HHS Public Access

Author manuscript

Curr Drug Abuse Rev. Author manuscript; available in PMC 2018 April 11.

Published in final edited form as:

Curr Drug Abuse Rev. 2017 ; 9(2): 87–92. doi:10.2174/1874473710666170125151410.

A Review on the Sex Differences in Organ and System Pathology with Alcohol Drinking

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Abstract

Hazardous consequences of alcohol consumption adversely influence overall health, specifically physical and mental health. Differences in alcohol consumption and manifestations in pathology have been observed between males and females, however research on understanding these differences is limited. Negative consequences of alcohol consumption have now been studied including sex as a significant factor. Some studies have shown differences in the severity of consequences of alcohol consumption between the sexes, both in the mental consequences and changes/ injury in various organ systems. Over time, reports in females on both the dynamics of drinking and on the hazardous consequences of alcohol consumption have grown, primarily because of more awareness, better observation, and the inclusion of sex as a factor in scientific investigations. This paper reviews role of sex differences in pathophysiological and behavioral consequences of alcohol drinking.

Keywords

Alcohol; organ injury; pharmacology; sex difference; pathology; addiction

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Conflict of Interest: The authors confirm that this article content has no conflict of interest.

1. Introduction

There are several biological risk factors that influence the negative outcomes of alcohol drinking including sex differences [1-3]. How the influence of pharmacological variability, consumption rates, and cues of alcohol drinking behavior (visual, olfactory, peer pressure, pre-drinking environment and arousal) have impacted men and women differentially is not clear yet. Further, the variable manifestation of these pathophysiological and psychopathological changes (mechanisms of onset and progression) resulting in organ injury and neurobehavioral changes has not been determined [4]. Sex differences in alcohol pharmacokinetics could increase susceptibility to pathophysiological changes, resulting in altered stimulatory and inhibitory patterns of neurobehavioral mechanisms [5, 6], liver-brain-endocrine axis hormones [7], and cardiac physiological markers [8, 9]. Early and acute changes can persist and progress into chronic status resulting in organ specific and/or multi-organ system injury/failure [10-13].

In this article, we examined the role of sex-based differences in the development of drinking behavior, organ injury, and changes in neurobehavioral mechanisms and organ injury. We also reviewed genetic predisposition and epigenetic mechanisms, as well as environmental adaptations in alcohol consumption and its consequences that may be differentially influenced and characterized by sex.

2. Sex Differences in Alcohol Pharmacology

2.1. Alcohol Pharmacokinetics

Few studies have investigated the underlying effects of sex differences in alcohol pharmacokinetics [14, 15]. Due to their lower body water content and generally smaller size, females absorb alcohol differently than men and their blood alcohol concentration (BAC) is higher than males after consuming the same amount of alcohol [16]. Females also have lower activity of the alcohol metabolizing enzyme, alcohol dehydrogenase (ADH), in the stomach. This causes a greater proportion of ingested alcohol to directly reach and thereby directly expose various organ systems [17]. Therefore, females have an increased vulnerability to organ injury, even with moderate drinking.

2.2. Alcohol Pharmacodynamics and Pathophysiology by Organ/System

2.2.1. Neurological and Psychiatric Conditions—Some of the most profound changes that are observed with alcohol consumption are neuropathological alterations [18, 19], decline in mental health [20], and development/progression of mental disorders [21] (Table 1). Changes in these neuropathological pathways due to sex differences are not clear and the etiological predisposition and differences in manifestations in alcoholic males and females are not yet understood clearly. Due to the complex nature of endocrine mechanisms and clear differences in the endocrine responses in men and women, the neuro-endocrine system has a significant role in the neuro-adaptations in alcohol addiction [22]. Astrocytes are known for their involvement in some types of brain insult. Increased *Tnf* gene expression in females showed sex dimorphism with chronic alcohol exposure in animal models; no activity was observed in males, suggesting vulnerability to alcohol induced neurotoxicity in

females [23]. Brain damage and decrease in the size of corpus callosum have been identified more commonly in females who drink heavily [24, 25]. In alcohol dependent women, longer sobriety has been associated with larger white matter volumes compared to the abstaining alcoholic males [26]. Significant correlations between various conditions and sex have been found in several corticostriatal-limbic circuits that are involved in emotional modulations, and men showed higher activation than women [27]. We see a consistent pattern in susceptibility to adverse neurobehavioral manifestations and progression of addictive behavior in women who drink alcohol compared to men.

2.2.2. Liver—Large epidemiological and clinical studies have shown levels of alcohol intake, sex, weight and age to be the most commonly present predictors of liver disease [28, 29]. Sex differences are gradually being recognized as a leading risk factor involved in development/progression and prognosis of Alcoholic Liver Disease (ALD) [30]. Sex-differences in liver disease have been detailed in a recently published book chapter documenting greater vulnerability in females in the development, progression, severity, prognosis and treatment of ALD [31]. Fibrosis progression in chronic ALD is more rapid in females than the males [32]. Interaction of drinking pattern and sex has been reported as a major contributing factor in developing alcoholic liver cirrhosis and in the progression of ALD [33]. The interaction of alcohol consumption and sex has also been reported to play a significant role in progression of liver cancer [34, 35], and in the development of liver injury in Hepatitis C virus infection [36]. In ALD, mortality rates in alcoholic cirrhosis showed a significant difference by both ethnicity and sex [37]. A review from the 1970's described the sex-differences in the incidence of ALD in 293 patients (males were higher in number, 215 to 78 women) and discussed the fatty liver infiltration that occurs predominantly in men. However, the same study also discussed susceptibility in women for central sclerosing hyaline necrosis, and a higher incidence rate of alcoholic hepatitis, with or without cirrhosis, thus indicating how different pathologies and mechanisms could affect men and women differently [38]. Differences in the level of sex hormones (primarily in the female sex hormones) have also been studied for their role as a pathogenic factor (Table 1) in the development of hepatocellular carcinoma among patients with alcohol related cirrhosis [39]. In a study evaluating the survival and prognostic indicators of compensated and decompensated cirrhosis, alcohol was confirmed as the etiology of cirrhosis in 33% of males and only 6% of females [40]. Previous reports on the more severe progression of chronic ALD and challenges of stopping alcohol abuse in females have been documented previously, suggesting that women are more susceptible to alcohol-related liver disease [41]. One recent study showed that light drinking in females does not produce any significant elevation in ALT or liver injury [42], consistent with the studies in males. Another study on hepatic encephalopathy showed that increased risk for the condition was associated with female sex [43]. It seems possible that males may have better protective mechanisms than females in response to alcohol exposure.

2.2.3. Cardiovascular—A broad meta-analysis of the hazardous consequences of alcohol consumption on the heart has shown a robust association between excessive drinking and coronary heart disease. Notably, that analysis also showed lower protective effects and more harmful effects in women compared to men in the development, progression and severity of

coronary heart disease [44]. In the Framingham study, left ventricular hypertrophy and valvular heart disease were more prevalent in women than men among those who drank more than 36 g of alcohol per day [45]. Evaluation of cardiac responses to acute alcohol ingestion showed that the heart rate variability measure, pNN50, exhibited significant alcohol and sex interaction, with females showing higher values than the males [9]. Higher levels have been associated with a decrease in autonomic vagal activity in heart [46]. Thus, alcoholic females may have a higher susceptibility than their male counterparts for developing cardiovascular conditions as a result of alcohol consumption.

2.2.4. Endocrine—Several endocrine systems are differentially affected in a sex-specific manner by alcohol [47]. For example, alcohol consumption has different effects on sex hormone levels in male and female subjects. Acute alcohol consumption in low doses causes an increase in testosterone levels in males, while higher acute doses of alcohol consumption and chronic alcohol consumption decrease testosterone levels in men [48]. On the other hand, both acute and chronic alcohol consumption increases testosterone and estrogen levels in females [49]. At puberty, changes in hormones and sex have been correlated with patterns of heavy drinking and with modulation of associated neural circuitry responsible for the reward mechanism that could lead to alcohol abuse and dependence [50]. Alcohol consumption increases the Hypothalamic-Pituitary axis activation in females and decreases it in males, and these effects are probably mediated by estrogens and androgens, respectively [22]. It is also important to recognize that the relationship between sex hormone activity and alcohol intake is bidirectional and is mediated by both the Hypothalamic-Pituitary-Gonadal and Hypothalamic-Pituitary-Adrenal axes [22]. Even with acute alcohol administration, sex-associated changes in liver and pituitary hormones have been noted, with women having increases in estradiol levels and men showing suppression of testosterone levels [7]. The adolescent phase of life, especially early onset of puberty, has been shown to be a risk factor for developing alcohol use disorder (AUD) [50, 51]. Some studies have reported increased alcohol intake in young adult females during menses (the luteal and premenstrual phase of the menstrual cycle) [52-54]. Furthermore, in postmenopausal women, there was a positive association between alcohol consumption and diabetes risk, which was influenced by estradiol and sex hormone binding globulin levels. However, one study suggested that alcohol increases insulin sensitivity in women who have not reached menopause, but not in men [55]. In a recent large meta-analysis of the effects of alcohol consumption on incidence of diabetes, it was noted that a reduction in the incidence of diabetes among moderate alcohol users was found only in women [56]. Thus, there are significant differences between males and females in endocrine responses to alcohol consumption.

2.2.5. Renal—Studies in animal models support sex differences in renal physiology, specifically in ADH activity, but the studies are contradictory. Female rats have more androgenic and estrogenic receptors and higher activity than male rats, but when alcohol metabolism is evaluated, an interspecies difference is observed, wherein male mice have higher ADH activity than the females, however female rats show stronger ADH response than the males [57]. One study examining the effects of alcohol intake on renal function in patients with IgA glomerulonephritis found that a mild amount of alcohol in women (4-5 drinks per week) and moderate amount of intake in men (5-14 drinks per week) was

associated with better renal function [58]. Albuminuria seems to be higher in females compared to males in the renal patient cohort who reported alcohol intake at moderate to heavy levels [59]. Another study found an inverse association between high alcohol consumption and the risk for developing chronic kidney disease in males, possibly due to increased high-density lipoprotein [60]. However, it is possible that sex difference might not play a role with end-stage renal disease associated with alcohol consumption. Thus, the effects of sex on renal consequences of alcohol consumption are not clear.

2.2.6. Gastrointestinal Tract—Several negative effects of alcohol drinking have been reported in the gastrointestinal (GI) tract [61, 62]. Alcoholic liver disease, alcoholic pancreatitis, and gastrointestinal cancers are some of the significant conditions resulting from excessive alcohol drinking [63]. We have addressed the sex differences in ALD in the Liver section above. Increasing alcohol consumption was associated with increased risks of cancers of the oral cavity and pharynx, esophagus, larynx, and rectum in a study conducted only on females [64]. Alcoholic pancreatitis has been reported primarily in males [65]. In one European study, the prevalence of alcoholic pancreatitis was more than six-fold higher in males than in females [65]; however such studies probably were not originally designed to capture sex-differences (patients included 61 males and only eight females). In chronic pancreatitis, alcoholism and female sex were found to be independent risk factors in South Asian communities [66]. However, in a large US study, alcoholism was correlated to developing chronic pancreatitis at twice the rate in men (59.4% men vs. 28.1% women) compared to the females where there were even numbers of males and females included [67]. However, the source of this difference is unclear. Lastly, gut barrier dysfunction with subsequent endotoxemia is an important mechanism for many alcohol-induced organ injuries, especially ALD. Thurman reported that female rats fed alcohol had significantly higher plasma endotoxin levels that were associated with greater hepatic inflammation and fatty liver compared to male rats [68]. To summarize, there appear to be significant differences in the manifestation of alcohol-related GI diseases in males and females.

2.2.7. Musculoskeletal System—Individuals with a history of alcohol abuse have a higher risk of developing malnutrition, including vitamin D deficiency, and the consequent decreased absorption of calcium from the gut is commonly observed [69]. Alcohol abuse is associated with decreased peak bone mass and development of osteoporosis [70, 71] that predisposes to fractures [72]. Clinical studies have shown that alcohol increases the levels of the parathyroid hormone, which causes withdrawal of calcium from bones for other functions [73]. Alcohol also raises cortisol levels, which slow bone formation and speed up bone breakdown [74]. On the other hand, some studies show beneficial effects of moderate alcohol intake, especially in postmenopausal women, who exhibit a decreased risk of fracture with moderate alcohol intake [75, 76]. While the effects of increased alcohol drinking on the female skeleton show a linear negative relationship, increasing level of alcohol drinking has a positive J-shaped association with bone mass density (BMD) in males [77].

Many studies have reported BMD loss with heavy alcohol use regardless of sex [78]. Decrease of BMD and skeletal muscle myopathy may be an outcome of altered protein

metabolism due to alcohol abuse [79, 80]. Notably, this has also been observed in alcoholics without evidence of malnutrition [81]. Low estrogen production in teenage girls has a lifelong impact on the reproductive system and bone formation. Females who have lower bone production in early life tend to have increased risk of developing osteoporosis later in life [69]. Women under treatment for alcoholism showed more severe myopathy in the muscle biopsy results and in clinical presentation. Physiological assessments for strength and ejection fractions (even with lower threshold dose of alcohol drinks) in females showed higher prevalence and greater severity compared to their male counterparts [82]. Alcohol may have a protective role in maintaining bone density in women and men, however heavy drinking could cause loss of BMD in women. Alcohol may also have harmful effects on muscles even at low doses in women [83].

3. Summary

Access and availability of alcohol has grown, and that has contributed to the higher prevalence of pathophysiological consequences of alcohol consumption in both males and females. Several studies support identifying sex differences both in alcohol consumption (levels of intake and patterns of intake), and its consequences. Due to differences in body composition and physiological response, even within a similar pattern of drinking, the effects of exposure to alcohol might be more severe in females than males.

The ability to understand the sex differences is limited due to many methodological issues. Further, drinking patterns might be very important in evaluating what kind of drinking/how much drinking is associated with the specific organ injury and pathophysiological changes. Low sample size significantly reduces the scope and understanding of studies and affects the generalizability of study results to a larger population. Apart from patient retention, another concerning issue is the lower enrollment rate of affected women in most studies. Thus, the need for having females in the studies is obvious. Nonetheless, the potential important interactions of alcohol consumption and sex are becoming clear, and women seem to be more vulnerable to alcohol addiction/drinking and more susceptible to organ injury than men.

Acknowledgments

This investigation was supported by the following grant: U01-AA021901-01 (CJM). Research reported in this publication was supported by the National Institute on Alcohol Abuse and Alcoholism of the National Institutes of Health under Award Number P50AA024337 (CJM). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Table 1

Description of sex-differences in published articles related to neurological and psychiatric conditions, liver, and endocrine system. Most studies show increased susceptibility to alcohol injury in women.

Study	Mechanism	Males	Females	Comments
Neurological and Psychiatric conditions				
Lenz, 2012 [22] #	Sensitization of brain reward system; Neuro-adaptive reinforcements	Vigorous withdrawal; lesser physiological harmful effects	Fewer withdrawal symptoms; more severe physiological harmful effects	Diversion in sex-specific pattern by age 18 yr.
Wilhelm, 2015 [23] #	Astrocyte dysfunction in hippocampus region	No astrocyte activation; reduced GFAP expression	Astrocyte activated; Increased TNF, reduced Tgfb1	Severity in females was more pronounced
Hommer, 1996 [24]#	Alcohol-induced brain damage in corpus callosum	No change comparable to non-alcoholics	Increased sensitivity	Corpus callosum was smaller in alcoholic females
Neiman, 1998 [25]*	Brain shrinkage, extensive neuropsy-chological deficits	Longer duration of drinking	Shorter duration of drinking	Enhanced risk to develop Central Nervous System complications in females
Seo, 2011 [27]#	Alcohol cues and stress	Greater stress-related activations	Greater alcohol-cue-related activity	Different pathways involved by specific sex
Liver				
Marsano, 2016 [31]*	Role of alcohol pharmacokinetics and free radical, endotoxins and fatty acid derivatives in alcoholic cirrhosis and hepatitis	Higher dose, rate and cumulative exposure	Lower rates, lower cumulative exposure	Greater risk for women
Askgaard, 2015 [33]#	Role of drinking pattern in Alcoholic Liver Disease	Drinking pattern predictable for alcoholic cirrhosis	Dose dependent association, when drinking <14 drinks	Variable drinking pattern and dose for men and women
Stepien, 2016 [34]#	Biomarkers useful hepatocellular carcinoma (HCC)	Higher cut-off for liver enzymes namely Bilirubin, ALT, AST; and GGT	Lower cut-off for liver enzymes namely Bilirubin, ALT, AST; and GGT	Women might be prone to HCC even with milder expression of liver injury
Farinati, 1995 [39]*	Sex hormone imbalance in HCC	Estradiol to testosterone ratio (ETR) was higher	Estradiol to testosterone ratio was significantly lower	Variable response in both sexes for ETR in HCC
Vatsalya, 2016 [83]#	Recent drinking pattern in the onset of ALD, role of fatty acids	Heavy drinking days past 90 days play role in ALD, higher Omega 3	Total drinks past 90 days was closely associated with liver injury in females; DHA significantly lowered	Women more vulnerable to heavy drinking, lowered omega 3 associated with onset of

Study	Mechanism	Males	Females	Comments
				liver injury in women

#Original article: *Review article; “[ ]” denotes citation in “References’ section.