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DENTISTRY

Associations Between Longitudinal Fluoride Intake and Bone Densitometry Outcomes at 23 Years

Gurjot K. Bhatia, Dr. Steven M. Levy, Chandler Pendleton, Dr. John J. Warren, Dr. Erliang Zeng, Dr. Punam K. Saha
The University of Iowa, College of Dentistry and Dental Clinics, College of Engineering, College of Medicine, Iowa City, IA

Introduction

- **Fluoride for Caries Prevention**
- **Community Water Fluoridation**
  - The most cost-effective method of delivering fluoride[1]
  - Reduces tooth decay by 25% in children and adults[2]
- **Fluoride and Bone Fracture Outcomes**
  - Conflicting findings for associations between long-term fluoride exposure and the risk of bone fracture[3-8]
  - Insufficient evidence to establish that water fluoride levels of 2 mg/L are associated with higher fracture rates[9] (US National Academy of Sciences' review of fluoride in drinking water (2006))
- **Fluoride and Non-Fracture Bone Outcomes**
  - Few age-stratified studies on the associations between fluoride intake and bone densitometry outcomes:
  - **Childhood:** 4 studies from 1982-2018[10-13]
  - **Adolescence:** 5 studies from 1982-2018[10-11,14-16]
  - **Early adulthood:** 2 studies from 1997 and 2021[17-18]

Background

- Most studies were ecological- conflicting results concerning effects of fluoride on bone.
- The few longitudinal studies that assessed relationships between fluoride intake and bone development in children, adolescents, or young adults had:
  - Small sample sizes
  - Less refined densitometry methods
- Substantial gaps in understanding of the effects of F and other factors on bone development during the adolescent-adult transition period[19].

Purpose

- To investigate the effects of period-specific and cumulative daily fluoride intake from birth to 23 years of age on cortical and trabecular bone microstructural outcomes.
  - Secondary data analysis of previously-collected and de-identified data from the Iowa Fluoride Study (IFS) and the Iowa Bone Development Study (IBDS) (prospective cohort study).

Methods

- The Iowa Fluoride Study (IFS) began in 1992 with the recruitment of 1,882 newborn participants from postpartum wards of 8 Iowa hospitals.
  - In 1998, the families that were still a part of IFS were invited to join the IBDS[12]
- Approved by the Institutional Review Board (IRB) of the University of Iowa.
- Informed consent was obtained from the parents and then later the adult subjects.
- For this study, distal tibia multi-detector computed tomography (MDCT) scans were obtained from 330 participants.
- Information about fluoride intake from each individual source and combined from all sources (water, beverages other than water and selected foods, dietary fluoride supplements, and dentifrices) obtained through the Iowa Fluoride Study (IFS) Questionnaires at:
  - 1. Specific time points (Point-specific) (mgF/day)
  - 2. Over defined periods of time (Period-specific) (in mg F/day using the area-under-the-curve (AUC) estimates.
- These anthropometric measurements were obtained: height, weight, Tanner Staging of development, years since peak height velocity (PHV)
- Data on dietary calcium, vitamin D and protein intake obtained through Modified Iowa Fluoride Study (IFS) Questionnaire, Diet History Questionnaire-II (DHQ-II), and Healthy Eating Index Version-2010 (HEI-2010)
- Data on physical activity obtained through Physical Activity Questionnaire (PAQ)
  - MDCT Protocol:
    - Developed by Dr. Saha and colleagues in his laboratory at the University of Iowa
    - 4 steps:
      1. Region of Interest (ROI) Selection
      2. CT Image Processing and Bone Measures
      3. Post-Image Processing
      4. Computation of Bone Microstructural Measures

Statistical Analyses

- **Univariate analysis:** Sex-specific descriptive statistics generated.
- **Bivariate analysis:** Sex-specific unadjusted one-variable linear regression conducted between MDCT distal tibia measures (dependent variables) and period-specific and cumulative fluoride intake variables (independent variables).
- **Multivariable analysis:** Sex-specific multivariable linear regression conducted between MDCT distal tibia measures (dependent) and period-specific and cumulative fluoride intake variables (independent), adjusted for covariates*.
  - Statistical significance level was set at $p<0.01$ due to multiple statistical tests conducted, while suggestive associations were defined as $0.01<p<0.05$.

*Covariates were: height, weight, years since peak height velocity (PHV), dietary calcium intake, HEI-2010 scores, and PAQ scores.

Results

Table 1. Average daily estimated fluoride intakes (AUC mg F) stratified by sex.

Variable (Time Period)	N	Mean	Min.	1st pctl	5th pctl	10th pctl	25th pctl	Med.	75th pctl	90th pctl	95th pctl	99th pctl	Max.
FEMALES													
0 - 8 years	159	0.67	0.29	0.16	0.27	0.31	0.36	0.49	0.62	0.80	1.01	1.48	2.41
8 - 15 years	137	0.70	0.31	0.16	0.21	0.32	0.35	0.48	0.64	0.85	1.07	1.66	1.82
15 - 23 years	124	0.93	0.46	0.23	0.25	0.34	0.39	0.63	0.84	1.14	1.56	2.17	2.58
0 - 23 years	138	0.76	0.29	0.25	0.33	0.41	0.46	0.55	0.69	0.92	1.15	1.62	2.19
MALES													
0 - 8 years	114	0.73	0.31	0.13	0.19	0.35	0.39	0.50	0.68	0.89	1.14	1.54	1.97
8 - 15 years	108	0.81	0.39	0.21	0.25	0.35	0.39	0.55	0.72	1.01	1.34	2.00	2.04
15 - 23 years	89	1.12	0.58	0.33	0.36	0.43	0.54	0.71	1.00	1.38	1.78	3.28	3.30
0 - 23 years	101	0.91	0.36	0.28	0.35	0.44	0.50	0.64	0.87	1.08	1.41	1.95	2.07

Table 2. Multivariable associations* between period-specific fluoride intakes and MDCT bone measures – FEMALES

		Age 0-8 F intake (mg)		Age 8-15 F intake (mg)		Age 15-23 F intake (mg)		Age 0-23 F intake (mg)	
Group	Characteristic	Beta (95% CI)	pval	Beta (95% CI)	pval	Beta (95% CI)	pval	Beta (95% CI)	pval
Trabecular	Tb.vBMC (mg)	56.80 (-178.43, 292.03)	0.64	203.01 (-30.63, 436.64)	0.09	114.46 (-50.33, 279.24)	0.18	197.07 (-58.25, 452.40)	0.13
	Tb.vBMD (mg/cc)	6.02 (-12.13, 24.18)	0.52	-2.15 (-20.07, 15.77)	0.82	3.99 (-8.87, 16.86)	0.54	7.47 (-12.31, 27.25)	0.46
	Tb.tBMD (mg/cc)	8.24 (-34.00, 50.49)	0.71	-10.16 (-52.36, 32.05)	0.64	7.67 (-22.74, 38.09)	0.62	17.26 (-29.88, 64.41)	0.47
	Tb.pBMD (mg/cc)	3.05 (-83.24, 89.34)	0.95	-25.06 (-109.33, 59.20)	0.56	2.96 (-58.21, 64.13)	0.93	12.52 (-80.82, 105.85)	0.80
	Tb.NA (mm^2)	0.01 (-0.12, 0.15)	0.83	-0.04 (-0.17, 0.09)	0.54	6.30×10^{-3} (-0.09, 0.10)	0.90	0.03 (-0.12, 0.18)	0.71
	Tb.PW (mm)	-36.37 (-173.80, 101.07)	0.61	-38.30 (-180.05, 103.45)	0.60	12.76 (-88.15, 113.67)	0.81	30.65 (-126.44, 187.74)	0.70
	Tb.Th (micrometers)	-2.84 (-10.00, 4.33)	0.44	-2.31 (-9.22, 4.59)	0.51	-0.02 (-5.04, 4.99)	1.00	-0.52 (-8.23, 7.19)	0.90
	Tb.Sp (micrometers)	-31.27 (-112.41, 49.87)	0.45	34.64 (-43.59, 112.86)	0.39	-16.83 (-72.17, 38.52)	0.55	-27.52 (-116.37, 61.34)	0.55
	EI (no unit)	-0.04 (-0.24, 0.16)	0.72	0.04 (-0.15, 0.24)	0.68	-0.01 (-0.15, 0.12)	0.84	-0.05 (-0.27, 0.16)	0.64
Cortical	Cb.Poro10P (no unit)	0.03 (-5.70×10^{-3}, 0.07)	0.10	0.02 (-0.02, 0.05)	0.37	8.10×10^{-3} (-0.02, 0.04)	0.56	0.04 (-5.60×10^{-3}, 0.08)	0.09
	Cb.Poro15P (no unit)	0.02 (-6.70×10^{-3}, 0.05)	0.13	0.01 (-0.02, 0.04)	0.41	4.30×10^{-3} (-0.02, 0.03)	0.71	0.02 (-8.70×10^{-3}, 0.06)	0.15
	Cb.Poro (no unit)	1.40×10^{-3} (-4.40×10^{-3}, 7.10×10^{-3})	0.65	-9.30×10^{-6} (-5.70×10^{-3}, 5.70×10^{-3})	1.00	-2.00×10^{-3} (-5.90×10^{-3}, 2.00×10^{-3})	0.33	2.10×10^{-4} (-5.70×10^{-3}, 6.20×10^{-3})	0.95
	Cb.Th (micrometers)	9.50×10^{-4} (-0.10, 0.11)	0.99	-0.01 (-0.12, 0.10)	0.85	-0.03 (-0.10, 0.05)	0.51	-0.04 (-0.16, 0.08)	0.50

Table 3. Multivariable associations* between period-specific fluoride intakes and MDCT bone measures – MALES

		Age 0-8 F intake (mg)		Age 8-15 F intake (mg)		Age 15-23 F intake (mg)		Age 0-23 F intake (mg)	
	Characteristic	Beta (95% CI)	pval	Beta (95% CI)	pval	Beta (95% CI)	pval	Beta (95% CI)	pval
Trabecular	Tb.vBMC (mg)	79.80 (-247.45, 407.06)	0.63	40.72 (-251.34, 332.78)	0.79	-12.96 (-261.61, 235.70)	0.92	-1.93 (-352.21, 348.36)	1.00
	Tb.vBMD (mg/cc)	-6.54 (-26.68, 13.61)	0.53	-5.19 (-21.54, 11.17)	0.54	0.86 (-12.51, 14.22)	0.90	-3.77 (-23.60, 16.06)	0.71
	Tb.tBMD (mg/cc)	-13.64 (-58.31, 31.03)	0.55	-10.46 (-47.09, 26.18)	0.58	5.58 (-25.11, 36.26)	0.72	-3.69 (-48.87, 41.49)	0.88
	Tb.pBMD (mg/cc)	-14.55 (-106.37, 77.27)	0.76	-16.93 (-90.64, 56.78)	0.65	16.46 (-15.92, 78.85)	0.61	3.91 (-87.64, 95.46)	0.94
	Tb.NA (mm^2)	-0.04 (-0.17, 0.10)	0.61	-0.03 (-0.14, 0.08)	0.58	0.02 (-0.07, 0.12)	0.66	2.80×10^{-3} (-0.14, 0.14)	0.97
	Tb.PW (mm)	-34.24 (-208.90,140.42)	0.70	-24.05 (-170.58, 122.49)	0.75	22.50 (-88.80,133.80)	0.69	6.22 (-160.94, 173.39)	0.95
	Tb.Th (micrometers)	0.89 (-8.17, 9.95)	0.85	-0.05 (-7.48, 7.37)	0.99	2.20 (-3.33, 7.73)	0.44	1.08 (-7.24, 9.40)	0.80
	Tb.Sp (micrometers)	19.02 (-32.30, 70.35)	0.47	24.71 (-16.63, 66.05)	0.24	19.72 (-42.11, 81.56)	0.53	66.81 (-17.34, 150.95)	0.12
	EI (no unit)	4.60×10^{-3} (-0.12, 0.13)	0.95	0.02 (-0.08, 0.11)	0.75	-0.05 (-0.14, 0.03)	0.22	-0.05 (-0.18, 0.00)	0.45
Cortical	Cb.Poro10P (no unit)	-0.02 (-0.06, 0.02)	0.38	-0.01 (-0.05, 0.02)	0.52	-8.80×10^{-3} (-0.04, 0.02)	0.55	-0.02 (-0.06, 0.02)	0.42
	Cb.Poro15P (no unit)	-0.01 (-0.05, 0.02)	0.45	-7.90×10^{-3} (-0.04, 0.02)	0.64	-7.30×10^{-3} (-0.03, 0.02)	0.58	-0.01 (-0.05, 0.02)	0.51
	Cb.Poro (no unit)	-6.40 x 10-5 (-7.20×10^{-3}, 7.10×10^{-3})	0.99	2.90 x 10-4 (5.30×10^{-3}, 5.90×10^{-3})	0.92	1.10 x 10-4 (-4.10×10^{-3}, 4.30×10^{-3})	0.96	1.00×10^{-3} (-5.10×10^{-3}, 7.20×10^{-3})	0.75
	Cb.Th (micrometers)	0.03 (-0.12, 0.18)	0.69	0.04 (-0.09, 0.16)	0.59	0.04 (-0.06, 0.14)	0.45	0.05 (-0.11, 0.20)	0.56

Results Summary

- **TABLE 1**
  - The sex-stratified descriptive statistics for the fluoride intake AUC variables show that they increased as participants got older for both the sexes, with slightly higher values for males.
  - **For Females:** Daily fluoride intake increased from 0.67 to 0.70 to 0.93 mg F/day for 0 to 8 years, 8 to 15 years and 15 to 23 years, respectively.
  - **For Males:** Daily fluoride intake – increased from 0.73 to 0.81 to 1.12 mg F/day for 0 to 8 years, 8 to 15 years and 15 to 23 years, respectively.
- **TABLES 2 AND 3**
  - For each table, associations of period-specific and cumulative fluoride intakes with 9 trabecular bone measures are listed on the top, followed by associations with 4 cortical bone measures at the bottom.
  - No associations at $p<0.01$ or $0.01<p<0.05$ were found between any of the 36 associations between period-specific and cumulative fluoride intake with trabecular measures for each of males and females, adjusted for for height, weight, years since peak height velocity (PHV), dietary calcium intake, HEI-2010 scores, and PAQ scores.
  - No associations at $p<0.01$ or $0.01<p<0.05$ were found between any of the fluoride intakes and any of the 4 cortical measures for each of males and females, adjusted for for height, weight, years since peak height velocity (PHV), dietary calcium intake, HEI-2010 scores, and PAQ scores.

Discussion

- Longitudinal period-specific and cumulative fluoride intakes were associated weakly and mostly positively with MDCT bone measures at age 23 years.
- Results consistent with previous IBDS analyses and other studies[12, 13, 15, 16, 18]
- Limitations:
  - Limited external validity/generalizability:
    - IFS/IBDS participants recruited from the specific parts of Iowa, and most were non-Hispanic whites from relatively high socioeconomic families.
    - F intakes generally modest to moderate and not extreme, with mean intakes generally consistent with the recommended levels.
  - Validity and reliability challenges: Indirect method of quantifying fluoride intake based on parental/adolescent reports of intakes of foods and beverages and ingested F-containing dentifrice
- Strengths:
  - Cohort followed for a long period of time from birth to age 23
  - Collection of comprehensive, age-specific individual data to estimate the cumulative intakes of fluoride starting at birth
  - Consideration of factors other than fluoride that could affect bone development: calcium intake, Healthy Eating Index scores, vertical jump, height, weight, and years since peak height velocity.

Future Directions

- It would be desirable to replicate this study in other samples/populations and geographic settings
- Researchers can use the IBDS data to explore potential sex differences in bone health and development and the factors that may contribute to these differences.
- Use of Finite Element Analysis (FEA) modeling to estimate bone strength and better understand the relationships between longitudinal fluoride intakes and bone strength.
- Overall, the foundational knowledge laid by the project can be used to inform public health policy and promote the bone health of young adults.

Conclusion

- Fluoride intakes within the optimal range do not appear to have adverse impacts on bone health in young adults in the Midwest region of the United States.
- Thus, efforts should be continued to preserve community water fluoridation.

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