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EDITORIAL

Alcohol use and cirrhosis in women: An underestimated risk

Consumo de alcohol y cirrosis en mujeres: un riesgo subestimado

In the last few decades, alcohol use has remained at harmful levels worldwide, including Latin America.[1] It is one of the main risk factors for the development of chronic diseases, disability, and premature death.[1,2] In addition, alcohol-associated liver disease (ALD) is currently the primary cause of cirrhosis in Latin America and is the predominant etiology in Argentina, Brazil, Chile, Mexico, and Peru.[3] In Mexico, close to 50% of cases of cirrhosis are attributed to chronic alcohol use.[4] Similarly, in the United States, a 36% increase in prevalence and 79% increase in mortality have been observed, between 2000 and 2021, respectively.[5]

In such a context, the study conducted by Pérez-Hernández et al.[6] that described a retrospective cohort of 192 patients with cirrhosis due to decompensated ALD, who were hospitalized at a referral center in Mexico City, acquires particular relevance. They aimed to evaluate alcohol use patterns and mortality rates, with special emphasis on differences between men and women. One of the most striking findings of the study was the high mortality rate in women hospitalized due to cirrhosis secondary to ALD (61.9%), compared with that of men (38.9%). In addition, the survival age in women (33.8 years) was significantly lower than in men (37.0 years). This is even more significant considering that women reported an older age at alcohol use onset (18 years vs 16.5 years), as well as a shorter period of use (24.5 years vs 30 years) and consuming significantly smaller quantities (140 g vs 275 g per day in excessive use and 196 g vs 320 g per episode of binge drinking). Even though age was a mortality factor for both sexes, it was even less protective in women.

Traditionally, ALD has been more related to male sex,[7] but over the last few decades an increase has been observed in the incidence of alcohol use disorder in women and a greater complication and mortality burden due to alcohol-associated cirrhosis in the female population.[1] The findings of the study described herein show a greater biologic susceptibility in women to alcohol-induced liver damage. In fact, a systematic review of nine studies that included 2,629,272 participants with 5,505 cases of cirrhosis showed that the consumption of one alcoholic drink daily, compared with long-term abstinence, resulted in a higher risk of cirrhosis in women, but not in men.[8] Furthermore, the risk for women was also consistently higher, compared with men. For example, the consumption of $\geq$5 alcoholic beverages a day was associated with a substantial increase in the relative risk (RR) of 12.44 (95% CI 6.65–23.27) for 5–6 drinks for women, whereas the RR for the same number of alcoholic drinks was only 3.80 (95% CI 0.85–17.02) in men.[8]

Multiple pathophysiologic mechanisms that could explain said difference have been documented in the medical literature. For example, less gastric alcohol dehydrogenase activity has been reported in women, limiting the pre-systemic metabolism of ethanol and increasing plasma concentrations after similar ingestion.[9] In addition, the lower body mass and higher percentage of adipose tissue in women produce a lower distribution volume for alcohol, increasing cell injury.[10] Female sex hormones, particularly estrogen, have also been postulated to possibly potentiate oxidative stress, modulate gene transcription, and alter mitochondrial function, exacerbating ethanol-induced liver injury.[11,12] At the immunologic level, women have a greater inflammatory response to molecular patterns derived from the gut microbiota (pathogen-associated molecular patterns [PAMPs]) in the presence of alcohol-induced dysbiosis, which amplifies the activation of Kupffer cells and the release of proinflammatory cytokines.[13]

The study by Pérez-Hernández et al.[6] provides relevant information from the epidemiologic perspective, but several points should be highlighted. The first aspect is the quantification of alcohol use, given that self-reporting is subject to a risk of underestimation due to the stigma associated with alcohol consumption, as well as recall biases and the effect of dropout due to illness (patients who reduce alcohol use due to advanced liver disease).[14] In fact, alcohol use underestimation can reach 10% in participants enrolled in clinical trials and be higher than

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55% of patients in habitual clinical practice.[15] Therefore, future studies should incorporate additional tools to better objectify the different levels of alcohol consumption between men and women, including questionnaires, such as the Timeline Followback and the Lifetime Drinking History, as well as the use of objective biomarkers, such as phosphatidylethanol.[14]

It is also necessary to look in detail at the specific causes of hospitalization in this cohort, given that conditions, such as alcohol-associated hepatitis, have a higher mortality rate than cirrhosis due to decompensated ALD, reaching 6-month survival rates close to 50% in severe episodes. Likewise, it is important to review the therapeutic strategies employed in all patients, because malnutrition, the development of infections, and organ failure may condition greater mortality in severe ALD phenotypes, and particularly in alcohol-associated hepatitis.[16] It should also be mentioned that even though there were no statistically significant differences in the Child-Pugh or Model for End-Stage Liver Disease (MELD) scores between sexes at hospital admission, MELD was an independent mortality predictor only in women. Given that MELD is one of the primary mortality predictors, this could reflect an insufficient sample size or the presence of confounding variables in the models.

Finally, it is worth noting that the present study results are in line with previous data showing a sustained increase in alcohol use disorder in women worldwide. In the United States, there was an 80% increase in excessive alcohol use in women between 2001–2003 and 2012–2013, compared with only a 30% increase in men.[17] In Mexico, the *Encuesta Nacional de Consumo de Drogas, Alcohol y Tabaco* (*ENCODAT*) *2016* revealed a significant increase in regular and excessive alcohol use in women, particularly in younger age groups. This epidemiologic change has important public health implications. In particular, the recognition that women not only consume more alcohol but also present with greater biologic vulnerability to liver injury, should prompt healthcare systems to develop specific public policies for reducing alcohol use, as well as strategies for the prevention, early detection, and treatment of ALD.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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