ARIC Manuscript Proposal # 1769

PC Reviewed: 3/8/11	**Status: <u>A</u>**	**Priority: <u>2</u>**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Diabetes, Glycemia, and Incident Fracture Risk: The Atherosclerosis Risk in Communities (ARIC) Study

  b. Abbreviated Title (Length 26 characters): **Fracture Risk Factors**

2.   Writing Group:
      Writing group members: Emma Williams, Andrea Christman, Frederick L. Brancati, Saul Blecker, Josef Coresh; Elizabeth Selvin; **others welcome**

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __EW___

        F**irst author**:   **Emma Williams**
        Address:

                            Department of Epidemiology and the
                            Welch Center for Prevention, Epidemiology and Clinical
                            Research
                            Johns Hopkins Bloomberg School of Public Health
                            2024 E. Monument Street, Suite 2-600
                            Baltimore MD 21287
                  Phone: 410-502-2509   Fax: 410-955-0476
                  Email: emwillia@jhsph.edu

ARIC author to be contacted if there are questions about the manuscript and the first author   does not respond or cannot be located (this must be an ARIC investigator).
        Name: **Elizabeth Selvin**
        Assistant Professor
                            Department of Epidemiology and the
                            Welch Center for Prevention, Epidemiology and Clinical
                            Research
                            Johns Hopkins Bloomberg School of Public Health
                            2024 E. Monument Street, Suite 2-600
                            Baltimore MD 21287
                  Phone: 410-614-3752   Fax: 410-955-0476
                  Email: lselvin@jhsph.edu

3.   Timeline: Analysis to start in March 2010. Our goal would be to submit for ARIC review in October 2010.

4.   Rationale:

Bones fractures represent a significant burden of morbidity, particularly among women and persons aged ≥65 [1, 2]. Serious fractures, such as hip fractures, are associated with significant health care costs, reductions in quality of life, and increased mortality risk.

Some evidence suggests that persons with diabetes are at increased risk for bone fractures. On the other hand, prediabetes and type 2 diabetes are associated with higher body mass index (BMI), which may have some protective effect against fracture [3, 4]. Studies examining the association between type 2 diabetes and bone mineral density have been mixed, with some studies showing a protective effect [5]. In one 2007 meta-analysis, type 2 diabetes was associated with an increased risk of hip fracture (relative risk 1.38; 95% confidence interval (CI) 1.25-1.53) and wrist fracture (relative risk 1.19; 95% CI 1.01-1.41), but no association was observed with spine fracture or fracture at any other site in the body [3], after adjustment for body mass index (BMI). In another 2007 meta-analysis, Janghorbani et al found that type 2 diabetes was associated with a relative risk for fracture of 1.2 (95% CI 1.01-1.5), based on 8 studies with a mixed age range of adult participants [6]. For hip fracture, type 2 diabetes was associated with a relative risk of 1.7 (95% CI 1.3-2.2), based on 12 studies. Most of the studies adjusted for BMI.

The mechanism for the relationship between type 2 diabetes and fracture is unclear. One hypothesis is that hyperglycemia and the ensuing exposure to advanced glycation endproducts has a weakening effect on the bones [7]. Some animal studies and small scale studies of humans support this hypothesis [4]. However, few studies examining the association between diabetes and fracture risk have included glycated hemoglobin (HbA1c) or other measures of glycemic control. The Blue Mountains Eye Study reported that persons with a fasting plasma glucose concentration of ≥126 mg/dl (≥7 mmol/l) had an adjusted relative risk of 2.8 (95% CI 1.4-5.8) for any type of fracture after two years' follow-up when diabetic retinopathy, diabetes duration, and type of diabetes treatment were included in the model; however, this category included persons with both diagnosed and undiagnosed diabetes [8]. In contrast, a model with five years' follow-up showed no significant associations between fasting plasma glucose concentration and fracture risk. However, neither analysis was adjusted or BMI, bone mineral density, or other anthropometric measures. Among diabetics, the Health, Aging and Body Composition study found no association between hemoglobin A1C ≥7% and fracture in the crude analysis [9].

Other hypotheses suggest that diabetes may increase fracture risk through reduced Vitamin D and calcium metabolism, increasing risk of osteoporosis, or through increased risk of falls due to neuropathy, retinopathy, hypoglycemia incidents, or a combination of these factors. It is also known that thiazolidinediones (TZDs)—which came to market in the late 1990s—increase fracture risk and that people with diabetes are more likely to be prescribed other drugs that increase fall risk [7]. Kidney disease may also lead to osteopenia.

The relationship between prediabetes and fracture risk has not been well-described. In a population-based prospective study in Australia (AusDiab), among persons not diagnosed with diabetes, no association was observed between 2-h plasma glucose among men, but the number of fractures was small [10]. Among women in the same study, those in the 4th quartile for 2-h plasma glucose (equivalent to 6.9-11.0/mmol/L) were at decreased risk of fracture (odds ratio 0.65, 95% CI 0.43-0.99), after controlling for BMI. Similarly, in the same study, those with pre-diabetes (impaired fasting glucose or impaired glucose tolerance based on 1999 World Health Organization criteria) showed a non-significant or marginally significant reduction in fracture risk. In the Health, Aging and Body Composition study, persons with impaired fasting glucose showed no evidence of increased risk of fracture, in models including or excluding measurements of bone mineral density and adiposity [9]. Among persons never diagnosed with diabetes in the Malmo Preventive Project, no association or a negative association among women was found between glycemia quartiles and fracture risk, depending of the type of test used (fasting plasma glucose or 2-hour glucose) and the statistical models employed [11]. The models were adjusted for age, BMI and smoking status. In the Rotterdam Study, persons with impaired fasting glucose were found to have a lower risk of nonvertebral fracture (0.80; 95% CI 0.63-1.00) and wrist fracture (0.49; 95% CI 0.29-0.82) compared to those with normal glucose tolerance , controlling for age gender, BMI, smoking, serum creatinine, visual acuity, falling frequency and limb disability [5].

5.   Main Hypothesis/Study Questions:
We propose to examine the relationship between diabetes, hyperglycemia and fracture risk among those with and without diagnosed diabetes at visit 2 in the ARIC cohort and to examine whether glycated hemoglobin may be a clinically useful predictor of fracture risk in this community-based population.

H1: Diagnosed diabetes will be independently associated with an increased risk of incident hospitalization for fracture, after controlling for body mass index and other known confounders.

H2: Elevated HbA1c, will be positively associated with risk of incident fracture hospitalization in persons with diabetes and will show no association with fracture among those with elevated HbA1c (5.7-6.4%), after controlling for BMI, waist-to-hip ratio and other anthropometric measures.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Data Source and Study Population:
Inclusions: The study population will include all individuals who completed ARIC visit 2 examination, had a valid HbA1c measurement, have non-missing data on covariates of interest, and whose race was identified as either black or white.

Exposure: Diagnosed diabetes at visit 2 will be defined as a self-reported physician diagnosis of diabetes or medical treatment for diabetes at either visit 1 or 2. HbA1c was measured from visit 2 stored whole blood samples using HPLC methods (Tosoh 2.2 and Tosoh G7). We do not plan to use fasting plasma glucose levels as a measure of glycemia; rather, we primarily aim to examine whether glycated hemoglobin alone is a useful predictor of fracture risk.

Outcome: Fracture Hospitalizations
Hospitalizations are assessed via self-report by participants during the annual follow-up phone calls, and hospital records are subsequently acquired. Data are currently available through the year 2007. Primary and secondary ICD9 codes for all discharge diagnoses associated with hospitalization events will be obtained from the hospital record abstraction forms.

Relevant ICD-9 Codes:
        Fracture due to injury - 800-829, C818, C819,
        Pathologic fractures – 733.1 – 733.19 and V13.51

Initially, we will examine incident hospitalization for fracture due to injury as the outcome. Pathologic fractures will likely be excluded, although for comparison we will run analyses including these events, as there is some evidence the fractures due to injury as sometimes coded as pathologic fractures. We will also compare the results using various definitions of osteoporotic fractures that have been presented in the literature [12, 13]. The number of events will prevent sufficiently powered analysis of hip fractures or other fractures in specific sites.

Covariates
Sociodemographic variables, such as age, sex, race, ARIC field center, education level
Body mass index, waist-to-hip ratioSerum creatinine
Drugs not specific to diabetes but associated with fracture risk, which include those in the following categories: antiepileptic, diuretics, sedatives, anxiolytics, hypnotics, neuroleptics, antidepressants, antihypertensives, cholesterol-lowering drugs, glucocorticoids [14], hormone replacement therapy [8]
Insulin use
Use of TZDs and other diabetes medications (using visit 3, visit 4 and annual follow-up data)
Physical activity
 Alcohol intake

Data Analysis
We will quantify the fracture burden (cumulative incidence) among ARIC cohort participants with and without diabetes. We will compare the cumulative incidence of fracture during follow-up among persons without diabetes, with undiagnosed diabetes, and with diagnosed diabetes at baseline. Using Cox proportional hazards models, we will

investigate the independent association between diabetes and incident fracture hospitalization risk. In analyses stratified by diabetes status, we will quantify the association between HbA1c value and incident fracture hospitalization. We will examine HbA1c as (a) a continuous variable and (b) a categorical variable based on current clinical cut-points. In persons with diabetes, we will compare clinical categories of HbA1c of: ≥8%, 7-8%, and <7%. In persons without diabetes, we will compare clinical categories: ≥6.5%, 5.7-6.4%, and <5.7% [15].

We will test for age- and race-interactions in the association of diabetes and HbA1c with fracture risk and conduct analyses stratified by age and race if there is evidence of effect modification. The associations between diabetes and incident fracture may be modified by use of TZDs; calendar time may be used as a proxy to examine this, given that TZDs were introduced in the late 1990s.

We will also conduct sensitivity analyses utilizing data on self-reported fracture available from visit 4.

Among persons with diabetes, if a positive association with incident fracture is found, we will examine the possibility of microvascular disease and kidney disease as a possible explanatory factor, using retinal data and serum creatinine levels, respectively.

Limitations and challenges
With >800 cases of incident fracture due to injury among the 14,348 ARIC participants who participated in visit 2, this will be one of the larger analyses of this subject that will benefit from the inclusion of both men and women and persons with and without diagnosed diabetes. Our main outcome will include only fractures severe enough to cause hospitalization. Given that hospitalization for fracture is a relatively rare event, we may have limited statistical power for the stratified analyses even in this large cohort. We will also be unable to exclude fractures due "excessive trauma" or "high trauma", as some other studies have done in an attempt to better capture osteoporosis-related fractures. Nonetheless, our primary outcome will capture fractures with the greatest burden of morbidity and associated health care costs. We can conduct a quasi-validation study using the visit 4 self-reported data, but self-reported assessment of fracture has its own major limitations.

Observational studies are always limited by the possibility of residual confounding. Possible sources of confounding in this example include unmeasured differences in bone mineral density and frailty

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

b. If Yes, is the author aware that the file ICTDER03 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? ____
Yes ____ No
(This file ICTDER03 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**
X__ No

**8.b. If yes, is the author aware that either DNA data distributed by the
Coordinating Center must be used, or the file ICTDER03 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://www.cscc.unc.edu/ARIC/search.php

_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)**
Proposal #1133 ("Association between obesity and hospitalizations")
Proposal #1323r ("Glycemia and hospitalization")
Proposal #1348 (Chronic kidney disease and risk of hospitalization)
Matsushita, K., S. Blecker, et al. (2010). "The association of hemoglobin a1c with
incident heart failure among people without diabetes: the atherosclerosis risk in
communities study." Diabetes **59**(8): 2020-2026.
Selvin, E., J. Coresh, et al. (2010). "Measurement of HbA1c from stored whole blood
samples in the Atherosclerosis Risk in Communities study." Journal of Diabetes
2(2): 118-124.
Selvin, E., Y. Ning, et al. (2010). "Glycated Hemoglobin and the Risk of Kidney Disease
and Retinopathy In Adults with and Without Diabetes." Diabetes.
Selvin, E., M. W. Steffes, et al. (2010). "Performance of Glycated Hemoglobin for the
Classification and Prediction of Diabetes." Diabetes Care.
Selvin, E., M. W. Steffes, et al. (2010). "Glycated hemoglobin, diabetes, and
cardiovascular risk in nondiabetic adults." The New England Journal of Medicine
362(9): 800-811.
Selvin, E., H. Zhu, et al. (2009). "Elevated A1C in adults without a history of diabetes in
the U.S." Diabetes Care **32**(5): 828-833.

**11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use
any ancillary study data?** _X ___ **Yes** ____ **No**

11.b. If yes, is the proposal

_X__   A. primarily the result of an ancillary study (list number* #2003.5 and #2006.15)
___   B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. **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.**

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