Published in final edited form as:
Obesity (Silver Spring). 2015 February ; 23(2): 488–494. doi:10.1002/oby.20974.

Covariation of Change in Bioavailable Testosterone and Adiposity in Midlife Women

Imke Janssen, PhD#1, **Lynda H. Powell**#1,2,3, **Mateusz S. Jasielec**#1, and **Rasa Kazlauskaite**#1,2

[1]Department of Preventive Medicine, Rush University Medical Center, Chicago, IL 60612

[2]Department of Medicine, Rush University Medical Center, Chicago, IL 60612

[3]Behavioral Sciences, and Pharmacology, Rush University Medical Center, Chicago, IL 60612

# These authors contributed equally to this work.

Abstract

Objective—To determine whether menopause-related changes in reproductive hormones are associated with change in adiposity and whether these relationships are independent of important covariates.

Design and Methods—Annual assessments of adiposity measures [CT-assessed visceral adipose tissue (VAT), subcutaneous abdominal adipose tissue (SAT), and DXA-assessed total body fat (TBF)] over 4 years from an ancillary study at the Chicago site of the Study of Women's Health Across the Nation (SWAN) were paired with reproductive hormones collected by SWAN. Included were 243 women (44% African American, 56% Caucasian), who were eligible participants in a population-based cohort with a 72% participation rate.

Results—VAT increased by 3.8% annually, and SAT increased by 1.8% per year. Change in bioavailable testosterone was significantly positively associated with changes both inVAT and in SAT but was not related to change in total body fat. The associations were independent of age, race, physical activity, smoking, baseline TBF, baseline bioavailable testosterone, and change in TBF. Change in estradiol were unrelated to changes in any adiposity measure.

Conclusion—Bioavailable testosterone may play an important role in menopause-related redistribution of visceral and subcutaneous fat in the central abdominal region.

Address for Correspondence: Imke Janssen, PhD Department of Preventive Medicine Rush University Medical Center 1700 W. van Buren, Suite 470 Chicago, IL 60612-3244 Phone: (312) 942-8122 Fax: (312) 942-8119 Imke_Janssen@rush.edu.
Lynda_Powell@rush.edu
Mateusz_Jasielec@rush.edu
Rasa_Kazlauskaite@rush.edu

The authors declare no conflicts of interest.

Introduction

Women's cardiovascular risk increases after menopause (1-3). Whereas gain of weight and total fat has been attributed mainly to aging (4), menopause has been associated with a redistribution of fat towards the abdominal region in the form of subcutaneous abdominal (SAT) and visceral (VAT) adipose tissue. Although the amount of VAT relative to total fat is small, VAT accumulation is a strong, independent predictor of cardiovascular disease (CVD) and diabetes (5-9), and a hallmark of the metabolic syndrome (10). Structural and functional differences between VAT, SAT, and other adipose tissue depots have been documented (11). Structurally, adipose tissue depots differ in vascular supply, innervation, and cellular composition. Functionally, there is heterogeneity in fatty acid handling, adipokine and adipose hormone production, other hormone responsiveness, including differential responsiveness to androgens (11). VAT is a preferential source of inflammatory cytokines which have been associated with premature atherosclerosis and risk of CVD events (12-14).VAT increases with menopause, independently of age and total body fat (TBF) as has been shown in cross-sectional (15-18) and longitudinal studies (14,19-22).

The best known hormonal change during the menopausal transition is the decrease in estrogen, especially estradiol (E2). Bioavailable testosterone (BioT) increases with menopause in most (15,23), although not in all studies (24). Since total testosterone stays constant, the increase in BioT is due to a menopause-related decline in sex hormone binding globulin (SHBG) (23). BioT is strongly associated with VAT cross-sectionally, whereas the correlation between E2 and VAT is weak (15). Change in BioT but not in E2 is significantly positively related to VAT at follow-up (16). In younger menstruating women, change in SHBG (but not change in BioT) was significantly inversely related to concurrent changes in BMI and waist circumference (25).

A meta-analysis of observational studies (26) found that increased androgenicity, characterized by high testosterone and low SHBG levels, is related to an adverse CVD risk factor profile in post-menopausal women, leading the authors to postulate that increased androgenicity contributes to the accumulation of visceral fat and impairment of glucose metabolism. The impact of BioT on VAT was further supported by a clinical trial where administration of a weak androgen (nandrolone decanoate), resulted in an increase of VAT in obese women (27).

Potential covariates are lifestyle factors, in particular physical activity (PA) and smoking. Lack of PA is strongly associated with fat accumulation, and increasing PA reduces VAT even in the absence of weight loss (13). Smokers have more VAT and less TBF than non-smokers (28). In summary, cross-sectional studies suggest a link between reproductive hormones which change across the menopausal transition and differential accumulation of fat, but longitudinal studies have either been based on small samples or lacked precise adiposity measures. The purpose of this study is to determine: (1) the rates of change in VAT, SAT, and TBF as women traverse the menopause; (2) how these changes relate to the baseline concentration and change in BioT and E2, respectively; and (3)whether these changes are independent of age, race, smoking, physical activity, TBF, and change in TBF.

Methods and procedures

Participants

Participants were women who enrolled in an ancillary study of the Study of Women's Health Across the Nation (SWAN) at the Chicago site, the “SWAN Fat Patterning Study”. SWAN is a 7-site multiethnic longitudinal study of women transitioning through menopause, featuring ongoing annual interviews. Women were eligible for SWAN if they were between the ages of 42 and 52, not pregnant or breastfeeding, had an intact uterus and at least 1 ovary, had menstruated within 3 months, and were not using hormone therapy. The Chicago SWAN site employed a population-based design drawing on a complete community census to recruit African American and Caucasian women with a 72% participation rate. Recruitment featured comparability on socioeconomic status (SES) within the African American and Caucasian women, thus minimizing any confound between ethnicity and SES. Details of SWAN recruitment and study protocol have been reported (29).

Women enrolled in the SWAN Fat Patterning Study between August 2002 and December 2005 coincident with their annual SWAN follow-up visit. They were eligible if they had no history of diabetes, chronic liver disease, renal disease, anorexia nervosa, alcohol or drug abuse, were not currently pregnant or planning to become pregnant, and had not undergone surgical menopause (hysterectomy and/or bilateral oophorectomy). Because of equipment limitations, women with breast implants, hip replacements, or weight exceeding 299 pounds (136 kg) could not participate. Seventy-seven percent of the 386 eligible Chicago SWAN participants enrolled in the Fat Patterning Study. Because few SWAN participants were pre- or early peri-menopausal at the Fat Patterning baseline visit, we refreshed the cohort by recruiting additional pre- and peri-menopausal women who were screened as part of the original SWAN recruitment effort but were too young in 1996 to participate. The final cohort consisted of 435 women.

Follow-up visits were conducted between December 2003 and January 2008 (follow-up time, mean±SD=2.5±0.9 years). We excluded women for the following reasons: surgical menopause (n=23), hormone therapy use (n=56), steroid use (n=6), ≤1 VAT assessments (n=55), or ≤1 BioT assessments (n=51). One woman experienced dramatic weight loss after the baseline visit and was removed leaving 243 women for the current analysis. Women in the analytic sample were more likely to be post-menopausal at baseline compared to those excluded. They did not differ significantly on any other measure.

Procedures—All SWAN participants completed a standard protocol annually; full details have been reported (29). Women recruited uniquely to the Fat Patterning Study completed the same protocol as the SWAN participants. Covariates were taken from SWAN visits closest to the fat assessments. The study was approved by the Rush University Medical Center Institutional Review Board, and all women provided written, informed consent.

VAT and SAT

were assessed by computed tomography (CT) by a trained technician using a General Electric Lightspeed VCT scanner (General Electric Medical Systems, Milwaukee, WI), with the participant in the supine position and arms folded across her chest. Following a scout view, a single 10-mm thick image of the abdomen at the L4-L5 vertebral space was obtained. Images were read by a single trained radiologist blind to the participant's characteristics, at the reading center at the University of Colorado Anschutz Medical Campus, using software developed by the center (RSI Inc., Boulder, CO) and used in large cohort studies (30,31). Total abdominal adipose tissue area (TAT) was defined within this planimetric area using fat attenuation range between 1190 and 130 Hounsfeld Units (32). The manual segmentation method was used to define VAT area delineating the area within the muscle wall surrounding the abdominal cavity (30). VAT was subtracted from TAT to quantify SAT.

Total body fat (TBF)

mass was expressed as a percent of a total soft tissue mass, measured by whole body dual-energy X-ray absorptiometry (DXA) using a General Electric Lunar Prodigy scanner (GE-Lunar, Madison, WI) and analyzed using GE-Lunar enCORE software (Madison, WI). DXA scans were completed the same day as the CT with the participant in the supine position, arms by her side, wearing a hospital gown.

Reproductive Hormones

Phlebotomy was performed in the morning following an overnight fast. Subjects were scheduled for venipuncture on days 2-5 of a spontaneous menstrual cycle (in cycling women). All assays were performed on the ACS-180 automated analyzer (Bayer Diagnostics Corporation, Tarrytown, NY) utilizing a double-antibody chemiluminescent immunoassay with a solid phase anti-IgG immunoglobulin conjugated to paramagnetic particles, anti-ligand antibody, and competitive ligand labeled with dimethylacridinium ester (DMAE). Serum testosterone (T) concentrations were determined by competitive binding of a DMAE-labeled T derivative to a rabbit polyclonal anti-T antibody premixed with monoclonal antirabbit immunoglobulin G antibody immobilized on the solid phase paramagnetic particles. Inter- and intraassay coefficients of variation were 10.5% and 8.5%, respectively, with a lower limit of detection (LLD) of 2.19 ng/dL. The two-site chemiluminescent assay for serum SHBG concentrations involved competitive binding of DMAE-labeled SHBG to a commercially available rabbit anti-SHBG antibody and a solid phase of goat antirabbit IgG conjugated to paramagnetic particles. Inter- and intraassay coefficients of variation for SHBG were 9.9% and 6.1%, respectively, with LLD 1.95 nM. Estradiol (E2) was measured with a modified ACS-180 (E2–6) immunoassay with LLD of 1.0 pg/mL. Inter- and intra-assay coefficients of variation averaged 10.6% and 6.4%, respectively. Duplicate E2 assays were conducted with results reported as the arithmetic mean for each subject, with a CV of 3-12%. All other assays were single determinations. Bioavailable testosterone was calculated as T (ng/dL)*100/[28.84*SHBG (nM)].

Covariates

Age was calculated as the difference between exam date and self-reported date of birth. Race was self- reported as African American or Caucasian. Smoking was self-reported annually as yes or no. Physical activity was measured with an adapted version of the Kaiser Physical Activity Survey as described previously (15).

Other Characteristics

Height and weight were measured with participants wearing light clothes and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. The highest educational degree was self-reported at the screening visit: high school or less, some college, college degree, or graduate school. Bleeding criteria were used to characterize menopausal status as pre-menopausal (normal cycling), early peri-menopausal (irregular cycles but bleeding within the past 3 months), late peri-menopausal (irregular cycles with bleeding in the past 11 months but not within the last 3 months), post-menopausal (no menses for at least 12 months).

Data Analyses

Analyses were conducted using PC-SAS ® (SAS Institute Inc., Cary, NC), version 9.2. We used descriptive statistics to characterize participants on fat measures, reproductive hormones, and demographic variables. Adiposity measures and reproductive hormones followed skewed distributions and were transformed by natural logarithm for analysis.

Analyses used linear mixed models which account for the dependence of observations measured on the same individual across time (33). Models with a random intercept and a random time slope were examined. The selection of the covariance structure was based on the Akaike Information Criterion which assesses the fit relative to the complexity of the model (34). Fixed parameter estimates were obtained using restricted maximum likelihood estimation and tested using the Wald chi-square statistic. Residual analysis and influence statistics were used to assess adherence to model assumptions and robustness of results.

To test whether hormones (BioT or E2) changed over time, models with a first-order autoregressive covariance structure were used. To test whether fat (VAT, SAT, TBF) increased over time, models with an independence covariance structure were selected. Quadratic and cubic terms of time were used to test for the nonlinear evolution of hormones and fat, respectively. Models were adjusted for age at baseline and race.

We outline the analysis for BioT and VAT. Analyses using E2 or other adiposity measures followed the same scheme. The hypothesis that increases in BioT were related to VAT progression was analyzed using a model where the dependent variable was the change in VAT (ΔVAT) from baseline to each of the three follow-up visits. The independent variable of interest was annual change in BioT. For each visit, this change score was computed as the difference of logarithmically transformed BioT (ΔBioT) at this visit and baseline divided by the time between baseline and this follow-up visit. Since ΔBioT was a time-varying covariate, it was decomposed into two components representing the between-subjects (the average change from baseline across visits) and the within-subject effect (the difference between the individual change and the average change from baseline across visits). Adjustments were made for baseline level of the hormone, TBF, race, age, change in TBF, and the time elapsed from the baseline visit. Smoking and physical activity were used as time-varying covariates. Sensitivity analyses were conducted: excluding women who (a) were already post-menopausal at the first adiposity assessment (N=88), (b) changed physical activity level (slope more than 2 SD above or below the mean, N=16), or (c) changed smoking status (N=11).

Results

The black and white middle-aged women in this cohort were overweight on average, and 37% were obese at baseline. Most women contributed 3 or 4 observations to the longitudinal analyses with about a year between consecutive assessments (Table 2). In unadjusted analyses (Table 3), TBF did not change; VAT increased more than SAT . Figure1 illustrates the development of the two abdominal adiposity measures across the study with baseline age added to the time of assessment. BioT increased significantly over time, whereas E2 and SHBG showed a significant decrease, and total testosterone was stable. Quadratic and cubic terms were not significant in any of these analyses. Decreases in physical activity and smoking over 4 years were not significant.

Table 4 presents the results of the linear mixed models relating change in hormone (ΔBioT and ΔE2) to change in fat (ΔVAT, ΔSAT, ΔTBF), adjusted for covariates. ΔVAT increased significantly by 4.99 cm^2 per year (time effect). For example, for a typical Caucasian woman, the average ΔVAT from baseline to first follow-up (the intercept of the model) was 2.73 cm^2, 2.73+ 4.99*(1) = 7.72 cm^2 from baseline to second follow-up, and 12.71 cm^2 from baseline to the third follow-up visit. These estimates confirm that, on average, VAT increased by more than 3% annually. The two ΔBioT components were both positively associated with increased ΔVAT, indicating that higher increases in BioT are related to larger increases in VAT. Specifically, for a woman with an average ΔBioT (the between-subjects effect) 1 SD above the population mean, the model predicted marginally significant higher ΔVAT across time (1.86 cm^2, p=0.080). Participants with an annual ΔBioT 1 SD above their time-averaged personal mean would experience a 7.20 cm^2 higher ΔVAT across time than participants whose BioT did not change but was at the same average level across time (p=0.027).

Although SAT increased more slowly than VAT (Figure 1), ΔBioT was more strongly related to ΔSAT; both ΔBioT components were significantly associated with higher ΔSAT. Changes in E2 were unrelated to ΔVAT and in ΔSAT with the exception of a trend (p=0.078) for a within-subject effect of ΔE2 on ΔSAT. Change in TBF was unrelated to both BioT and E2 and their changes.

Excluding women who were post-menopausal at the first fat assessment yielded slightly stronger estimates of the within-subject ΔBioT in ΔVAT and ΔSAT models (Supplemental Table 1). Excluding women who changed smoking status or their physical activity level yielded similar estimates for the ΔBioT components and the same conclusions as the complete analysis.

Discussion

This is the first study showing a significant longitudinal relationship between change in hormones and change in adiposity measures, extending our previous finding of cross-sectional associations. In light of the large differences between pre- and post-menopausal women in E2 as well as adiposity, the lack of association between E2 and adiposity measures, although surprising, confirms previous findings (16). Increase in BioT reflects a change from an estrogen-dominated hormonal milieu to one dominated by testosterone; that is, a shift in the balance between these two hormones over the course of the menopausal transition toward increased androgenicity. The significance of this finding is that the testosterone and adipose tissue association may be key in the understanding of hormonal changes observed during the menopausal transition that link to diabetes and CVD risk.

Decomposing ΔBioT into a between-subjects and a within-subject component enabled us to examine the relationship between hormone change and adiposity change. Women with more rapidly changing BioT experience a larger increase in adiposity compared to their more stable counterparts. By the same token, women with slowly changing BioT experience less increase in adipose tissue. We found the relationship between ΔBioT and ΔSAT to be similar to the relationship between ΔBioT and ΔVAT. However, ΔBioT was not related to ΔTBF. Our results support the hypothesis that the adipose tissue distribution rather than total fat *per se* changes due to menopause, and that this redistribution is related to change in the hormonal balance.

In this large bi-racial sample of middle-aged women, VAT and SAT increased significantly over four years, independently of initial age. Although African American women had less VAT and more SAT than Caucasian women at baseline, the increase over time was similar in both races, consistent with a previous smaller study (20). The annual increase in VAT was about 3.8%, much larger than annual changes in SAT and TBF observed in this study as well as previously reported increases (≤1%) of BMI (35,36) and waist circumference (37) over the menopausal transition.

Change in VAT was not associated with baseline BioT in the current analysis in contrast to a recent study (22) which found a significant inverse association between baseline BioT and ΔVAT over 2 years. However, that study was conducted in non-obese women only, and the sample size was too small to allow for covariate adjustment. When we reran our model without ΔBioT in the non-obese subset of our cohort, baseline BioT was significantly inversely related to ΔVAT (p=0.02). Adjusting for TBF eliminated this significant inverse relationship between baseline BioT and ΔVAT.

The link between testosterone and adipose tissue is biologically plausible. Women with polycystic ovary syndrome (PCOS), a condition characterized by high levels of testosterone, tend to have obesity of the abdominal phenotype. Weight loss programs in women with PCOS are more efficient when antiandrogens are utilized in the program. On the other hand, for women receiving hormone therapy, the addition of testosterone reduced the beneficial estrogen effect on weight reduction (38).

Strengths of the study include the longitudinal design, the precise assessment of adipose tissue, and the large, representative, bi-ethnic cohort of middle-aged women with design control for the commonly encountered bias between race and socio-economic status. Only 7 (2.9%) of the participants were still pre-menopausal at last follow-up, and 82 (33.7%) participants transitioned to post-menopause (Table 5). When we excluded women who were post-menopausal at study start, results were similar to the complete analysis. Therefore it would be unlikely that results would have changed if more women had started the study in pre- menopause.

Hormonal changes may start well before becoming postmenopausal and may continue for a number of years (39). The use of reproductive hormones instead of bleeding criteria to characterize the menopausal transition is a strength of the study. The longitudinal design of the parent SWAN study with its annual assessments enabled us to track changes across the entire menopausal transition.

Limitations of the study include the observational nature that does not allow us to conclude that change in BioT causes change in adiposity. However, this longitudinal study shows the covariation of BioT and adiposity changes and provides stronger evidence for the link between hormonal changes and change in adiposity than cross-sectional analyses.

This study was limited to women who were either African American or Caucasian, and who lived in the large metropolitan area of Chicago. We therefore cannot determine whether the observed associations apply to women of other ethnicities or in more rural areas.

In summary, an increase in adipose tissue was significantly associated with menopause-related change in hormones, independent of aging. This menopause effect was characterized by increasing BioT. Since central adiposity is a major predictor of CVD and diabetes (5-9), testosterone predominance during the menopausal transition may be an important target for cardiometabolic disease prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The Study of Women's Health Across the Nation (SWAN) has grant support from the National Institutes of Health (NIH), DHHS, through the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR) and the NIH Office of Research on Women's Health (ORWH) (Grants U01NR004061; U01AG012505, U01AG012535, U01AG012531, U01AG012539, U01AG012546, U01AG012553, U01AG012554, U01AG012495). The SWAN Fat Patterning Study is supported by the National Heart, Lung, and Blood Institute (grant HL067128) and the Charles and Margaret Roberts Trust. The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the NIA, NINR, ORWH or the NIH.

Clinical Centers: University of Michigan, Ann Arbor – Siobán Harlow, PI 2011 – present, MaryFran Sowers, PI 1994-2011; Massachusetts General Hospital, Boston, MA – Joel Finkelstein, PI 1999 – present; Robert Neer, PI 1994 – 1999; Rush University, Rush University Medical Center, Chicago, IL – Howard Kravitz, PI 2009 – present; Lynda Powell, PI 1994 – 2009; University of California, Davis/Kaiser – Ellen Gold, PI; University of California, Los Angeles – Gail Greendale, PI; Albert Einstein College of Medicine, Bronx, NY – Carol Derby, PI 2011 – present, Rachel Wildman, PI 2010 – 2011; Nanette Santoro, PI 2004 – 2010; University of Medicine and Dentistry – New Jersey Medical School, Newark – Gerson Weiss, PI 1994 – 2004; and the University of Pittsburgh, Pittsburgh, PA – Karen Matthews, PI.

NIH Program Office: National Institute on Aging, Bethesda, MD – Winifred Rossi 2012 - present; Sherry Sherman 1994 – 2012; Marcia Ory 1994 – 2001; National Institute of Nursing Research, Bethesda, MD – Program Officers.

Central Laboratory: University of Michigan, Ann Arbor – Daniel McConnell (Central Ligand Assay Satellite Services).

Coordinating Center: University of Pittsburgh, Pittsburgh, PA – Maria Mori Brooks, PI 2012 - present; Kim Sutton-Tyrrell, PI 2001 – 2012; New England Research Institutes, Watertown, MA - Sonja McKinlay, PI 1995 – 2001.

Steering Committee: Susan Johnson, Current Chair Chris Gallagher, Former Chair

We thank the study staff at each site and all the women who participated in SWAN.

References

1. Fujioka S, Matsuzawa Y, Tokunaga K, Tarui S. Contribution of intra-abdominal fat accumulation to the impairment of glucose and lipid metabolism in human obesity. Metabolism. Jan; 1987 36(1):54–59. [PubMed: 3796297]
2. Albu JB, Murphy L, Frager DH, Johnson JA, Pi-Sunyer FX. Visceral fat and race-dependent health risks in obese nondiabetic premenopausal women. Diabetes. Mar; 1997 46(3):456–462. [PubMed: 9032103]
3. Goodpaster BH, Thaete FL, Simoneau JA, Kelley DE. Subcutaneous abdominal fat and thigh muscle composition predict insulin sensitivity independently of visceral fat. Diabetes. Oct; 1997 46(10):1579–1585. [PubMed: 9313753]
4. Davis SR, Castelo-Branco C, Chedraui P, Lumsden MA, Nappi RE, Shah D, et al. Understanding weight gain at menopause. Climacteric. 15(5):419–429. 20-2 10/01; 2012/12. [PubMed: 22978257]
5. Despres JP, Nadeau A, Tremblay A, Ferland M, Moorjani S, Lupien PJ, et al. Role of deep abdominal fat in the association between regional adipose tissue distribution and glucose tolerance in obese women. Diabetes. Mar; 1989 38(3):304–309. [PubMed: 2645187]
6. Peiris AN, Sothmann MS, Hennes MI, Lee MB, Wilson CR, Gustafson AB, et al. Relative contribution of obesity and body fat distribution to alterations in glucose insulin homeostasis: predictive values of selected indices in premenopausal women. Am J Clin Nutr. May; 1989 49(5):758–764. [PubMed: 2655411]
7. Zamboni M, Armellini F, Milani MP, De Marchi M, Todesco T, Robbi R, et al. Body fat distribution in pre1 and post-menopausal women: metabolic and anthropometric variables and their inter-relationships. Int J Obes Relat Metab Disord. Jul; 1992 16(7):495–504. [PubMed: 1323546]
8. Rader DJ. Effect of insulin resistance, dyslipidemia, and intra-abdominal adiposity on the development of cardiovascular disease and diabetes mellitus. Am J Med. Mar; 2007 120(3 Suppl 1):S12–8. [PubMed: 17320517]
9. Nicklas BJ, Penninx BWJH, Cesari M, Kritchevsky SB, Newman AB, Kanaya AM, et al. Association of Visceral Adipose Tissue with Incident Myocardial Infarction in Older Men and Women: The Health, Aging and Body Composition Study. Am J Epidemiol. Oct 15; 2004 160(8):741–749. [PubMed: 15466496]
10. Goodpaster BH, Krishnaswami S, Harris TB, Katsiaras A, Kritchevsky SB, Simonsick EM, et al. Obesity, Regional Body Fat Distribution, and the Metabolic Syndrome in Older Men and Women. Arch Intern Med. Apr 11; 2005 165(7):777–783. [PubMed: 15824297]
11. Lee M, Wu Y, Fried SK. Adipose tissue heterogeneity: Implication of depot differences in adipose tissue for obesity complications. Mol Aspects Med. 2013; 34(1):1–11. [PubMed: 23068073]
12. Berg AH, Scherer PE. Adipose Tissue, Inflammation, and Cardiovascular Disease. Circ Res. May 13; 2005 96(9):939–949. [PubMed: 15890981]
13. Tchernof A, Despres JP. Pathophysiology of human visceral obesity: An update. Physiol Rev. 2013; 93(1):359–404. doi: 10.1152/physrev.00033.2011 [doi]. [PubMed: 23303913]
14. Lee CG, Carr MC, Murdoch SJ, et al. Adipokines, inflammation, and visceral adiposity across the menopausal transition: A prospective study. J Clin Endocrinol Metab. 2009; 94(4):1104–1110. doi: 10.1210/jc.200810701. [PubMed: 19126626]
15. Janssen I, Powell LH, Kazlauskaite R, Dugan SA. Testosterone and visceral fat in midlife women: the Study of Women's Health Across the Nation (SWAN) fat patterning study. Obesity (Silver Spring). Mar; 2010 18(3):604–610. [PubMed: 19696765]
16. Guthrie JR, Dennerstein L, Taffe JR, Ebeling PR, Randolph JF, Burger HG, et al. Central abdominal fat and endogenous hormones during the menopausal transition. Fertil Steril. Jun; 2003 79(6):1335–1340. [PubMed: 12798880]

17. Kanaley JA, Giannopoulou I, Tillapaugh-Fay G, Nappi JS, Ploutz-Snyder LL. Racial differences in subcutaneous and visceral fat distribution in postmenopausal black and white women. Metabolism. Feb; 2003 52(2):186–191. [PubMed: 12601630]
18. Tchernof A, Desmeules A, Richard C, Laberge P, Daris M, Mailloux J, et al. Ovarian Hormone Status and Abdominal Visceral Adipose Tissue Metabolism. J Clin Endocrinol Metab. Jul 1; 2004 89(7):3425–3430. [PubMed: 15240626]
19. Carr MC. The Emergence of the Metabolic Syndrome with Menopause. J Clin Endocrinol Metab. Jun 1; 2003 88(6):2404–2411. [PubMed: 12788835]
20. Lovejoy JC, Champagne CM, de Jonge L, Xie H, Smith SR. Increased visceral fat and decreased energy expenditure during the menopausal transition. Int J Obes (Lond). Jun; 2008 32(6):949–958. [PubMed: 18332882]
21. Ho SC, Wu S, Chan SG, Sham A. Menopausal transition and changes of body composition: a prospective study in Chinese perimenopausal women. Int J Obes (Lond). Mar 2.2010
22. Goss AM, Darnell BE, Brown MA, Oster RA, Gower BA. Longitudinal associations of the endocrine environment on fat partitioning in postmenopausal women. Obesity (Silver Spring). May; 2012 20(5):939–944. [PubMed: 22173571]
23. Burger HG, Dudley EC, Cui J, Dennerstein L, Hopper JL. A prospective longitudinal study of serum testosterone, dehydroepiandrosterone sulfate, and sex hormone-binding globulin levels through the menopause transition. J Clin Endocrinol Metab. Aug; 2000 85(8):2832–2838. [PubMed: 10946891]
24. Davison SL, Bell R, Donath S, Montalto JG, Davis SR. Androgen levels in adult females: changes with age, menopause, and oophorectomy. J Clin Endocrinol Metab. Jul; 2005 90(7):3847–3853. [PubMed: 15827095]
25. Sternfeld B, Liu K, Quesenberry CP Jr, et al. Changes over 14 years in androgenicity and body mass index in a biracial cohort of reproductive-age women. J Clin Endocrinol Metab. 2008; 93(6): 2158–2165. doi: 10.1210/jc.20071 2203. [PubMed: 18334590]
26. Brand JS, van der Tweel I, Grobbee DE, Emmelot-Vonk MH, van der Schouw YT. Testosterone, sex hormone1 binding globulin and the metabolic syndrome: a systematic review and meta-analysis of observational studies. Int J Epidemiol. Feb; 2011 40(1):189–207. [PubMed: 20870782]
27. Lovejoy JC, Bray G, Bourgeois M, Macchiavelli R, Rood J, Greeson C, et al. Exogenous androgens influence body composition and regional body fat distribution in obese postmenopausal women--a clinical research center study. J Clin Endocrinol Metab. Jun 1; 1996 81(6):2198–2203. [PubMed: 8964851]
28. Demerath EW, Rogers NL, Reed D, et al. Significant associations of age, menopausal status and lifestyle factors with visceral adiposity in african-american and european-american women. Ann Hum Biol. 2011; 38(3):247–256. doi: 10.3109/03014460.2010.524893. [PubMed: 21175300]
29. Sowers, MF.; Crawford, S.; Sternfeld, B. SWAN: A Multicenter, Multiethnic, Community-Based Cohort Study of Women and the Menopausal Transition.. In: Lobo, RA.; Kelsey, J.; Marcus, R., editors. Menopause: Biology and Pathobiology. Academic; San Diego, Calif. ; London: 2000. p. 175-188.
30. Wagenknecht LE, Langefeld CD, Scherzinger AL, Norris JM, Haffner SM, Saad MF, et al. Insulin sensitivity, insulin secretion, and abdominal fat: the Insulin Resistance Atherosclerosis Study (IRAS) Family Study. Diabetes. Oct; 2003 52(10):2490–2496. [PubMed: 14514631]
31. Hill JO, Sidney S, Lewis CE, Tolan K, Scherzinger AL, Stamm ER. Racial differences in amounts of visceral adipose tissue in young adults: the CARDIA (Coronary Artery Risk Development in Young Adults) study. Am J Clin Nutr. Mar; 1999 69(3):381–387. [PubMed: 10075320]
32. Yoshizumi T, Nakamura T, Yamane M, Islam AH, Menju M, Yamasaki K, et al. Abdominal fat: standardized technique for measurement at CT. Radiology. Apr; 1999 211(1):283–286. [PubMed: 10189485]
33. Fitzmaurice, GM.; Laird, NM.; Ware, JH. Applied longitudinal analysis. 2nd ed.. Wiley; Hoboken, N.J.: 2011.
34. Verbeke, G.; Molenberghs, G. Linear mixed models for longitudinal data. Springer; New York, NY: 2009.

35. Lewis TT, Everson-Rose SA, Sternfeld B, Karavolos K, Wesley D, Powell LH. Race, education, and weight change in a biracial sample of women at midlife. Arch Intern Med. Mar 14; 2005 165(5):545–551. [PubMed: 15767531]
36. Sowers MF, Zheng H, Tomey K, Karvonen-Gutierrez C, Jannausch M, Li X, et al. Changes in Body Composition in Women over Six Years at Midlife: Ovarian and Chronological Aging. J Clin Endocrinol Metab. Mar 1; 2007 92(3):895–901. [PubMed: 17192296]
37. Janssen I, Powell LH, Crawford S, Lasley B, Sutton-Tyrrell K. Menopause and the Metabolic Syndrome. Arch Intern Med. 2008; 168:1568–1575. [PubMed: 18663170]
38. Mayes JS, Watson GH. Direct effects of sex steroid hormones on adipose tissues and obesity. Obesity Reviews. 2004; 5(4):197–216. 11/30. [PubMed: 15458395]
39. Tepper PG, Randolph JF Jr, McConnell DS, Crawford SL, El Khoudary SR, Joffe H, et al. Trajectory Clustering of Estradiol and Follicle-Stimulating Hormone during the Menopausal Transition among Women in the Study of Women's Health across the Nation (SWAN). J Clin Endocrinol Metab. Aug; 2012 97(8):2872–2880. [PubMed: 22659249]

Bullet points

What is known about the subject?

1. Menopause is associated with weight gain and central fat redistribution.
2. Menopause is associated with hormonal changes.
3. Visceral adiposity is positively associated with testosterone in cross-sectional studies.

What does this study add?

1. The rate of change across the menopausal transition is higher for visceral adipose tissue than for subcutaneous abdominal adipose tissue or total body fat.
2. Change in bioavailable testosterone, but not change in estrogen, is significantly related to change in visceral adipose tissue as well as change in subcutaneous abdominal adipose tissue.
3. Neither change in bioavailable testosterone nor change in estradiol is related to change in total body fat.

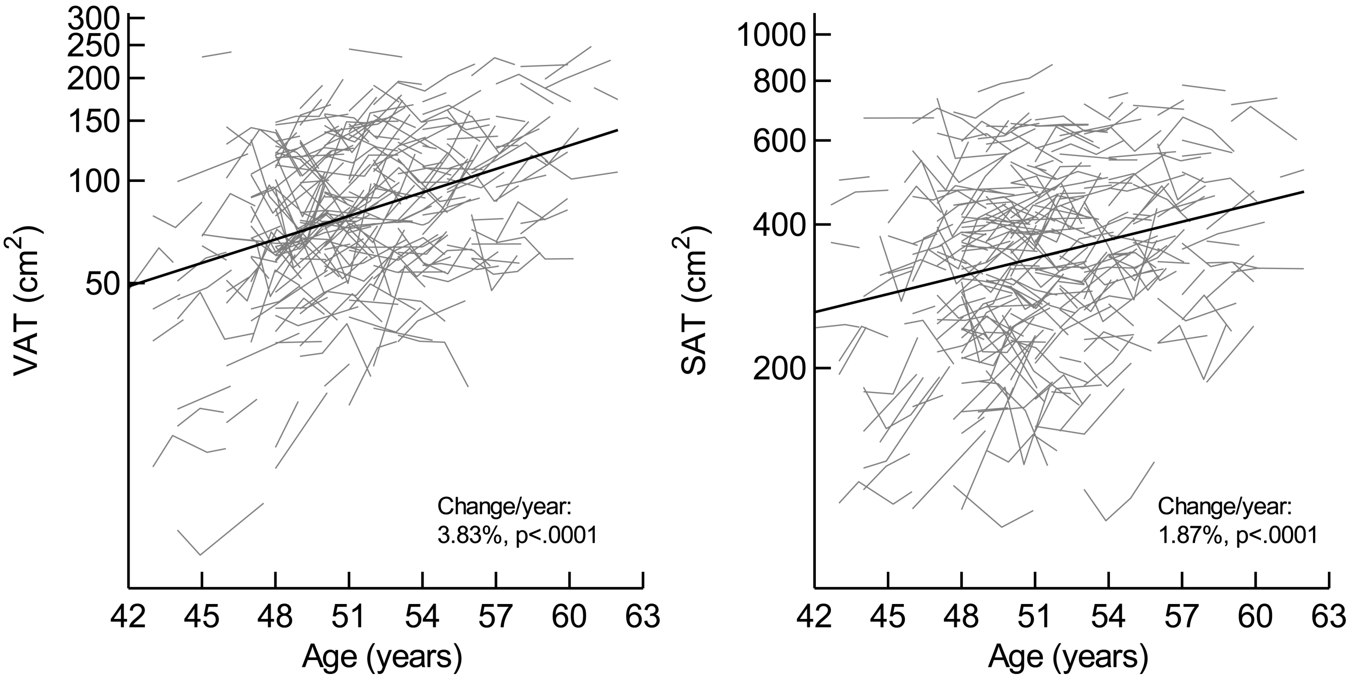

Figure 1.

Visceral adipose tissue (VAT) and subcutaneous abdominal adipose tissue (SAT) by age at assessment – individual trajectories and overall trend

Table 1

Characteristics of the cohort at baseline

N	243
African American, N (%)	106 (43.6)
Caucasian, N (%)	137 (56.4)
Age, years, mean (SD)	51.1 (3.7)
Education $\leq$ HS, N (%)	31 (12.8)
Menopausal Status, N (%)	
Pre	28 (11.5)
Peri	127 (52.1)
Post	88 (36.2)
BMI, kg/m^2, mean (SD)	28.6 (6.1)
Obese (BMI$\geq$30kg/m^2), N (%)	89 (36.6)

Table 2

Number of adiposity assessments

Number of assessments, N (%)	
2	68 (28.0)
3	103 (42.4)
4	72 (29.6)
Number of assessments, mean (SD)	3.0 (0.8)
Time between consecutive assessments (years)	1.1 (0.3)

Table 3

Baseline statistics and annual change for hormones and adiposity measures

	Baseline	change, % (p-value)
Reproductive Hormones median (IQR)		
Testosterone, bioavailable	2.9 (1.9 – 4.8)	9.14 (<.0001)
Testosterone, total (ng/dL) (0.0347 nmol/l)	40.9 (30.0 – 53.4)	0.57 (0.736)
Estradiol (pg/mL)	29.2 (16.8 – 65.3)	−7.35 (0.043)
Sex hormone-binding globulin (μg/ml) or nmol/l	47.0 (33.0 – 68.1)	−7.59 (<.0001)
Adiposity Measures, median (IQR)		
Visceral Adipose Tissue (VAT), cm^2	82.4 (59.7 - 123.8)	3.83 (<.0001)
Subcutaneous Adipose Tissue (SAT), cm^2	358.3 (262.3 - 487.6)	1.87 (<.0001)
Total Body Fat (TBF), %	44.0 (38.1 – 48.7)	0.02 (0.920)
Lifestyle factors		
Physical Activity, mean (SD)	8.2 (1.6)	−0.72 (0.061)
Smoking, N (%)	48 (19.8)	−1.00 (0.590)

VAT and SAT were measured by computed tomography, and TBF was measured using dual-energy X-ray absorptiometry.

Table 4

Linear mixed model relating change in bioavailable testosterone (BioT) and estradiol (E2) to change in adiposity measures[a] [visceral adipose tissue (VAT), subcutaneous abdominal adipose tissue (SAT), and total body fat (TBF)], adjusted for baseline age, race/ethnicity, and time-varying covariates of physical activity and smoking

	Δ VAT		Δ SAT		Δ TBF	
Effect	**Estimate (SE)**	**P-value**	**Estimate (SE)**	**P-value**	**Estimate (SE)**	**P-value**
Intercept	2.73 (1.45)	0.061	2.59 (3.76)	0.491	−0.38 (0.29)	0.194
Baseline BioT[b]	−0.87 (1.08)	0.425	−1.27 (2.70)	0.640	−0.20 (0.21)	0.330
Δ BioT[b] between-subject effect[c]	1.86 (1.05)	0.080	**5.46 (2.68)**	**0.046**	0.04 (0.21)	0.849
Δ BioT[b] within-subject effect[c]	**7.20 (3.16)**	**0.027**	**26.72 (8.18)**	**0.002**	0.22 (0.57)	0.709
Time (Years)	**4.99 (0.82)**	**<.0001**	**8.07 (1.83)**	**<.0001**	**−0.25 (0.13)**	**0.049**
Intercept	2.39 (1.48)	0.108	1.42 (3.84)	0.711	−0.35 (0.29)	0.230
Estradiol (E2)[b]	0.30 (1.41)	0.835	0.92 (3.55)	0.797	0.18 (0.27)	0.502
Δ E2[b] between-subject effect[c]	0.57 (1.27)	0.656	0.07 (3.26)	0.983	−0.38 (0.25)	0.128
Δ E2[b] within-subject effect[c]	0.24 (1.04)	0.819	4.87 (2.72)	0.078	−0.17 (0.19)	0.379
Time (Years)	**5.15 (0.84)**	**<.0001**	**8.99 (1.87)**	**<.0001**	−0.24 (0.13)	0.058

N=243 women, n=450 observation pairs or 675 observations total.

Significant results (p<0.05) are bolded.

[a] Change in adiposity from baseline

[b] Transformed by natural logarithm

[c] Standardized

Table 5

Transitions between menopausal statuses

Transition		**%**
Pre → Peri	21	20.4
Pre → Post	4	3.9
Peri → Post	78	75.7
Total	103	