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Association of serum sex steroid hormone hemodilution and body mass index among healthy postmenopausal women

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Abstract

Purpose—Hemodilution refers to reduced concentrations of analytes in the blood secondary to increased fluid volume. Given that obesity is associated with expanded vascular volume, hemodilution may result in a lower ratio of blood concentrations of analytes among heavier subjects. Assessing the relationship of hormone concentration to total mass varies by body mass index (BMI) is etiologically important because obesity is related to hormone metabolism and cancer risk.

Methods—We evaluated data for 194 postmenopausal controls in an endometrial cancer case-control study. Height, weight, and serum hormone concentrations were measured previously. We estimated serum hormone mass from concentration based on estimates of calculated plasma volume. We assessed the effect of BMI on relationships of sex steroid hormone concentration and mass using multivariate linear regression.

Results—Higher BMI was associated with increased estrone, estrone sulfate, estradiol, and albumin-bound estradiol concentrations and masses (p-trend <0.001). With increasing BMI, androstenedione concentration did not change significantly (p-trend=0.548), but its mass increased (p-trend=0.024).

Conclusions—Relationships of sex steroid hormone concentration and mass were generally similar, except for androstenedione in which the relationship was only significant for mass. Future studies to assess both sex steroid hormone concentration and mass may have value in etiological research.

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Keywords

sex steroid hormones; obesity; hemodilution

Introduction

Clarifying relationships between body mass index (BMI) and production of sex steroid hormones is important for understanding the etiology of obesity-related malignancies such as endometrial cancer. Among postmenopausal women, elevated BMI is associated with higher circulating estrogen concentrations (1–2) and endometrial cancer risk (3–5). However, in multivariate analyses that include BMI and estrogen measurements, both factors remain significantly related to endometrial cancer risk (6–8), suggesting that elevated circulating estrogen concentrations may not fully mediate the obesity-endometrial cancer association. A possible explanation for these data is that obesity drives non-hormonal mechanisms of endometrial carcinogenesis, such as chronic inflammation, abnormal insulin metabolism and irregular ovulation (4). However, an alternative proposal is that values for hormone concentration and mass may diverge among obese women secondary to expanded blood volume, and that mass may be a better marker of risk than concentration.

Sex steroid hormone levels are highly regulated among normal cycling women through complex feedback loops involving the ovaries and hypothalamic-pituitary axis. After menopause, these homeostatic mechanisms are no longer operative, and excess hormone production among obese women may lead to increased endometrial cancer risk. Studies demonstrate that BMI and vascular volume are positively correlated, although relationships vary by body habitus (9–10). Therefore, the ratio of concentration to total body mass for some sex steroid hormones may be lower among heavier women. Given that postmenopausal obesity increases estrogen production and lowers the concentration through hemodilution, total body mass might represent a stronger measure of endometrial cancer risk. Previous analyses have suggested that elevated BMIs may reduce blood concentrations of prostate specific antigen relative to mass (11–13) and dilution of biomarkers has also been found during blood volume expansion with pregnancy (14).

We hypothesized that BMI related hemodilution could yield different relationships between body size and sex-hormone measurements when expressed as concentration compared with mass. Hormone mass can be computed from concentration by adjusting for plasma volume, which is a function of body surface area. To assess this hypothesis, we compared serum concentration and mass of sex-steroid hormones among healthy postmenopausal controls in an endometrial cancer study.

Materials and Methods

We analyzed data from an endometrial cancer case-control study conducted during 1987–1990 in five regions in the US. This study has been described previously (15). Controls were defined as women with intact uteri who did not have endometrial cancer and identified using two methods. One group included women identified through random-digit-dialing or Health Care Financing Administration records that were matched to incident endometrial cancer cases on age, race, and area of residence. A second group of controls, who had undergone hysterectomies for benign conditions, were selected at one of the seven participating recruitment hospitals. In total, 297 postmenopausal controls (70% of total) provided interviewed-based questionnaire data.

Anthropometric measures

Anthropometric measures were obtained in duplicate by trained interviewers (16). If repeat measurements were discrepant, a third measure was taken. Several indices of adiposity and adipose tissue distribution including BMI (kg/m^2) were calculated.

Sex steroid hormone concentration measurements

Details of the standardized procedures for blood collection, laboratory analysis of serum hormone levels, and reproducibility of laboratory assays have been previously reported (6). In brief, fasting serum sex steroid hormones concentrations were measured using in-house radioimmunoassays at Nichols Institute, Inc. (San Juan Capistrano, CA). Levels of estrone (E_1), estradiol (E_2), and androstenedione were measured following extraction with 20% ethyl acetate in hexane and separation by celite chromatography (17) and E_1 sulfate (E_1SO_4) was measured after extraction with an organic solvent (18), enzymatic hydrolysis, and celite chromatography (17). Sex hormone-binding globulin (SHBG) was measured by a commercially-available radioimmunoassay (Diagnostic Systems Laboratory Inc, Webster TX) and albumin-bound E_2 levels were calculated from E_2 levels and SHBG-bound E_2 levels (6). A pilot study of repeated testing of pooled specimens over a 10-day period demonstrated acceptable reliability (19). Analysis of 34 masked quality control samples included in all batches of study assays yielded the following coefficients of variation (CV): 16.6%, 11%, 11.4%, 45.1% and 15.2% for E_2 , E_1 , E_1SO_4 , androstenedione and SHBG, respectively (6). The high CV for androstenedione was reduced to 10.8% with the removal of a single outlier. Women who had recently used exogenous estrogens or oral contraceptives or were pregnant at the time of the interview analysis were excluded (6).

Sex steroid hormone mass calculation

Hormone mass was computed as presented for PSA mass calculation by Grubb et al (13). First, body surface area (m^2) was calculated as $\text{weight (kg)}^{0.425} \times \text{height (m)}^{0.725} \times 0.2025$. Next, plasma volume (L) was computed as body surface area $\times 1.670$. Finally, mass was computed by multiplying concentration $\times$ plasma volume. In this analysis, we substituted serum concentrations for plasma concentrations, assuming proportionality. As a sensitivity analysis, we applied a formula derived specifically for women (plasma volume (ml) = $1,395 \times$ body surface area (m^2)) (20).

Study participants

The current analysis is based on 194 postmenopausal women who had undergone natural menopause for whom anthropometric data and serum levels of E_1 , E_1SO_4 , E_2 , androstenedione, and albumin-bound E_2 were available. There were some differences in mean hormone levels between community ($N=135$) and hysterectomy controls ($N=59$), but we present the results of the combined controls because the patterns of associations were similar.

Statistical analysis

Using linear regression models, we regressed log transformed sex hormone concentrations and body masses against each BMI category (underweight/normal weight $<25 \text{ kg}/\text{m}^2$; overweight $25\text{--}30 \text{ kg}/\text{m}^2$ and obese $\geq 30 \text{ kg}/\text{m}^2$) to calculate the geometric mean hormone value and corresponding 95% confidence interval (CI). We tested for trends in sex steroid hormone concentration and mass across BMI categories. BMI groupings were entered as a continuous variable in the model and the Wald test of the coefficient was assessed. The adjusted model included age (years), smoking status at time of interview (smoker/nonsmoker), and average alcohol consumption (grams/week). After determining the relationships between BMI and log-transformed sex steroid hormone concentration and

mass for each BMI category, values were back-transformed for ease of interpretation. In addition, we used the Spearman rank correlation coefficient (r_s) and associated p-value to determine the correlations between hormone concentration and mass by BMI category. We also plotted log transformed hormone mass and concentration against BMI (continuous) for each sex steroid hormone. For all analyses, *P*-values of < 0.05 were considered statistically significant. All tests of statistical significance were two-tailed. Analyses were performed using Stata 10.1.

Results

Subject characteristics by BMI are provided in Table 1. Obesity was associated with less alcohol intake, White race, and less frequent history of ever smoking ($p < 0.03$). BMI and plasma volume were positively associated (p -trend < 0.001), albeit in a non-linear relationship (Supplementary Figure 1); women with a BMI of ≥ 30 kg/m² had approximately 20% larger plasma volume compared with women with BMI < 25 kg/m². The variance in plasma volume was higher among women with elevated BMIs.

Higher BMI was associated with increased concentration and mass of E_1 , E_1SO_4 , E_2 , and albumin-bound E_2 (p -trend < 0.001). However, whereas increasing BMI was not significantly associated with higher androstenedione concentrations (p -trend = 0.548), it was significantly related to greater mass (p -trend = 0.024). For each analyte, we found that the relative percentage increase among obese compared to normal weight women was higher for mass as opposed to concentration: E_1 23% vs. 3%; E_1SO_4 83% vs. 53%; E_2 133% vs. 95%; and for albumin-bound E_2 297% vs. 218%. We also assessed the strength of the correlation between log transformed concentration and mass by calculating the r_s and associated p-value, and all were 0.97 or greater with a p -value < 0.0001 . We observed similar Spearman rank correlation coefficients when limiting to extreme BMI values, corresponding to underweight and morbidly obese women (data not shown).

Figure 1 plots the log transformed concentrations and masses against BMI for each sex steroid hormone. We observed a linear relationship with BMI for both log transformed mass and concentration. Overall across all the hormones, the slopes were larger for mass as compared to concentration. In addition, we observed similar associations between steroid hormone mass and BMI when we calculated the hormone mass using an alternative plasma volume formula as proposed by Pearson et al (20), although the absolute plasma volume values differed (data not shown).

Discussion

Our analysis demonstrates that concentration and mass of estrogens among postmenopausal control women are highly correlated and relate similarly to BMI. However, as BMI increases, total body mass of hormones rises more steeply than concentration. In contrast to relationships for estrogens, higher BMI was related only to androstenedione mass, but not to concentration. This may represent a chance finding, but could indicate that concentration and mass associations with BMI vary by analyte, reflecting differences in homeostatic mechanisms, hormone interconversions or other factors. In particular, conversion of androgens to estrogens in peripheral adipose tissue may blunt the rise in androgen concentrations relative to total body mass among heavier women.

The mathematical conversion of concentration to mass is derived from computation of body surface area and plasma volume (13). We acknowledge that the masses of the sex steroid hormones were calculated and not measured. However, we suspect that our estimation is based on a reasonable formula and assessment using an alternative method (20) yielded the

same interpretation. Estimation of plasma volume is more strongly related to height than weight, raising the possibility that differences in body habitus might differentially influence total body mass of analytes. Recently, Baglietto et al reported that fat mass was the strongest anthropometric determinant of estradiol concentration, whereas waist circumference was the best indicator of estrone sulfate and androstenedione (2). Given that anthropometry adds information about the variance in hormone concentrations, continued assessment of different hormone metrics may also be warranted.

Although we applied the same formula to convert hormone concentration to hormone mass for each hormone, it is plausible that relationships between BMI and these metrics might vary by analyte. Adiposity is related to both hormone metabolism and hemodilution, consistent with our finding that total body mass rises more quickly than concentration with increasing BMI. Mechanisms that maintain sex steroid hormones levels may be more closely tied to plasma concentrations, irrespective of blood volume or total body mass (11). Furthermore, limited data suggest that hormone concentrations in blood and tissues of benign atrophic endometrium, endometrial cancer precursors and cancer are not correlated (21). Thus, a more comprehensive understanding of hormonal biology may require simultaneous analysis of levels in multiple tissue compartments and new strategies for comparing measurements in fluids and compositionally heterogeneous solid tissues.

Biologically, the homeostatic mechanisms that control sex steroid hormone production after menopause are poorly understood and may differ among analytes. Among postmenopausal women, most androgens are produced in the adrenal cortex and to a much lesser degree in the ovaries (22), but there may be considerable variation among women with regard to production, inter-conversion to estrogens and regulatory mechanisms. One study reported that elevated concentrations of free androgens was associated with weight gain during the menopausal transition among obese women (23), suggesting that understanding relationships between hormone concentrations and total body hormone mass may be important. Our findings suggest the possible importance of considering concentrations in combination with other metrics in assessing such questions.

The major strengths of our study include the use of measured BMI and the availability of extensive epidemiological data and valid serum hormone measurements. However, we used a cross-sectional design with only a modest number of subjects and relatively few obese patients. We also measured serum rather than plasma hormones, but given the strong correspondence of these measurements this would be unlikely to have affected our conclusions. Finally, we estimated plasma volume from surface area rather than performing direct measurements, but this conversion has been previously validated and represents a much more feasible approach for large epidemiologic studies (13).

In conclusion, we found that relationships of sex steroid hormone concentrations and mass were generally related similarly to BMI. However, there was some indication that the mass of sex steroid hormone, which accounts for obesity related hemodilution, might differentially affect relationships for certain analytes, such as androstenedione. Future prospective studies in which circulating hormones are measured at multiple time points, expressed as concentrations and masses, and compared with morphometric values may shed light on obesity, steroid hormone biology and endometrial cancer risk. Continued efforts to assess different metrics of hormone levels in multiple body compartments, including target tissues, may also contribute to increased understanding of hormonal carcinogenesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Sex steroid hormone log transformed mass and concentration among 194 postmenopausal control subjects stratified by body mass index

Note: β is the coefficient of an unadjusted linear regression between BMI (continuous) and hormone mass and concentration (continuous).

Table 1
Characteristics of 194 postmenopausal control subjects stratified by body mass index

	All women N=194			Underweight/Normal (BMI<25 kg/m ²) N=99			Overweight (BMI 25-29.9 kg/m ²) N=57			Obese (BMI ≥30 kg/m ²) N=38			P-value ^a
	Mean (SD)	Range		Mean (SD)	Range		Mean (SD)	Range		Mean (SD)	Range		
Age (years)	62.4 (6.4)	45-78		63.3 (6.1)	51-78		61.0 (6.1)	45-75		62.3 (7.4)	49-76		0.199
Age at menarche (years)	13.0 (1.5)	9-18		13.2 (1.4)	10-17		12.8 (1.6)	9-16		13.1 (1.5)	10-18		0.295
Time since menopause (years)	13.4 (7.8)	1-35		14.2 (7.8)	1-35		12.4 (7.8)	1-35		12.7 (7.1)	1-35		0.222
Parity (number)	3.3 (1.9)	0-13		3.3 (1.8)	0-7		2.9 (1.3)	0-7		3.7 (2.8)	1-13		0.605
Current alcohol/week (grams/week)	23.5 (60.7)	0-420		31.5 (70.8)	0-420		20.8 (55.5)	0-360.5		6.6 (27.8)	0-171.9		0.029
			Percent			Percent			Percent			Percent	
Race													
White (%)	93%			94%			100%			76%			0.008
Ever smoke regularly (% yes)	44%			52%			40%			29%			0.014

* Wald test p-value of each characteristic from linear regression using ordinal value of BMI.

Table 2
Sex steroid hormone concentration and mass in 194 postmenopausal control subjects stratified by body mass index

	All Female Controls			Underweight/Normal (BMI<25 kg/m ²)			Overweight (BMI 25-29.9 kg/m ²)			Obese (BMI ≥30 kg/m ²)			P-trend ^a	P-trend ^β
	Mean ^γ	95% CI	N=194	Mean ^γ	95% CI	N=99	Mean ^γ	95% CI	N=57	Mean ^γ	95% CI	N=38		
Plasma Volume (L)	2.88	(2.84–2.92)		2.72	(2.68–2.76)		2.93	(2.88–2.99)		3.23	(3.15–3.31)		<0.001	
Androstenedione														
Concentration (ng/dL)	62	(57.6 – 66.7)		61	(54.8 – 68.5)		63	(54.7 – 71.5)		63	(54.5 – 73.2)		0.741	0.548
Mass (ng)	1782	(1,652 – 1,923)		1662	(1,483 – 1,864)		1834	(1,603 – 2,097)		2047	(1,758 – 2,382)		0.037	0.024
Estrone														
Concentration (pg/mL)	34	(31.1 – 36.1)		30	(27.0 – 33.5)		33	(29.1 – 36.8)		46	(39.0 – 54.3)		<0.001	0.001
Mass (ng)	96	(88.9 – 104.4)		82	(73.2 – 91.1)		96	(84.9 – 108.4)		149	(125.7 – 177.2)		<0.001	<0.001
Estrone sulfate														
Concentration (pg/mL)	357	(316 – 405)		305	(254 – 367)		335	(277 – 406)		594	(453 – 779)		<0.001	<0.001
Mass (ng)	1,027	(904 – 1,168)		828	(689 – 995)		983	(811 – 1,192)		1,926	(1,460 – 2,540)		<0.001	<0.001
Estradiol														
Concentration (pg/mL)	7.4	(6.7 – 8.2)		5.8	(5.1 – 6.5)		7.9	(6.7 – 9.3)		13.4	(11.1 – 16.1)		<0.001	<0.001
Mass (ng)	21	(19.3 – 23.8)		16	(13.73 – 17.78)		23	(19.5 – 27.4)		43	(35.7 – 52.5)		<0.001	<0.001
Albumin-bound Estradiol														
Concentration (pg/mL)	1.6	(1.4–1.8)		1.1	(0.9–1.3)		1.8	(1.5–2.3)		3.5	(2.8–4.5)		<0.001	<0.001
Mass (ng)	4.6	(4.0–5.2)		2.9	(2.4–3.4)		5.4	(4.4–6.7)		11.5	(9.1–14.6)		<0.001	<0.001

^aWe calculated p-trend from unadjusted linear regression model using log transformed concentration and log transformed mass of sex steroid hormones and assuming a continuous variable for categories of BMI, coding 0 as normal weight, 1 overweight, 2 obese.

^βAdjusted for age, current smoke status, current alcohol/week, and White/non-White.

^γGeometric mean