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Gender differences in alcohol affection on an individual

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SUMMARY
It is a well-known fact that after drinking the same amount of alcohol, women show more signs of the effects of alcohol than men of the same weight. It seems that the main factors responsible for sex differences in alcohol metabolism and influence are the relatively lower amount of body water related to body fat in women than men and lower gastric ADH activity in women, both of which enable women to reach higher BAC after drinking equivalent amounts of alcohol with men. On the other hand, first-pass metabolism of alcohol during passing through the liver is more rapid in women, probably due to bigger liver mass in women than in men. It is proven that alcohol and sex hormones have bilateral influence on each other. Women with more rapid alcohol elimination ability show higher levels of sex hormones in blood than the rest. It seems that the specific body constitution of the female organism as well as the unique combination of their sex hormones is responsible for the gender differences in alcohol influence.

Keywords: alcohol metabolism – gender differences – gastric ADH – blood alcohol concentration.

Pohlavní rozdíly v ovlivnění jedince alkoholem

SÚHRN
Je známou a medicínsky overenou skutočnosťou, že po vypití rovnakej dávky alkoholu pri rovnakej telesnej hmotnosti sa u žien prejavujú výraznejšie známky alkoholového ovplyvnenia ako u mužov. Najdôležitejšou determinantou tohto javu je habituálny dimorfizmus muža a ženy. Ide najmä o nižšie pomerné zastúpenie telesnej vody v ženskom tele voči tukovému tkanivu, ktorá poskytuje vhodné biofyzikálne prostredie pre distribúciu vstrebaného a fyzikálne rozpusteného alkoholu v organizme. Významnú úlohu zohráva aj nižšia aktivita gastrickej frakcie alkoholdehydrogenázy (ADH) u žien v porovnaní s mužmi, zodpovedná za dosiahnutie vyšších krvných koncentrácii alkoholu (BAC) u žien po vypití ekvivalentného množstva alkoholu oproti mužom. Tento enzým s rozhodujúcou úlohou pre biotransformáciu molekuly alkoholu má nižšiu afinitu k alkoholu z nápojov s 10–40 % vol., a preto je aj následný „first-pass" metabolizmus nižší a do krvného obehu sa u žien tak dostáva relatívne väčšie množstvo chemicky nezmeneného alkoholu, ktorý sa potom podieľa na samotnom alkoholovom ovplyvnení jedinca. Aktivita tohto enzýmu sa ešte viac znižuje so stúpajúcim vekom subjektu, u mužov dokonca výraznejšie. U jedincov vyššieho veku preto dochádza k zotretiu intersexuálnych rozdielov v BAC, ba až k preklopeniu sa do vyšších hodnôt BAC u mužov v porovnaní so ženami pri požití ekvivalentných množstiev alkoholu. Prekvapivou skutočnosťou je, že alkohol sa pri prechode pečeňou vo „first-pass" metabolizme u žien metabolizuje rýchlejšie ako u mužov. Podľa niektorých autorov je za to zodpovedný relatívne väčší objem pečeňového tkaniva žien vo vzťahu k čistej tkanivovej hmote. Ak sa však porovnáva metabolizmus muža a ženy s rovnakým pomerom objemu pečeňového tkaniva k čistej tkanivovej hmote tela, ukazuje sa, že metabolická rýchlosť spracovania alkoholu sa u oboch pohlaví vyrovnáva. Bolo preukázané, že alkohol a pohlavné hormóny sa reciprocne ovplyvňujú. U žien s rýchlejšou elimináciou alkoholu sa pri testoch preukázali vyššie hladiny pohlavných hormónov ako u mužov. Ženský estrogén potencuje aktivitu hepatálnej frakcie ADH a súčasne mužský dihydrotestosterón prispieva k nižšiemu alkoholovému ovplyvneniu mužov inhibíciou gastrickej ADH. Zdá sa teda, že špecifická konštitúcia ženského organizmu ako aj jedinečná kombinácia pohlavných hormónov sú zodpovedné za rozdielne účinky alkoholu na ľudských jedincov opačného pohlavia.

Kľúčové slová: metabolizmus alkoholu – pohlavné rozdiely – žalúdočná ADH – koncentrácia alkoholu v krvi

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It is widely reported that although women use to drink less than men they still are more vulnerable and have more easily detectable signs of alcohol influence on their mental and physical functions than men (1). Study of Walter et al. says that female chronic alcoholics die twice more often than men (2). Epidemiological studies have found about 14 million U.S. adults show positive criteria for alcohol abuse or dependence from which approximately one-third are women (3). In the USA in 1970s, the age-specific rate of initiation of alcohol use in 10- to 14-year-olds showed a male female ratio of 2:1, which had equalized to 1:1 by the 1990s and has remained equal (4,5). Even among studies done in Turkey, authors report that although alcohol related disorders are more common in males, alcohol abuse in women has increasing tendencies (6). From all the facts stated above it is clearly visible that there certainly are differences between the two genders in alcohol consumption and it's effects on the body. Their importance is of a high impact on female morbidity and mortality and that's why it still requires attention and further research of this field.

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LITERATURE REVIEW AND DISCUSSION

a) Gender differences in alcohol resorption and distribution

It has long been recognized that consumed equal doses of al-

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cohol result in a higher blood alcohol concentration (BAC) in women than in men of the same body weight (7,8).

The only biological difference consistently related to peak BAC which is easily measurable is body water. Ethanol's pharmocokinetics depends strongly on the value of the distribution factor which accurately reflects the body composition. Women have, on average, a lower volume of body water per kg of body weight and bigger amount of body fat than men of the same weight. The lower volume of body water in women gives them a smaller volume for distribution of alcohol than in men thus alcohol is dispersed in body fluids (9) and so higher BAC can be reached.

b) Gender differences in alcohol elimination

Possible mechanisms to explain the gender difference in BAC include gender differences in the metabolism of alcohol - the interaction of alcohol dehydrogenase (ADH) with female sex hormones, but mainly decreased 'first-pass' metabolism in women because of lower levels of gastric ADH (10). Up to Ely et al. women have less first-pass metabolism when are given 10% or 40%, but not 5% alcohol which is associated with lower gastric ADH activity and its lower afinity for high concentrations of ethanol (11). Karch's research team states that gastric metabolism of ethanol is of a significant importance in the ethanol disposal, others say that the amount of gastric ADH is only a small fraction of hepatic ADH (12). Gastric ADH activity is lower in women than in men as stated above. Scientific study done by Nolen-Hoeksema found that for a given particular alcohol dose, men's gastric ADH levels were two times higher than women's, and in turn, women's blood alcohol levels were higher than those in men (13). It also confirmed that this gender difference in metabolism of alcohol appears to be stable in younger adults but not in the older ones. Gastric ADH activity decreases with age, particularly in men, leading to similar BAC in older men and women, or even higher concentrations in older men than older women (13).

Highest gastric ADH activity was measured by Parlesak et al. at given ethanol concentrations between 150 and 500 mM/l (14). Results of the authors' study mentioned above showed that ADH activity was higher in antral specimens than in those taken from the gastric corpus of the same subject. ADH activity decreased with increasing age in males, while the values in females aged 41–60 years were higher than those in women aged 20–40 or 61–80 years (14). In men aged 20–40 years, consumption of larger quantities of alcohol (>0.8 g/kg body weight/day) was associated with reduced ADH activity (14). The results also indicate that ADH activity in human gastric mucosa is negatively associated with consumption of larger quantities of alcohol (14).

Alcohol gastric emptying was 42% slower and hepatic oxidation was 10% higher in women (15). A 7,3% smaller volume of alcohol distribution contributed to the higher ethanol levels in women, but it did not account for the route-dependent effects (15).

Liver volume has been found to correlate directly with alcohol metabolic rate even in experimental animals. It's quite surprising that eliminative metabolism of alcohol in the liver in women is more rapid than in men. This fact is supported by Jones who states that the declining phase of BAC slope is steeper in women compared to men which is probably related to their different relation of liver weight to lean body mass (15). Lean body mass measured for the sake of Mumenthaler's study was 42-percent greater in men than in women. Thus, compared with men, women had a 33-percent higher mean alcohol elimination rate and a 38-percent higher liver volume per kg of lean body mass (16). Opposite opinion comes from a study published by Kwo et al. which says that women have greater clearance of ethanol per unit lean body mass and they have approximately the same liver volume as men, explaining the equivalent alcohol elimination rates seen when men and women are compared on the basis of liver size (17).

Alcohol disappearance/elimination rate should be the preferred elimination measure for pharmacokinetic gender comparisons, where different body composition is one of the major aspects that prevents equal dosing. Mumenthaler et al present a review of 13 studies measuring gender differences in terms of β60 using moderate alcohol doses (0.3 to 0.8 g/kg). 9 of them concluded that women reach higher β60 than do men. Higher peak BAC in women might accelerate alcohol metabolism by activating MEOS (16). Also York et al. estimated that the higher elimination rate of alcohol may be seen in women, although his research did not confirm gender difference in reached peak BAC (18). Dettling et al. found out that maximum BAC after obtaining the same amount of alcohol per kg were higher in women than in men, even hourly ethanol elimination rate was confirmed to be higher in females, but surprisingly difference in hourly elimination rates in relation to the liver weight were not statistically significant (19).

c) Sexhormones' influence on alcohol metabolism

Some evidences suggest that slower alcohol disappearance in men may reflect inhibition of alcohol metabolism by the male reproductive hormone – dihydrotestosterone. Dihydrotestosterone appears to inhibit hepatic ADH in rats and decreases liver alcohol dehydrogenase content in humans. Hypothesis says estrogen administration repeatedly increased hepatic ADH activity and estrogen and progesterone administered together, but not estrogen alone, significantly increased BAC. In some human studies, women taking oral contraceptives (OC), which suppress the natural monthly hormonal cycle, reached significantly lower peak BAC and eliminated alcohol more slowly than women not taking OC (16).

Another authors' research of the influence of sex hormones on the elimination kinetics of ethanol investigated the mean hourly elimination rate (β60) which showed to be significantly higher in women than in men, especially the mean hourly elimination rate was 0.2044 ± 0.0414 g/kg/h in the high progesterone group and 0.1850 ± 0.0276 g/kg/h in the low progesterone group. These results allow to conclude that the gender differences in the pharmacokinetics of ethanol can partly, but not completely, be explained by progesterone levels (20). Results of a few studies which are summarised in the work of Gariott state that research on oral contraceptives influencing hourly elimination rate are conflicting and show increasing/decreasing/no change tendencies and so any exact conclusion can be drawn from them (21). And on the other hand, consumption of ethanol influences sex hormones levels in return. In women, alcohol metabolism may contribute to increased production of a form of oestrogen called estradiol (which contributes to increased bone density and reduced risk of coronary artery disease) and to decreased estradiol metabolism, resulting in elevated estradiol levels (22).

d) Gender differences in damage caused by chronic alcohol consumption

A) Central nervous system changes

Nixon says that women tend to be more vulnerable to developing heart and brain damage when drinking heavily than do men (23). Men and women who use to drink alcohol chronically show different brain morphological changes compared to subjects of the same sex. Women show less cortical grey and white matter and smaller third ventricles volume than men, which is consistent with sex-related differences in intracranial volume (24). Diagnosis by sex interactions for cortical white matter and sulcal volumes were due to abnormalities in alcoholic men but not alcoholic women, relative to the subjects of the same sex (24).

B) Hepatic diseases

Female drinkers have lower threshold for alcohol toxicity so they tend to develop alcoholic liver injury more easily than men. That is mainly because oestrogen has influence on the susceptibility of

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Kuppfer cells to gut-derived lipoproteinase which results in increased production of proinflammatory cytokines (25). There are very important gender differences in cirrhosis mortality risk and mortality rates. Cirrhosis mortality rates are about two times higher in men than in women (26). These rates reflect the fact that men typically drink more than women, and that the proportion of heavy drinkers and alcoholics is much higher among men. It seems that at any given level of alcohol consumption, women have a higher likelihood of developing cirrhosis than men. One explanation is that levels of alcohol dehydrogenase may be lower in the stomachs of females than in males (as stated above). Because damage to the liver is a function of blood alcohol levels and exposure time, factors that lead to higher BAC could at least partially explain females' higher risk for alcohol-related cirrhosis. Another possible explanation is that oestrogen may increase the susceptibility of the liver alcohol-related damage (26).

C) Psychical problems Results of some studies confirmed that female alcoholics significantly tend to develop greater depression and/or anxiety disorder and neuroticism compared to their male counterparts. Female problem drinkers reported significantly greater depressive symptoms and health-related stressful events compared to male problem drinkers (27).

CONCLUSION

Alcohol pharmacokinetics differs between women and men. Some of the factors that may contribute to these sex differences in absorption, distribution and metabolism include variation of body mass and total body water, liver size and differences in activity of alcohol metabolizing enzymes in the stomach and livers of women and men. A fundamental difference between men and women is in the levels of the sex hormones oestrogen and testosterone, which can influence several of the above factors. Many studies have been published dealing with alcoholism in men but desperately few are related to female alcoholism. Retrospective registered-based forensic study from Slovakia has been done recently on 171 cases of female deaths due to alcohol intoxication where the authors noticed 150% elevation (28). Mortality in women population in Slovak republic due to alcohol intoxication reached 5% from total amount of deaths due to cancer of the cervix (29). This shows that although female alcoholism increases and reaches mortal sizes, it still remains partially unclear. That is why there should be an additional area of interest in sex- and age-related differences in sensitivity to the effects of alcohol.

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