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Interrelationship between alcohol intake and endogenous sex-steroid hormones on diabetes risk in postmenopausal women

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Abstract

Objective—We examined whether circulating concentrations of sex hormones, including estradiol, testosterone, sex hormone-binding globulin (SHBG), and dehydroepiandrosterone sulfate (DHEAS), were associated with alcohol intake or mediated the alcohol-type 2 diabetes (T2D) association.

Methods—Among women not using hormone replacement therapy and free of baseline cardiovascular disease, cancer, and diabetes in the Women's Health Study, 359 incident cases of T2D and 359 matched controls were chosen during 10 years of follow-up.

Results—Frequent alcohol intake (≥1 drink/day) was positively and significantly associated with higher plasma estradiol concentrations in an age-adjusted model (β=0.14, 95% CI, 0.03, 0.26), as compared with rarely/never alcohol intake. After adjusting for additional known covariates, this alcohol-estradiol association remained significant (β=0.19, 95% CI, 0.07, 0.30). Testosterone (β=0.13, 95% CI, −0.05, 0.31), SHBG (β=0.07, 95% CI, −0.07, 0.20), and DHEAS (β=0.14, 95% CI, −0.04, 0.31) showed positive associations without statistical significance. Estradiol alone or in combination with SHBG appeared to influence the observed protective association between frequent alcohol consumption and T2D risk, with a 12–21% reduction in OR in the multivariate-adjusted models.

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Conclusions—Our cross-sectional analysis showed positive associations between alcohol intake and endogenous estradiol concentrations. Our prospective data suggested that baseline concentrations of estradiol, with or without SHBG, might influence the alcohol-T2D association in postmenopausal women.

INTRODUCTION

Recent data indicate that endogenous sex hormones play an important role in the pathogenesis of type 2 diabetes (T2D) [1]. Sex hormones, including estrogen [1;2], testosterone [3–5], sex hormone-binding globulin (SHBG) [4;6;7], and dehydroepiandrosterone sulfate (DHEAS) [4;8] have been linked with insulin resistance, impaired glucose tolerance (IGT), and T2D risk. There is evidence to indicate significant sex differences for the associations between endogenous testosterone and risk of type 2 diabetes [1,7]. High testosterone levels were associated with higher risk of type 2 diabetes among women but decreased risk of type 2 diabetes among men. With the onset of menopause and the concurrent decrease in estrogen, T2D risk increases among postmenopausal women [2]. High estradiol levels may be associated with high risk of diabetes in both women and men while low SHBG levels were consistently associated with increased diabetes risk.

There is some evidence suggesting that alcohol might be associated with increased concentrations of estrogen [9;10] and DHEAS [11–14]. Previous prospective studies have documented an inverse association between moderate alcohol consumption and the incidence of T2D [15–24]; however, the mechanisms underlying this potential benefit from alcohol intake are not completely understood. Given these interrelationships among alcohol intake, sex hormones, and T2D, it seems reasonable to hypothesize that sex hormones may, at least in part, explain the inverse relations between alcohol consumption and T2D risk. However, there is as yet no study directly testing these hormone-mediating pathways linking alcohol intake to T2D risk.

The objective of this study was to investigate whether alcohol consumption was associated with circulating concentrations of endogenous sex hormones. Also, we aimed to examine whether circulating levels of endogenous sex hormones mediate the association between alcohol consumption and T2D risk.

MATERIALS AND METHODS

Study Population

The Women's Health Study (WHS) is a randomized, double-blind placebo-controlled clinical trial of aspirin and vitamin E for the primary prevention of cardiovascular disease (CVD) and cancer. The participants are 39,876 female health professionals who were 45 years or older, had no history of CVD and cancer (except nonmelanoma skin cancer). Details of this trial have previously been described [25–27]. Among a total of 27,962 postmenopausal women in the WHS who had not used hormone replacement therapy (HRT) and were free of CVD, cancer, and diabetes at baseline, 359 incident cases of T2D and 359 matched controls were chosen using risk set sampling strategy during a median of 10 year

follow-up [28]. Controls were matched on age, race, fasting status at time of blood draw, and follow-up time.

Written informed consent was obtained from all participants in the WHS. This study was approved by the Institutional Review Boards of Brigham and Women's Hospital, Harvard Medical School, and the University of California at Los Angeles (UCLA).

Assessment of alcohol consumption and other covariates

Baseline information on usual diet, including alcohol intake, was provided by 39,310 (99%) of the randomized participants, who completed a 131-item, validated, semiquantitative food-frequency questionnaire (SFFQ). For each food, a commonly used unit or portion size was specified on the questionnaire, and the participants were asked how often on average during the previous year they had consumed that amount. The portion sizes for beverages containing alcohol were "1 glass, bottle, can" for beer and light beer, "4 oz. glass" for red wine and white wine, and "1 drink or shot" for liquor. Nine responses were possible, ranging from "never or less than once per month" to "6 or more times per day." These 9 categories were condensed into 4 categories because of the few women who reported frequent alcohol consumption. The 4 categories are rarely/never, 1–3 drinks/month, 1–6 drinks/week, and 1+drinks/day. These 9 categories were also used to calculate alcohol consumption as a continuous variable in g/day. We scaled the continuous alcohol variable, measured in grams/day by the US standard for one alcoholic beverage, 14 g, according to the International Center for Alcohol Policies (ICAP). Women who did not respond to any of the alcohol questions were excluded. A detailed description of the SFFQ and procedures used to calculate nutrient intake as well as data on its reproducibility and validity in a similar cohort was previously reported [29,30]. In brief, Spearman's correlation coefficient between total alcohol consumption as measured by four 1-week diet records and the SFFQ was 0.90 [4].

Other covariates, including body weight, height, family history of diabetes, smoking status, and physical activity, were assessed using questionnaires at study entry. Body mass index (BMI) was calculated as weight (in kg)/height^2 (in m^2). Physical activity was assessed using a validated questionnaire. At baseline, participants were asked, "How often do you exercise vigorously enough to work up a sweat?" The possible responses were rarely or never, one to three times a month, once a week, two to four times a week, five or six times a week, or daily.

Biomarker measurements

Baseline blood samples were centrifuged and stored in liquid nitrogen freezers until the time of laboratory analysis. Matched case-control pairs were handled identically and assayed in random sample order in the same analytical run. Laboratory personnel were blinded to case-control status during all assays. Hankinson and colleagues [31;32] reported that a single measurement of plasma levels of sex hormones can reliably reflect average long-term hormone levels over a 3-year period, with correlations ranging from 0.66 to 0.92 for plasma levels of sex hormones, including estradiol, estrone, estrone sulfate, androstenedione, testosterone, dehydroepiandrosterone (DHEA), DHEAS, and SHBG. Details have been previously reported. In brief, Chemiluminescent immunoassays (Elecsys autoanalyzer 2010,

Roche Diagnostics, Indianapolis, IN) were used to measure sex hormones and SHBG. As reported previously, the coefficients of variation from blinded quality control samples were 5.2% for estradiol, 7.4% for testosterone, 2.8% for DHEAS, and 2.8% for SHBG [33–36].

Statistical Analysis

Age-adjusted, age-and BMI-adjusted, and multivariate linear regression models were used to examine the associations between alcohol intake and biomarker concentrations. Adjusted geometric means of biomarkers were calculated using a multivariable adjusted regression model while controlling for age, smoking, BMI, physical activity, and family history of diabetes. To adjust for confounding effects, we included these covariates in the models because they are traditional well-established T2D risk factors. Linear regression modeling was also conducted with alcohol as a continuous variable.

Conditional logistic regression was performed to assess the impact of sex hormone concentrations on the association of alcohol intake with T2D risk. We first adjusted for matching factors such as age, ethnicity, and fasting status at time of blood draw. In multivariate analyses, we adjusted for BMI (continuous), family history of diabetes (yes or no), smoking (never, past, and current smokers), and physical activity (continuous). To evaluate whether sex hormone concentrations mediate the association between alcohol intake and T2D risk, each sex hormone biomarker (estradiol, testosterone, SHBG, and DHEAS) was added individually to the alcohol-T2D model. A change in the OR towards the null (OR=1) in estimates of the parameter between the models was used to indicate how various sex hormone biomarkers may mediate the pathway between alcohol consumption and reduced diabetes risk.

All statistical analyses were conducted using SAS (version 9.2; SAS Institute, Cary, NC). All p-values were two-tailed (α=0.05). Figures were constructed using GraphPad Prism Software (version 4.0, GraphPad Software Inc., La Jolla, CA).

RESULTS

The amount of alcohol consumption was significantly different between cases and controls. Cases tended to consume less alcohol than controls (Table 1). Overall, there were linear trends towards positive associations of alcohol consumption with all sex hormone biomarker concentrations (Figure 1). Nonetheless, the estradiol linear trend was largely influenced by the highest alcohol consumption category and the testosterone trend was not linear, as we observed a bimodal trend. These linear trends were adjusted for age, case/control status, BMI, smoking physical activity, and family history of diabetes. Specifically, geometric means of estradiol (p=0.002), SHBG (p<0.001), and DHEAS (p<0.001) significantly increased across increasing alcohol consumption category.

In the linear regression models adjusting for age and case/control status (Model 1) or BMI, age and case/control status (Model 2), levels of estradiol were positively associated with alcohol consumption (β=0.14, 95% CI,0.03, 0.26 from Model 1 and β=0.17, 95% CI, 0.06, 0.29 from Model 2) (Table 2). Beta (β) indicates the amount that the sex hormone increases in concentration with alcohol consumption compared to rarely/never consumption. Upon

further adjustment for smoking, physical activity and family history of diabetes (Model 3), estradiol remained significantly associated with alcohol consumption (β=0.19, 95% CI, 0.07, 0.30). Testosterone, SHBG, and DHEAS were not significantly associated with frequent alcohol consumption, although each showed evidence of positive associations in the unadjusted model (Model 1). In the full model including alcohol consumption as a continuous variable, there were significantly positive associations of alcohol intake with estradiol (β=0.07, 95% CI, 0.02, 0.12) and DHEAS (β=0.10, 95% CI, 0.03, 0.18). Beta (β) for the continuous variable indicates the amount that the sex hormone increases in concentration with each additional alcoholic beverage (14 g alcohol) consumed in a day.

We examined and confirmed the inverse association between alcohol consumption and T2D risk in our population. As compared with women who rarely/never drank alcohol, women who drank alcohol ≥ 1 drink/day had reduced T2D risk (OR=0.43, 95% CI, 0.19, 0.99) (Table 3). Furthermore, we tested for mediation of the alcohol-diabetes association by sex steroid hormones. The addition of SHBG in the unadjusted model only suggested mediation between alcohol consumption and T2D risk, however this difference was not observed in the full model. The addition of DHEAS in the full model did slightly shift the OR towards the null value (unadjusted: 3% change; full model: 5% change). Although estradiol did not seem to mediate the alcohol-T2D association with a shift in OR towards the null value, it did influence the association with a 12% reduction in the OR. In the model with both estradiol and SHBG, we observed a 21% reduction in the OR.

DISCUSSION

Our cross-sectional analysis of 718 postmenopausal women suggested a positive association between alcohol intake and concentrations of endogenous estradiol, independent of age, BMI, physical activity, race, family history of diabetes and smoking. In our nested case-control study, we found that concentrations of endogenous estradiol alone or together with SHBG may influence the prospective association of alcohol consumption and T2D.

Diabetes risk increases in middle-aged women when menopause occurs (with a pronounced decrease in estrogen) [2]. As previously reported, circulating concentrations of estradiol and testosterone were higher in cases, while SHBG and DHEAS were lower in cases than matched controls in our study population [37]. Both DHEAS and estradiol increase insulin secretion through their effects on pancreatic β-cells [2;38] and DHEAS improves insulin sensitivity by inducing an increase in glucose transport activity [8]. Testosterone was reported higher in T2D women in cross-sectional studies and may be positively associated with T2D risk in postmenopausal women in prospective studies [1]. Additionally, higher SHBG levels have been significantly associated with decreased diabetes risk in women and women, although the inverse association appeared to be stronger in women than in men [1]. These observations of T2D risk highlight the importance of the sex hormones in the T2D biologic pathway in postmenopausal women.

The inverse association between alcohol consumption and type 2 diabetes risk observed in our study population is consistent with previous reports [15–24]. Correspondingly, alcohol has been suggested to influence the levels of sex hormones. Early reports had mixed results

for the association of alcohol consumption and increased estradiol in postmenopausal women [39]. HRT was thought to modify this association; only those women taking HRT tended to have increased estradiol with alcohol consumption in a majority of the reports [39]. The increased estradiol was thought to be due to the inhibition of the conversion of estradiol to estrone [39]. More recently, results from a large cross-sectional study showed that postmenopausal women who drank more than 25 g alcohol per day had higher estradiol and DHEAS concentrations compared to nondrinkers independent of HRT [40]. Possible mechanisms for the increased estradiol include decreased catabolism of the sex hormones by the liver, increased aromatase activity, causing increased conversion of estradiol from androgens, or increased signaling of the adrenal gland to produce DHEAS (a precursor of estradiol) [41].

Our study provided suggestive evidence that the beneficial effect of alcohol on type 2 diabetes risk might occur through its influence on sex hormones, especially estradiol and DHEAS. Experimental data indicate that estradiol increases insulin secretion through its effects on pancreatic β-cells [2;38]. Given the observed association between alcohol consumption and estradiol concentration in this study, it is possible that estradiol exerts its modulating effects on the protective effect of alcohol consumption on type 2 diabetes risk. Our study results provided some suggestive evidence, but further mechanistic studies are warranted to elucidate the causal interrelationships. In addition, since SHBG binds estradiol and regulates the amount of available estradiol [42], the interaction of these sex hormones may influence the association of alcohol with T2D risk.

DHEAS might be involved in the mechanisms underlying the effect of alcohol consumption on T2D risk as well. DHEAS has been shown to enhance insulin secretion in β-cells in vitro and in vivo [8] and improve insulin sensitivity by inducing an increase in glucose transport activity [8]. We observed an association between alcohol consumption and DHEAS concentration in this study. Similar to estradiol, it is conceivable that increased DHEAS induced by alcohol consumption may be one pathway by which alcohol exerts its protective effect on T2D risk. DHEAS is a precursor of estrogen [43], DHEAS concentrations may also be influenced in this pathway. The mediation analysis provided a weak hint of mediation, suggesting that DHEAS may be a surrogate of estradiol or other sex hormone metabolisms in the pathway by which alcohol consumption reduces T2D risk.

Our study showed mixed results for the association or mediation of SHBG with alcohol intake and T2D. This may be explained in part -by the evidence for a possible “U-shaped” relationship between alcohol consumption and T2D for both sexes, where moderate alcohol consumption was significantly associated with lower risk of T2D with a nadir for diabetes risk at the 24 g/day level, and heavy alcohol drinking (above ~50 g/day for women and 60 g/day for men) were associated with increased diabetes risk [44]. Another explanation could be SHBG’s strong correlation with BMI ($\beta = -0.51$, p-value=0.008) [45]. Due to this strong correlation, the effect of each constituent alone cannot be distinguished from the other. A third explanation for the mixed results could be due to low statistical power when small numbers of subjects consumed alcohol frequently.

This study is a risk-set sampled matched nested case-control study within the WHS. It has several strengths, including a validation of the food frequency questionnaire, baseline biomarker concentration measurements, and prospectively collected disease diagnosis. However, there are some limitations that merit consideration. First, cross-sectional associations cannot tease out the causal relation between alcohol consumption and biomarker concentrations. Second, there may be some measurement error in the biomarkers with single measures, due to assay variability or degradation of the biomarkers. This bias should be non-differential among cases and controls, and therefore may cause bias to the null. Food frequency questionnaires, although validated in this study, may also produce some measurement error in the assessment of alcohol consumption. There remains the possibility of residual confounding due to unmeasured or poorly measured confounders in our observational study. Third, there is a possibility of potential bias using a mediation analysis by comparing two regression models [46]. Although such a conventional model provided suggestive evidence, development of alternative mediation analysis based on longitudinal data and evidence-based causal interrelationship will have potential to extract more accurate information about whether sex hormone biomarkers truly mediate the relation between alcohol intake and T2D. Finally, the results had wide confidence intervals, indicating the presence of instability in the estimates, partially due to inadequate statistical power with the small numbers of women who consumed alcohol frequently.

CONCLUSION

The cross-sectional analysis in our study suggested a positive association between alcohol intake and endogenous estradiol concentrations. Our prospective results also suggested that baseline concentrations of estradiol alone or with SHBG may contribute, in part, to the alcohol-T2D association in postmenopausal women. Further investigation of our findings and possible biological mechanisms is warranted.

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Abbreviations

BMI	body mass index
CVD	cardiovascular disease
DHEAS	dehydroepiandrosterone sulfate
HRT	hormone replacement therapy
ICAP	International Center for Alcohol Policies
IGT	impaired glucose tolerance
SFFQ	semiquantitative food-frequency questionnaire
SHBG	sex hormone-binding globulin

T2D	type 2 diabetes
UCLA	University of California Los Angeles
WHS	Women's Health Study

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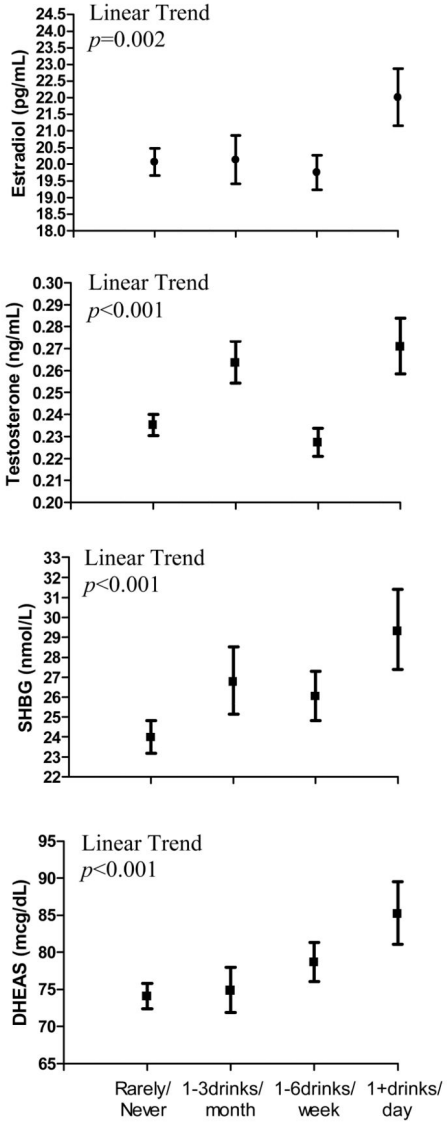

Figure 1.

Adjusted baseline sex hormone concentrations across categories of alcohol consumption. Geometric mean and 95% confidence intervals are presented. Geometric mean was adjusted for case/control status, age, BMI, smoking, physical activity, and family history of diabetes.

Table 1

Baseline characteristics of 718 postmenopausal women participated in this prospective case-control study of type 2 diabetes

Variable	Cases (n=359)	Controls (n=359)	*p*
Mean±SD Age (years)	59.6 ± 6.1	59.6 ± 6.1	—
Race/Ethnicity			
White	332 [93]	332 [93]	—
Black	8 [2]	8 [2]	
Hispanic	5 [1]	5 [1]	
Asian/Pacific Islander	9 [3]	9 [3]	
Other/Unknown	5 [1]	5 [1]	
Mean±SD BMI (kg/m^2)	30.9 ± 6.1	26.0 ± 5.0	<0.001
Strenuous Physical Activity			
Rarely/Never	183 [51]	142 [40]	0.002[1]
<1 time/week	65 [18]	78 [22]	
1 time per week	28 [8]	28 [8]	
2–3 times/week	50 [14]	70 [19]	
4–6 times/week	23 [6]	27 [7]	
7+ times/week	9 [3]	14 [4]	
Smoking			
Never	52 [15]	49 [14]	0.57[1]
Past	136 [38]	132 [37]	
Current	170 [47]	178 [49]	
Total alcohol consumption			
Rarely/Never	218 [61]	169 [47]	<0.001[1]
1–3 drinks/month	49 [14]	55 [15]	
1–6 drinks/week	74 [20]	94 [26]	
≥ 1 drinks/day	18 [5]	41 [12]	

Presented as frequency [percent] unless otherwise noted as Mean ± SD. Age and Race/Ethnicity were matching variables and therefore were the same for cases and controls.

[1]Mantel Haenszel Chi Square test for differences between cases and controls.

Table 2

Linear regression coefficients (95% CIs) for the increment in circulating concentrations of four endogenous sex hormone biomarkers according to each of the alcohol intake categories (as compared with never/rarely alcohol drinkers) among 718 postmenopausal women

N=718 Model	Alcohol consumption	Estradiol	Testosterone	SHBG	DHEAS
Model 1	1–3 drinks/month	0.02 [−0.08, 0.11]	0.10 [−0.04, 0.24]	0.06 [−0.04, 0.17]	0.01 [−0.12, 0.14]
	1–6 drinks/week	0.02 [−0.06, 0.10]	0.01 [−0.12, 0.13]	0.02 [−0.07, 0.11]	0.03 [−0.03, 0.20]
	1+ drink/day	**0.13 [0.01, 0.25]**	0.14 [−0.05, 0.33]	0.08 [−0.06, 0.22]	0.11 [−0.06, 0.23]
Model 2	1–3 drinks/month	0.03 [−0.06, 0.12]	0.10 [−0.04, 0.24]	0.04 [−0.06, 0.14]	0.01 [−0.12, 0.14]
	1–6 drinks/week	0.04 [−0.04, 0.12]	0.01 [−0.12, 0.14]	−0.03 [−0.11, 0.06]	0.08 [−0.03, 0.20]
	1+ drink/day	**0.16 [0.04, 0.28]**	0.14 [−0.05, 0.33]	0.00 [−0.13, 0.14]	0.11 [−0.07, 0.28]
Model 3	1–3 drinks/month	0.04 [−0.05, 0.13]	0.12 [−0.03, 0.26]	0.04 [−0.06, 0.14]	0.03 [−0.11, 0.16]
	1–6 drinks/week	0.05 [−0.03, 0.13]	0.01 [−0.11, 0.14]	−0.02 [−0.11, 0.07]	0.03 [−0.02, 0.21]
	1+ drink/day	**0.17 [0.05, 0.29]**	0.12 [−0.07, 0.31]	0.02 [−0.11, 0.15]	0.11 [−0.02, 0.30]

Values presented are beta-coefficient [95% CIs]. Sex hormone concentrations were log-transformed. **Bolded** values have $p<0.05$.

Model 1: Adjusted for case/control status and age

Model 2: Adjusted for case/control status, age, and BMI

Model 3: Adjusted for case/control status, age, BMI, race, family history of diabetes, physical activity, and smoking.

Table 3

Prospective associations of alcohol intake with T2D risk and mediation by endogenous sex hormone concentrations

Alcohol Intake (Rarely/Never vs. ≥1 Drink/Day)	Un-adjusted[1]			Adjusted[2]		
Model	**OR**	**95% CI**	**Percent Difference**	**OR**	**95% CI**	**Percent Difference**
Model A	0.30	0.16, 0.58	--	0.43	0.19, 0.99	--
[Model A] + Estradiol	0.25	0.13, 0.50	−17	0.38	0.16, 0.89	−12
[Model A] + Testosterone	0.29	0.15, 0.57	−3	0.44	0.19, 1.01	2
[Model A] + SHBG	0.41	0.18, 0.93	37	0.44	0.18, 1.09	2
[Model A] + DHEAS	0.31	0.16, 0.59	3	0.45	0.20, 1.03	5
[Model A] + Estradiol + SHBG	0.35	0.15, 0.82	17	0.34	0.13, 0.90	−21
[Model A] + Testosterone + SHBG	0.40	0.18, 0.90	33	0.44	0.18, 1.09	2
[Model A] + Estradiol + Testosterone + SHBG	0.35	0.15, 0.83	17	0.34	0.13, 0.90	−21

[1] Adjusted only for matching

[2] Adjusted for age, BMI, smoking, physical activity, and family history of diabetes