Racial Differences in the Association between Sex Hormone Binding Globulin and Adiposity in Premenopausal Women: The BioCycle Study

Short title: Association between SHBG and adiposity by race

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Objective: To assess the associations between measures of adiposity and sex hormone binding globulin (SHBG) and to evaluate whether such associations differ by race.

Research Design and Methods: Adiposity was measured by anthropometry and dual energy x-ray absorptiometry among women (146 White, 50 Black, and 25 Asian) aged 18-44 years in the BioCycle study. SHBG was repeatedly measured over 1-2 menstrual cycles. The ratio of trunkal to leg fat (T/L) was used to assess upper to lower body adiposity.

Results: Among Whites, all adiposity measures were significantly and inversely associated with SHBG. Among Blacks, BMI (beta=-0.032), waist circumference (beta=-0.016), and T/L (beta=-.033), were significantly associated with SHBG whereas total and trunkal fat were not (p-interaction with race <0.04). Among Asians, measures of central and upper body fat were significantly associated with SHBG (e.g. T/L, beta=-0.84) but not BMI.

Conclusions: Associations between SHBG and adiposity differs by race among premenopausal women.

Racial differences in type 2 diabetes risk have been incompletely accounted for by differences in adiposity, partly due to disparities in the relationships between adiposity and other risk factors such as insulin and lipid levels.(1) Obesity is associated with a decreased level of sex hormone binding globulin (SHBG), which is associated with the development of type 2 diabetes.(2) However, data on the associations between SHBG and adiposity in premenopausal women are sparse and unknown whether such associations differ by race/ethnicity.

RESEARCH DESIGN AND METHODS
The BioCycle study, originally designed to investigate the association between endogenous sex hormones and oxidative stress, followed 259 premenopausal women aged 18-44 years old for 1-2 menstrual cycles, with up to 8 clinic visits per cycle timed using fertility monitors.(3,4) The inclusion/exclusion criteria have been published.(4) Over 94% of the participants attended at least 7 visits. For these analyses, we excluded women missing body composition measurements (n=11), leaving 146 White, 50 Black, 25 Asian, and 25 women of other race. The University of Buffalo Health Sciences Institutional Review Board approved the study. All women provided informed consent.

Demographics and lifestyle information were self-reported.(4) Anthropometry was measured by trained personnel. A dual energy x-ray absorptiometry (DXA) scan (Hologic, Waltham, MA), as previously validated in other studies (5,6), was performed to measure total body (%BF) and trunkal fat (%TF). Trunkal fat mass was divided by leg fat mass to assess upper to lower body fat ratio (T/L). Fasting estradiol, SHBG, insulin, and glucose had inter-assay coefficients of variation of <10%, <10%, <8%, and <3%, respectively. (4) Insulin resistance and beta-cell function were calculated based on the homeostasis model (HOMA).(7)

Associations between all repeated measures of SHBG and adiposity measures measured at a single time point were estimated using mixed models with a random intercept, which accounted for repeated
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measures and adjusted for age and cycle. In additional models, we adjusted for caloric intake, total physical activity, and repeated measures of estradiol (E2), and HOMA-IR. To test for interaction we included a cross-product term between each adiposity measure and race. Spearman correlations were calculated using values from the follicular phase visit of cycle 1. Analyses were performed using SAS 9.1 (SAS Institute Inc., NC).

RESULTS

33% of the women were overweight or obese (BMI $\geq 25$). (Supplemental Table A1 in the online appendix available at http://care.diabetesjournals.org) . Black women had higher ovulatory E2, insulin, HOMA-IR, and HOMA-beta levels than other women. Differences remained after adjusting for age and BMI or %BF ($p<0.01$). Other hormones did not differ significantly by race.

SHBG in White women were consistently inversely associated with adiposity. (Table 1) Results from mixed models show all adiposity measures except hip circumference were also inversely associated with SHBG in non-white women. However, the Spearman correlations and significant interactions suggest weaker associations between adiposity and SHBG among them.

Total and trunkal fat among Black women were not significantly associated with SHBG (Table 1). Adjusting for age, caloric intake, physical activity, E2, HOMA-IR, did not eliminate racial differences. T/L was associated with SHBG in both Blacks (beta=-0.33, p=0.003) and Whites (beta=-0.36, p<0.001); as were BMI and waist circumference. Among Asians, %BF was not associated with SHBG, whereas waist (beta=-0.022), and T/L (beta=-0.85) remained associated.

CONCLUSIONS

Among healthy premenopausal women, SHBG was inversely associated with measurements of body fat in Whites. In Blacks, correlations of SHBG with adiposity were weak with the strongest inverse association observed with upper to lower body fat ratio (i.e. T/L) Among Asians, the strongest inverse association was with central and upper adiposity (by T/L or waist).

Upper or total body adiposity do not carry the same type 2 diabetes inducing “toxic” affects among women of different race/ethnicity.(1,8) It has been observed that despite occasions of similar adiposity, Blacks have higher insulin levels than Whites whether during fasting or in response to a glucose challenge.(9) Here we found the same phenomena with fasting insulin and HOMA-IR. These differences could be through the mechanism of greater beta-cell activity among Blacks in compensation of higher insulin resistance (7), as confirmed here by HOMA-beta.

We add to this body of research the racial differences seen between the associations of SHBG, a type 2 diabetes risk factor(2), and adiposity. Despite the Black-White difference in insulinemia and the documented relationship between hyperinsulinemia and SHBG,(10,11) we found no significant difference in levels of SHBG by race. Studies are inconsistent on absolute differences in SHBG by race; Blacks have been observed to have higher SHBG than Whites in one study(1) and lower levels in others.(12-14) Despite the lack of racial difference in absolute SHBG levels in our study, measures of adiposity in Blacks were not as strongly correlated with SHBG as in Whites. These observations agree with previous investigations among pre- (1,12) and postmenopausal women.(15) However, unlike previous studies we were able to adjust for E2 and insulin and found that these hormones do not account for the racial differences. Studies among Asian women
are lacking but our observation that central adiposity was strongly inversely associated with SHBG levels here requires replication in a larger sample.

Our study was limited by different sample sizes of racial groups, which affected the precision of estimates and may have led to non-significant associations among minority groups. However, using mixed models on repeated measurements decreased the effects of intra-individual variability on results, and helped to increase power. We also lacked information on testosterone. However, previous investigation observed that SHBG is associated with adiposity independent of testosterone.(10) We could not determine directionality of the association between adiposity and SHBG due to single measures of adiposity. The strengths of our study comes from a wealth of information including measures of adiposity by DXA and repeated measures of hormone levels timed to capture cycle phase.

These findings suggest that despite having similar levels of SHBG, racial differences exist for the relationships between SHBG and adiposity among premenopausal women, adding to the evidence that the metabolic and reproductive influence of adipose tissue may differ by race.

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## Table 1. Age adjusted associations between SHBG and adiposity measures by race among premenopausal women in the BioCycle Study

| Measures | β(SE) from mixed models | p-interaction | Spearman Correlations |
|----------|-------------------------|---------------|-----------------------|
|          | White (n=146) | Minority* (n=100) | Black (n=50) | Asian (n=25) | (Minority* vs. White) | (Black vs. White) | White (n=146) | Minority* (n=100) | Black (n=50) | Asian (n=25) |
| %BF      | -0.031 (0.006) | -0.016 (0.007) | -0.010 (0.010) | -0.025 (0.026) | **p=0.041** | **p=0.021** | -0.35 | -0.13 | -0.04 | -0.08 |
| %TF      | -0.029 (0.004) | -0.020 (0.006) | -0.014 (0.008) | -0.039 (0.020) | **p=0.11** | **p=0.032** | -0.43 | -0.22 | -0.12 | -0.32 |
| T/L      | -0.363 (0.057) | -0.474 (0.090) | -0.333 (0.114) | -0.837 (0.250) | **p=0.49** | **p=0.72** | -0.43 | -0.34 | -0.28 | -0.51 |
| BMI      | -0.051 (0.008) | -0.027 (0.012) | -0.032 (0.015) | -0.077 (0.045) | **p=0.059** | **p=0.19** | -0.42 | -0.16 | -0.21 | -0.38 |
| Waist    | -0.026 (0.004) | -0.016 (0.005) | -0.016 (0.007) | -0.023 (0.012) | **p=0.048** | **p=0.15** | -0.43 | -0.18 | -0.22 | -0.44 |
| Hip      | -0.022 (0.004) | -0.007 (0.005) | -0.011 (0.007) | 0.007 (0.018) | **p=0.013** | **p=0.10** | -0.35 | -0.10 | -0.18 | 0.25 |
| WHR      | -3.231 (0.692) | -1.692 (0.719) | -2.102 (1.43) | -1.89 (1.01) | **p=0.068** | **p=0.41** | -0.32 | -0.13 | -0.18 | -0.6 |

All values are beta-coefficients (standard error) unless otherwise indicated. Measures of adiposity were taken at one time point - either at the beginning of the study for BMI, WC, WHR, or at the end of the study by DXA for %BF, %TF, T/L. Models tested associations with measures of adiposity singularly and were not mutually adjusted for each other. Bolding indicates significance of p<0.05. *Minority includes all women of non-white race