Commentary: Metabolic associated liver disease: an inevitable terminological evolution in real practice

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Abstract. – In real practice, the patient with liver disease is often the carrier of multiple etiological factors, such as metabolic syndrome (MS) and alcohol consumption (AC). Their co-presence is often underestimated as AC is not adequately studied.

AC is a contributing cause of MS and alcoholic and nonalcoholic liver disease have a substantially overlapping histopathological picture. Moreover, AC and MS are the cause (and the contributing cause) of extra-hepatic morbidity and mortality.

It can be concluded that the possible simplification of terminology at metabolic associated liver disease (MALD) facilitates better communication and cooperation between scientific societies and specialists belonging to different medical sectors, facilitates early identification of related hepatic and extra-hepatic pathology, allows to “see the person in a unitary way”, to create leaner healthcare pathways, to reduce the hospitalization rate with relative cost-benefit advantage and to create unitary prevention and health promotion policies.

Key Words:
Alcohol consumption, Metabolic syndrome, Non-alcoholic fatty liver disease, Type 2 diabetes mellitus.

Brief Commentary

Unlike what happens in the world of controlled studies, in the routine outpatient activity, the patient with liver disease is often the carrier of multiple etiological factors, such as metabolic syndrome (MS) and alcohol consumption (AC).

The reasons for further simplifying the terminology at metabolic associated liver disease (MALD) are proposed in this brief commentary.

The prevalence and incidence of MS, insulin resistance (IR), obesity, type 2 diabetes mellitus (T2DM) and NAFLD are also closely linked

Traditionally to diagnose NAFLD, AC must not exceed 30 gr for men and 20 gr for women per day. In reality, lower doses of alcohol (light-moderate consumption) cause liver damage.

A recent meta-analysis found for one drink/day (12 gr of ethanol) a risk ratio (RR) increase, for incidence of liver cirrhosis, equal to 1.40 (95% confidence interval [CI]: 1-1.97), while the intake of two drinks/day increased the RR to 3.02 (95% CI: 1.95-4.07).

The assertion of non-acceptability is determined by the assessment of the “acceptable daily intake” (ADI). This safety threshold derives from the combination of the dose-response curve with a “safety factor”. The ADI calculated for ethanol (morbidity/mortality from liver cirrhosis) is 2.6 gr/day.

We think that this limit should still be reduced, especially in relation to the AC and fibrogenesis ratio, and also, frequent misestimation of AC or unrecognized MS may underestimate multi-caused liver injury.

Therefore, in real practice metabolic NAFLD and AC are coexisting. Cohort studies estimate that 20% of patients may have characteristics of both NAFLD and alcohol related liver disease (ALD) due to alcohol use disorders.

The link between fatty liver disease/steatohepatitis, cardiovascular disease (CVD) and cancer is known.

Both NAFLD and ALD are associated with extra-epatic risk factors and complications: increase
IR, T2DM, arterial hypertension, coronary heart disease, cardiomyopathy and cardiac arrhythmias which clinically result in increased CV morbidity and mortality.

Epidemiological data show us that AC and MS can be present simultaneously. People with T2DM and obesity have a high prevalence of NAFLD (40-80%). In the Western Europe, 60-70% of the adult population consumes alcohol.

ALD and NAFLD are substantially indistinguishable in their histopathological manifestations and regardless of whether there is NAFLD or ALD, short- and long-term mortality increases significantly. Scholars have shown that fibrosis stage, but not other histopathological parameters, determines the future risk of mortality in NAFLD patients.

Fibrosis stage correlates significantly with both hepatic and extrahepatic pathology. Eckstedt et al recorded a 10-year mortality rate of 20% in case of advanced fibrosis (F3/F4 based on Metavir Score) and NAFLD stages and 45% in case of ALD.

AC is often self-reported by direct interview. This is a limitation as many adult drinkers may be unaware of their risk of alcohol related harm. Hence, it is recommended to use alcohol use disorder identification test (AUDIT). The test’s sensitivity and specificity (92% and 93%, respectively) are very high, this fact allows identifying patients affected by hazardous or harmful consumption (AUDIT>8) who are not alcohol addicted.

In MALD patients it is mandatory to assess smoking and/or AC to achieve cessation. Furthermore, it is mandatory to identify light-moderate consumption. AASLD affirms: “patients with ALD or other liver diseases, in particular NAFLD, non-alcoholic steato hepatitis, viral hepatitis and hemochromatosis should be counseled that there is no safe level of drinking and that they should abstain”.

In the case of AUDIT equal/< 8, simple information on AC will be provided to the subject, enhancing the usefulness of the abstention. If AUDIT is >8 addiction program and a liver diagnostic examination are necessary. It is also necessary to detect signs of MS and or T2DM. It is worth pointing out that non-alcoholic and ALD are diagnosed with significant delay with respect to viral liver disease.

Both in the presence of MS, T2DM or AUDIT >8 the patient will be studied by biochemistry (often silent), and ultrasonography (US) will be performed. In the case of focal liver lesions the hepatologist can better identify their nature through contrast-enhanced ultrasound. After appropriate study, in case of hepatocellular carcinoma (HCC), Milan and Up to Seven Criteria will be followed.

Except in cases where there is a manifest clinical picture, biochemical or US signs of cirrhosis, elastography is mandatory (in our case diagnosed by 2-dimensional-shear wave elastography/2D-SWE). If liver stiffness (LS) values are equal/lower than 6 kilopascal (kPa) education in correct lifestyles is necessary. If LS is >6 kPa it will be advisable to evaluate the presence of confounding factors. In case of active AC, 2D-SWE must be repeated after 15 days of abstinence, or the AST adapted cutoffs if alcohol withdrawal is not feasible can be used.

In case of confirmation of 6-7 kPa, annual US surveillance is recommended. This is suggested by the direct carcinogenetic action of ethanol/acetaldheyde regardless of the degree of fibrosis and by the evidence that HCC can occur in case of NAFLD/ALD without cirrhosis (incidence rates from 7 to 44%).

Tamaki et al demonstrated that liver fibrosis was associated with CV risk independent of already known CV risk comorbidities. AASLD and Japanese Society of Gastroenterology recommend CV surveillance.

In case of kPa >7, six-monthly US surveillance/checks for digestive varices must be provided (Figure 1).

**Conclusions**

The metabolic patient, regardless of the pre- eminent etiological factor, has a determining factor in the global risk of mortality in liver disease.

In real clinical practice it is not always practicable to subdivide NAFLD from ALD. MALD definition could guarantee an optimal diagnostic-therapeutic process and facilitates early identification of related hepatic and extra-hepatic pathology.

**Conflict of Interest**

The Authors declare that they have no conflict of interests.
Figure 1. Metabolic syndrome and/or alcohol use disorder: a possible care pathway.

References


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