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A BRIEF ORIGINAL CONTRIBUTION

Caffeine Intake and Endogenous Sex Steroid Levels in Postmenopausal Women

The Rancho Bernardo Study

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Caffeine intake has been associated with risk of osteoporosis, breast cancer, endometriosis, and fibrocystic breast disease and has been hypothesized to exert its effects through alteration of endogenous hormone levels. This study examined the cross-sectional association of caffeine intake with endogenous androgens, estrogens, and sex hormone-binding globulin in 728 white postmenopausal women aged 42–90 years in the Rancho Bernardo community-based study in 1984–1987. Caffeine intake was inversely associated with age and waist/hip ratio and positively associated with alcohol consumption. Significant inverse associations were noted between caffeine intake and bioavailable testosterone, which persisted after adjustment for age, waist/hip ratio, body mass index, alcohol intake, cigarette smoking, and physical activity ($r = -0.10$, $p = 0.02$). At high doses (equivalent to more than 2 cups of coffee or four cans of caffeinated soda daily), caffeine intake was positively associated with plasma estrone before and after adjustment for confounders ($r = 0.26$, $p = 0.05$). Sex hormone-binding globulin levels were positively associated with increasing caffeine intake (adjusted $r = 0.09$, $p = 0.03$). The positive association of caffeine with estrone and its inverse association with bioavailable testosterone suggest that caffeine's reported association with several chronic conditions may be mediated by an effect on endogenous sex steroids. *Am J Epidemiol* 1996;144:642–4.

caffeine; cohort studies; estradiol; estrogens; estrone; sex hormone-binding globulin; testosterone; women

It has been hypothesized that intake of caffeine-containing beverages may play a role in the development of hormone-dependent conditions such as osteoporosis (1), breast cancer (2, 3), fibrocystic breast condition (4), and endometriosis (5). One large cross-sectional study of perimenopausal women reported a negative correlation between caffeine and the percentage of bioavailable estradiol (but not total estradiol or estrone levels) (6). In another study, however, age-adjusted caffeine consumption was not associated with estradiol or estrone levels in pre- or postmenopausal women (7). Some studies suggest differential effects of caffeine depending on body weight with an inverse association with caffeine intake and breast cancer in lean women and a positive association between caffeine intake and breast cancer in heavier women (8). Some studies of daily or intermittent caffeine intake in male animals report elevations of testosterone levels (9, 10). Associations in humans may be further confounded because caffeine consumption is negatively associated with age and positively associated with cigarette smoking and alcohol intake (7, 11).

The community-based Rancho Bernardo study of older adults in southern California provided an opportunity to study whether caffeine intake in postmenopausal women is independently associated with endogenous sex hormone levels.

MATERIALS AND METHODS

Participants were part of an ongoing community-based study designed to examine lifestyle and healthy aging among middle- to upper-middle-class older adults in Rancho Bernardo, California. From 1984 through 1987, 1,385 women aged 24–90 years completed a standard questionnaire on diet, smoking, physical activity, and alcohol consumption by telephone or clinic visit. Self-reported physical activity

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was ascertained by asking participants whether they engaged in strenuous activity three or more times a week (yes/no). Caffeine intake was ascertained using the Harvard-Willett semiquantitative food frequency questionnaire (12). Height, weight, and waist and hip circumference were measured at a clinic visit. Sex hormone levels were measured in all 728 postmenopausal women not taking exogenous hormones. Venipuncture was performed in fasting subjects between 7 and 11 a.m.; plasma was stored at −70°C until first thawed for sex hormone analyses in 1990–1991. Previous work has demonstrated no deterioration of hormone levels over 15 years when samples are frozen and stored in tightly sealed containers (S. S. C. Yen, unpublished data). Estrone, estradiol, and testosterone were measured by radioimmunoassay (13). Bioavailable testosterone and bioavailable estradiol (non-sex hormone-binding globulin bound) were measured using the method of Tremblay and Dube (14). Sex hormone-binding globulin, which binds testosterone and estradiol, was determined by the method of Rosner (15). Women with estrone levels greater than 76 pg/ml ($n = 5$) or estradiol levels greater than 35 pg/ml ($n = 10$) were excluded because these hormone levels are consistent with premenopausal status or undisclosed estrogen use.

For estradiol and bioavailable estradiol, 14 percent (101 of 728 women) had values below the sensitivity of the assay. Four women (0.5 percent) had values below the sensitivity of the assay for testosterone and its bioavailable fraction; 0.4 percent of women had values below assay sensitivity for estrone. Undetectable levels were converted to levels just below the sensitivity of the assay for analysis. Intraassay coefficients of variation and sensitivity were as follows: testosterone (4.00 percent, 20 pg/ml), estrone (6.00 percent, 3 pg/ml), estradiol (5.87 percent, 3 pg/ml), sex hormone-binding globulin (7.50 percent, 0.10×10^8), bioavailable testosterone (5.80 percent, 20 pg/ml × percent free), and bioavailable estradiol (3.70 percent, 3 pg/ml × percent free).

Testosterone and bioavailable testosterone analyses used natural log transformation to correct for skewed distribution. Statistical analyses used analysis of variance and two-tailed Pearson's and partial correlations to adjust for covariates.

RESULTS

The average age was 73.6 (standard deviation = 8.3; range = 42–90) years with average caffeine intake of 65.8 mg/week (standard deviation = 152.2, range = 0–880.8). Caffeine intake was inversely correlated with age ($r = -0.26, p < 0.001$) and waist/hip ratio (age-adjusted $r = -0.11, p = 0.002$) and positively correlated with alcohol consumption (grams/week) (age-adjusted $r = 0.14, p = 0.03$), but it was not associated with cigarette smoking (cigarettes/day) (age-adjusted $r = 0.07, p = 0.31$), physical activity (age-adjusted $r = -0.07, p = 0.06$), or body mass index (weight (kg)/height $(m)^2$) (age-adjusted $r = -0.03, p = 0.48$).

Caffeine intake (mg/week) was significantly associated with bioavailable testosterone (pg/ml) after controlling for age, waist/hip ratio, body mass index, alcohol intake, cigarette smoking, and physical activity (multiply adjusted $r = -0.10, p = 0.02$; table 1). Neither estrone nor total or bioavailable estradiol was significantly associated with caffeine intake. However, a post hoc analysis of 61 women consuming more than 7 g/month of caffeine (approximately equal to more than 2 cups of coffee or four cans of caffeinated cola daily) revealed an association between increasing caffeine intake (grams/month) and estrone (pg/ml) inde-

TABLE 1. Adjusted* mean sex hormone levels by usual caffeine intake (mg/day) in 728 postmenopausal women aged 42–90 years, Rancho Bernardo, California, 1984–1987

	No.	Hormone (pg/ml)				
		Estradiol	Bioavailable estradiol	Testosterone†	Bioavailable testosterone†	Estrone
Caffeine intake (mg/day)						
None	512	5.84	3.25	138.8	39.77	18.8
0.1–60	49	6.52	3.76	146.35	36.78	19.74
60.1–144	49	5.5	2.84	122.12	27.88	18.28
144.5–234	54	6.01	3.13	123.35	26.71	18.24
234.1–880.8‡	64	5.42	2.87	134.29	30.08	18.46
p for trend§		0.50	0.21	0.58	<0.001	0.93

* Adjusted for age, body mass index, waist/hip ratio, cigarette smoking, alcohol consumption, and exercise participation.
† Analyses performed using natural logarithm and then reconverted for tabular presentation.
‡ This represents >7 g/month of intake.
§ Calculated using analysis of variance with covariates.

pendent of adjustment for age, body mass index, waist/hip ratio, cigarette smoking, alcohol consumption, and physical activity (multiply adjusted $r = 0.3, p = 0.05$). Levels of sex hormone-binding globulin tended to increase with increasing caffeine intake (multiply adjusted $r = 0.09$, $p = 0.03$). Analyses repeated after excluding women with estradiol levels below the sensitivity of the assay did not change the results.

DISCUSSION

A literature survey revealed no previous work examining the effect of caffeine intake on testosterone levels in postmenopausal women. In this analysis, bioavailable testosterone was negatively and independently associated with caffeine intake, while estrone was positively associated with high levels of caffeine consumption. Sex hormone-binding globulin was positively associated with caffeine intake, replicating findings of London et al. (6). Sex hormone-binding globulin is the major carrier of steroid hormones in the circulation and an important moderator of bioavailable hormone levels. The higher level of binding globulin probably explains the observed reduction in bioavailable testosterone levels. A similar reduction in bioavailable estradiol may not be apparent because these levels are already very low in postmenopausal women. Because sex hormone-binding globulin is produced in the liver, the results suggest a caffeine effect on hepatic metabolism. These findings are compatible with the effect of caffeine on medications metabolized by the liver (16).

These intriguing caffeine-hormone associations may explain some of the previously reported associations between hormone-related conditions and the intake of caffeinated beverages. If caffeine increases sex hormone-binding globulin levels, this may result in decreased levels of bioavailable estradiol and testosterone, providing one possible mechanism for both a diminished breast cancer risk (8) and an increased risk of osteoporosis (17) reported among caffeine users. The finding of higher levels of estrone in those with high caffeine intake may partially account for the association between caffeine consumption and endometriosis, even though the present study examined postmenopausal women (5). The absent expected associations with cigarette smoking and body mass index probably reflect the small number of smokers (12 percent) and overweight women (body mass index ≥ 27 = 22 percent) in this older population.

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