



# Alcohol and the Liver: The Return of the Prodigal Son

Octavio Campollo

Center of Studies on Alcohol and Addictions, Hospital Civil de Guadalajara FAA, Universidad de Guadalajara. Guadalajara, Jalisco, Mexico.

## ABSTRACT

With the discovery of direct-acting antivirals and the prospective of viral hepatitis becoming curable, alcohol liver disease (ALD) is back to primetime. In the last 20 years, there have been many advances in the understanding of the biology, the psychology and the social and environmental factors associated with this long-known medical problem. Recent information about regional, ethnic, cultural and genetic factors seem to be relevant for the Latin American (LA) population. New approaches based on the new concepts and current information will render better results in the overall management of patients with this problem. Considering alcohol use disorder and ALD as part of the same entity managing it in a multidisciplinary approach seems to be best way to deal with this disease.

**Key words.** Alcohol liver disease. Cirrhosis. Hispanic. Alcohol use disorder.

## INTRODUCTION

Nowdays with the discovery of direct-acting antivirals<sup>1</sup> and one of the most common causes of chronic liver disease (i.e. viral hepatitis) becoming curable on old foe, (alcohol) is back. Alcoholic liver disease or alcohol-related liver disease (ALD) as it is also referred (European Association for the Study of the Liver, EASL) is perhaps the “oldest form of liver injury known to humankind”.<sup>2,3</sup> At this point we should bear in mind that a patient with ALD has two main problems: alcoholism (more relevant when active) and ALD, both of which have to be dealt with at the same time.

Perhaps the interest in the relation between alcohol and liver disease had some downfall during the period when most liver specialists were more focused with diagnosis and treatment of viral hepatitis<sup>1</sup> but that did not mean that ALD was forgotten, not even neglected but it's been on stage but perhaps paid less attention to it (many researchers have kept on studying the problem for decades). There is no doubt ALD morbidity and co-morbidity are familiar terms to all physicians specially among general internists, gastroenterologists and hepatologists. Nevertheless when it comes the time to deal with the specific problem of al-

coholism a more complex situation arises as to what is the best approach to deal with it and whether how or when to start dealing with the problem: immediately including referring the patient to the psychologist-psychiatric team right away or defer it for next consultation, and still it's not as simple as that.

An important consideration is that as the only definitive treatment for advanced alcoholic cirrhosis is liver transplantation, an option which is not readily available in the majority of Hospitals and clinics or for the majority of cases, the strategies to prevent transition to an irreversible stage and prolong survival are most important. As for the pathology, diagnosis and therapy of ALD excellent reviews have been published in this<sup>4</sup> and other journals.<sup>2,5</sup>

In concordance with the current scope of *Annals of Hepatology*, some current essential aspects for the approach and control of this complex long-known disease are presented herein.

## A NOTE ON EPIDEMIOLOGY

Liver cirrhosis is among the top 10 causes of death in adults (4th and 6th place) around the world and between the 3rd and 5th in Latin America (LA) depending on the

age group studied.<sup>6</sup> There is extensive evidence to support the high prevalence and mortality due to cirrhosis as well as for alcohol as one of the leading causes of cirrhosis.<sup>7</sup> According to the WHO alcohol accounts for 48 % liver cirrhosis deaths (53% in men and 45% in women) around the world (WHO), and in some populations it is the second cause of cirrhosis after viral hepatitis<sup>3</sup> or non-alcoholic fatty liver disease (NAFLD) according to some recent reports.<sup>7</sup> These are some of the reasons why ALD is considered as a public health problem.<sup>6,8</sup> Nevertheless, perhaps the important message related to the epidemiological characteristics of ALD is that most of the risk factors are preventable and so the importance of studying this area.<sup>9</sup>

In the last 30 years liver cirrhosis deaths increased from 1.54% to 1.95% of global deaths of which male deaths double female's (2:1).<sup>9</sup> In Latin America, Mexico has the highest liver cirrhosis age-standardized mortality rate (38.3 per 100,000 person-years)<sup>9</sup> reaching the fourth-leading cause of death in 2016.<sup>10</sup> Liver cirrhosis changed from the 15th general cause of death in Mexico in the 50's ascending to 9th place in the 70's and up to the 4th place in 2016.<sup>10</sup> In Mexico and in Latin America, similar to other countries, the level and pattern of alcohol consumption are related to the increase in liver cirrhosis mortality.<sup>11</sup> The variations in mortality among different countries may be explained in part by alcohol consumption levels, type and quality of alcohol consumed, the presence of hepatitis C and hepatitis B infections among other factors.

## BURDEN OF DISEASE

Another important point to consider is that alcohol is a risk factor not only for the liver but for at least 200 diseases and injuries<sup>6</sup> with the largest mortality found in cardiovascular diseases, injuries, gastrointestinal diseases (mainly liver cirrhosis) and cancers.<sup>5</sup> A consequence of ALD to bear in mind is the level of disability or disease burden associated with it. That is measured with "lost healthy years" or disability-adjusted life years (DALYs) which is 53% and 44% (men and women respectively) from cirrhosis caused by alcohol.<sup>6</sup> In LA cirrhosis and use of alcohol are the leading causes of lost healthy years (DALYs).<sup>12</sup>

## ALCOHOL CONSUMPTION, DRINKING PATTERNS AND DISEASE RISK

The worldwide alcohol consumption in 2016 was 6.4 liters of alcohol *per capita* (person) (APC) per year<sup>6</sup> with wide geographical variations. In Europe for instance the mean total APC was 9.8 Litres (world highest).<sup>6</sup> In North America the average is 8.9 Liters *per capita* in Canada and 9.8 Liters in the USA.<sup>6</sup> Latin America has the second highest

APC consumption in the world with a mean APC of 8.4 liter,<sup>6</sup> ranging from 2.4 L in Guatemala to 10.8 L in Uruguay with a median of 6.5 L *per capita* (e.g. Mexico).<sup>6</sup> The 10 Latin American countries with the higher alcohol consumption are Trinidad and Tobago, Chile, Grenada, Saint Kitts and Nevis, Barbados, Argentina, Saint Lucia and Uruguay.<sup>6</sup>

As described above, alcohol consumption is higher in rich countries but morbidity and mortality associated to alcohol are higher in those countries with lower economic wealth.<sup>5,6</sup> There is also a good correlation between the level of alcohol consumption and the prevalence of alcohol-related harm including mortality from alcohol-related cirrhosis.<sup>3,5,11</sup>

For many years researchers have been trying to find out why not all the people who drink alcohol even in large amounts develop alcohol-related liver disease<sup>2</sup> without a clear answer. It is reported that 40-60% of patients who drink between 40-80 g/daily or more for an average of 25 years develop changes characteristic of cirrhosis.<sup>3,5</sup> Nevertheless, some patients develop cirrhosis with lesser amounts or in less time while up to 60% of them may not develop liver cirrhosis at the amounts mentioned.<sup>2</sup>

An important aspect to be considered in the understanding of the natural history of ALD is the drinking pattern which tends to vary depending on several factors and the phases of alcoholism.<sup>13</sup> Those factors include geographic, gender, genetic and socio-demographic factors.<sup>13</sup> Some drinking patterns are associated with higher risk of ALD.<sup>11</sup> The WHO (on the other hand) uses patterns of drinking score to determine how people drink instead of how much people drink.<sup>11</sup> Four Latin American countries (Belize, Grenada, Guatemala and Mexico) are in the group of most risky drinking pattern.<sup>6</sup>

Heavy episodic drinking is defined by WHO as drinking (the equivalent of) at least 60 g or more of pure alcohol on at least one occasion in the past 30 days.<sup>6</sup>

Binge drinking (BD) has been defined as 5 or more drinks for men and 4 or more drinks for women within 2 hours.<sup>5,6</sup> BD also increases the risk of ALD,<sup>2</sup> like in the case of the Mexican alcoholics where there is more binge drinking, particularly during weekends.<sup>13</sup>

## TYPE OF ALCOHOLIC BEVERAGE AND LIVER DAMAGE

There has been a long-standing argument about different toxic effects on the liver depending on different types of alcoholic beverages. Presence of toxic substances and method of production (i.e. home, non-certified) seem to be related to that in some cases.<sup>2,13,15</sup>

In Latin America, as in other parts of the world<sup>6</sup> in small towns of several countries, local produced alcoholic

drinks, including those produced in Amerindian communities, are also consumed even more frequently than commercial beverages.<sup>14</sup> In some countries like Mexico where most Tequila in the world is produced, that was the most frequent alcoholic beverage in the acute phase of alcoholism in cirrhotic patients.<sup>13</sup>

## ALCOHOL USE DISORDER (ALCOHOLISM)

Excessive alcohol use is a public health problem.<sup>8,16</sup> DSM-V defines alcohol use disorder (AUD) as a problematic pattern of alcohol use leading to clinically significant impairment or distress, with graded levels of severity depending on the number of diagnostic criteria met.<sup>5</sup> The DSM-V includes 11 diagnostic criteria and anyone meeting at least two of them during the last year qualifies for a diagnosis of AUD.<sup>5</sup>

The world prevalence of alcohol use disorder is 4.1%, with the European WHO region showing the highest (7.5%). In the American continent the prevalence is 6.0%.<sup>6</sup> On the other hand the world prevalence of alcohol dependence is 2.9% with the highest in the Europe WHO region (4%) whereas in the American continent it is 3.4%.<sup>6</sup>

## ALCOHOLIC LIVER DISEASE

ALD covers a spectrum of liver injuries from simple steatosis to cirrhosis including alcohol-related fatty liver disease (AFLD) and alcoholic hepatitis which have been previously reviewed in this journal.<sup>4</sup> It has been estimated that ALD accounts for almost 50% of all deaths from cirrhosis in the world.<sup>11</sup>

Although the effects of alcohol on the liver have been well studied, in subjects with acute or chronic alcohol consumption an important point is that the alcohol-related morbidities should always be kept in mind when a patient is attended at the physician's office or at the clinic.<sup>2</sup>

Another important aspect of ALD is that from a wide variety of therapies available (medical, pharmacological, psychological, holistic) for the main cause of ALD i.e. alcoholism, there is no "magic bullet" to achieve abstinence (or control) and any of those mentioned will usually require an integral approach which most of the times is multidisciplinary.

The above seems to be a straight forward approach but one of the problems lays on the traditional way of thinking of many medical doctors and specialists that tend to work with the patients up into one main track of therapy: medical, psychiatric, psychological and so forth and leave the integral approach for later. In that sense we should learn from the medical teams (literally not just one) that evaluate, follow up and prepare alcohol-related patients for a

liver transplant following a truly multidisciplinary approach.<sup>5</sup> That approach should cover all the other factors mentioned in other sections that affect susceptibility to alcohol.

## FACTORS ASSOCIATED WITH ALD OTHER THAN ALCOHOL

As mentioned before there are several factors associated with the development of ALD. Some of them already mentioned. They include biologic, genetic, gender, ethnic, environmental and social-demographic factors. From those biologic and pathological factors a special mention is made to obesity, iron overload, viral hepatitis, nutritional deficiencies, hepatitis B, hepatitis C, and HIV viruses, and diabetes.<sup>2,16</sup>

Studies on cultural aspects associated with ALD particularly relevant to LA populations have also being reported.<sup>13,14</sup>

## ETHNICITY

The LA population has been shown to have higher risk factors for chronic liver disease including high alcohol consumption, diabetes, elevated aminotransferase levels, hepatitis B and hepatitis C and, obesity.<sup>3,4,14</sup> Ethnic factors play a role as evidenced by epidemiological studies comparing different ethnic groups observing that the rates of alcoholic cirrhosis are higher in African-American and Hispanics compared to Caucasian males.<sup>2,7</sup>

## GENDER

Gender is another associated factor with ALD as women have been found to be twice as sensitive to alcohol-mediated liver injury than men. After drinking the same amount of alcohol women have shown higher levels of alcohol than men.<sup>5</sup> That situation seems to be related to differences in the concentration of alcohol dehydrogenase in the stomach leading to a higher absorption of alcohol through the gut on the one hand and to a higher proportion of body fat in women and to differences in absorption during the menstrual cycle.<sup>2,5</sup>

## GENETIC FACTORS

There are genetic and epigenetic factors that influence susceptibility to and development of liver damage. Early studies on genes related to liver physiology and pathology can be dated to the 90's in the past century<sup>14</sup> but a significant advancement has occurred in the last 16 years in the areas of AUD and ALD.<sup>14</sup> More recently a whole new spectrum of genetic factors have been discovered and

studied in the last 10-20 years including differences in mestizo populations and Amerindians compared with European and North American populations.<sup>14</sup> From a long and always increasing list of genes associated to AUD and ALD there are those that encode enzymes that metabolize alcohol or acetaldehyde, genes related to the development of alcohol dependence, genes encoding for proteins and inflammatory cytokines, genes involved in lipid metabolism and genes involved in the immune response to mention a few.<sup>14</sup> The future in this area is promising and getting close to what is now called precision medicine.

## APPROACH TO THE PATIENT WITH AUD AND ALD

When the clinician suspects that the diagnosis can be ALD he or she has to look for direct and indirect evidence of previous or current alcohol use and abuse using all sources of information and evidence at hand (period). That involves interviewing family members and use of alcohol questionnaires apart from direct information from the patient, the medical history and laboratory tests. AUD is suspected upon documentation of regular alcohol consumption of > 20 g/d 1.5 standard drinks in females and > 30 g/d two standard drinks in males or binge drinking.<sup>5</sup>

Nevertheless a common pitfall among clinicians is that they frequently fail to recognize or treat alcoholism appropriately, early enough or both. That is to say that the physician or specialized consultant has to go further deep in the medical history and investigate the pattern of alcohol use, the type, amount and frequency of alcohol ingestion relying on screening tests (i.e. questionnaires) proven not only useful but instrumental to detect alcohol abuse or dependence which are relatively easy to apply. Among those instruments the most commonly used are the CAGE and the AUDIT (alcohol use disorders identification test) among others which are very useful to identify a pattern of alcoholism.<sup>13</sup> The CAGE questionnaire is short (4 items), simple and easy to perform with good sensitivity and specificity.<sup>2,5</sup> It should be familiar to all physicians if it is not already. The AUDIT is a 10-item questionnaire used by the World health organization<sup>6</sup> with higher sensitivity and specificity and is used to identify heavy drinkers and drinkers at risk.<sup>6</sup> Nowadays there are also Apps (e.g. Drinkaware) available for this purpose.<sup>5</sup> The DSM-V is still the gold standard for diagnosis of AUD.<sup>2,5</sup> A psychiatric evaluation is recommended when alcoholism is suspected.<sup>5</sup> More recently the use of direct alcohol markers such as ethyl glucuronide (EtG), ethyl sulfate (EtS) in urine or hair, phosphatidylethanol (PEth) and fatty acid ethyl esters (FAEEs) which are products of non-oxidative metabolism of ethanol and can be measured in urine or hair, have high specificity and are used in Europe.<sup>5</sup>

A general protocol for the diagnosis of ALD includes clinical history and physical examination, psychological evaluation and laboratory tests of which liver function tests are fundamental including a measure of liver fibrosis (scan). Indications for liver biopsy are well described in most guidelines as well as recommendations for screening and management of ALD complications.<sup>5</sup>

## UNANSWERED QUESTIONS

Other aspects of ALD should be reviewed thoroughly including those related to therapy where there are still several issues to clarify or answer like the question of is there a cure for advanced ALD apart from liver transplant? What is the critical factor or factors in order to develop ALD? Could we identify those people who may drink large amounts of alcohol and not developing its disease and then focus our efforts in preventing its development in those who will? Would that or those factor(s) be genetic or environmental? Are there nutritional factors which could intervene? Thus we still have lots of work to do in answering those questions and so we should take this opportunity to start answering them.

## CONCLUSIONS

We should start considering alcohol use disorder and alcohol-related liver disease as part of the same entity and approach it in a multidisciplinary setting which seems to be the best way to deal with this disease. As a part of the general work up the use of questionnaires like the CAGE and AUDIT is instrumental in the initial diagnosis of AUD-ALD and that can be done by most health professionals in primary care to start with as well as in emergency departments. In any setting, patients with AUD or patients at risk should receive a brief intervention and be referred to a multidisciplinary team. We can now go back to the future where ALD is one of leading causes of chronic liver disease because it seems like the prodigal son is back.

## ABBREVIATIONS

- **AFLD:** alcohol-related fatty liver disease.
- **ALD:** alcohol liver disease.
- **APC:** alcohol *per capita* (person).
- **AUD:** alcohol use disorder.
- **BD:** Binge drinking.
- **DALYs:** disability-adjusted life years.
- **EASL:** European Association for the Study of the Liver.
- **EtG:** ethyl glucuronide.
- **EtS:** ethyl sulfate.
- **FAEEs:** fatty acid ethyl esters.

- **LA:** Latin American.
- **NAFLD:** non-alcoholic fatty liver disease.
- **Peth:** phosphatidylethanol.
- **WHO:** World Health Organization.

## CONFLICT OF INTEREST

The author declares that there is no conflict of interest regarding the publication of this article.

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### Correspondance and reprint request:

Dr. Octavio Campollo R., M en C, PhD  
 Centro de Estudios de alcoholismo y Adicciones. Servicio de Biología Molecular en Medicina. Hospital Civil de Guadalajara. Calle Hospital, No. 278. Col. El Retiro. C.P. 44280. Guadalajara, Jalisco, Mexico.  
 Tel. (55) 33 3614-2179  
 E-mail: [calcohol@hotmail.com](mailto:calcohol@hotmail.com)