ARIC Manuscript Proposal # 1006

PC Reviewed: 05/06/04   Status: A   Priority: 2
SC Reviewed: 05/07/04   Status: A   Priority: 2

1. a. Full Title: Associations of dairy products, dietary calcium and calcium supplementation with the incidence of metabolic syndrome and its components

b. Abbreviated Title (Length 26 characters): Calcium and metabolic syndrome

2. Writing Group (list individual with lead responsibility first):
   Lead:
   Eric Nowicki, MPH, RD
   137 E. Franklin St. Suite 400
   Chapel Hill, NC 27599
   Phone: 919-966-1065
   FAX: 919-962-3265
   Email: nowicki@unc.edu

   Eric Nowicki is a doctoral student in the Department of Epidemiology at the University of North Carolina at Chapel Hill. He has an academic and professional background in nutrition and is currently part of the Obesity and Physical Activity program area in the doctoral program. He has also published two papers in peer-reviewed journals on the topic of obesity and its associated morbidities.

   Writing group members:
   June Stevens, PhD, is a Professor in the Departments of Nutrition and Epidemiology in the School of Public Health at the University of North Carolina at Chapel Hill and an experienced ARIC investigator who specializes in nutrition and obesity epidemiology.

   Jianwen Cai, PhD, is an Associate Professor in the Department of Biostatistics in the School of Public Health at the University of North Carolina at Chapel Hill and an experienced ARIC Investigator.

3. Timeline:
   Dataset preparation and analysis will start immediately upon approval. The manuscript development will be completed within 18 months of approval of the proposal.

4. Rationale:
   Criteria have been proposed for Metabolic Syndrome by the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). According to the ATP III criteria, the metabolic syndrome is identified by the presence of three or more of the following components:
   - Central obesity as measured by waist circumference:
     Men - Greater than 40 inches
     Women - Greater than 35 inches
   - Fasting blood triglycerides greater than or equal to 150 mg/dL
   - Blood HDL cholesterol:
     Men - Less than 40 mg/dL
     Women - Less than 50 mg/dL
Blood pressure greater than or equal to 130/85 mmHg
Fasting glucose greater than or equal to 110 mg/dL

There are several proposed mechanisms by which calcium may affect the components of metabolic syndrome. Calcium may affect blood pressure and insulin function through several mechanisms, including reduced membrane permeability and intracellular calcium, changes in calcium-regulating hormones, modulation of the sympathetic nervous system, and altering the metabolism of other electrolytes [Hatton, 1995]. The possible hypolipidemic mechanisms of calcium include the inhibition of: intestinal absorption of cholesterol; absorption of bile acids; and absorption of fat [Shahkhalili, 2001]. Hypothesized explanations for an anti-obesity affect of dietary calcium are: dietary calcium may form soaps with fatty acids and thereby prevent the absorption of some of the fatty acids released during lipid digestion; and/or dietary calcium may bind bile acids, which would decrease micelle formation and thus reduce lipid absorption and digestible energy of the diet [Makynan, 1996].

The following briefly summarizes the current evidence on the possible role of calcium in the prevention of metabolic syndrome and its components.

**Blood pressure**
A meta-analysis of 23 observational studies estimated that each 100 mg increase in daily calcium intake would produce a lowering of 0.39 mmHg in systolic and 0.35 mmHg in diastolic blood pressure [Birkett, 1998]. A meta-analysis of 43 randomized controlled studies found that both dietary and supplemental increase in calcium intake to more than 1000 mg/day for at least two weeks leads to a significant reduction in blood pressure [Griffith, 1998]. Thus, the antihypertensive effect of increased intake of calcium is supported by a large body of data [McCarron, 1999].

**Lipids and triglycerides**
There has been relatively little attention given to possible lipid-lowering effects of an increased intake of calcium. The first clinical studies in the 1960’s and 1970’s were small, but showed a consistent serum cholesterol- and triglyceride-lowering effect of increased dietary calcium intake. In healthy adults on normal diets, a moderate 890 mg/day calcium supplementation produced a mean 15.4 mg/dL (0.4 mmol/L) decrease in serum total cholesterol and 32.2 mg/dL (0.83 mmol/L) decrease in triglycerides [Yacowitz, 1965]. The decreases were greater (up to 15 to 30%) in those whose baseline lipid levels were elevated. In a recent study, a 1 g/day calcium supplement was reported to produce a 7% increase in HDL cholesterol and 6% decrease in LDL cholesterol in a study on 223 healthy postmenopausal women [Reid, 2002].

Epidemiologic evidence in favor of the hypothesis of dietary calcium as a lipid-lowering agent is limited and somewhat inconsistent. Some ecological studies have found that higher calcium intake correlated with higher serum cholesterol levels and incidence of coronary heart disease [Artaud-Wild, 1993]. One explanation is that dietary calcium usually comes from milk products, which often contain high saturated fat and cholesterol, which may override the effects of calcium. A cross-sectional study in 5,394 men and 4,800 women found a linear increase of both total cholesterol and HDL cholesterol with serum calcium levels, independent of confounding factors such as age, blood pressure, body weight, fat and cholesterol intake [De Bacuquer, 1994]. Conversely, a recent longitudinal analysis of CARDIA data suggested an inverse association between higher calcium intake and the development of dyslipidemia in young (18-30 years), overweight black and white men and women [Pereira, 2002].

Results from the Dietary Approaches to Stop Hypertension (DASH) Trial suggest that a diet higher in calcium may reduce LDL and total cholesterol, increase HDL, but have no effect on triglycerides. However, other components of the DASH study diet, which is high in fruits, vegetables, and low-fat dairy products, may have contributed to these effects. A recent cross-sectional study found similar results in subjects with a dietary calcium intake of >1000 mg/day compared to <600 mg/day [Jacmain, 2003].

**Glucose and Insulin**
Only a few experimental or observational studies have studied the effect of calcium intake on glucose metabolism and insulin resistance. A longitudinal analysis of CARDIA data suggested an inverse association
between higher calcium intake and the development of abnormal glucose homeostasis in young (18-30 years), overweight black and white men and women [Pereira, 2002]. A study using the DASH diet (high in fruits, vegetables, and low-fat dairy products) in a community setting found that subjects in the DASH diet group had improved insulin sensitivity and a significant decrease in fasting insulin and glucose compared to controls [Ard, 2004]. However, it is possible that other components of the DASH diet contributed to these differences.

Central obesity

Reductions in body weight have been observed in some experimental and clinical calcium supplementation studies. More work needs to be done on associations between calcium and body weight, and even less work is available on associations between calcium and fat distribution. We know of one cross-sectional study which examined the effect of calcium intake on central obesity as measured by both waist circumference (WC) and abdominal adipose tissue (AT) using CT scans. Subjects with the highest dietary calcium intake had significantly lower WC and abdominal AT compared to subjects with the lowest intake [Jacqmain, 2003].

Conclusion

The possible role of calcium in the prevention of the components of metabolic syndrome has a plausible physiological basis, and support from experimental, as well as clinical and population studies. However, the data are particularly sparse for African Americans, who tend to have a lower intake of dietary calcium and dairy products. We are not aware of any epidemiologic study in middle-aged adults that has examined the association of dietary calcium and the incidence of metabolic syndrome, or all of the components of metabolic syndrome. Analysis of ARIC data would fill this gap. This paper will build on (and not repeat) the work we plan to do on calcium and anthropometry, which was submitted as a separate proposal.

5. Main Hypothesis/Study Questions:

A. Is dietary calcium intake associated with the incidence of metabolic syndrome and its components after adjusting for confounding factors?
B. Is the association of dietary calcium with metabolic syndrome and its components mediated by changes in body composition?

6. Data (variables, time window, source, inclusions/exclusions):

Identification information:
Participant identification number (visit 1 - 4)
Visit date (visit 1 & 4)
ARIC field center (visit 1)

Demographics:
Ethnicity (visit 1)
Gender (visit 1)
Date of birth (visit 1)
Age (visit 1 & 4)
Marital status (visit 4)
Number of household members (visit 4)

Anthropometrics (visit 1 - 4):
Weight
Height
BMI
WC
WHR
Tricep skinfold

**Diet (visits 1 & 3):**
Frequencies of consumption of foods and nutrients from 66-item FFQ

**Others:**
- Date of annual follow-up
- Smoking (visit 1 & 4):
  - Smoking status and # of cigarettes
- Physical activity (visit 1 & 3)
- Education (visit 1)
- Prevalent CHD (visit 1)
- Incident CHD (visit 2-4, annual follow-up)
- Prevalent cancer (visit 1)
- Incident cancer (visit 2-4, annual follow-up)
- Prevalent stroke (visit 1)
- Incident stroke (visit 2-4, annual follow-up)
- Hypertension (visit 1-4)
- Diabetes (visit 1-4)

**Laboratory (Visits 1-4):**
- Fasting glucose
- Fasting insulin
- LDL
- HDL total cholesterol
- Triglycerides
- Diastolic BP
- Systolic BP
- Diabetes
- Hypertension

7.a. Will the data be used for non-CVD analysis in this manuscript?  
  - X Yes  ____ No

b. If Yes, is the author aware that the file ICTDER02 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used?  
  - X Yes  ____ No

(This file ICTDER02 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript?  
  ____ Yes  ____ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 must be used to exclude those with value RES_DNA = “No use/storage DNA”?  
  ____ Yes  ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at:

http://bios.unc.edu/units/csecc/ARIC/stdy/studymem.html

  X Yes  ____ No
10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

737
Dietary intake as a predictor of incidence of type 2 diabetes in African-Americans (AAs) and Whites
Stevens J
09/19/00

461D
Dietary patterns and blood pressure over time in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) study
Wang C
01/10/03

274B
Development of the multiple metabolic syndrome in the ARIC cohort: Joint contribution of insulin, BMI and WHR
Liese A
05/29/96

11. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.