Matt Scherer

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FAT DISTRIBUTION AND BONE MASS DENSITY IN HIV POSITIVE POST-MENOPAUSAL WOMEN

1. Study Purpose and Rationale

As the population with HIV achieves greater longevity, a greater understanding of the incidence of and risk factors for the diseases associated with aging is necessary in this population. One such disease is osteoporosis. HIV- infected patients tend to have diminished bone mineral density (BMD) when compared with non-infected individuals, and the association between HIV and osteopenia and osteoporosis persists in post-menopausal women. [1-9] This is of direct clinical relevance. A recent large population-based study showed that fracture rates are higher in HIV infected individuals than in non-infected patients; in patients over the age of 60, those with HIV had more than double the risk of fracture.[10] The etiology of and risk factors for decreased BMD in this population remain poorly defined. A recent meta-analysis attributed much of the diminished BMD to low BMI.[11] This relationship may be partially mediated by antiretroviral therapy (ART).[12-19] Although earlier studies have shown an association between HIV and low BMD that is independent of ART use,[12, 16] others have noted up to a 6% decline in BMD during the first 2 years on ART.[20, 21] One mechanism by which the relationship between ART and BMD might be mediated is through redistribution of fat.

The relationships between fat mass in different compartments of the body and BMD remains unclear in the population with HIV. A redistribution of total body fat, known at the "HIV-infection, HAART treatment-associated lipodystrophy syndrome" associated with ART use, has been well-described in HIV positive patients, and still effects around half of all patients on ART, even on newer regimens.[19, 22, 23] The relationship between this distribution of fat and diminished BMD remains unclear. Two prior studies have shown a relationship between increased area of central adiposity and diminished

bone density[3, 24] while a more recent study failed to find such a relationship but showed a positive association between SAT and BMD.[25] Although a negative relationship between VAT and BMD has been reported in populations without HIV, this relationship has not been consistently described by all investigators, which may be due to methodological differences among studies.[26-29] One prior study in post-menopausal women found that increased abdominal fat was actually associated with increased BMD, although body fat was not differentiated into its different compartments.[30] No prior study has attempted to characterize this relationship in post-menopausal HIV-positive women.

The goal of this study is to describe the relationship between different compartments of body fat in a cohort of African-American and Hispanic post-menopausal HIV-positive women and compare this to that relationship in HIV negative controls. We use quantitative CT of the abdomen to quantify VAT and SAT areas and DEXA to quantify BMD. We hypothesized that because the relationship between ART and lower BMD might be mediated by higher levels of visceral fat in subjects with HIV, increased visceral adiposity will be associated with lower BMD in HIV-positive individuals, as it is in subjects without HIV.

2. Study Design and Statistical Procedures

The study will be a cross-sectional analysis of a baseline visit of a larger longitudinal prospective study looking at the relationship between body composition, bone mass density, cytokine levels, and markers of bone turnover in a population of HIV-infected postmenopausal minority women and non-infected controls.

This study is primarily descriptive in nature. We will first characterize the nature of the population in terms of medical comorbidities, non-ART medication use, reproductive history, and history and type of ART use. We anticipate a normal distribution of VAT and SAT in this population, and will report the mean levels and distributions of these measures in our two populations. Bone density will be described as both an absolute number in grams/square centimeters and as a T-score. Average BMD at each of the

anatomic locations (see part 3) will be calculated for both of the groups and will be compared by an unpaired T-test. Based upon 95 subjects in each group, and an expected standard deviation of approximately 0.15, the study has 80% power to detect an absolute difference of 0.06 g/cm^2 between the two groups. This represents approximately a 5% relative difference, given the expected values for mean BMD in the two groups.

Next, we will perform separate univariate linear regressions of VAT area, SAT area, and VAT/SAT ratio on bone density at each of the anatomic sites for both the subjects with and without HIV. Our final and main analysis will be a series of multivariable regressions of each of the above measures on BMD, adjusting for BMI, age, and race. Then to assess whether the relationship between VAT and BMD is mediated by ART use, we will adjust for a factor taking into account years of ART use.

3. Study Procedures

Subjects will have had non-contrast computed tomography (CT) of the abdomen from L1 through L4. Cross-sectional VAT and SAT areas will be measured at the level of L4 using the automated method of Zhao, et al.[31] Each area will be expressed in cm^2. BMD will be assessed by DEXA at the hip, lumbar spine, and femoral neck. Blood will be drawn for CD4 count, HIV RNA viral load, and basic metabolic measurements.

4. Study Drugs or Devices

N/A

5. Study Questionnaires

Subjects will be asked to answer questions about their medical and surgical history and comorbidities, reproductive/gynecological history and time since menopause, social history, current and prior

medication use, and history of ART use. More detailed questions regarding HIV history will be asked, including CD4 nadir and history of opportunistic infections.

6. Study Subjects

Eligible study subjects must be over the age of 40, Hispanic or African-American, and post-menopausal. Exclusion criteria include history of metabolic bone disease, cancer, chronic kidney disease, inflammatory bowel disease, current glucocorticoid, hormone replacement, or anticonvulsant use, and current or past treatment for osteoporosis. 92 HIV positive women and 95 HIV negative controls have been enrolled. In order to enroll the above number of subjects, 110 HIV positive and 108 HIV negative women were screened.

7. Recruitment

Subjects have been recruited from the General Internal Medicine and Infectious Diseases Clinics of Columbia University Medical Center. They are volunteers who have been recruited through their providers, who had been asked to refer postmenopausal minority women for whom they were caring. Control subjects were recruited with the intention of having a control population with medical illnesses and comorbidities that are similar to those in the HIV positive group and common in an inner-city minority population.

8. Confidentiality of Study Data

All data will be coded so that the investigators do not have access to identifying information of the individuals enrolled in the study. Investigators will be required to keep any data which may allow them to potentially identify an individual as confidential. Information on individual subjects will not be released to anyone outside of the study. Only investigators will have access to the data.

9. Potential Risks

There is no risk associated with this study with the exception of the minimal exposure to radiation incurred as part of the partial CT of the abdomen.

10. Potential Benefit

There is no immediate direct benefit to be expected as a result of participation in this study, although participants may be contributing to advances in knowledge that will help patients similar to them in the future. Participation is voluntary.

11. Alternatives

Non-participation

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