The Association Between Reported Dietary Intake of Vitamin D and Cow's Milk Proteins in the Development of Islet Autoimmunity (IA)

M.D. Simpson, K. Barriga, X. Yin, H. Brady, M. Rewers, J.M. Norris

Department of Preventive Medicine and Biometrics and The Barbara Davis Center for Childhood Diabetes, University of Colorado Denver

Study Objective

To investigate the associations between infant diet, current vitamin D intake, and current cow's milk intake and the risk for islet autoimmunity (IA)

Background

- Islet autoimmunity
  - Condition preceding clinical type 1 diabetes (T1D)
  - Used as a surrogate outcome because it is highly predictive of T1D
- Vitamin D
  - Preferentially stimulates a Th1 immune response, T1D is mediated by a Th1 response
  - Published literature shows a protective association between vitamin D and T1D
- Cow's milk
  - Has been hypothesized as diabetogenic
  - In our cohort ~48% of total vitamin D intake is from fluid milk
- Infant diet
  - Interactions between infant diet and current diet have not been explored prospectively

Population

- Study population assembled from the Diabetes Autoimmunity Study in the Young (DAISY)
- DAISY is a prospective study following children at increased risk for development of type 1 diabetes
  - The goal of the study is to identify environmental etiologies for T1D
  - Increased risk defined by having a first degree relative with type 1 diabetes or having a high risk genotype (HLA-DR3/4, DQB1*0302)

Methods

- Current intake of vitamin D (in international units, IU) and cow's milk protein (in grams) measured by annual food frequency questionnaire given to parents
- Infant diet assessed while study subjects were infants via telephone and in clinic interviews of parents at 3, 6, 9, 12, and 15 months of life
- IA is defined by having insulin, glutamic acid decarboxylase, or insulinoma-associated antigen-2 autoantibodies on 2 consecutive visits and still autoantibody positive or diagnosed with type 1 diabetes at their last follow up visit
- Survival analysis using IA as the outcome was performed to estimate hazard ratios (HR) and 95% confidence intervals (C.I.)
- In these analyses:
  - 1785 children with complete dietary data
  - 57 have developed IA

Description of Dietary Intakes in DAISY Cohort

Dietary intake variable	3 - Year olds (n = 1083)	5 - Year olds (n = 862)	7 - Year olds (n = 657)	9- Year olds (n = 357)
Cow's milk protein (g/day)	30.76 (19.96)	27.65 (17.59)	24.63 (15.57)	24.16 (13.62)
Vitamin D (IU/day)	428.77 (222.58)	409.99 (207.13)	373.40 (182.43)	383.39 (192.49)

Study Population Characteristics

Characterstic	Children positive for IA n = 57(%)	Children negative for IA n = 1728(%)	Unadjusted HR (95% CI)	*P* Value
Age years (mean)	4.6 (2.5)	6.7 (3.5)	NA	NA
HLA-DR3/4, DQB1*0302 genotype	25 (44)	350 (20)	2.77(1.64-4.68)	<0.0001
Family history of type 1 diabetes	37 (65)	864 (50)	1.96(1.14-3.40)	0.02
Female	38 (58)	822 (48)	1.52(0.90-2.57)	0.12
Non-hispanic white ethnicity	47 (82)	1318 (46)	1.22(0.62-2.43)	0.56
Maternal education > high school (mean)	51 (89)	1353 (79)	1.76(0.24-12.70)	0.58
Maternal age at subject's birth (mean)	31.2 (4.7)	30.2 (5.6)	1.02(0.97-1.07)	0.39
Breast feeding duration < 3 months	23(40)	641(380)	1.26(0.97-1.07)	0.39
Cow's milk introduction < 3 months	32(49)	832(49)	0.96(0.77-1.62)	0.88
Cereal introduction ≤ 3months or ≥ 7 months	16(28)	466(28)	1.07(0.60-1.90)	0.83

Results

- Adjusting for having a high risk genotype, having a first degree relative with T1D, daily caloric intake, and n3 and n6 polyunsaturated fatty acids, both vitamin D and cow's milk protein were associated with IA when they were included in the same model
  - Vitamin D HR: 0.71 (95% CI: 0.51-0.99)
  - Cow's milk protein HR: 1.37 (95% CI: 1.07–1.74)
  - Neither one of these variables was associated with IA in the absence of the other in the model
- Exploration of effect modification revealed two interactions with current vitamin D intake
- The interaction between the age at introduction to cow's milk and current vitamin D intake was significant (p = 0.02). See figure 1
  - Adjusting for cow's milk and the variables listed above, the hazard ratio for vitamin D intake was 0.49 (95% CI: 0.31-0.79) in children who were exposed to cow's milk at 3 months of age or older
  - The hazard ratio for vitamin D intake was 0.99 (95% CI: 0.67-1.50)
- The interaction between the age at introduction to cereal and current vitamin D intake was marginal (p = 0.05). See figure 2
  - Adjusting for current cow's milk intake and the variables listed above, the hazard ratio for vitamin D intake was 0.59 (95% CI: 0.39 – 0.88) in children who were exposed to cereal at 4-6 months of age
  - The hazard ratio for vitamin D intake was 1.05 (95% CI: 0.65 – 1.70) in children who were exposed to cereal younger than 3 months of age or 7 months of age and older
- Effect modification between infant diet variables and cow's milk protein was tested and none was detected

Figure 1: Interaction Between Current Vitamin D Intake and Age at Introduction to Cow's Milk

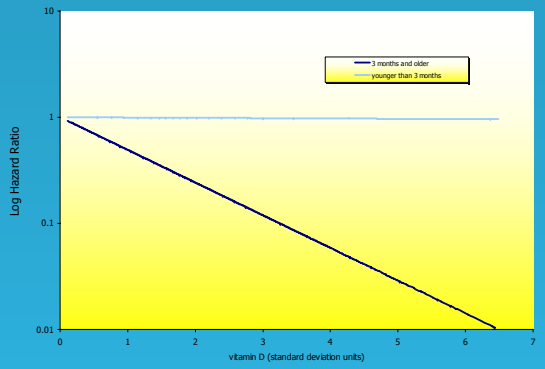
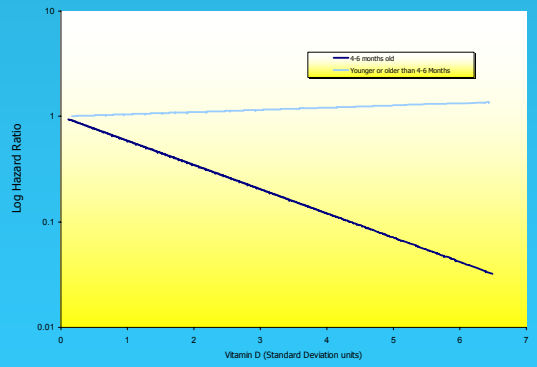


Figure 2: Interaction Between Current Vitamin D Intake and Age at Introduction to Cereal



Summary and Conclusion

- Our results highlight the complexity of the relationship between cow's milk and vitamin D, given that protein from cow's milk and vitamin D from cow's milk appear to have opposite associations with the risk for IA
- The association between the risk for IA and current vitamin D intake appears to be modified by the timing of dietary exposures during infancy
  - Possible interpretation: The timing of dietary exposures in infancy may lead to early nutritional programming that influences the way children in this population are able to utilize nutrients later in life