Long-term Calcium Carbonate Antacid Use, Hip Fracture, and Bone Mineral Density in Men and Women Age 50+: Analysis of NHANES 2003-2010

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Burden of Hip Fracture

$^1/_3$ of adults aged 65+ fall each year, of which $^1/_4$ suffer severe injury or fracture

Hip fracture is the most common cause of all fall-related deaths

Risk of fracture increases dramatically with age

Reduced mortality from CVD → longer life expectancy → higher burden of hip fracture

Risk Factors for Hip Fracture

RISK FACTORS

Osteoporosis/reduced bone mineral density (BMD)

Older age

Female

White or Asian

Low BMI

Smoking

Long-term daily-dose corticosteroid use

Cancer/Cancer treatments

Post-menopausal status

Proton Pump Inhibitors (Acid Reflux)

Social Factors

PROTECTIVE FACTORS

High BMI

Weight-bearing Exercise

Post-menopausal Estrogen Therapy

Calcium & Vitamin D

Calcium and Bone Health

Calcium is a major component of the mineral portion of bone

Consumption of foods high in calcium improves bone health

- Dairy, leafy greens, etc.

Results from literature regarding calcium intake and bone health are inconsistent

- Calcium intake misclassification
- Consideration of vitamin D intake

Results from randomized controlled trials of calcium/vitamin D supplementation also inconsistent

- Short duration of RCTs
- Not well studied in men

Although not conclusive, study results generally suggest protective effect of calcium and of calcium/vitamin D supplementation

Gastroesophageal Reflux Disease (GERD)

Reflux of stomach acid into the esophagus

- Heartburn

Prevalence estimated 15-20%

Symptoms greatly reduced by avoiding acidic foods and beverages

- Red meat, fried foods, dairy, coffee, tea

Isn't there a pill for that?

- Proton pump inhibitors
  - Reduces production of stomach acid
- Antacids
  - Increases stomach pH (less acidic)

Calcium Carbonate Antacids

Carbonate is an excellent buffer

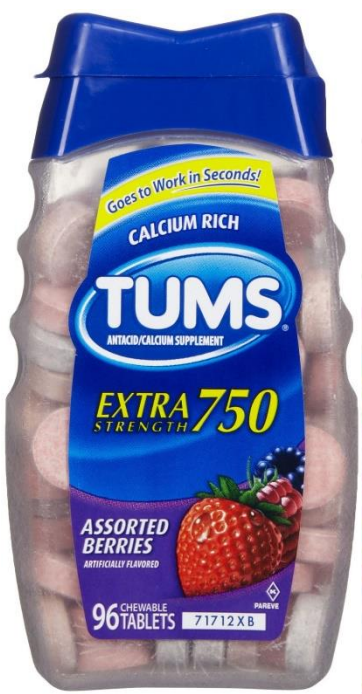
- Increases and maintains stomach pH

Antacids often used in combination with PPIs

Both typically used long-term since nobody wants to commit to a lifestyle change

Calcium 600 mg

- 60% Daily Value



Hypotheses and Objectives

Summary

- High calcium intake may increase BMD and reduce risk of hip fracture
- Many people use antacids to alleviate symptoms of acid reflux
- Antacids are an excellent source of dietary calcium

Hypotheses

- Long-term use of antacids reduces risk of hip fracture
- Long-term use of antacids increases BMD

Objectives

- Use publicly available NHANES data to investigate the independent effects of antacid use on history of hip fracture

National Health and Nutrition Examination Survey (NHANES)

Annual cross-sectional survey conducted by the Center for Disease Control since 1999

Nationally representative sample of the non-institutionalized US civilian population

Datasets are publicly available online and released in 2-year cycles

- Demographic Questionnaire
- Health and Medications Questionnaire
- Dietary History Questionnaire
- Physical Examination
- Laboratory Analysis

Survey Weights

- Adjustment for sampling error/biases
- Apply a weight to each person based on demographic profile

Study Population

NHANES 2003-2010

- Only cycles with information on hip fracture

NHANES 2005-2010

- Only cycles with measured BMD

Primary Analysis Sample

- Men and women age 50+

Sensitivity Analysis Subsample

- Men and post-menopausal women age 50+ without history of cancer, prednisone/cortisone use, or female hormone therapy

Methods

Descriptive Analysis

- Compare prevalence of antacid use among covariate strata
- Compare prevalence of hip fracture among covariate strata
- Compare mean BMD among covariate strata

Logistic Regression Modelling

- Calculate crude and adjusted measures of association between hip fracture and antacid use
- Calculate crude and adjusted effect of antacids on BMD
- Stratified by gender
- Both primary and sensitivity samples

Logistic Regression Model Parameters

Hip Fracture (Ever, Never)

Antacid Use
- Use within the last 30 days (Yes/No)
- Duration of use if used within the last 30 days (Continuous, log-transformed)

PPI Use
- Use within the last 30 days (Yes/No)
- Duration of use if used within the last 30 days (Continuous, log-transformed)

Age + Age^2 (Continuous)

BMI (Continuous)

Race/Ethnicity (White, Black, Mexican-American, Other)

History of Any Cancer (Ever, Never)

History of Prednisone or Cortisone Use (Ever, Never)

Menopausal Status (Post, Pre)

History of Estrogen Therapy (Ever, Never)

Descriptive Analysis of Antacid Use

	Men			Women		
	n	Antacids	p-value	n	Antacids	p-value
Hip Fracture						
Yes	109	26 (23.6%)	0.056	112	15 (11.6%)	0.2111
No	5024	646 (15.7%)		5071	753 (17.1%)	
PPI Use						
Yes	661	101 (17.4%)	0.458	807	146 (20.9%)	0.01*
No	4474	571 (15.6%)		4379	622 (16.3%)	
Age						
50-60	1540	211 (16.8%)	0.212	1493	216 (16.2%)	0.261
60-70	1627	181 (14.3%)		1667	250 (19.0%)	
70-80	1226	160 (15.4%)		1176	172 (16.1%)	
80+	742	120 (17.3%)		850	130 (16.5%)	
BMI						
Normal/Under	1252	139 (15.1%)	0.293	1381	189 (14.3%)	0.024*
Overweight	2071	274 (15.2%)		1615	259 (18.1%)	
Obese	1694	245 (17.3%)		2068	301 (18.1%)	
Race/Ethnicity						
White	2879	487 (17.8%)	<0.0001**	2780	521 (19.1%)	<0.0001**
Black	983	72 (7.2%)		1004	111 (11.3%)	
Mexican American	780	69 (9.8%)		840	96 (11.6%)	
Other	493	44 (9.9%)		562	40 (6.3%)	
Cancer						
Ever	867	141 (16.5%)	0.601	824	125 (15.5%)	0.223
Never	4260	530 (15.7%)		4351	642 (17.2%)	
Prednisone/Cortisone Use						
Ever	226	44 (21.4%)	0.006**	289	50 (21.5%)	0.051
Never	3740	448 (14.1%)		3653	506 (16.0%)	
Post-Menopausal						
Yes		N.A.		4373	682 (17.8%)	0.014*
No				813	86 (13.0%)	
Hormones						
Ever		N.A.		1843	378 (21.5%)	<0.0001**
Never				2832	348 (14.3%)	

Descriptive Analysis of Hip Fracture

	Men			Women		
	n	Hip Fracture (%)[a]	p-value[b]	n	Hip Fracture (%)[a]	p-value[b]
Antacid Use						
Yes	672	26 (3.0%)	0.056	768	15 (1.2%)	0.211
No	4461	83 (1.8%)		4415	97 (1.9%)	
PPI Use						
Yes	661	17 (3.0%)	0.214	806	23 (2.2%)	0.422
No	4472	92 (1.8%)		4377	89 (1.7%)	
Age						
50-60	1540	19 (1.4%)	<0.0001**	1493	10 (0.7%)	<0.0001**
60-70	1626	29 (2.0%)		1666	25 (1.1%)	
70-80	1226	20 (1.6%)		1175	31 (2.7%)	
80+	741	41 (5.6%)		849	46 (5.4%)	
BMI						
Normal/Under	1252	33 (2.2%)	0.225	1380	52 (2.9%)	0.0001**
Overweight	2070	36 (1.4%)		1614	32 (1.8%)	
Obese	1694	33 (2.4%)		2068	24 (0.8%)	
Race/Ethnicity						
White	2878	83 (2.1%)	0.111	2279	71 (1.9%)	0.183
Black	983	9 (0.9%)		1004	12 (1.1%)	
Mexican American	779	8 (1.0%)		839	18 (1.9%)	
Other	493	9 (2.8%)		561	11 (1.3%)	
Cancer						
Ever	867	23 (2.6%)	0.115	824	24 (2.4%)	0.154
Never	4258	86 (1.9%)		4348	88 (1.6%)	
Prednisone/Cortisone Use						
Ever	226	6 (4.2%)	0.088	289	11 (2.4%)	0.489
Never	3738	68 (1.7%)		3652	68 (1.8%)	
Post-Menopausal						
Yes	N.A.			4371	91 (1.8%)	0.993
No				812	21 (1.8%)	
Hormones						
Ever	N.A.			1843	35 (1.6%)	0.63
Never				2829	60 (1.8%)	

Descriptive Analysis of Mean BMD

	Men			Women		
	n	Mean BMD[a] (SD)	p-value	n	Mean BMD[a] (SD)	p-value
Antacid Use						
Yes	428	0.809 (0.006)	0.510	2621	0.727 (0.003)	0.429
No	2956	0.814 (0.004)		460	0.733 (0.008)	
PPI Use						
Yes	441	0.800 (0.009)	0.441	471	0.732 (0.007)	0.517
No	2943	0.816 (0.003)		2610	0.727 (0.003)	
Age						
50-60	1095	0.838 (0.005)	<0.0001**	975	0.767 (0.005)	<0.0001**
60-70	1101	0.813 (0.005)		1018	0.728 (0.005)	
70-80	766	0.779 (0.007)		680	0.689 (0.004)	
80+	422	0.736 (0.008)		408	0.633 (0.006)	
BMI						
Normal/Under	837	0.745 (0.005)	<0.0001**	894	0.666 (0.004)	<0.0001**
Overweight	1456	0.808 (0.004)		1053	0.725 (0.004)	
Obese	1066	0.867 (0.005)		1116	0.794 (0.005)	
Race/Ethnicity						
White	1869	0.807 (0.003)	<0.0001**	1657	0.718 (0.003)	<0.0001**
Black	643	0.894 (0.006)		554	0.814 (0.006)	
Mexican American	498	0.819 (0.008)		493	0.743 (0.007)	
Other	374	0.792 (0.011)		377	0.715 (0.008)	
Cancer						
Ever	585	0.786 (0.007)	<0.0001**	483	0.711 (0.007)	0.012*
Never	2793	0.819 (0.003)		2594	0.731 (0.003)	
Prednisone/Cortisone Use						
Ever	183	0.799 (0.011)	0.185	222	0.725 (0.010)	0.695
Never	3168	0.815 (0.003)		2828	0.729 (0.003)	
Post-Menopausal						
Yes	N.A.			2706	0.720 (0.003)	<0.0001**
No				375	0.771 (0.008)	
Hormones						
Ever	N.A.			1160	0.729 (0.004)	0.933
Never				1745	0.729 (0.005)	

Logistic Regression Model Results

Model Results for Current Antacid Use (yes/no)

		Hip Fracture		BMD			
Sample	Gender	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude Estimate	p-value	Adjusted Estimate	p-value
Primary	Men[a]	1.69 (0.88-3.26)	1.58 (0.73-3.40)	-0.005	0.510	-0.009	0.851
	Women[b]	0.65 (0.27-1.56)	0.57 (0.21-1.55)	-0.006	0.429	-0.002	0.245
Sensitivity[c]	Men	2.78 (1.41-5.48)*	2.51 (1.46-4.29)*	-0.004	0.621	-0.001	0.766
	Women	0.91 (0.25-3.26)	1.06 (0.41-2.73)	0.012	0.362	-0.009	0.817

Model Results for Duration of Antacid Use (log-years)

		Hip Fracture		BMD			
Sample	Gender	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude Estimate	p-value	Adjusted Estimate	p-value
Primary	Men[a]	1.20 (0.80-1.81)	1.11 (0.70-1.77)	-0.002	0.738	-0.003	0.653
	Women[b]	0.81 (0.39-1.66)	0.78 (0.34-1.77)	-0.004	0.581	-0.002	0.684
Sensitivity[c]	Men	1.52 (1.00-2.31)	1.58 (1.05-2.37)*	-0.001	0.867	0.003	0.689
	Women	0.96 (0.34-2.67)	1.00 (0.36-2.80)	0.014	0.301	-0.004	0.651

Summary of Results

Among men age 50 and older with no history of cancer or prednisone/cortisone use, the odds of hip fracture was 1.58 (1.05-2.37) times higher among individuals using antacids for 5 years compared to non-users of antacids

Results consistent with descriptive analysis and “current use” analysis

Association attenuated if cancer and prednisone/cortisone included

No association among women in either exposure or either sample

No association of antacid use and BMD in any analysis

Study Limitations

Alcohol Consumption Data
- Heavy alcohol consumption reduces vitamin D uptake

Ambiguous weighting of study subjects
- 80/20 gender split for hip fracture in literature
- 50/50 gender split for hip fracture in NHANES

Small number of study subjects reporting both hip fracture and antacid use

Cross-sectional design

Large amount of self-reported data

Potential for exposure misclassification
- Duration of exposure is based on only current users (last 30 days)
- Major assumption – Individuals who use antacids regularly to treat symptoms of GERD are not likely to discontinue use

NHANES is not the ideal dataset for this analysis

Conclusions

First study to examine association of long-term antacid use and hip fracture

Given the limitations, results should be interpreted with some skepticism

- Heavy drinking may be confounding these results

Future research should focus on

- Improved methods for antacid use
- Longitudinal or retrospective study design
- Representative sample of the elderly population
- Investigation of potential confounding by heavy alcohol consumption