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Evaluation of Atherosclerotic Risk by Oxidative Contributors in Alcohol Use Disorder

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Objective: Alcohol Use Disorder (AUD) is a condition described as the inability to control or stop alcohol consumption. The patients with AUD have an increased risk of developing atherosclerosis-related diseases. The present study aimed to evaluate oxidative contributors of atherosclerotic risk factors in patients with AUD.
Methods: The male subjects diagnosed with AUD (n = 45) and the male subjects as control (n = 35) were enrolled in this study. All participants were undergone psychiatric evaluation and sociodemographic tests. Also, serum oxidative contributors of atherosclerosis including myeloperoxidase (MPO), ferroxidase, catalase (CAT), and lipid hydroperoxides (LOOH) were measured. Additionally, serum lipid profile tests and atherogenic indicators including atherogenic index of plasma (AIP) and non-high-density lipoprotein (HDL) cholesterol were also analyzed.
Results: The AUD subject had significantly elevated MPO activity and LOOH levels with decreased antioxidant capacity. AIP and non-HDL cholesterol levels, the atherogenic indicators, were also higher in AUD group compared to the control group. We found the MPO activity and LOOH levels were positively correlated with AIP, non-HDL cholesterol levels, and amount of alcohol consumption. Additionally, CAT activity was negatively correlated with duration of alcohol consumption.
Conclusion: Our results revealed that MPO and LOOH levels were elevated by severe alcohol intake and the atherogenic indicators, AIP and non-HDL cholesterol, were significantly correlated alcohol induced elevated oxidative risk factors. Therefore, it can be suggested that MPO activity and LOOH levels may be useful to determine jeopardy of atherosclerotic and the therapeutic interventions that reduce oxidative load could be taken into account to prevent atherosclerotic diseases before clinical manifestation.

KEY WORDS: Alcohol use disorder; Atherosclerosis; Lipid hydroperoxide; Myeloperoxidase; Oxidative stress.

INTRODUCTION

Alcohol use disorder (AUD) is defined as a non-compatible consumption of alcohol that causes clinically significant impairment in a person's life in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) which is published by the American Psychiatric Association (APA). AUD is subclassified into mild, moderate, and severe based on several criteria met for the diagnosis [1]. The adverse effect of alcohol on a person' health depends on the dose and pattern of alcohol consumption. It has been attributed that alcohol-related deaths to cardiovascular disease (CVD) are up to 19% coming after cancer and liver diseases [2,3]. Although recent studies have focused that light to moderate alcohol intake reduces the risk of atherosclerotic process on vessels, a well-known cause of CVD is alcohol dependency and a leading cause of death in males aged 15−59 years [4]. Heavy alcohol consumption is one of the reasons for secondary hypertriglyceridemia, which leads to initiation of the atherosclerotic process by causing dyslipidemia [5].

The oxidative stress hypothesis is suggested to initiate

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atherosclerosis in arteries following chronic inflammation and there is an unbalanced state between oxidants and antioxidants in atherosclerosis. It has been proved that myeloperoxidase (MPO) has multiple roles including congenital heart diseases, damaging vascular wall structure, inducing endothelium inflammation by producing reactive oxygen species (ROS), and oxidizing low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol molecules [6,7]. Lipid hydroperoxides (LOOH) resulting from free radical attacks on polyunsaturated fatty acids in lipoproteins involve immune responses and cell deaths in atherosclerosis [8].

There is a gap in the knowledge of the relationship between heavy alcohol consumption and oxidative contributors of atherosclerosis. Therefore, this study aims to illuminate the relationship between heavy alcohol drinking and oxidative risk factors of atherosclerosis in AUD. Also, atherogenic dyslipidemia indicators including non-HDL cholesterol and atherogenic index of plasma (AIP) were examined.

METHODS

Study Design

The 45 male subjects diagnosed with AUD according to DSM-5 and 35 male healthy subjects as a control group were included in this study as shown in Figure 1. A priori power analysis was performed to determine the sample size for detecting a difference between the study groups. The sample size was calculated to give a statistical power of 80%. All participants were examined by a psychiatrist and the following criteria; regular consumption of alcohol for at least three months, 18−65-year-old, not diagnosed with any metabolic or chronic diseases (including cardiac, endocrinological, neurological, and metabolic diseases), and not any administered regular treatments were admitted as including criteria. The exclusion criteria were using other substances with alcohol except smoking and having comorbid psychiatric disorders such as mental retardation, mood disorders, and anxiety disorders. Informed consent was obtained from all subjects. Clinical Research Ethical Committee of Istanbul Bilgi University (approval no: 2021- 40034-34) approved this study.

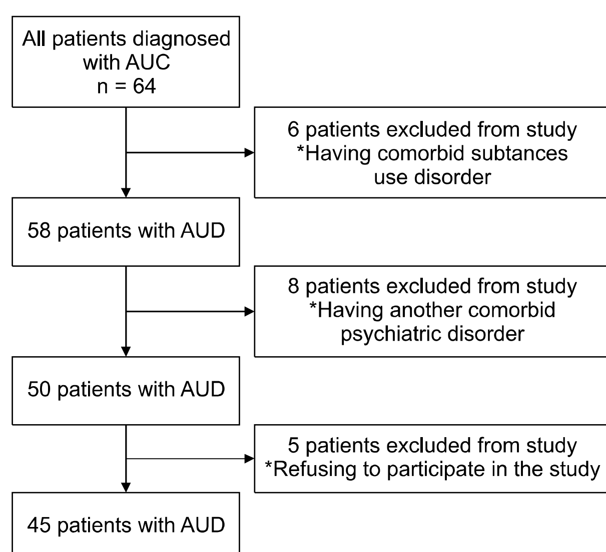

Fig. 1. The flow chart to show patients selection.
AUD, Alcohol Use Disorder.

Procedures and Measurements

All subjects were evaluated by the Michigan Alcohol Screening Test (MAST). The MAST form, consisting of 25 items, was used to evaluate drinking behavior and examine significant alcohol use problems in medical, legal, and interpersonal life areas and the total score of MAST indicates the severity of alcohol-related problems [9]. Turkish version of the MAST scale was carried out for validity and reliability of this scoring [10].

One standardized drink was accepted as 10−14 g of ethanol which is equivalent to a bottle of beer (350 ml), a glass of wine (150 ml), or a shot of tequila, raki, vodka, or whiskey (44 ml) [11]. Also, the total duration of drinking (years) and amount of weekly average alcohol consumption (standard drinks-per week) for the last three months of subjects were recorded. The drinking years cover the years between starting drinking and on the day of admission.

Venous blood samples of all subjects were drawn into tubes following at least 8 hours of fasting. Then all samples were centrifuged at 1,500 × g for 10 minutes. The obtained serum samples were aliquoted and stored at −80°C until the day of analysis.

Rutin chemical analysis including Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Gamma Glutaminase (GGT), and serum lipid profile tests were measured on Siemens Advia 1800 chemistry analyzer. Serum LDL cholesterol levels were calculated by using Friedewald formulas follows; (LDL cholesterol) = (total cholesterol) − (HDL cholesterol) − (triglyceride) / 5.

Friedewald formula was used for the samples with triglyceride levels under 400 mg/dl. Non-HDL cholesterol was calculated as total cholesterol minus HDL cholesterol. Also, spectrophotometric tests were measured on Advia 1800 chemistry systems Siemens Healthineers (Erlangen, Germany), including follows: MPO activity was determined according to modified Bradley *et al.* [12]. Siotto *et al.* [13] method was used for ferroxidase activity. Catalase activity was measured by Goth's method [14]. Lastly, LOOH levels were determined according to the fox2 assay [15]. The atherogenic index of plasma (AIP) was a logarithmically transformed ratio of triglyceride (TG)/HDL cholesterol [16].

Statistical Analysis

All statistical analysis was done with SPSS software version 23.0 (IBM Co.). The Kolmogorov–Smirnov test was used to determine the normality of variables. Variables normally distributed were indicated as mean ± standard deviation (SD). The variables not normally distributed were shown as medians (inter-quartile range [IQR]: 25th−75th percentile), while categorical variables were shown as the number of cases (percentage [%]). Independent sample *t* and Mann–Whitney *U* tests were performed for parametric and non-parametric variables, respectively. Correlation analysis was done with Spearman's correlation analysis. Also, linear regression analysis with a mixed model was used to show the relationship between atherosclerotic risk factors and demographic and clinic characteristics of subjects. The model was built with an additional adjustment covering age, body mass index (BMI), and smoking to explore their potential impact on atherosclerotic risk factors. The effect estimates were shown as regression coefficients (β) and odds ratios (OR) and their corresponding 95% confidence intervals (CI). The statistical significance value was accepted as 0.05.

RESULTS

The psychiatric, sociodemographic, and clinical characteristics of all participants are summarized in Table 1. There were no statistical differences between the AUD

Table 1. Characteristics of psychiatric, sociodemographic, clinical, and the oxidative contributors of atherosclerosis in all subjects

Variable	AUD (n = 45)	Control (n = 33)	*p* value
Age (yr)	37.7 ± 10.2	36.9 ± 8.50	0.726
Body mass index (kg/m^2)	24.6 ± 2.24	23.6 ± 2.44	0.056
History of smoking (package/yr)	12.5 (6−17.5)	5 (1−8.7)	0.001
Education status (yr)	9 (6.5−12)	8 (6.5−12)	0.514
Amounts of alcohol (std/wk)	50 (35.5−84)	0	<0.0001
Alcohol consumption duration (yr)	14.4 ± 7.8	0	<0.0001
Main type of consumed alcohol			
Beer	24 (53.3)	0	
Vodka/whiskey	13 (28.8)	0	
Wine	8 (17.7)	0	
MAST score	13 (11−14.5)	1 (0−2)	<0.0001
AST (U/L)	31.5 (23.3−42)	26 (17−29.5)	<0.0001
ALT (U/L)	38 (20.5−44.3)	20 (17−27)	0.001
GGT (U/L)	70 (56−192)	26 (19−119)	<0.0001
Total cholesterol (mg/dl)	184 ± 38.6	136 ± 27.6	<0.0001
Triglyceride (mg/dl)	159 ± 25.1	142 ± 17.2	0.001
LDL cholesterol (mg/dl)	138 ± 25.6	140 ± 42.2	0.796
HDL cholesterol (mg/dl)	54.2 ± 10.5	52.5 ± 8.2	0.442
Non-HDL cholesterol (mg/dl)	129 ± 39.6	83 ± 27.3	<0.0001
Atherogenic index of plasma (AIP)	0.15 ± 0.11	0.08 ± 0.07	0.001
Myeloperoxidase (U/L)	140 ± 31.7	94 ± 20.3	<0.0001
Ferroxidase (U/L)	85.3 (72.8−102)	98 (77−121)	0.020
Catalase (U/L)	113 ± 24.5	128 ± 17.9	0.008
Lipid hydroperoxides (μmol/L)	4.43 ± 0.94	2.83 ± 0.74	<0.0001

Values are given as a mean ± standard deviation, median (25th−75th percentile), or number (%).
MAST, Michigan Alcohol Screening Test; AUD, Alcohol Use Disorder; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutaminase; LDL, low-density lipoprotein; HDL, high-density lipoprotein; AIP, atherogenic index of plasma.

and control groups regarding age, BMI, and education status ($p = 0.726$, $p = 0.056$, and $p = 0.514$ respectively). As expected, the amount of alcohol consumption per week, and the total duration of the alcohol use were found significantly higher in the subjects diagnosed with AUD than in the control group ($p < 0.0001$ for all). In addition, MAST scores were higher in patients with AUD than in the control group ($p < 0.0001$).

Serum lipid profile was dysregulated in the AUD group. Serum triglyceride, total cholesterol, non-HDL cholesterol, and AIP values were significantly higher in the AUD subject compared to the control group ($p = 0.001$, $p < 0.0001$, $p < 0.0001$, and $p = 0.001$ respectively). However, LDL and HDL cholesterol levels were not different between AUD and control group ($p = 0.796$ and $p = 0.442$)

MPO activity and LOOH levels were significantly elevated in the AUD group ($p < 0.0001$ for both), while catalase ($p < 0.0001$) and ferroxidase activities were decreased ($p = 0.02$). All results are shown in Table 1.

All correlation analysis results are summarized in Tables 2, 3, and also Figure 2. MPO, LOOH, non-HDL levels, and AIP were strongly correlated with the amount of alcohol consumption and duration of the alcohol use. Also, MPO and LOOH levels had strongly correlated with AIP and non-HDL cholesterol levels as shown in Figure 2. The antioxidant capacity of the patients with AUD was lower than the control group. Besides, the CAT activity had an inverse relationship with the duration of alcohol consumption.

Linear regression analysis was performed to explore the effects of covariates in a mixed model including age, BMI, and smoking. According to the result, age, BMI, and smoking did not have a statistically significant effect on atherosclerotic risk factors. All values are shown in Table 4.

Table 2. Correlation analysis between AUD characteristics and atherosclerotic contributors

Variable	Amounts of alcohol (std/wk)	Total duration of alcohol consumption (yr)
MPO (U/L)	r = 0.410 $p < 0.0001$	r = 0.573 $p < 0.0001$
Ferroxidase (U/L)	r = −0.151 $p = 0.188$	r = −0.262 $p = 0.021$
Catalase (U/L)	r = −0.243 $p = 0.046$	r = −0.528 $p < 0.0001$
LOOH (µmol/L)	r = 0.534 $p < 0.0001$	r = 0.528 $p < 0.0001$
Non-HDL (mg/dl)	r = 0.458 $p < 0.0001$	r = 0.458 $p < 0.0001$
AIP	r = 0.327 $p = 0.004$	r = 0.265 $p = 0.020$

AUD, Alcohol Use Disorder; MPO, myeloperoxidase; LOOH, lipid hydroperoxides; HDL, high-density lipoprotein; AIP, atherogenic index of plasma.

DISCUSSION

The patients diagnosed with AUD are vulnerable to atherosclerotic vascular damage which is a complex process including atherogenic dyslipidemia, oxidative stress, and inflammation [17]. Our results showed increased MPO activity and LOOH levels versus decreased ferroxidase and catalase activities in the AUD group compared to control subjects. Also, the participant with AUD had laboratory results in consonance with atherogenic dyslipidemia; increased triglycerides, total cholesterol, and non-HDL cholesterol levels, and additionally significantly higher AIP value than the control subjects. These results are supported by studies in the literature that reports the adverse effect of heavy alcohol consumption on serum lipid profile [5,18]. It has been shown that ethanol has a net effect on lipogenesis via activating the lipogenic enzymes and contributing de novo synthesis of lipids mole-

Table 3. Correlation analysis between atherogenic risk parameters and oxidative contributors of atherosclerosis

Variable	AIP	Non-HDL	Triglycerides	Total cholesterol
MPO (U/L)	r = 0.314 $p = 0.005$	r = 0.433 $p < 0.0001$	r = 0.257 $p = 0.023$	r = 0.471 $p < 0.0001$
LOOH (µmol/L)	r = 0.390 $p = 0.001$	r = 0.510 $p < 0.0001$	r = 0.218 $p = 0.059$	r = 0.524 $p < 0.0001$
Catalase (U/L)	r = −0.119 $p = 0.335$	r = −0.179 $p = 0.143$	r = −0.375 $p = 0.002$	r = −0.184 $p = 0.133$
Ferroxidase (U/L)	r = 0.098 $p = 0.396$	r = −0.170 $p = 0.137$	r = 0.053 $p = 0.644$	r = −0.229 $p = 0.044$

AIP, atherogenic index of plasma; HDL, high-density lipoprotein; MPO, myeloperoxidase; LOOH, lipid hydroperoxides.

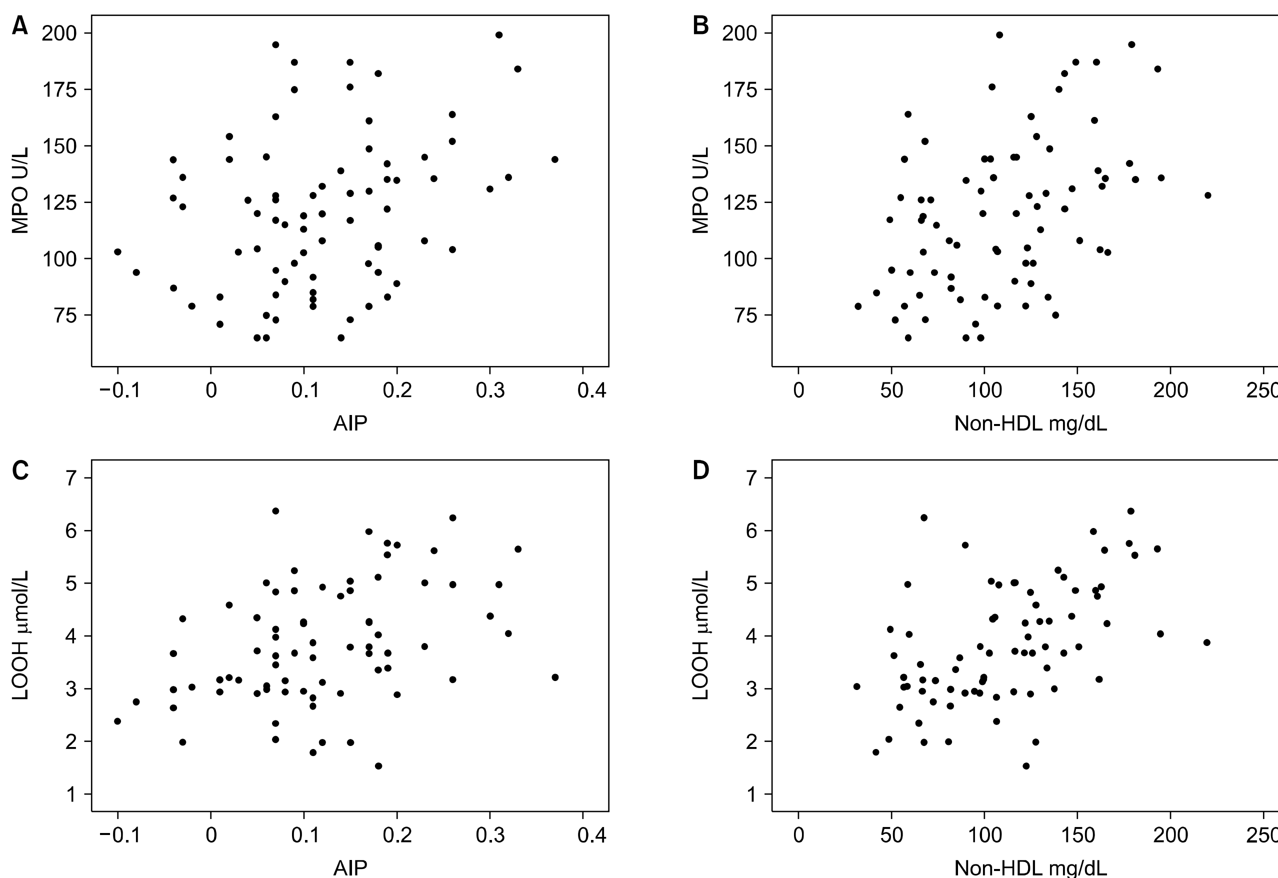

Fig. 2. The correlation graphic: (A) between MPO and AIP (r = 0.314, p = 0.005), (B) between MPO and non-HDL mg/dl (r = 0.433, $p < 0.0001$), (C) between LOOH and AIP (r = 0.390, p = 0.001), (D) between LOOH and non-HDL (r = 0.510, $p < 0.0001$).
MPO, myeloperoxidase; AIP, atherogenic index of plasma; HDL, high-density lipoprotein; LOOH, lipid hydroperoxides.

cules. Heavy alcohol drinking causes dyslipidemia [19]. On the other hand, MPO, one of the most important oxidative risk factors of atherosclerosis, provides a robust contribution to dyslipidemia by oxidizing LDL molecules and disturbing interactions with hepatic LDL receptors. The contribution of MPO to atherosclerosis includes oxidizing LDL, impairing HDL function, decreasing the bioavailability of nitric oxide, leading to endothelial dysfunction, and producing a thrombogenic matrix to generate atherosclerotic lesions [20]. Our results showed that significantly elevated MPO activity and LOOH levels accompanying increased AIP and non-HDL cholesterol levels remarkably increase the jeopardy of atherosclerosis related diseases. Additionally, The AIP and non-HDL cholesterol levels showed a statistically significant relationship with not only the amount of alcohol intake also duration of consumption.

HDL cholesterol with multifunctional effects including antioxidant and anti-inflammatory is a key factor for protecting atherosclerosis. But oxidative attacks or inflammation causes impaired HDL functionality. HDL dysfunction is associated with oxidized LDL molecules, impaired vasodilatation pathways, endothelial damages, and finally atherosclerotic plaque formation on vessels [21]. Recently, it has been proven that apolipoprotein-A1 (apo-A1), the major protein of HDL cholesterol, is a selected target of MPO-catalyzed nitration and chlorination reactions and MPO modifies HDL molecules by oxidating the functional protein structure of HDL. These modifications impair HDL functionality and contribute to atherosclerosis [22]. In our results, although HDL cholesterol levels were not different between AUD and control groups, alcohol induced oxidative modification of HDL cholesterol molecules by elevated MPO activity and LOOH levels may provide a strong contribution to initiating or developing atherosclerotic process.

Table 4. Linear regression analysis for oxidative atherosclerotic risk factors

Parameters	Independent variables	B (95% CI)	OR	p value	R^2/adjusted R^2	p value for F change
MPO	Model				0.13/−0.28	0.816
	Age	0.237 (−0.728 to 1.202)	0.063	0.626		
	BMI	−0.308 (−4.18 to 3.56)	−0.20	0.875		
	Smoking	0.368 (−8.91 to 1.16)	0.079	0.562		
Catalase	Model				0.282/0.080	0.103
	Age	0.530 (−0.204 to 1.265)	0.179	0.154		
	BMI	1.472 (−1.47 to 4.42)	0.124	0.323		
	Smoking	−1.15 (−2.11 to 0.195)	−0.312	0.019		
Ferroxidase	Model				0.029/−0.01	0.534
	Age	−0.397 (−0.972 to 0.179)	−0.175	0.174		
	BMI	0.808 (−1.504 to 3.120)	0.089	0.488		
	Smoking	0.002 (−0.749 to 0.753)	0.001	0.996		
LOOH	Model				0.025/−0.015	0.602
	Age	0.003 (−0.028 to 0.035)	0.026	0.839		
	BMI	0.017 (−0.109 to 0.144)	0.035	0.784		
	Smoking	0.019 (−0.022 to 0.060)	0.125	0.352		
Non-HDL	Model				0.063/0.025	0.181
	Age	0.175 (−0.916 to 1.26)	0.040	0.750		
	BMI	−1.73 (−6.11 to 2.65)	−0.099	0.433		
	Smoking	1.41 (−0.013 to 2.83)	0.259	0.052		
AIP	Model				0.039/−0.001	0.407
	Age	−0.001 (−0.004 to 0.001)	−0.126	0.328		
	BMI	0.007 (−0.004 to 0.019)	0.165	0.203		
	Smoking	0.001 (−0.003 to 0.005)	0.076	0.570		

CI, confidence intervals; OR, odds ratio; B, regression coefficients; MPO, myeloperoxidase; LOOH, Lipid hydroperoxides; HDL, high-density lipoprotein; AIP, atherogenic index of plasma; BMI, body mass index.

There are hardly any studies about the direct relationship between MPO and AUD. The studies have reported that MPO was involved in cellular invasion via alcohol-induced oxidative damage [23] and MPO emerged as a key component of atherothrombosis from vascular damage to developing atherosclerotic plaques and rupture of it [24]. In parallel with the reports in the literature, the MPO activity was significantly elevated in the AUD group. Additionally, MPO and LOOH levels were positively correlated with the amount of alcohol and duration of alcohol consumption. Alcohol induced increased MPO activity in AUD patients causes oxidative attacks on lipid molecules and results in elevated LOOH levels. Besides the both MPO activity and LOOH levels were statistically correlated with atherogenic indicators AIP and non-HDL cholesterol. These data showed that the subject who had no clinical symptoms of atherogenesis but had significantly elevated oxidative risk factors for initiation vascular dysfunction.

It has been known that ceruloplasmin, which has a ferroxidase activity, shows a high affinity for MPO to form a complex. The complex structure between ceruloplasmin and MPO strongly masks halogenating and peroxidase function of MPO [25]. Similar to the literature, decreased ferroxidase activity in patients with AUD caused increased MPO activities in the present study. Ferroxidase, a physiologic inhibitor of MPO, did not neutralize MPO and its oxidative hazards. LOOH levels are oxidation products of lipid molecules. Asano *et al.* [26] have shown that LOOH levels were significantly increased after one-shot moderate alcohol consumption, and a strong correlation was found between blood alcohol and LOOH levels. Additionally, another report has presented that LOOH levels were elevated due to alcohol consumption [27]. Our study demonstrated elevated LOOH levels in concordance with increased MPO activity in subjects with AUD. Also, higher non-HDL and AIP values in subjects with AUD indicate to the risk of the pro-atherosclerotic condition.

Another antioxidant enzyme we study, CAT, is a peroxisomal enzyme that converted H_2O_2 to water and involves alcohol metabolism [28]. Similar to our study results, pre-

vious reports have revealed decreased catalase activity in alcoholic liver disease and explained reduced CAT activity due to overproduction of oxygen radicals which inactivates the CAT enzyme [29,30]. In the present study, CAT activity decreased in AUD subjects compared to the control group. Also, CAT activity showed a negatively significant correlation between the total duration of alcohol consumption.

We performed linear regression analysis to explore the effects of some covariates including age, BMI, and smoking as a mixed model. Age, BMI, and smoking did not have a significant effect on MPO, ferroxidase, CAT, and LOOH levels likewise AIP and non-HDL cholesterol. Correlation analysis revealed important relationships between oxidative atherogenic contributors and lipogenic risk factors. On the other hand, the enzymatic antioxidant system weakens through the duration of alcohol consumption.

There are some limitations in the present study. Although the participants did not have known cardiovascular diseases, they were not undergone a radiologic assessment for atherosclerotic findings and a larger study population may be indicated stronger results. Also, we evaluated only male subjects because both prevalence of AUD and the risk of cardiovascular diseases are higher in the male compared to the women may be another limited part of our study. On the other hand, our limited results have put forward strong relationships between atherogenic dyslipidemia indicators such as AIP and non-HDL cholesterol levels and oxidative contributors of atherosclerosis.

In conclusion, it is known that MPO involves and has multifunctional roles in atherosclerosis similar to LOOH, the patients diagnosed with AUD have increased MPO activity and LOOH levels accompanying weakened antioxidant system, oxidative risk factors of atherosclerosis, and atherogenic lipid profile. Our data indicates that heavy alcohol consumption critically increases MPO activity and LOOH levels which positively correlated with AIP and non-HDL cholesterol. These important relationships were confirmed after adjustment for age, BMI, and smoking. Therefore, it can be concluded that MPO and LOOH tests may be useful to evaluate the risk of atherosclerosis-related diseases in AUD subjects before clinic manifestation.

■ Funding

None.

■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: Almila Senat, Esra Kabadayi-Sahin, Ibrahim Sogut. Data acquisition: Almila Senat, Esra Kabadayi-Sahin, Ibrahim Sogut. Formal analysis: Almila Senat, Ibrahim Sogut. Funding: Almila Senat, Esra Kabadayi-Sahin, Ibrahim Sogut. Tomris Duymaz, Ozcan Erel. Supervision: Ozcan Erel. Writing—original draft: Almila Senat. Writing—review&editing: Almila Senat, Esra Kabadayi-Sahin, Ibrahim Sogut, Tomris Duymaz, Ozcan Erel.

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