EARLY SUPPLEMENTATION OF NON-OBESE DIABETIC MICE WITH OLIGOSACCHARIDES ISOLATED FROM HUMAN MILK REDUCES SPONTANEOUS AUTOIMMUNE DIABETES DEVELOPMENT LATER IN LIFE

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HUMAN MILK OLIGOSACCHARIDES: EFFECTS ON THE IMMUNE SYSTEM

Breastfeeding is associated with immunological benefits (less allergies, less infections)

Human milk oligosaccharides (HMOS) can modulate the immune system directly or indirectly

Research questions:
→ Can HMOS affect the development of autoimmune disease?
→ Can early exposure to HMOS affect disease in later life (programming)?

EVERY BABY NEEDS A SUGAR MAMA
L. Bode, Glycobiology 22(9):1147–1162, 2012
EXPERIMENTAL SETUP

Non-obese diabetic (NOD/ShiLtJ) mice: spontaneous autoimmune (type I diabetes) development, sensitive to dietary influences

HMOS: isolated from a pooled mature human milk sample and reduced in lactose (84% HMOS, 16% lactose; method: Geisser et al, J Chromatogr A, 2005)

- Comparison: AIN-93M control diet versus AIN-93M diet + 1% (w/w) HMOS
- Primary readout: urine glucose detection (>300 mg/dL)
- Secondary readouts: blood glucose, pancreas histology, flow cytometric analysis of splenocytes

Weeks 0-29:

1. Control diet (n=20)
2. HMOS wk 4-10 (n=20)
EARLY HMOS DIETARY EXPOSURE REDUCES DIABETES DEVELOPMENT

**Diabetes development**

![Graph showing diabetes-free survival over weeks of follow-up for control and HMOS groups.](image)

* p=0.031

**Endpoint measurements**

**Urine glucose score results**

- Non-diabetic
- Diabetic

Fisher exact: p=0.04

**Blood glucose levels**

- Diabetic
- Non-diabetic

food intake & body weight were similar between experimental groups
REDUCED ACTIVATION OF SPLEEN CD4 T-CELLS AND REGULATORY T-CELLS IN HMOS GROUP

Reduced T-regulatory cells

Reduced activated T-helper cells

Related to decreased overall immune activation marker expression?

No increase in Tregs was observed, in contrast to effects of breastfeeding on T1D in BB rats (Brugman et al. 2009, Diabetes Metab Res Rev, 25(4):380-7)

No differences were observed in % of Th1, Th2 or Th17 cells between dietary groups
Each islet of each section was scored by this system:

0 = No Insulitis
1 = Peri-Insulitis
2 = Insulitis affecting less than 50% of the islet area
3 = Insulitis affecting more than 50% of the islet area
4 = Complete Insulitis

Average of 46 islets per animal were analyzed
DECREASED INSULITIS IN HMOS GROUP

Most prevalent insulitis score per animal

- Complete Insulitis
- Insulitis>50%
- Insulitis<50%
- Peri-insulitis
- No insulitis

Normalized score (range 0-4)

Insulitis scores showed a partial correlation with urine glucose values, but many normoglycemic animals showed variable levels of insulitis.
CONCLUSIONS

Low level supplementation with the complex mixture\(^1\) of HMOS in early life reduces autoimmune diabetes development in NOD mice later in life

- Urine & blood glucose levels
- Pancreas inflammation

Analysis of systemic immune cell populations revealed lower CD4 T-cell activation levels and lower percentages of Tregs

- Lower Treg levels may be related to lower immune activation

HMOS in early life modulate immune responses in later life: an example of immunological programming

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