Can We Prevent Type 1 Diabetes: The TRIGR Study

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## DISCLOSURES

<table>
<thead>
<tr>
<th>Organisations</th>
<th>Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novo Nordisk Pharma, Finland</td>
<td>Consultant</td>
</tr>
<tr>
<td>Eli Lilly Finland</td>
<td>Consultant</td>
</tr>
<tr>
<td>Valio Ltd</td>
<td>Consultant</td>
</tr>
<tr>
<td>Vactech Ltd</td>
<td>Board Member, Minor Shareholder</td>
</tr>
<tr>
<td>Mead Johnson Nutritionals</td>
<td>Provision of Study Formulas</td>
</tr>
</tbody>
</table>
INTEGRATED HYPOTHESIS

Type 1 diabetes is an immune-mediated disease, in which

- the genetic susceptibility is conferred by HLA and non-HLA genes;
- the disease process is triggered by an exogenous factor, most likely an infectious agent;
- driven by an exogenous antigen, potentially a dietary antigen;
- modified by a series of host-related and exogenous factors; and
- affected by gene-gene and gene-environmental interactions in each phase of the process.
PATHOGENESIS OF TYPE 1 DIABETES

Insulin secretory capacity, %

100

II. Trigger(s)

- IAA
- ICA
- GADA
- ZnT8A
- IA-2A

II. Trigger(s)

- FPIR
- IGT

2 months - >20 years

Modyfying factors

Clinical diabetes

IAA

ICA

GADA

ZnT8A

IA-2A

FPIR

IGT

III. Beta-cell autoimmunity

IV. Driving antigen(s)

I. Genetic susceptibility
CUMULATIVE INCIDENCE OF ICA, IAA, GADA, AND IA-2A

Kimpimäki et al. J Clin Endocrinol Metab 2002; 87: 4572-4579
NUTRITIONAL AGENTS OR FACTORS WITH A POTENTIAL ROLE IN THE DEVELOPMENT OF TYPE 1 DIABETES

- Breast-feeding
- Cow’s milk proteins, including bovine insulin
- Cereals
- Early introduction of complex foreign proteins
- Early introduction of fruits, berries and root vegetables
- Vitamin D deficiency
- Deficiency of omega-3 fatty acids
- Deficiency of major phospholipids
- Agents decreasing intestinal butyrate production
- High intake of branched-chain amino acids
RELATIVE RISK OF TYPE 1 DIABETES IN RELATION TO EARLY EXPOSURE TO COW’S MILK AND SHORT DURATION OF BREAST-FEEDING

Odds ratio

Exposure to cow’s milk < 4 mo of age

Breast-feeding < 3 mo

EFFECT OF EXCLUSIVE AND NON-EXCLUSIVE BREAST-FEEDING ON T1D RISK: A POOLED ANALYSIS OF 43 STUDIES

Cardwell et al. *Diabetes Care* 2012; 35: 2215-25
STRUCTURE OF HUMAN AND BOVINE INSULIN

A-chain

B-chain

HI: Thr
HI: Ile
HI: Thr
BI: Ala
BI: Val
BI: Ala
IgG antibodies to bovine insulin in formula-fed and breast-fed infants at the age of 3 months

$p<0.0001$

IgG antibodies to bovine insulin at the age of 3, 12 and 18 months in three groups of infants.

- **Infants with beta-cell autoimmunity**
- **Formula-fed infants**
- **Breast-fed infants**

FOREIGN FOODS TO WHICH INFANTS ARE FIRST EXPOSED IN FINLAND AND IN DENVER, COLORADO

**FINLAND**
Virtanen et al. 2002 (n=429)
- Potatoes and fruits: 13.5%
- Potatoes and carrots: 15%
- Fruits and berries: 5.5%
- CM only: 66%

**COLORADO, USA**
Norris et al., ADA 2002 (n = 1009)
- CM only: 55%
- CM + soy formula: 4%
- Soy formula only: 13%
- Cereal only: 15%
- Potatoes and fruits: 13.5%
- Potatoes and carrots: 15%
- CM + cereal: 6%
- Other: 7%
Early and late exposure to cereals and appearance of beta-cell autoimmunity

Norris et al. *JAMA* 2003; 290; 1713-1730
Ziegler et al. *JAMA* 2003; 290: 1721-1727
EARLY EXPOSURE TO FRUITS AND BERRIES AND ROOT VEGETABLES AND APPEARANCE OF BETA-CELL AUTOIMMUNITY

Subjects with beta-cell autoimmunity

- Fruits and berries (≤ 4 mo of age)  N=104
- Root vegetables (< 3 mo of age)      N=222

EARLY AND LATE EXPOSURE TO SUPPLEMENTARY FOODS IN INFANCY AND PROGRESSION TO T1D (N=53)

Norris et al. *JAMA Pediatrics* 2013; 167: 808-15
INTAKE OF COW’S MILK BEYOND INFANCY, BETA-CELL AUTOIMMUNITY AND PROGRESSION TO CLINICAL T1D


Hazard Ratio

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>High intake</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-cell autoimmunity</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>T1D</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Beta-cell autoimmunity</td>
<td>232</td>
<td></td>
</tr>
</tbody>
</table>
VITAMIN D AND RISK OF TYPE 1 DIABETES


Rate Ratio

Regular vs. no supplementation

Irregular vs. no supplementation

Suspected rickets

9.0
Odds ratios of effect of vitamin D supplementation in infancy on development of type 1 diabetes – a meta-analysis

Odds ratio meta-analysis plot (fixed effects)

Stene et al (2000)²¹ 1.01 (0.51 to 2.17)
Tenconi et al²⁶ 0.42 (0.17 to 0.95)
EURODIAB²⁰ Austria 1.26 (0.49 to 3.83)
EURODIAB²⁰ Bulgaria 2.09 (0.47 to 19.14)
EURODIAB²⁰ Latvia 1.21 (0.56 to 2.87)
EURODIAB²⁰ Lithuania 0.77 (0.19 to 3.67)
EURODIAB²⁰ Luxembourg 0.42 (0.21 to 0.83)
EURODIAB²⁰ Romania 0.67 (0.39 to 1.13)
EURODIAB²⁰ N. Ireland 0.55 (0.37 to 0.82)
Stene et al (2003)²² 0.78 (0.59 to 1.05)
Combined (fixed) 0.71 (0.60 to 0.84)
Odds ratio of vitamin D supplementatation in infancy and maternal supplementation during pregnancy: The most recent meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D Intake during Early Life</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EURODIAB study (1999)</td>
<td>0.67 (0.53, 0.85)</td>
<td>18.22</td>
</tr>
<tr>
<td>Stene (2000)</td>
<td>0.82 (0.47, 1.43)</td>
<td>12.84</td>
</tr>
<tr>
<td>Hypponen (2001)</td>
<td>0.22 (0.05, 0.93)</td>
<td>4.15</td>
</tr>
<tr>
<td>Stene (2003)</td>
<td>0.74 (0.56, 0.98)</td>
<td>17.48</td>
</tr>
<tr>
<td>Visalli (2003)</td>
<td>1.22 (0.82, 1.82)</td>
<td>15.48</td>
</tr>
<tr>
<td>Tenconi (2007)</td>
<td>0.27 (0.10, 0.72)</td>
<td>7.23</td>
</tr>
<tr>
<td>Ahadi (2011)</td>
<td>0.26 (0.11, 0.62)</td>
<td>8.34</td>
</tr>
<tr>
<td>Simpson (2011)</td>
<td>1.30 (0.91, 1.86)</td>
<td>16.26</td>
</tr>
<tr>
<td>Total (I-squared = 74.9%, p = 0.000)</td>
<td>0.71 (0.51, 0.98)</td>
<td>100.00</td>
</tr>
<tr>
<td>Maternal Vitamin D Intake during Pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stene (2000)</td>
<td>0.38 (0.12, 1.24)</td>
<td>8.74</td>
</tr>
<tr>
<td>Stene (2003)</td>
<td>1.00 (0.69, 1.45)</td>
<td>54.80</td>
</tr>
<tr>
<td>Marjamaki (2010)</td>
<td>1.08 (0.65, 1.79)</td>
<td>36.46</td>
</tr>
<tr>
<td>Total (I-squared = 23.7%, p = 0.269)</td>
<td>0.95 (0.66, 1.36)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
CIRCULATING 25-OH-VITAMIN D CONCENTRATIONS IN FINNISH AND ESTONIAN 4-YEAR OLD CHILDREN

INTAKE OF OMEGA-3 FATTY ACIDS AND DEVELOPMENT OF BETA-CELL AUTOIMMUNITY

Endpoint Persistent positivity for at least one AB or at least two ABs out of IAA, GADA and/or IA-2A

Norris et al. JAMA 2007; 298: 1420-8
USE OF COD LIVER OIL AND RISK OF TYPE 1 DIABETES

GLOBAL CHANGES IN UMBILICAL CORD LIPIDOME IN RELATION TO DIFFERENT TYPE 1 DIABETES-ASSOCIATED OUTCOMES

A

B

C

<table>
<thead>
<tr>
<th>Name</th>
<th>n</th>
<th>General LC description</th>
<th>Most abundant representative lipids</th>
<th>Case group vs. controls (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LC1</td>
<td>4</td>
<td>Unknown lipids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LC2</td>
<td>49</td>
<td>Major phospholipids</td>
<td>PC(36:4), PC(16:0/18:1), PC(34:2), PC(36:5), PC(38:5), SM(d18:1/24:1), SM(d18:1/16:0), PC(18:1/20:4), PC(38:5e)</td>
<td>0.484, 0.656, 0.569, 0.142</td>
</tr>
<tr>
<td>LC3</td>
<td>14</td>
<td>LPCs</td>
<td>LPC(16:0), LPC(18:1), LPC(20:4), LPC(22:6)</td>
<td>0.664, 0.869, 0.730, 0.821</td>
</tr>
<tr>
<td>LC4</td>
<td>10</td>
<td>Minor phospholipids</td>
<td>PC(40:3), PC(33:1), SM(d18:1/23:0)</td>
<td>0.380, 0.309, 0.473, 0.587</td>
</tr>
<tr>
<td>LC5</td>
<td>10</td>
<td>Primarily unknown</td>
<td>PC(34:4e)</td>
<td>0.750, 0.710, 0.257, 0.666</td>
</tr>
<tr>
<td>LC6</td>
<td>17</td>
<td>PUFA containing phospholipids</td>
<td>PC(38:4), PC(38:6), PE(38:4)</td>
<td>0.776, 0.504, 0.173, 0.446</td>
</tr>
<tr>
<td>LC7</td>
<td>7</td>
<td>Minor SMs</td>
<td>SM(d18:0/16:0), SM(d18:0/18:0)</td>
<td>0.092, 0.752, 0.048, 0.577</td>
</tr>
<tr>
<td>LC8</td>
<td>16</td>
<td>Major TGs containing SFAs and MUFAs</td>
<td>TG(16:0/18:1/18:1), TG(16:0/16:1/18:1), TG(16:0/16:0/18:1)</td>
<td>0.726, 0.720, 0.425, 0.794</td>
</tr>
<tr>
<td>LC9</td>
<td>23</td>
<td>Major TGs containing MUFAs and PUFAs</td>
<td>TG(16:0/18:2/18:1), TG(16:0/18:2/18:2)</td>
<td>0.757, 0.379, 0.803, 0.602</td>
</tr>
<tr>
<td>LC10</td>
<td>9</td>
<td>Long-chain TGs containing PUFAs</td>
<td>TG(56:7), TG(56:8), TG(58:8)</td>
<td>0.812, 0.032, 0.420, 0.264</td>
</tr>
</tbody>
</table>

The trend of upregulation or downregulation in cases vs. pooled controls is marked as ↑ or ↓, respectively, if \( P < 0.25 \). \( P < 0.05 \) in bold. Aab, autoantibody; MUFA, monounsaturated fatty acid; PUFAs, polyunsaturated fatty acid; SFA, saturated fatty acid.
DEARTH OF *BIFIDOBACTERIUM ADOLESCENTIS* AND *PSEUDOCATENULATUM*

AMONG CHILDREN WITH SIGNS OF BETA-CELL AUTOIMMUNITY

de Goffau et al. *Diabetes* 2013;62:1238-44
DECREASED DIVERSITY OF GUT MICROBIOTA AMONG PROGRESSORS

Giongo et al. *ISME J* 2010; 5: 82-91

DIPP 2011
Mining of 16S rRNA data suggests case/control functional differences

Hypothesis: a healthier gut microbiome in healthy children

Four lines of evidence:

2. More reads from species with pathogenic potential in autoimmune children.
3. Bacterial diversity higher in healthy children.
4. Microbiomes from healthy children more closely related to each other than those from autoimmune children.

Giongo et al. ISME J 2010; 5: 82-91
NUTRITIONAL AGENTS AND PREVENTION OF TYPE 1 DIABETES: POTENTIAL INTERVENTION ALTERNATIVES I

- Breastfeeding: *Intervention studies not feasible of ethical reasons*

- Cow’s milk proteins, including bovine insulin: *No or reduced intake of bovine insulin (FINDIA)*

- Cereals: *No or decreased intake of cereals (BABYDIET)*

- Early introduction of complex foreign proteins: *Postponed introduction of complex foreign proteins (TRIGR)*

- Vitamin D deficiency: *Increased vitamin D supplementation*

- Early introduction of fruits, berries and root vegetables: *Delayed introduction of fruits, berries and roots*
Deficiency of omega-3 fatty acids: *Supplementation of the diet with relevant fatty acids (The TrialNet Nutritional Intervention to Prevent type 1 diabetes, NIP)*

Deficiency of major phospholipids: *Supplementation of the diet with major phospholipids or their precursors*

Agents decreasing intestinal butyrate production: *Supplementation of the diet with starch that escapes digestion in the small intestine. Such starches enhance the abundance of butyrate-producing bacteria in colon*

Reduced intake of branched-chain amino acids: *Reduced intake of branched-chain amino acids*
EFFECT OF WEANING TO AN INSULIN-FREE FORMULA ON THE APPEARANCE OF BETA-CELL AUTOIMMUNITY

The insulin-free formula

$P=0.01$

BABYDIET: EFFECT OF DELAYED EXPOSURE TO DIETARY GLUTEN ON THE APPEARANCE OF BETA-CELL AUTOIMMUNITY

Any autoantibody out of IAA, GADA and/or IA-2A

Late exposure (12 mo)
Early exposure (6 mo)

P = 0.6

Multiple autoantibodies

P = 0.7

TRIGR PILOT RESEARCH QUESTION

IS IT POSSIBLE TO REDUCE THE FREQUENCY OF DIABETES-ASSOCIATED AUTOANTIBODIES BY EXCLUDING DIETARY COW’S MILK PROTEINS OVER THE FIRST 6-8 MONTHS OF LIFE IN SUBJECTS AT INCREASED RISK OF T1D?

The TRIGR Pilot
THE APPEARANCE OF AT LEAST ONE AUTOANTIBODY

THE APPEARANCE OF TWO OR MORE AUTOANTIBODIES

HAZARD RATIOS FOR WEANING TO AN EXTENSIVELY HYDROLYZED FORMULA

Table 1. Hazard Ratios with Highly Hydrolyzed Infant Formula, as Compared with Conventional Cow’s-Milk–Based Formula, for Seroconversion to Positivity for Autoantibodies Predictive of Type 1 Diabetes.*

<table>
<thead>
<tr>
<th>Autoantibodies</th>
<th>No. Who Underwent Seroconversion</th>
<th>Hazard Ratio with Highly Hydrolyzed Formula (95% CI)</th>
<th>P Value</th>
<th>Adjusted Hazard Ratio with Highly Hydrolyzed Formula (95% CI)†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Islet-cell antibodies</td>
<td>37</td>
<td>0.38 (0.18–0.77)</td>
<td><strong>0.006</strong></td>
<td>0.37 (0.17–0.75)</td>
<td><strong>0.005</strong></td>
</tr>
<tr>
<td>Insulin autoantibodies</td>
<td>23</td>
<td>0.72 (0.30–1.64)</td>
<td>0.45</td>
<td>0.61 (0.25–1.42)</td>
<td>0.26</td>
</tr>
<tr>
<td>GAD autoantibodies</td>
<td>23</td>
<td>0.87 (0.37–1.97)</td>
<td>0.74</td>
<td>0.80 (0.34–1.85)</td>
<td>0.61</td>
</tr>
<tr>
<td>IA-2 autoantibodies</td>
<td>20</td>
<td>0.36 (0.12–0.94)</td>
<td><strong>0.04</strong></td>
<td>0.32 (0.10–0.83)</td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td>ZnT8 autoantibodies</td>
<td>14</td>
<td>0.61 (0.19–1.77)</td>
<td>0.37</td>
<td>0.61 (0.19–1.79)</td>
<td>0.37</td>
</tr>
<tr>
<td>≥1 Antibody</td>
<td>50</td>
<td>0.54 (0.29–0.95)</td>
<td><strong>0.03</strong></td>
<td>0.51 (0.28–0.91)</td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td>≥2 Antibodies</td>
<td>25</td>
<td>0.52 (0.21–1.17)</td>
<td>0.12</td>
<td>0.47 (0.19–1.07)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

QUESTION OF TRIGR STUDY PROPER

IS IT POSSIBLE TO REDUCE

(i) THE FREQUENCY OF DISEASE-ASSOCIATED AUTO-
   ANTIBODIES AND/OR CLINICAL DIABETES BY THE
   AGE OF 6 YEARS AND

(ii) THE CUMULATIVE INCIDENCE OF DIABETES BY
   THE AGE OF 10 YEARS

BY WEANING TO A HIGHLY HYDROLYZED FORMULA
OVER THE FIRST 6-8 MONTHS OF LIFE?

Knip et al. JAMA 2014; 311: 2279-87
TRIGR: Population

- Newborn infants with a first-degree relative with type 1 diabetes
- HLA genotype conferring increased risk for type 1 diabetes
- Gestational age ≥ 35 weeks
- No cow’s milk protein prior to randomization
- No major anomalies, life threatening conditions, or abnormal karyotype

Knip et al. *JAMA* 2014; 311: 2279-87
TRIGR: Sample Size

- 2,032 infants to receive intervention, HLA screen around 5,200
- 95% confidence level
- 80% statistical power
- 40% reduction of type 1 diabetes by 10 years
- 20% dropout rate
- 10% exclusive breastfeeding to 6 months

Knip et al. JAMA 2014; 311: 2279-87
CURRENT STATUS OF TRIGR

- 77 PARTICIPATING CENTERS FROM 15 COUNTRIES
- 2159 RANDOMIZED PARTICIPANTS, THE OLDEST CHILD HAS TURNED 12 YEARS AND THE YOUNGEST IS 7-YEAR-OLD AND WILL TURN 10 IN EARLY 2017
TRIGR: Intervention

**6 Months**
- Breast milk
- Study formula for at least 60 days
  - Intact cow’s milk protein + 20% casein hydrolysate
  - Casein hydrolysate
- No cow or soy milk or bovine protein

**6-8 Months**
- If exclusive breastfeeding up to the age of 6 months, study formula to be used for 2 months

Knip et al. *JAMA* 2014; 311: 2279-87
TRIAL PROFILE OF TRIGR

5156 Newborn infants screened for HLA risk and randomized

2159 Were eligible

2841 Infants excluded based on their HLA genotype

156 Infants excluded based on exclusion criteria other than HLA

1078 Were assigned to be weaned an extensively hydrolyzed formula

43 Withdrew without providing any follow-up samples

1035 Provided at least one follow-up sample

1081 Were assigned to be weaned to a regular cow’s-milk-based formula

1035 Provided at least one follow-up sample

46 Withdrew without providing any follow-up samples

Knip et al. JAMA 2014; 311: 2279-87
FOLLOW-UP TIME BY THE TIME OF THE ANALYSIS OF THE AUTOANTIBODY DATA

- Mean 7.0 years

- Median 6.3 years (range 0.3-10.3 years)

Knip et al. JAMA 2014; 311: 2279-87
### Demographic Characteristics of the Trial Participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Casein Hydrolsate Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, % male</td>
<td>53.3</td>
<td>52.4</td>
</tr>
<tr>
<td>Gestational age, weeks, mean (SD)</td>
<td>38.7 (1.6)</td>
<td>38.8 (1.6)</td>
</tr>
<tr>
<td>Birth weight, g, mean (SD)</td>
<td>3585 (539)</td>
<td>3625 (558)</td>
</tr>
<tr>
<td>Birth length, cm, mean (SD)</td>
<td>50.9 (2.8)</td>
<td>51.1 (2.8)</td>
</tr>
<tr>
<td>Family history of type 1 diabetes;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>affected mother</td>
<td>49.1</td>
<td>48.6</td>
</tr>
<tr>
<td>affected father</td>
<td>32.9</td>
<td>34.0</td>
</tr>
<tr>
<td>affected sibling</td>
<td>14.0</td>
<td>14.6</td>
</tr>
<tr>
<td>more than one affected family member, %</td>
<td>4.0</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Knip et al. *JAMA* 2014; 311: 2279-87
## HLA Genotypes in the Trial Participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Casein Hydolysate Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA genotype, %;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLADQB1<em>02/DQB1</em>03:02;</td>
<td>24.1</td>
<td>23.7</td>
</tr>
<tr>
<td>HLA-DQB1<em>03:02/x (x not DQB1</em>02, DQB1<em>03:01 or DQB1</em>06:02);</td>
<td>44.2</td>
<td>44.1</td>
</tr>
<tr>
<td>HLA-DQA1<em>05-DQB1</em>02/y (y not DQA1<em>02:01-DQB1</em>02, DQB1<em>03:01, DQB1</em>06:02 or DQB1*06:03);</td>
<td>30.7</td>
<td>31.2</td>
</tr>
<tr>
<td>HLA-DQA1<em>03-DQB1</em>02/y (y not DQA1<em>02:01-DQB1</em>02, DQB1<em>03:01, DQB1</em>06:02 or DQB1*06:03);</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Knip et al. *JAMA* 2014; 311: 2279-87
## Intervention Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Casein Hydrolysate</th>
<th>Standard formula</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed to the study formula, %</td>
<td>80.0</td>
<td>80.9</td>
<td>NS</td>
</tr>
<tr>
<td>Age at introduction of study formula, months,</td>
<td>2.0 (2.3)</td>
<td>1.8 (2.2)</td>
<td>0.05</td>
</tr>
<tr>
<td>Duration of study formula feeding, weeks,</td>
<td>10.2 (9.3)</td>
<td>11.7 (9.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume of study formula consumed, mean (SD)</td>
<td>42.3 (59.4)</td>
<td>48.7 (60.1)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Knip et al. *JAMA* 2014; 311: 2279-87
IgA CLASS ANTIBODIES TO COW’S MILK IN TRIGR

Casein hydrolysate

Standard formula

Knip et al. JAMA 2014; 311: 2279-87
THE APPEARANCE OF AT LEAST ONE AUTO-ANTIBODY IN TRIGR
THE APPEARANCE OF AT LEAST TWO AUTO-ANTIBODIES IN TRIGR

Knip et al. JAMA 2014; 311: 2279-87
HAZARD RATIOS (HR; 95% CI) FOR WEANING TO A HIGHLY HYDROLYZED CASEIN-BASED FORMULA

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted HR</th>
<th>Adjusted HR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positivity for at least one</td>
<td>1.06 (0.93;1.22)</td>
<td>1.09 (0.94;1.24)</td>
</tr>
<tr>
<td>autoantibody</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positivity for at least two</td>
<td>1.21 (0.94;1.54)</td>
<td>1.23 (0.96;1.58)</td>
</tr>
<tr>
<td>autoantibodies</td>
<td></td>
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</tbody>
</table>

*adjusted for for HLA risk, duration of breast-feeding, study formula duration and consumption, and region (Finland, Canada, USA, and other)

Knip et al. *JAMA* 2014; 311: 2279-87
<table>
<thead>
<tr>
<th>Event</th>
<th>Casein Hydrolysate</th>
<th>Control Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Respiratory Infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>0.0136</td>
<td>0.0127</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>0.0013</td>
<td>0.0012</td>
</tr>
<tr>
<td>Middle Ear Infection</td>
<td>0.0172</td>
<td>0.0185</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0.0010</td>
<td>0.0011</td>
</tr>
<tr>
<td>Other Infection</td>
<td>0.0286</td>
<td>0.0285</td>
</tr>
<tr>
<td>Suspected Study Formula Intolerance</td>
<td>0.0007</td>
<td>0.0008</td>
</tr>
<tr>
<td>Asthma, Other Forms of Allergy</td>
<td>0.0056</td>
<td>0.0063</td>
</tr>
<tr>
<td>Malignancy</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>Accident (Not Requiring Hospitalization)</td>
<td>0.0015</td>
<td>0.0015</td>
</tr>
<tr>
<td>Accident (Requiring Hospitalization)</td>
<td>0.0002</td>
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<tr>
<td>Death</td>
<td>0.0001</td>
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<tr>
<td>Other</td>
<td>0.0406</td>
<td>0.0398</td>
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<tr>
<td>Hypoglycemia requiring IV glucose</td>
<td>0.0001</td>
<td>0.0003</td>
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<td>Event requiring inpatient hospitalization or prolongation of existing hospitalization</td>
<td>0.0007</td>
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<tr>
<td>Life-threatening event</td>
<td>0.0000</td>
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<tr>
<td>Persistent or significant disability/incapacity</td>
<td>0.0000</td>
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<tr>
<td>Any Infection</td>
<td>0.0978</td>
<td>0.0997</td>
</tr>
<tr>
<td>Serious Event (Onset &lt;= April 26, 2006)*</td>
<td>0.0124</td>
<td>0.0119</td>
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<tr>
<td>Serious Event (Onset &gt;= April 27, 2006)*</td>
<td>0.0010</td>
<td>0.0009</td>
</tr>
<tr>
<td>Study Related Serious Event (Onset &lt;= April 26, 2006)*</td>
<td>0.0001</td>
<td>0.0000</td>
</tr>
<tr>
<td>Study Related Serious Event (Onset &gt;= April 27, 2006)*</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
</tbody>
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The intervention is safe

The compliance with the dietary intervention has been good

There are no significant differences in the appearance of diabetes-associated autoantibodies between the two groups by the age of 7 years

Currently there is no conclusive evidence to revise the dietary recommendations for infants at increased risk for type 1 diabetes

There is a definite need to continue the follow-up of all TRIGR participants as planned (until the youngest one turns 10 years of age)

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PATHOGENESIS OF TYPE 1 DIABETES

I. Genetic susceptibility

II. Trigger

IIA. Beta-cell autoimmunity

IIA.1. IAA

IIA.2. ICA

IIA.3. GADA

IIA.4. ZnT8A

IIA.5. IA-2A

IIA.6. FPIR

IIA.7. IGT

III. Beta-cell autoimmunity

IV. Driving antigen

Modyfying factors

Clinical diabetes

Insulin secretory capacity, %

Healthy

Clinical disease
Lesson I from the NOD mice: The casein hydrolysate prevents autoimmune diabetes

Karges et al. *Diabetes* 1997;46:557-64
Lesson II from the NOD mice: The casein hydrolysate does not prevent insulitis

Karges et al. *Diabetes* 1997;46:557-64
THANKS

All participating TRIGR children and families
All TRIGR Study Group members
- Local study center staff
- TRIGR investigators
- ICC staff
- DMU staff
- TRIGR laboratory staff
- IEC members
- DSMB members
GENERAL CONCLUSIONS I

- Dietary interventions aimed at primary prevention of type 1 diabetes should be started early in life, possibly already during pregnancy.

- All dietary interventions performed so far have turned out to be safe, which is of outermost importance when treating infants and young children.

- So far very few dietary intervention trials aimed at secondary prevention of type 1 diabetes have been performed.
GENERAL CONCLUSIONS II

- A variety of diet-related factors have been implicated to increase the risk of developing signs of beta-cell autoimmunity and/or clinical type 1 diabetes

- Of those tested so far in randomized clinical pilot trials early elimination of bovine insulin have shown promising results

- There are some novel approaches that have to be tested in future randomized clinical trials
JOINPOINT REGRESSION ANALYSIS OF THE INCIDENCE OF TYPE 1 DIABETES IN FINNISH CHILDREN UNDER THE AGE OF 15 YEARS 1980-2012

Vitamin D, 1000 IU/day
Supplementation of milk products, 20 IU/dl 40 IU/dl
400 IU/day

Harjutsalo et al. JAMA 2013; 310: 427-428
<table>
<thead>
<tr>
<th>Research Group</th>
<th>National</th>
<th>International</th>
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<tbody>
<tr>
<td>Hans K. Åkerblom</td>
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<td>Valma Harjutsalo</td>
<td>Hans-Michael Dosch</td>
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<tr>
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<td>Anu-Maaria Hämäläinen</td>
<td>John Dupretal</td>
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<td>Heikki Höyty</td>
<td>Natalya Dorshakova</td>
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<td>Samppa Ryhänen</td>
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<td>Olli Simell</td>
<td>Vallo Tillmann</td>
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<td>Raivo Uibo</td>
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<td></td>
<td>Riitta Veijola</td>
<td>DIABIMMUNE Study Group</td>
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<td></td>
<td>Suvi Virtanen</td>
<td>TEDDY Study Group</td>
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<td>DIPP Study Group</td>
<td>TRIGR Study Group</td>
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<td>Finnish Pediatric Diabetes Register and Biobank</td>
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Canadian Institute of Health Research

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