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Factors associated with the level of prolactin in patients under remission from Alcohol Use Disorder: A gender perspective

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Abstract

Background: Prolactin mirrors the dopaminergic activity in the brain which is key to understanding alcohol use disorders (AUD). Still, patients with AUD are a heterogenous group and there seem to be gender differences in the relationship between alcohol use and the level of prolactin. In this study, we examined gender-wise relationship of alcohol use trait- and state-related factors with the level of prolactin among AUD inpatients in remission.

Methods: This cross-sectional study examined the level of prolactin along with general patient characteristics and alcohol use trait- and state-related factors that could influence the level of prolactin in 112 AUD inpatients at three rehabilitation clinics in Norway. Logistic regression was performed to identify the gender-specific predictors of level of prolactin.

Results: Male and female AUD patients had similar level of prolactin. Among females, younger age, early alcohol debut, and absence of parental drinking problem predicted higher level of prolactin. In males, presence of other substance dependence predicted a lower level of prolactin.

Conclusions: There were gender differences in the factors associated with the level of prolactin among the AUD patients. Especially in the female AUD patients under remission, alcohol use trait-related factors were better predictors of the level of prolactin than the alcohol use state-related factors, indicating that individuals might characteristically have varying degree of dopamine reactivity.

KEYWORDS
alcohol use disorder, gender, prolactin, state factors, trait factors

1 | INTRODUCTION

Prolactin is a polypeptide hormone mainly secreted by the lactotrophs in the anterior pituitary and also by the extra pituitary sources like lymphocytes, the breast, the prostate, and the adipose tissue cells.[1] Although prolactin is well known for its role in lactation, mammary gland development, and reproduction, it also plays a vital role in the immune functions and behavioral functions of learning, memory, and adaptation.[2] The release of prolactin, to a major extent, is inhibited by the neurotransmitter dopamine produced in the hypothalamus.[3,4] To this end, the level of prolactin in the peripheral blood may be viewed as a reflection of the hypothalamic dopaminergic activity.

The dopamine system is considered to have an important role in the development and maintenance of alcohol use disorder (AUD). Alcohol intake increases dopaminergic activity, which induces dependence.[5-7] However, chronic heavy alcohol use downregulates the dopamine system, possibly through reduction in the availability and sensitivity of dopamine D2 receptors (D2R).[2,8-10] Different experimental[11-13] and naturalistic studies[14-16] indicate that a down regulation of the D2R increases the level of prolactin.

An animal study identified reduced hypothalamic dopamine as a possible cause of elevated serum prolactin after chronic alcohol administration.[11] However, studies also suggest that alcohol-induced proliferation of lactotrophs in the anterior pituitary gland may have fostered prolactin elevation.[17] Nevertheless, a neuroendocrine challenge test performed by administering the D2R blocker haloperidol to AUD patients revealed significant increase in the level of prolactin in patients when they underwent detoxification compared to the period of their usual alcohol consumption.[12] Such an increase in prolactin response to D2R blockage after undergoing detoxification signifies increased availability and responsivity of dopamine receptors indicating normalization from the previously downregulated dopamine system in these patients. However, increased level of prolactin in the absence of a neuroendocrine challenge is a sign of downregulated dopamine system.

Studies have shown that in addition to chronic heavy alcohol use, prolactin may also elevate in acute alcohol intoxication,[18] alcohol withdrawal, and early abstinence.[14] The elevation of prolactin during alcohol withdrawal is associated with the severity of alcohol dependence and withdrawal symptoms.[14] Also, it has been suggested that the elevated level of prolactin at the time of admission for treatment can serve as a biomarker that predicts increased risk of withdrawal seizures.[19] In addition, elevated level of prolactin is found to be associated with higher craving during early alcohol withdrawal in AUD patients with anxiety disorder who used alcohol for its anxiolytic effect.[20] Likewise, increased level of prolactin during alcohol withdrawal is significantly correlated with depressed mood.[21]

Generally, the level of prolactin is also influenced by use of certain drugs[1] and presence of diseases such as pituitary tumor, hypothyroidism, lung cancer, renal failure, and cirrhosis of liver. In addition, several physiological factors including body mass index (BMI),[22] menstrual cycle,[23] stress,[24] and sleep[25] influence the level of prolactin. One among such important factors that influences the level of prolactin is gender.[26] A study reported that increased level of prolactin is associated with lower craving during alcohol withdrawal but only in female AUD patients.[15] Another study which examined the alteration in the level of prolactin and its associated factors during alcohol withdrawal chose to include only male AUD patients so as to overcome the impact of gender difference.[14] In general, it is found that females have enhanced dopamine activity[27] and modulation of dopamine by sex hormones especially estrogen[28] implicates that the influence of alcohol on dopamine and prolactin may be sexually dimorphic. A previous study in AUD patients by our group found that a high level of prolactin was associated with relapse in a subgroup of patients with antisocial personality disorder, a disorder most often present in males (Pandey S. et al, 2020, unpublished data). Thus, there seem to be different predictors of level of prolactin in different subgroups of AUD patients.

Here, we aim to examine the gender-specific factors that influence the level of prolactin in AUD inpatients. Given the fact that the level of prolactin may be influenced by a plethora of factors, it is difficult to identify the role of alcohol on fluctuations of level of prolactin and also caution should be held while using prolactin as a surrogate marker to the dopaminergic activity. Furthermore, individuals' characteristics related to alcohol use determined by their genes, background, experiences, or the interactions among them (trait factors) may influence the level of prolactin, in addition to their current alcohol consumption status (state factors). We have therefore categorized the prolactin influencing factors into (a) general patient characteristics, (b) alcohol use trait-related factors, (c) alcohol use state-related factors, and (d) presence of other substance dependence in this study and have aimed to scrutinize whether the factors in these categories can predict the level of prolactin. We hypothesize that alcohol use trait- and state-related factors influence the level of prolactin in AUD patients but differently in males and females.

2 | MATERIALS AND METHODS

2.1 | Study participants

AUD patients (n = 112; 31 females) in treatment at three different rehabilitation clinics in Norway participated in the study. The median (25th, 75th percentiles) age of the participants was 53.3 (44.5, 57.8) years. The participants had been receiving inpatient treatment since median (25th, 75th percentiles) days of 7 (5, 12) and reported being abstinent since 19 (13, 30) days before data collection. Ethical approval to conduct the study was obtained from Norwegian Regional Ethics Committee (Reference number 2017/1314). The study abided by the Declaration of Helsinki. The participants provided written informed consent to participate in the study.

The inclusion criteria were adult above 18 years of age currently receiving inpatient treatment for AUD. The patients were also required to self-report abstinence for at least 5 days before data collection because the residential treatment in Norway does not necessarily confine the patients within the treatment center indicating that the patient may have a possibility to relapse even during the inpatient treatment. The exclusion criteria were unfamiliarity with a Scandinavian language, severe somatic illness, psychosis, and cognitive impairment that could hinder the patient's ability to provide informed consent and safely participate in the study. Furthermore, we did not include those patients from whom blood sample could not be obtained via superficial veins of arm.

2.2 | Measures

2.2.1 | General patient characteristics with possible influence on prolactin

Information on patient age, smoking status, height, and weight was obtained, and BMI (kg/m^2) was calculated. In addition, information on current regular use of dopaminergic drugs including antipsychotics, antihistamines, and stimulants was collected. The influence of all typical antipsychotics and mainly two atypical antipsychotics, risperidone and amisulpride, were our major focus because their effect on the dopamine receptors is well established and significant.[29] Furthermore, psychological distress and sleep condition of the patients were assessed. A Norwegian version of the 10-item Hopkins Symptom Checklist (HSCL), which has been previously used in AUD population,[30] was used to identify general psychological distress. The checklist required the respondents to rate their experience of symptoms related to anxiety and depression over the past week on a scale of 1 (not at all) to 4 (extremely). The mean score was calculated if 8 out of 10 items were answered. Higher score corresponds to more psychological distress. Participants' sleep condition over the last month was assessed using an 8-item Sleep Condition Indicator[31] which required the respondents to rate their sleep quality and its impact on their life in a scale of 0 to 4. The total score was generated by summing up the individual scores if 6 out of 8 items were answered and higher score represented better sleep conditions.

2.2.2 | Alcohol use trait-related factors with possible influence on prolactin

Alcohol use trait-related factors refer to those patient characteristics related to alcohol use which are determined by their genes, background, experiences, or the interactions among them. In this study, we collected information on participants' age (years) at first alcohol use, presence of alcohol problems in parents, and level of response to early alcohol use as alcohol use trait-related factors. The level of response to early alcohol use was examined using a Self-Rating of the Effects (SRE) of alcohol form.[32] This is a 12-item instrument from which we chose a single item that measured the number of standard drinks required to develop dizziness during the first five times the alcohol was imbibed. Higher number of drinks required to feel dizzy is interpreted as lower level of response to alcohol.

2.2.3 | Alcohol use state-related factors with possible influence on prolactin

Alcohol use state-related factors refer to the current alcohol-related characteristics of the patients mainly attributable to the actual action of alcohol consumption either current or over time. In this study, we collected information on hazardous alcohol use, duration of drinking (years), time since last drink (days), and presence of current alcohol

withdrawal symptoms as alcohol use state-related factors. Hazardous alcohol consumption was screened using the WHO-developed Alcohol Use Disorders Identification test (AUDIT) which measures the experience with alcohol within the last year using 10 questions.[33] The first 3 questions deal with the level of alcohol consumption (AUDIT-C) while the last 7 questions are related to alcohol dependence (AUDIT-dependence) and alcohol-related harms (AUDIT-harm) summed together and hereafter referred as AUDIT-problems.[34] Each response has scores that range from 0 to 4. The total score was calculated as sum of individual items if all three items were answered for AUDIT-C and if six out of seven items were answered for AUDIT-problems. The total score ranged from 0 to 12 for AUDIT-C and 0 to 28 for AUDIT-problems. A higher score indicates more hazardous alcohol use.

The presence of other substance dependence was identified using the Mini International Neuropsychiatric Interview (MINI) Norwegian translation version 6.0. which is a short structured diagnostic interview for DSM-IV psychiatric disorders. The nonalcohol psychoactive substance use disorders module of the MINI gives the diagnosis of current substance dependence and current substance abuse by asking questions about use of psychoactive substances within the period of past 12 months. The diagnosis of either current substance dependence or substance abuse was considered as presence of other substance dependence in our study.

2.2.4 | Prolactin and other biological measures related to alcohol use

Along with prolactin, we measured gamma-glutamyltransferase (γ-GT) and phosphatidylethanol (PEth; 16:0/18:1) of the participants. Venous blood samples from the superficial veins in the arm were collected. Serum gel tubes were used to collect blood sample for prolactin and γ-GT, and ethylenediaminetetraacetic acid tubes were used for PEth. The tubes were turned upside-down 8 to 10 times immediately after the samples were drawn and then set to rest in a blood tube stand. The serum gel tubes were centrifuged to separate serum. The blood samples were then sent to a laboratory to perform necessary analysis.

Prolactin was measured by chemiluminescence immunoassay using the ADVIA Centaur XPT immunoassay analyzer (Siemens, Erlangen, Germany), and the analytical and biological coefficients of variation of the assay were 3.7% and 23%, respectively. The prolactin secretion is greatest during the sleep,[35] and it is recommended that the blood sample for prolactin estimation should be collected 2-3 hours after waking up.[36] All our blood samples were drawn after 8:45 in the morning. The median (25th, 75th percentiles) time for sample collection was 10:38 AM (10:10 AM, 12:30 PM).

2.3 | Statistical analyses

Statistical analyses were performed using SPSS version 23.0 for Windows. Descriptive statistics were used to present the

TABLE 1 Gender differences in selected variables among AUD inpatients under remission (n = 112)

		Patient group				
		Female (n = 31)		Male (n = 81)		
		n		n		P-values
General patient characteristics						
Age (y)	Median (25th, 75th percentile)	31	51.7 (43.6, 57.1)	81	53.4 (44.7, 59.2)	0.318[a]
Body mass index (kg/m^2)	Median (25th, 75th percentile)	31	26.5 (23.1, 29.4)	81	26.5 (13.5, 28.9)	0.633[a]
Smoking	n (%)	31	21 (67.7)	81	68 (84.0)	0.057[b]
HSCL mean score	Median (25th, 75th percentile)	21	2.5 (1.9, 3.1)	64	1.9 (1.5, 2.4)	**0.002**[a]
Sleep condition	Median (25th, 75th percentile)	20	13.0 (7.8, 17.5)	62	18.0 (11.0, 25.0)	**0.036**[a]
Regular use of dopaminergic drugs (typical antipsychotics, risperidone and amisulpride)	n (%)	31	0 (0)	83	1 (1.2)	1.000[b]
Alcohol use trait-related factors						
Age at first drink (y)	Median (25th, 75th percentile)	31	15.0 (14.0, 17.0)	80	15.0 (13.0, 16.0)	0.214[a]
Parents having drinking problem	n (%)	31	18 (58.1)	80	43 (53.8)	0.682[b]
SRE (number of alcohol units to feel dizzy)	Median (25th, 75th percentile)	15	5.0 (2.0, 6.0)	46	4.3 (3.0, 7.0)	0.661[a]
Alcohol use state-related factors						
AUDIT-C	Median (25th, 75th percentile)	21	11.0 (8.5, 12.0)	63	11.0 (9.0, 12.0)	0.531[a]
AUDIT-problems	Median (25th, 75th percentile)	21	19.0 (15.0, 23.0)	64	19.0 (14.0, 22.0)	0.624[a]
Duration of drinking carrier (y)	Median (25th, 75th percentile)	31	9.0 (5.0, 15.0)	80	17.5 (10.0, 25.0)	<0.001[a]
Time since last drink (d)	Median (25th, 75th percentile)	31	16.0 (12.0, 30.0)	80	19.5 (13.0, 36.5)	0.202[a]
Current withdrawal symptoms present	n (%)	31	3 (9.7)	81	11 (13.6)	0.754[c]
Presence of other substance dependence						
Other substance dependence present	n (%)	31	3 (9.7)	80	21 (26.3)	0.057[b]
Biological measures of alcohol use						
γ-GT (U/L)	Median (25th, 75th percentile)	30	31.5 (22.0, 57.5)	81	41.0 (25.5, 89.5)	0.133[a]
PEth (μmol/L)	Median (25th, 75th percentile)	28	0.2 (0.1, 0.6)	79	0.3 (0.1, 0.6)	0.952[a]
Level of prolactin (mU/L)	Median (25th, 75th percentile)	31	125.0 (103.0, 202.0)	81	134.0 (98.0, 177.0)	0.743[a]

Note: Values in bold indicate statistically significant results.

Abbreviations: γ-GT, Gamma-glutamyltransferase; AUDIT, alcohol use disorders identification test; HSCL, Hopkins Symptom Checklist; PEth, Phosphatidylethanol; SRE, self-rating of the effects of alcohol.

[a]Mann-Whitney *U* test.

[b]Pearson chi-square.

[c]Fisher's exact test.

TABLE 2 Gender differences in the association of selected variables with prolactin levels among AUD inpatients under remission (n = 112)

Factors with possible influence on Prolactin		Female (n = 31) n		P-values	Male (n = 81) n		P-values
General patient characteristics							
Age (y)	r_s	31	−0.533	**0.002**[b]	81	−0.021	0.852[b]
Body mass index (kg/m²)	r_s	31	0.324	0.075[b]	81	0.023	0.839[b]
Smoking							
No	Median (25th, 75th percentile)	10	125.0 (88.0, 195.0)	0.485[a]	13	158.0 (126.0, 191.0)	0.163[a]
Yes	Median (25th, 75th percentile)	21	125.0 (103.5, 204.0)		68	132.0 (94.3, 168.8)	
HSCL mean score	r_s	21	−0.007	0.978[b]	64	−0.122	0.339[b]
Sleep condition	r_s	19	0.037	0.743[b]	62	0.047	0.719[b]
Alcohol use trait-related factors							
Age at first drink (y)	r_s	31	−0.423	**0.018**[b]	80	0.104	0.357[b]
SRE (number of alcohol units to feel dizzy)	r_s	15	0.402	0.138[b]	46	0.302	**0.041**[b]
Parents having drinking problem							
No	Median (25th, 75th percentile)	13	175.0 (115.5, 223.0)	0.075[a]	37	134.0 (99.5, 172.5)	0.772[a]
Yes	Median (25th, 75th percentile)	18	111.0 (99.3, 195.0)		43	139.0 (99.0, 188.0)	
Alcohol use state-related factors							
AUDIT-C	r_s	21	0.366	0.103[b]	63	−0.084	0.511[b]
AUDIT-problems	r_s	21	−0.184	0.424[b]	64	−0.119	0.351[b]
Duration of drinking carrier (y)	r_s	31	−0.134	0.471[b]	80	−0.127	0.261
Time since last drink (d)	r_s	31	−0.018	0.925[b]	80	0.091	0.422[b]
Current withdrawal symptoms							
Absent	Median (25th, 75th percentile)	28	124.5 (103.3, 197.0)	0.316[a]	70	133.5 (98.5, 175.5)	0.994[a]
Present	Median (25th, 75th percentile)	3	204.0 (103.0)		11	140.0 (91.0, 196.0)	
Other substance dependence							
Absent	Median (25th, 75th percentile)	28	122.5 (103.0, 190.0)	**0.018**[a]	59	140.0 (112.0, 180.0)	0.052[a]
Present	Median (25th, 75th percentile)	3	242.0 (204.0)		21	115.0 (70.0, 164.0)	
Biological measures of alcohol use							
γ-GT (U/L)	r_s	30	0.074	0.699[b]	81	0.048	0.669[b]
PEth (μmol/L)	r_s	28	−0.056	0.776[b]	79	−0.038	0.741[b]

Note: Values in bold indicate statistically significant results.

Abbreviations: γ-GT, Gamma-glutamyltransferase; AUDIT, alcohol use disorders identification test; HSCL, Hopkins Symptom Checklist; PEth, Phosphatidylethanol; SRE, self-rating of the effects of alcohol.

r_s, Spearman's rank order correlation coefficient.

[a]Mann-Whitney *U* test.

[b]Spearman's rank order correlation.

characteristics of the AUD patients stratified on gender. Our data were skewed and thus reported as medians and 25th, 75th percentiles in the tables. Groups were compared using Pearson's χ^2 test or Fisher's exact test for categorical variables and Mann-Whitney's U test for continuous variables. In addition, Spearman's Rho (r_s) was used to identify the gender-wise correlates of level of prolactin. Furthermore, a gender-wise logistic regression analysis of level of prolactin was performed, and odds ratios (OR) along with 95% confidence intervals (CI) were reported. Linear regression analysis was not performed because the assumptions of the test were not met. To obtain a dichotomous outcome variable for logistic regression, the prolactin values for each gender were split on median. Along with unadjusted logistic regression analysis, an age-adjusted logistic regression model was also constructed. All statistical tests were two-tailed with a significance level of $\alpha = 0.05$.

3 | RESULTS

Table 1 presents the gender differences of selected variables in the AUD patients. The male and female AUD patients had similar level of prolactin. The female AUD patients reported more psychological distress ($P = .002$), poorer sleep condition ($P = .036$), and shorter duration of drinking ($P < .001$) than their male counterparts.

Table 2 presents the association of the level of prolactin of AUD patients with general patient characteristics, alcohol use trait-related factors, alcohol use state-related factors and presence of other substance dependence stratified on gender. Among the general patient characteristics, in the females, younger age was associated with higher level of prolactin ($r_s = -0.533$, $P = .002$). On examining the influence of regular use of important dopaminergic drugs (all typical antipsychotics, risperidone, and amisulpride) on the level of prolactin, it was found that only one male AUD patient was on regular use of an atypical antipsychotic (levomepromazine)

which was not associated with the level of prolactin ($P = .146$). We also examined the individual influence of regular use of other dopaminergic drugs in the level of prolactin including atypical antipsychotics (quetiapine, aripiprazole, and olanzapine), antihistamines (trimeprazine and promethazine), and stimulant (Methylphenidate) and found that the use of these drugs was not associated with the level of prolactin in either gender. Among the alcohol use trait-related factors, those females who started drinking at earlier age had higher level of prolactin ($r_s = -0.423$, $P = .018$). In addition, the AUD females with the presence of other substance dependence measured higher on their level of prolactin ($P = .018$). Among the male AUD patients, an alcohol use trait-related factor, SRE had a weak positive correlation with the level of prolactin ($r_s = 0.302$, $P = .041$).

Table 3a presents the results from the logistic regression model ($n = 31$) of level of prolactin in the female AUD patients using variables that were significantly ($P < .05$) or marginally ($P = .075$) associated with the level of prolactin for either gender in Table 2. Substance dependence was an exception and was not included because of fewer number in the subgroups. A younger age (OR = 0.88, 95% CI: 0.79, 0.98) and early alcohol debut (OR = 0.59; 0.37, 0.95) increased the odds of having higher prolactin levels in the female AUD patients. On adjusting for age, having parents with drinking problem (OR = 0.13; 0.02, 0.88) decreased the odds of having higher level of prolactin in the female AUD patients.

Table 3b presents the results from a similar logistic regression model ($n = 81$) in the male AUD patients but also including other substance dependence as a covariate. Presence of other substance dependence decreased the odds of having higher level of prolactin in the male AUD patients also when adjusted for age (OR = 0.29; 0.09, 0.95).

Figure 1 presents the scatter plot between the level of prolactin and age at first drink in male and female AUD patients. There is a gender interaction in the relationship between the level of prolactin and age at first drink.

TABLE 3A Logistic regression model of prolactin level among female AUD patients (n = 31)

	n	Reference		Unadjusted	P-values	Adjusted[a]	P-values
Age (y)	31	Continuous	OR (95% CI)	0.88 (0.79, 0.98)	**0.022**		
Body mass index (kg/m²)	31	Continuous	OR (95% CI)	1.10 (0.97, 1.26)	0.151	1.14 (0.96, 1.35)	0.132
Parents having drinking problem	31	No drinking problem in parents	OR (95% CI)	0.22 (0.05, 1.03)	0.054	0.13 (0.02, 0.88)	**0.036**
Age at first drink (y)	31	Continuous	OR (95% CI)	0.59 (0.37, 0.95)	**0.030**	0.68 (0.42, 1.12)	0.678
SRE (number of alcohol units to feel dizzy)	15	Continuous	OR (95% CI)	1.34 (0.83, 2.17)	0.237	1.60 (0.84, 3.04)	0.153

Note: Values in bold indicate statistically significant results.

Abbreviations: CI, confidence interval; OR, odds ratio; SRE, self-rating of the effects of alcohol, the prolactin levels were dichotomized into high and low by splitting on the median value of 125 mU/L.

[a]Adjusted for age

TABLE 3B Logistic regression model of prolactin level among male AUD patients (n = 81)

	n	Reference		Unadjusted	P-values	Adjusted[a]	P-values
Age (y)	81	Continuous	OR (95% CI)	1.01 (0.97, 1.05)	0.688		
Body mass index (kg/m²)	81	Continuous	OR (95% CI)	1.03 (0.93, 1.14)	0.569	1.03 (0.93, 1.14)	0.582
Parents having drinking problem	80	No drinking problem in parents	OR (95% CI)	1.11 (0.46, 2.66)	0.823	1.12 (0.46, 2.71)	0.800
Age at first drink (y)	80	Continuous	OR (95% CI)	1.20 (0.98, 1.47)	0.085	1.20 (0.97, 1.47)	0.093
SRE (number of alcohol units to feel dizzy)	46	Continuous	OR (95% CI)	1.11 (0.88, 1.39)	0.381	1.11 (0.88, 1.39)	0.380
Other substance dependence present	80	Absence of other substance dependence	OR (95% CI)	0.32 (0.12, 0.93)	**0.036**	0.29 (0.09, 0.95)	**0.040**

Note: Values in bold indicate statistically significant results.

Abbreviations: CI, confidence interval; OR, odds ratio; SRE, self-rating of the effects of alcohol, the prolactin levels were dichotomized into high and low by splitting on the median value of 134 mU/L.
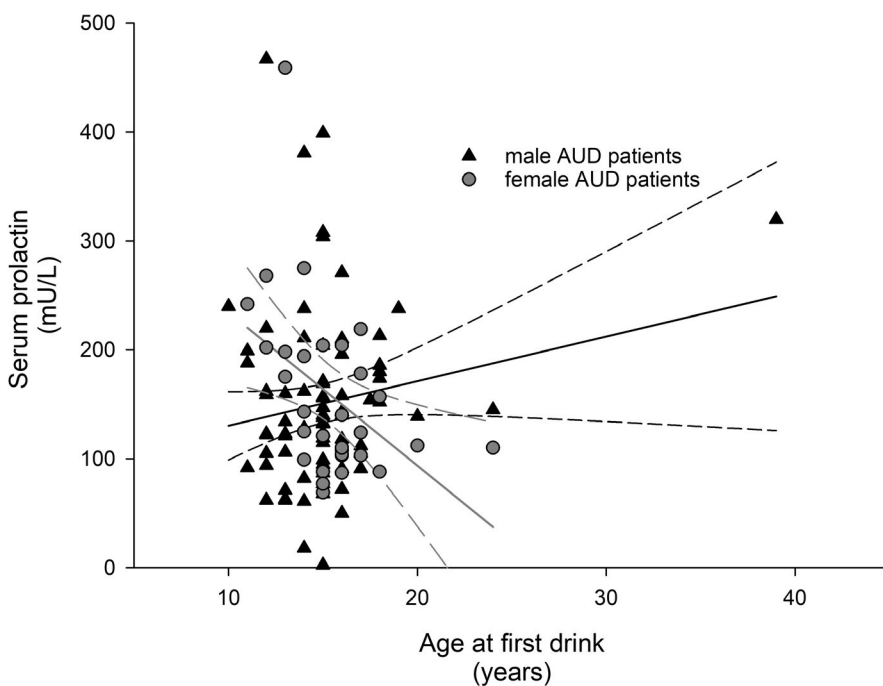
[a]Adjusted for age.

FIGURE 1 Scatter plot between the level of serum prolactin (milliunits per liter) and age at first drink (y) in male (n = 80) and female AUD patients (n = 31)

4 | DISCUSSION

This study of patients in remission from AUD identified similar level of prolactin in both genders. There were, however, gender differences in the factors associated with the level of prolactin. Among the general patient characteristics, a younger age predicted a higher level of prolactin among the female AUD patients. Among the alcohol use trait-related factors, an early alcohol debut and absence of parental drinking predicted higher level of prolactin in the female AUD patients. Among the male AUD patients, absence of other substance dependence predicted higher level of prolactin.

Among the general patient characteristics, in the female AUD patients, younger age predicted a higher level of prolactin. Estrogen increases prolactin secretion and its level begins to decrease before menopause and continues to decrease at a greater rate after menopause.[35] After menopause, female and male prolactin levels tends to be similar.[37] In the present study, we observed similar level of prolactin in both genders, which may reflect the age-span of the investigated patients.

Among the alcohol use trait-related factors, early alcohol debut predicted a higher level of prolactin only in the female AUD patients and a gender interaction was also observed in the relationship between the level of prolactin and age at first drink. Early alcohol use is found to be associated with externalizing and internalizing behaviors in childhood.[38] In the males, early alcohol debut is mainly attributed to the externalizing behaviors while in the females it is mainly attributed to the internalizing behaviors.[39] Some studies suggest that an excess of dopamine makes individual more reward oriented and

thus results in externalizing behavior while others suggest that dopamine deficiency in individuals drive them toward externalizing behavior.[40] As the direction of relationship between the level of dopamine and externalizing behavior is not conclusive, even in our study we did not find any association between age at first drink and level of prolactin in the male AUD patients. On the other hand, internalizing behaviors like anxiety and depression which are more related to early alcohol debut in the females are associated with reduced level of dopamine.[41] Our finding of higher level of prolactin in the female AUD patients being associated with early alcohol debut could be explained by this linkage. On adjusting for age, the presence of parental drinking problem also predicted lower level of prolactin in the female AUD patients. Schuckit et al studied sons of AUD patients and found that the participants with positive family history adapt more rapidly to the presence of alcohol by showing a faster decrease in level of prolactin following a high-dose alcohol challenge.[16] Possibly, for the same reason, we observed an association of positive family history of parental drinking with lower level of prolactin but only in the AUD daughters. Furthermore, we did not observe an association of alcohol use state-related factors with the level of prolactin possibly because the participants were abstinent for a long duration.

Among the male AUD patients, we found that the presence of other substance dependence predicted lower level of prolactin. Consistent with our findings, some literature suggests that the use of substances such as cannabis[42] and benzodiazepines[43] is associated with lower level of prolactin. In our study, the male AUD patients were more frequently dependent to cannabis (9 out of 21) but also to opiates (2 out of 21), cocaine/amphetamines (6 out of 21), and other prescription medicines (4 out of 21). However, studies in abstinent methamphetamine-[44] and cocaine-dependent subjects[45] demonstrated higher level of prolactin in the dependent subjects compared to the controls. This was also observed in the bivariate analysis of our female AUD patients where the presence of other substance dependence was associated with higher level of prolactin. However, caution should be held in interpreting the finding because there were only three patients in the group with other substance dependence where each of them were dependent to different substances. We suspect that rather than a gender influence, the nature of the substance abused might have attributed to the discrepant finding across genders.

The present medium-sized naturalistic study on patients in remission from AUD has some limitations. General factors of importance in interpreting prolactin values such as effect of food, stress, exercise, and phase of menstrual cycle were not examined. However, literature demonstrates major role of gender, age, and BMI in prolactin dynamics, all of which were examined in this study.[26] The blood samples for prolactin estimation were collected over a wide time frame (8:47 AM to 4:45 PM) allowing for bias based on diurnal variation. However, there was no correlation between time of blood sample collection and the level of prolactin in our patients. On splitting time of blood sample collection using 12:00 mid-day as cutoff, there was no difference in the level of prolactin between the morning and afternoon samples.

In patients recovering from AUD who were abstinent for a long duration, we did not find an influence of alcohol use state-related factors in the dopamine system. Nevertheless, we still found that the level of prolactin (extent of dopamine dysregulation) could be explained by the variation in the alcohol use trait-related factors in one subgroup of AUD patients (females). Level of prolactin may reflect some of the biological drive to alcohol addiction. Having an idea on the different factors influencing the level of prolactin may help identify workable areas to minimize this drive. While it is well known that the very action of alcohol consumption has influence on the level of prolactin, our finding that in the female patients under remission from AUD, even the presence of alcohol use trait-related factors had influence on the level of prolactin, might have some treatment implications. Knowing about the presence of trait-related factors may help us understand if and why these patients are different in terms of outcome for a given treatment although the AUD symptoms they exhibit may be similar. Future research could study the influence of trait versus state factors in the level of prolactin during acute alcohol intoxication, early abstinence, and withdrawal to see if our findings are replicable in AUD patients with more recent alcohol consumption. Adding to the literature, our study also conveys the importance of studying different homogenous subgroup of AUD patients separately because we found that the variation in alcohol use-related trait factor was more important for the dopamine system in the female AUD patients. Furthermore, future research could include prospective studies following individuals with alcohol use trait-related factors from a young age so that additional traits influencing dopamine system other than that observed in our study could be identified and on doing so a more distinct gender difference could possibly emerge.

The sum and substance of our study is that although there is no gender difference in the level of prolactin among the AUD patients, the factors associated with the level of prolactin are gender specific. Looking at the influence of alcohol use on the level of prolactin among patients at the stage of remission from AUD, we conclude that alcohol use *trait*-related factors are more related to the level of prolactin than alcohol use *state*-related factors and more so in the females.

CONFLICT OF INTEREST

The authors report no conflict of interest.

AUTHORS' CONTRIBUTIONS

JGB and LL designed this project. IB recruited participants and collected blood samples and data on psychometric measures. Data analysis was performed mainly by JGB and SP, and findings were interpreted by all the authors. SP prepared the first draft which

was revised by all authors. All authors read and approved the final manuscript.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

Ethical approval to conduct the study was obtained from Norwegian Regional Ethics Committee.

INFORMED CONSENT

The patients provided written informed consent to participate in the study.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

2017/1314

ANIMAL STUDIES

NA.

DATA AVAILABILITY STATEMENT

The data and materials of the study are not made publicly available due to confidentiality reasons. However, it will be shared upon reasonable request.

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