DEFINITION

Alcoholic liver disease (ALD) covers a large spectrum of structural and functional hepatic modifications, from benign and frequent forms (asymptomatic hepatomegaly) to the most severe ones (acute liver failure), modifications that share the same etiologic factor: systematic and long term consumption of alcoholic beverages (1-3). The spectrum of clinical manifestations and hepatic morphopathological modifications varies widely: from liver steatosis (alcoholic fatty liver) to inflammatory and necrotic lesions (alcoholic hepatitis), progressive fibrosis (hepatic cirrhosis) (4, 5, 6).

EPIDEMIOLOGY

ALD is probably one of the oldest forms of manifestation in chronic liver disease, considering that fermented alcoholic beverages have been consumed for hundreds of years, ever since the Neolithic Period (7, 8).

After 1970, many countries registered a fall in mortality by ALD; unfortunately, during the last decade, we have witnessed an increase in the incidence of this condition, and, implicitly in mortality, reaching 14.3/100,000 in France and 7.9/100,000 in the United States (9).

A lot of information concerning incidence, risk factors and ALD evolution are outdated, as while analyzing existing literature, we can easily see that most studies were carried out 15 or 20 years ago.

The real incidence and prevalence of ALD are difficult to evaluate, as many cases are asymptomatic, remaining thus
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undiagnosed and unreported. On a group of 1,604 patients with chronic alcohol consumption which underwent liver biopsy, in 20% of them morphopathological modifications in alcoholic hepatitis have been registered (10). Other studies estimate alcoholic hepatitis incidence in 10-35% of chronic alcohol consumers.

Although alcohol consumption is increasing, numbers related to mortality by ALD remained constant in the last 24 years, the United States even witnessing a reduction from 6.9/100,000 inhabitants in 1980, to 4.4%/100,000 in 2003 (11, 12).

Mortality by ALD mainly depends on the severity of hepatic affection, varying from 20% in light forms, to 30-60% in cases of severe alcoholic hepatitis (13). Acute hepatitis has the highest mortality rate, over 15% within 30 days and up to 39% within 1-year follow up (14,15). Great Britain is one of the countries where mortality by chronic liver disease has raised dramatically in the course of a few decades (1979-2005), the main cause of death by hepatic affection being ALD. In this area, mortality by ALD has jumped from 1.7 to 10.4/100,000 in men, and from 0.9 to 5.0/100,000 in women with alcoholic hepatitis, the increasing trend in alcohol consumption and mortality among young people aged between 25 and 34 years causing concerns (16).

On the long term, survival in patients with uncomplicated alcoholic hepatitis reaches 58%, and only 35% in patients with alcoholic hepatitis developed on cirrhotic background (17).

ALD patients who continue to consume alcohol have a reserved prognosis on the short term as well as on the long term: 5-year survival in compensated cirrhosis is almost 90% in abstinent and drops below 70% in those who continue to drink, while the occurrence of decompensation indicates a chance of survival under 30% (18).

A study carried performed on a group of patients with alcoholic hepatitis follow up during 5 years through annually evaluations by liver biopsy has shown the occurrence of cirrhotic morphopathological modifications in almost 40% of them (19), as well as the possibility that resolution of histological modifications be complete in 10% of abstinent (20). Regrettably, in many abstinent it can be noticed a certain progression towards liver cirrhosis, while women, even in conditions of total abstinence, seem to be more exposed to an aggravation of lesions.

In an earlier study, Bird specifies that the risk of developing hepatic cirrhosis in patients with alcoholic hepatitis is 10-20% every year, and in the end, over 70% of them, in time, develop cirrhosis with all its complications (21).

ALD occurrence is influenced by many factors, mainly alcohol consumption, thus geographic distribution and prevalence of the disease correlate with distribution of alcohol consumption.

ALCOHOL CONSUMPTION – A SOCIAL PROBLEM

Excessive alcohol consumption implies high economic and social costs. Alcohol accounts for 1.8 million deaths worldwide, while in Europe, alcohol consumption is responsible for more than 55,000 deaths amongst those aged between 15 and 29. In the United States, alcoholism prevalence is 20% in hospitalized adults (22). In Great Britain, 1 in 3 patients assisted through primary care services has an alcohol addiction.

ALD incidence is strongly correlated with geographic distribution of alcohol consumption. According to a recent WHO
report (Global Status Report on Alcohol and Health), published in 2011, alcohol consumption is a major global health issue (23). The WHO report estimates that 4% of deaths worldwide are caused by excessive alcohol drinking, totaling more deaths than AIDS, tuberculosis or violence (24). Alcohol consumption is considered to be the most important risk factor leading to death in men aged between 15 and 59.

The lowest mortality rate determined by alcohol-induced pathology is registered in regions with Islamic population, where alcohol consumption is reduced; in Western Europe also mortality is relatively low (in comparison with the East), although numbers referring to alcohol consumption are significant.

Globally, pathology determined by alcohol consumption accounts for 6.2% of registered deaths in males, beside 1.1% in females. Damaging alcohol drinking is fatal especially in youngsters.

Annually, 320,000 young people (15-29 years of age) worldwide die from alcohol consumption related causes, accounting for 9% of the total number of deaths at this age.

**Quantity of alcohol consumed**

The largest quantity of alcohol is consumed in developed countries. Although Western European countries report an important consumption of alcohol, alcohol induced mortality is significantly lower (while morbidity rate is considerable), as opposed to Eastern countries with the highest levels of alcohol consumption, and, probably, it is the type of beverages and consumption that determine much higher morbidity and mortality rates (9).

Alcohol drinking is largely spread, numbers are in some areas alarming, but a considerable percentage of the population is totally abstinent: almost half of men and over 2/3 of women have not drunk alcohol at all in the last years. From the point of view of the geographic distribution, populations in North African and South Asian regions are the most abstinent - areas with Muslim inhabitants, where alcohol is forbidden by religion.

In 2005, worldwide, the level of consumption of pure alcohol per inhabitant (persons over 15 years of age) was 6.13 liters. This largely varies geographically: developed countries, especially from the Northern hemisphere, report the highest values, but so do Argentina, Australia and New Zealand. South African, South and North American countries register a moderate level of consumption, while the North African and Sub Saharian, East Mediterranean and South-East Asia regions show reduced levels of alcohol drinking (23).

It must be underlined that an important percentage (28.6%) of this consumption, the equivalent of 1.76 liters, is represented by unregistered alcohol (homemade, produced in illegal conditions or sold without taxes (23). Consumption of illegal beverages is much more dangerous (to the hepatic toxic effect of alcohol that of noxious substances is added as well as the impurities contained by these inappropriately produced beverages).

Alcohol drinking in Eastern European countries exceeds the European average level, in Russia and the Community of Independent States (CIS) every fifth death is caused by excessive drinking. According to the WHO report, Romania is among the countries with the highest alcohol drinking levels in Europe: the national average is 15.3 liters/inhabitant compared to 12.2 liters, which is the EU average; we exceed by far the European average, while the ex-Soviet states are ahead of us.

**Type of alcohol**
Worldwide, spirits are the most consumed beverages: over 45% of the total quantity of alcohol consumed (23). However, as there are geographical differences in quantities consumed, so are in types of drinks: beer, wine, spirits etc.

Traditionally, in Europe there were marked differences concerning preferences: it was well known that Nordic countries preferred beer, while the South-East consumed mostly wine; at present, these practices tend to change (35). Spirits are consumed mostly in Asia and Eastern Europe, whereas wine tops the preferences list of South Americans, as well as of some European states. Beer is one of the most favorite alcoholic drinks, being consumed by most Westerns countries, Northern Europe, Australia and most Africans states.

Alcohol consumption may be: close to risk level, damaging consumption and alcohol addiction. In the United States, it is estimated that there are 4.65% persons that meet the criteria for damaging consumption and 3.81% alcohol addicts (24).

ALCOHOLIC LIVER DISEASE – RISK FACTORS

The occurrence of hepatic lesions in alcohol consumers is influenced by a series of risk factors pertaining to: alcohol consumption (quantity drunk, type of alcohol, duration, and frequency), constitutional factors (sex, ethnicity), risk factors for hepatic simultaneous affection (viral chronic hepatitis, iron overload syndrome, obesity, genetic factors etc.).

Alcohol consumption

Although there isn’t a linear progression type of relationship between ALD incidence and alcohol consumption, numerous data confirm the strong connection between the quantity of alcohol consumed and the debut of alcoholic liver cirrhosis (25, 40).

It is difficult to establish which of the chronic alcohol consumers will develop a severe liver disease. Though it is considered that the occurrence risk for liver cirrhosis is high in consumers with over 10 years of alcohol drinking, 60-80 grams/day in men and 20 grams/day in women, only 6-41% of them develop cirrhosis (8). Some studies show that after large quantities of alcohol consumed (approximately 120 g per day), only 13.5% of consumers are affected by cirrhosis (7). At the same time, an epidemiological study on a large scale proves that every liter of alcohol consumed in excess (irrespective of type) leads to an increase in cirrhosis incidence with 14% in males and 8% in females.

It is relatively difficult to say who will develop or not ALD according to the quantity of alcohol consumed. Nevertheless, risk thresholds as defined by WHO are 21 glasses per week in men (approximately 3 glasses per day, not more than 5 glasses on occasions) and 14 glasses per week in women (about two glasses per day). These thresholds are not risk-free, as there are differences according to nutrition, sex, physical and mental health, and consumption time.

While hepatic steatosis occurs in almost all persons with sustained alcohol consumption, only 10-35% of them develop alcoholic hepatitis, and less, 8-20%, develops liver cirrhosis (6). If the risk for cirrhosis occurrence is no more than 1% in those who consume 30-60 grams of alcohol per day, this risk increases to over 5.7% in persons who drink daily 120 grams of alcohol (23). There is clear and sufficient evidence to confirm that, irrespective of other risk factors associated, the quantity of alcohol consumed is the key element causing ALD.
*Beverage type and consumption pattern*

All alcoholic drinks are toxic to the liver, but it seems that the risk for ALD is greater in individuals that prefer beer and spirits, and more reduced in wine consumers (18). Also, the risk for liver damage is 2.7 higher in those who usually drink outside meals (9). Daily (or very frequent) alcohol consumption represents a more significant risk for the occurrence of severe forms of ALD than excessive periodical or occasional drinking; the earlier the start, the higher the risk to develop ALD (24).

*Sex*

The fact that the percentage of females with ALD is smaller than that of men does not mean that women are less likely to develop ALD, but it is a consequence of the fact that men drink alcohol more frequently. Female alcohol consumers are more exposed ALD than men, the main factors which favor the disease being: reduced level of gastric alcohol dehydrogenase, high fat mass, and hormone status (6). While in men the risk for hepatic disease is significant at 14-27 drinks per week, in women, the risk increases at a smaller number of drinks, 7-13 per week (11). Women are twice more sensitive to liver alcohol toxicity and usually develop more aggressive forms of ALD, though they drink less and for a shorter period of time as compared to men (51).

A number of studies showed that at the same quantity of alcohol consumed, blood alcohol content is significantly higher in women than in men (9). It is estimated that women without any other liver condition can consume 14 units of drink per week (one unit equals 8 grams of alcohol) without risk to develop ALD (in the case of men, the "risk-free" dose is 21 drinks per week) (23, 30); quantities mentioned are relative, as they do not give any warranty. Other studies lower the risk-free limit to 7 units per week.

*Race and ethnicity*

Some studies mention that African and Hispanic populations in America register higher rates in mortality and incidence of alcoholic liver cirrhosis as opposed to Caucasian population (23). As these differences do not seem to correlate with differences in alcohol quantity consumed, we are inclined to think of the role played by race or some genetic factors in favoring alcohol induced hepatic lesions.

*Obesity*

Obesity is an independent risk factor for hepatic disease, and non-alcoholic hepatic steatosis incidence, frequently associated to overweight, has been increasing in the past years. The association of the toxic effect of alcohol with non-alcoholic steatosis lesions raises the risk for ALD, with evolution towards cirrhosis; obesity intensifies ALD severity irrespective of the stage: steatosis, alcoholic hepatitis or liver cirrhosis. Taking that into account, for some years now, obesity has become an important health care problem for developed countries, with alarming rising incidence, and it is expected that in the following years we should face a significant increase in ALD cases, in number as well as severity (18).

*Nutritional deficiencies*

Many alcoholic patients are confronting with different nutritional deficiencies, and in those with alcoholic hepatitis it has been noticed that death risk is strongly correlated with the degree of nutrition (9, 12).

In these cases, mortality increases proportionately with malnutrition severity, reaching 80% in patients with severe nutritional deficiency, as compared to less than 50% in those with normal nutritional status. Malnutrition is a result of poor diet, anorexia, neuropsychological disorders, while
nutritional deficits of vitamin A and E are the most frequently met.

*Hepatitis C virus infection*

Almost 30% of ALD patients are infected with hepatitis C virus and more than 70% of those with viral chronic hepatitis C have previously consumed significant quantities of alcohol. The relationship between hepatitis C and ALD is proved, the infection with hepatitis C virus being directly involved in the occurrence of severe and advanced forms of ALD (27). The presence of lesions caused by hepatitis C virus is a major risk factor for hepatocellular carcinoma in patients with alcoholic cirrhosis, with a 10-year absolute cumulative incidence of 81% compared to 19% in those without VHC antibodies (28).

Alcohol drinking aggravates hepatic lesions in patients with viral chronic hepatitis C and accelerates the progression towards fibrosis and liver cirrhosis. It has also been noticed that in chronic alcohol consumers, ARN VHC level is significantly higher than in abstainers; last but not least, response to antiviral therapy in alcoholics is much weaker.

In viral hepatitis B, there is no certain data to confirm aggravation of hepatic lesions in patients which associate alcohol drinking (study results are even contradictory), but the effects of alcohol on an already damaged liver are very likely to be more significant than on undamaged liver.

*Iron overload syndromes*

There is irrefutable proof that hepatic iron overload is a frequent disorder in alcohol consumers; ALD patients have increased hepatic iron load, deposited at hepatocytes level and Kupffer cells. Hepatic iron overload in patients with ALD is considered a predictive factor for mortality (1).

Sinergical hepatotoxic effect of iron and alcohol is proved most convincingly by alcohol drinking association in patients with hereditary hemochromatosis: patients that drink alcohol have a significantly greater risk for severe hepatocytary lesions and cirrhosis occurrence at younger ages in comparison with abstainers (1, 9).

*Genetic factors*

There are numerous genetic factors that indicate a predisposition to alcoholism as well as to ALD; monozygotic twins are twice likely to become alcoholic and develop cirrhosis than are dizygotic twins (1, 11). It has been noticed that, generally, adopted children from alcoholic parents had a significantly higher alcohol addiction rate (18%) than adopted children with non-alcoholic parents (5%) (6, 11).

Recent studies have shown that variations of *patatin-like phospholipasedomain-containing protein 3* (*PNPLA3*) influence occurrence of alcoholic liver cirrhosis in Caucasian patients.

ALD ethiopathogenesis is not yet fully clear and has several unknown elements; still, one thing is certain: whatever may be the associated risk factors or genetic predisposition, the main triggering element in the genesis of the disease is alcohol consumption.

**REFERENCES**

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**NEWS**

**EVALUATION OF ADJUNCTIVE SYSTEMIC DOXYCYCLINE WITH NON-SURGICAL PERIODONTAL THERAPY WITHIN TYPE 2 DIABETIC PATIENTS**

The aim of a study realized by a group of researchers from King Abdulaziz University, King Saud University, Riyadh, Kingdom of Saudi Arabia was to evaluate the effects of systemic doxycycline on clinical and microbiological parameters of diabetic subjects with chronic periodontitis. The 9-month multi-center, randomized, parallel, single-blinded study was conducted from different hospitals in Riyadh, Saudi Arabia between April 2010 - December 2010. A total of 76 diabetic subjects with chronic periodontitis were randomized into 2 groups: control group (CG) received only scaling and root planing (SRP), and the treatment group (TG) receiving systemic doxycycline during the reevaluation visit 45 days after the completion of SRP. Probing pocket depth, clinical attachment level, gingival index, plaque index, and bleeding on probing were collected at baseline, 45 days after SRP, and one, 3, and 6 months after the use of systemic doxycycline. Microbiological analysis comprised the detection of *Tannerella forsythia* (Tf), *Aggregatibacter actinomycetemcomitans* (Aa), *Porphyromonas gingivalis* (Pg), and *Prevotella intermedia* (Pi) by polymerase chain reaction method. Sixty-eight (33 CG and 35 TG) subjects completed the study. Greater reduction in the population of Tf, Pg, and Pi were observed in TG compared with CG in the first month after the administration of systemic doxycycline. The TG showed a significant improvement in gingival index scores compared with the CG by the end of the first and 6 months after the administration of doxycycline. The conclusion of the study was that the adjunct systemic doxycycline can be associated with a reduction of Tf, Pg, and Pi in the first month after the administration of doxycycline with an improvement in the GI. (Al-Nowaiser AM, Al-Zoman H, Baskaradoss JK, Robert AA, Al-Zoman KH, Al-Sohail AM, Al-Suwyed AS, Ciancio SG, Al-Mubarak SA. Evaluation of adjunctive systemic doxycycline with non-surgical periodontal therapy within type 2 diabetic patients. *Saudi Med J*, 2014; 35 (10) :1203-1209)

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