RESEARCH ARTICLE

THE ASSOCIATION OF ALBUMINURIA WITH FRACTURE RISK

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ABSTRACT

Background: Large blood vessel atherosclerotic cardiovascular disease is associated with hip fracture risk. Here we summarize studies on the association of microvascular disease with hip fracture risk. We further assess whether the risk of hip fractures with microvascular disease is through reduced trabecular bone density or through markers of endothelial dysfunction.

Methods: We used albuminuria (>30 mg albumin/gram creatinine) as a marker of microvascular disease. Albuminuria is associated with microvascular disorders of the heart, lungs, eyes, skin, and brain. It is present in 30-40% of adults >70 years, the age at which hip fractures occur.

Results: In an observational study of the elderly, a doubling of albuminuria was associated with a hazard ratio (HR) of 1.12 (95 % CI, 1.001-1.25) for hip fractures among women. In a blood pressure study, macroalbuminuria (>299 mg/gram) had an adjusted HR of 2.01 (1.21, 2.15). In a population study of 360,000 people, the HRs for hip fractures were 1.30 (1.02-1.65) for microalbuminuria (30-299 mg/gram) and 1.58 (1.07-2.35) for macroalbuminuria. In a population study of 2.7 million people, macroalbuminuria had an increased odds ratio of hip fracture (odds ratio 1.37 [1.28, 1.47]). Despite these findings, volumetric trabecular bone density was not significantly reduced in association with albuminuria levels nor with markers of endothelial dysfunction.

Conclusions: Microvascular disease, as detected by albuminuria, is independently associated with hip fracture risk. However, this association is not through reduced trabecular bone density nor through endothelial dysfunction. Other mechanisms of fracture risk need to be explored.

Key Words: bone density, albuminuria, fracture risk, microcirculation

Introduction

The loss of bone density (osteoporosis) and the consequent increase in fracture risk are strongly related to aging. In women, the loss of estrogen production in the menopause also contributes to bone loss. Other factors associated with hip fracture risk in older individuals that we have described include: (1) increased circulating levels of advanced glycation end products[1] (AGEs); (2) increased levels of trans fats in the diet[2]; (3) carotid artery subclinical vascular disease in the absence of clinical cardiovascular disease[3]; and (4) reduced cardiac parasympathetic tone as derived from 24-hour Holter monitoring[4]. All these factors are age-related and may help to explain the high mortality associated with hip fractures in the elderly.

In this review article, we highlight yet another risk factor that we have identified for hip fracture: albuminuria. Aside from this being a "novel" risk factor, knowledge of its effect on bone broadens our understanding of the association of vascular disease with fracture risk. It is well known that coronary artery disease, stroke and heart failure are related to hip fracture risk[5,6]. What is not well appreciated is that microvascular disease – as represented by albuminuria - is also independently associated with hip fracture risk.

We divide this review into four sections:

1. A review of the osseous microcirculation and its association with bone loss.
2. Examination of albuminuria as a marker of extra-osseous microvascular dysfunction and its independent relationship with hip (and other osteoporotic) fracture risk.
3. A discussion of endothelial dysfunction which underlies albuminuria and microvascular disease.
4. Finally, a review of trabecular bone volume and markers of endothelial function as possible mechanisms explaining fracture risk in association with albuminuria.

I. Osseous Microcirculation and the Association of Disturbances of the Intra-Osseous Microcirculation with Bone Density

Bone is a highly vascularized tissue, receiving up to 10% of resting cardiac output[7,8]. In long bones, blood enters through three routes: (1) a central nutrient artery; (2) metaphyseal–epiphyseal arteries near the ends of the bones; and (3) periosteal arteries. The entry of an artery into the bone, where it divides into smaller arterioles, is the beginning of the osseous microcirculation. These arterioles provide vascular resistance which controls blood flow to meet tissue needs. Once inside the bone, blood flows through a dense capillary network of Haversian (longitudinal) and Volkmann's (transverse) canals, delivering nutrients, hormones, oxygen, and metabolic signals to bone tissue. Ultimately, blood egresses through periosteal, epiphyseal/metaphyseal, and central veins, removing metabolic waste products.

The vascularization of flat bones resembles that of long bones but includes a large periosteal vascular network that provides the majority of perfusion.

Two clinical studies indicate that disturbances of the intraosseous microcirculation are associated with osteoporosis. A pathology study of femoral head fracture specimens revealed a reduction in the number of arterioles and arterial capillaries compared to femoral heads removed for arthritis[10]. In another study of 120 post-menopausal, healthy female subjects (mean age, 74 years; age range, 67-89 years), perfusion indices in the femoral head [maximum enhancement, defined as the maximum percentage increase in signal intensity from baseline], and enhancement slope [the rate of enhancement between 10% and 90% of the signal intensity difference between baseline and maximum signal intensity] were significantly lower in subjects with osteoporosis compared to subjects with osteopenia or normal bone mineral density[11]. Together these studies show that disturbances in the number and function of the intraosseous circulation are associated

with osteoporosis. They do not indicate, however, if they are causally associated with osteoporosis or are epiphenomena of low bone density.

Rodent studies suggest a causal association of microvascular disease/dysfunction with bone loss. Nitric oxide knockout rodents, which exhibit reduced arterial and capillary vasomotor control, demonstrate decreased bone mineral density and cortical thickness[12]. Another study found that a reduction in a specific bone marrow capillary subtype (type H micro-vessels) declined with age with subsequent bone loss[13].

II. Albuminuria and Bone Health

In addition to disturbances of the intra-osseous microcirculation, abnormalities of the extra-osseous microcirculation are associated with bone disease and fractures. One such disorder is albuminuria—the excess excretion of protein in urine. This marker of extra-osseous microvascular disease is easily and inexpensively measured and is amenable for use in cohort and population studies. It is associated with microvascular disorders elsewhere in the body. These include the brain[14], lungs[15,16], skin[17], eyes[18,19], and myocardium[20]. Albuminuria is likely a manifestation of a systemic disorder affecting parts or the entirety of the microvascular system, making it a valid marker for assessing the association between extra-osseous microvascular disease and bone health and fracture risk.

In one of our early studies[21], done in a cohort of 3110 elderly participants with albuminuria testing, there were 313 hip fractures during follow-up (7.7 % of men; 11.7 % of women). The incidence rate for men, with and without albuminuria, was 1.43 and 0.93/100 person-years of follow-up (p = 0.02); for women, 1.84 and 1.33 (p = 0.04) (FIGURE). After adjustment for osteoporosis-related factors, frailty and falling, a doubling of albuminuria was significantly associated with hip fracture risk in women (hazard ratio, 1.12, 95 % CI, 1.001-1.25).

In a large blood pressure study (n=28,602),[22] participants with baseline albuminuria had a significantly increased risk of hip fracture compared with participants without albuminuria (unadjusted hazard ratio=1.62 [1.22, 2.15], P<0.001; adjusted hazard ratio=1.36 [1.01, 1.84], P=0.05). Participants with macroalbuminuria had a particularly high fracture risk (unadjusted hazard ratio=2.01 [1.21, 3.35], P=0.007; adjusted hazard ratio=1.71 [1.007, 2.91], P=0.05). In this cohort, estimated glomerular filtration rate was not a risk factor for hip fracture.

In a prospective cohort study of 352,624 Korean adults[23], the adjusted hazard ratios (HRs) for hip fracture were 1.30 (95% CI 1.02-1.65) for moderate albuminuria (albumin creatinine ratio [ACR] 30-299 mg/gram) and 1.58 (95% CI 1.07-2.35) for severe albuminuria (ACR >300) compared to no albuminuria (< 30 mg/gram ACR). This increased risk of hip fracture was independent of the estimated glomerular filtration rate, suggesting that it was albuminuria, and not kidney function, which was responsible for the hip fractures.

Finally, a study involving 2.7 million residents of Alberta, Canada[24], found that participants with albuminuria (ACR >300) had a significantly increased odds of hip fracture (adjusted odds ratio [OR] = 1.37; 95% confidence interval [CI] 1.28, 1.47), vertebral fracture (OR = 1.31; 95% CI 1.21, 1.41), and any-type fracture (OR = 1.22; 95% CI 1.17, 1.28) compared to individuals with no or mild albuminuria (ACR <300).

In support of the notion that albuminuria is a marker of a systemic disorder of the microvasculature, we reported that increasing amounts of abnormal white matter disease (AWMD) on brain MRI were associated with hip fracture risk. AWMD is a marker of cerebral small blood vessel disease[25]. Adjustment for albuminuria attenuated the association of AWMD with hip fracture, suggesting that AWMD and albuminuria are part of the same microvascular disorder that is linked to bone disease. Diabetic retinopathy, another microvascular complication, is also associated with hip fracture risk[26,27].

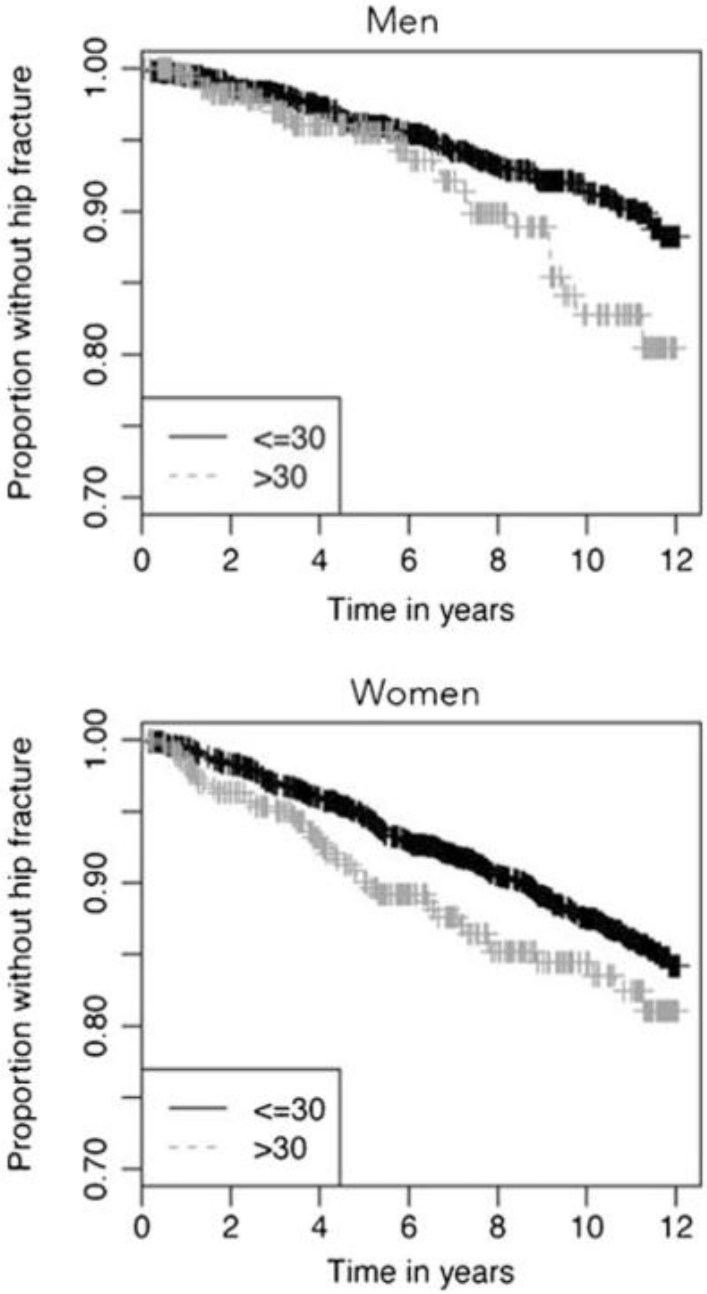

FIGURE: Kaplan-Meier plots for time without hip fracture categorized by the presence or absence of albuminuria (>30 mg / g creatinine) in men and women from the Cardiovascular Health Study. Reproduced with permission. Taken from Barzilay JI, Bůžková P, Chen Z, et al. Albuminuria is associated with hip fracture risk in older adults: the cardiovascular health study. Osteoporos Int. 2013;24(12):2993-3000. Reprinted with permission.

Albuminuria is commonly considered a complication of diabetes. However, in older individuals it is more often associated with hypertension, which is highly prevalent in the age group experiencing bone loss[28]. Based on a cross-sectional analysis of the Third National Health and Nutrition Examination Survey (NHANES III) from the United States, albuminuria is present in 30% of adults over the age of 70 years and in 40% of similarly aged adults with diabetes[29]. Thus, it is highly prevalent in the demographic group in which osteoporotic fractures occur.

III. Endothelial Dysfunction

Endothelial dysfunction (EndDys) underlies albuminuria. It is characterized by disturbances of vascular tone due to imbalanced release of endothelium-derived relaxing and contracting factors. EndDys also encompasses compromised endothelial cell functions that support an impermeable barrier between the circulation and the tissues it perfuses[30]. Abnormally increased permeability, excessive coagulation, fibrinolysis,

cell proliferation, and immune activation in the blood vessel wall characterize this aspect of EndDys.

Studies of bone physiology support the role of EndDys as a mechanism for bone loss. There is a crosstalk between bone cells and endothelial cells. Bone cells release factors that modulate blood vessel function (e.g., endothelin and TGF-β), while blood vessels release factors that stimulate bone cellular activity (e.g., insulin-like growth factor-1, nitric oxide). The impairment of this symbiotic relationship disrupts the arterial microcirculation, which regulates vascular resistance to control tissue blood flow, which in turn regulates bone cellular activities (e.g., recruitment, proliferation, differentiation). A discussion of these interactions is beyond the scope of this paper. The reader is referred to two recent reviews on these subjects [31,32].

A clinical example of how EndDys is associated with bone loss comes from a study of coronary vascular reactivity. A cohort of 194 postmenopausal women over 50 years of age with non-obstructive coronary arteries was administered intracoronary acetylcholine during diagnostic angiography[33]. Impaired reactivity was defined as a ≤50% increase in coronary blood flow from baseline. After a mean follow-up of 8.4±4.7 years, women with impaired response were more than twice as likely to report having osteoporosis compared to those without evidence of EndDys (relative risk, 2.4; 95% confidence interval [CI], 1.1, 5.6, P=0.02).

IV. Markers of Endothelial Dysfunction and Bone Density

Given that low bone mineral density and fracture risk are associated with intra- and extra-osseous microcirculatory disorders and EndDys, it is logical to deduce that metabolically active trabecular bone density — the site of vertebral and hip fractures — would be associated with microvascular disease. A study of ours does not support such a conclusion[34]. Among 6,814 participants in the Multi-Ethnic Study of Atherosclerosis (MESA), we opportunistically derived volumetric thoracic vertebral trabecular bone mineral density (BMD) from computer tomography scans of the chest and heart. We measured urine albumin to creatinine ratios (UACR), retinal arteriolar and venular widths, flow-mediated dilation (FMD) of the brachial artery after 5 minutes of ischemia, and levels of five soluble endothelial adhesion markers (ICAM-1, VCAM-1, L-selectin, P-selectin, and E-selectin). Linear regression models were used to examine the association of trabecular BMD with the markers of microvascular disease and endothelial dysfunction. We found no significant associations between UACR, retinal arteriolar or venular widths, or FMD with BMD. Additionally, we observed no statistically significant association of spine trabecular BMD with levels of endothelial adhesion markers. Men and women exhibited similar results.

This finding can be interpreted in several ways. First, one could conclude that extra-osseous microvascular disease and EndDys are not associated with fracture risk through reduced trabecular BMD. In our analysis from the Cardiovascular Health Study, increased urine albumin levels were not associated with decreased total hip BMD in women, despite women having a high risk of hip fracture[35]. In a Scandinavian study[36], DEXA-based BMD was also not associated with albuminuria, even though albuminuria was linked to fracture risk. Second, the markers of EndDys that we chose are not comprehensive and other markers may have a relationship with bone health. Last, markers of extra-osseous microvascular disease may be associated with loss of cortical bone density or decreased cortical bone quality. A study of diabetic individuals using high-resolution peripheral quantitative tomography (HR-pQCT) found that participants with diabetic microvascular disease (retinopathy, nephropathy, nerve disease) had lower cortical volumetric BMD in the radius and greater cortical porosity than participants without DM[37]. There were no differences in trabecular bone density or quality. Such findings suggest—but do not prove—that extra-osseous microvascular disease may have a pronounced impact on the periosteal microvasculature which is related to cortical bone health.

V. Conclusions

What are the implications of these findings? We believe there are several lessons to be learned.

1. Both intra- and extra-osseous microcirculations are associated with the risk of hip fractures. How they interact with one another requires further investigation.
2. Extra-osseous microvascular disease, as represented by albuminuria, is independently associated with hip fracture risk. The risk is 20-50% higher compared to the absence of albuminuria. This risk is lower than that associated with macrovascular disease, e.g., coronary artery disease, which can be associated with a two to five-fold increased risk[5]. Nonetheless the ubiquity of microvascular disease makes population attributable risk for fracture high.
3. How extra-osseous microvascular disease leads to fracture risk requires further investigation, given that albuminuria and measures of endothelial dysfunction are not related to trabecular bone density. Future studies with newer technologies[38] will further delineate the role of the vascular system with bone health.

Last, it should be remembered that albuminuria reflects many disease processes, e.g., inflammation and endothelial dysfunction. These basic cellular disturbances likely lie at the root of the association of microvascular disease and fracture risk.

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The authors do not have a financial or intellectual conflict of interest regarding the contents of this paper.

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