Translation from Romanian

ROMANIAN SOCIETY
OF GASTROENTEROLOGY
AND HEPATOLOGY

Position Paper on NAFLD treatment

Hepatic pathology is very frequent in Romania

- The treatment of chronic liver disease has made remarkable progress over the past 30 years. However, about 29 million people in the EU suffer from chronic liver conditions. Out of these, cirrhosis is the most daunting, due to its complications, among which hepatic cancer.
- Romania has one of the highest prevalence rates of mortality due to cirrhosis of the liver out of the European countries, ranking at the top as regards hepatitis B and C virus infections.
- The first causes of cirrhosis of the liver are alcohol consumption and viral hepatitis B and C. More recently, the cirrhogenic potential of fatty liver disease has also been noted, in the context of an increase in the prevalence of the metabolic syndrome.

Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease is a liver condition whose prevalence and incidence are growing continuously worldwide, becoming one of the most frequent causes of chronic liver conditions.

- In Romania, where obesity is growing from early ages, it is estimated that over 20% of the general population suffers from fatty liver disease.
- Over the next years, a quick increase in the prevalence of hepatic steatosis is estimated, along with a dramatic growth of diabetes and obesity.
- The histological spectrum of non-alcoholic fatty liver disease varies from mere fatty infiltration of the liver (steatosis) to hepatocyte lesion with focal necrosis and inflammation (steatohepatitis). In addition, the absence of specific symptomatology has been noted in over 50% of the patients, most of them having normal values of aminotransferase.
- The long asymptomatic evolution of hepatic conditions, in the absence of a correct therapeutic approach, exposes patients to the risk of evolving to serious forms of cirrhosis of the liver.
- Patients with chronic liver conditions, including fatty liver disease, have expectations regarding therapy. In the absence of an etiological treatment, there is the tendency of prescribing therapies with pathogenic focus (even though there are no convincing meta-analyses), generically named hepatoprotectives.
- These hepatoprotectives have membrane stabilising, antioxidant, anti-inflammatory, immuno-stimulating etc. effects. Experimental effects could not be extended successfully to real life in all cases. For this reason, the prescription of hepatotropic drugs should be made responsibly by the physician, and patients should be educated not to self-medicate, so as not to waste money on useless or even toxic drugs.

There is a worrying tendency of associating or replacing verified hepatoprotective therapy with non-verified food supplements

- In this context, **food supplements have taken the indications dedicated exclusively to drugs** (OTC or prescription medication), communicating to the population and to the medical community of Romania incorrect messages, from both a legal point of view and not correlated with the scientific reality.
- **The use of food supplements does not have a curative or preventive purpose.** According to the legislation in force, they are destined to oral consumption (administration) by healthy people who need a higher exogenous intake, due to specific nutritional requirements related to their physiological state.

- **The use of food supplements to treat liver conditions is controversial among the medical community** because sometimes their composition is incompletely known; frequently they contain non-standardised and non-investigated extracts according to the standards in force (good clinical practice, GCP) whose efficacy/safety evaluation in clinical studies does not exist.

- **Liver conditions require additional precautions,** which is why the additional charge of hepatic activity with uncertain compounds, possibly with a toxic potential with no therapeutic role is not recommended.

The general physicians acts as first line in the screening, primary and secondary prophylaxis of the NAFLD patient:

The conduct algorithm includes:

A. **Primary prophylaxis** – maintaining a healthy lifestyle, a rational diet, avoiding a sedentary lifestyle.
   a. healthy diet;
   b. maintaining the BMI = 18.5 – 24.9 kg/m^2;
   c. avoiding a sedentary lifestyle.

B. **Screening of risk categories:**

High risk categories are: alcohol consumers, patients with obesity, type II diabetes mellitus, dyslipidaemia, metabolic syndrome and those using drugs with an adipogenic potential (amiodarone, methotrexate, tamoxifen, glucocorticoids, oestrogen, valproic acid, antiretroviral drugs, nifedipine, tetracycline, etc.).

Screening method: must include the clinical examination of persons in the risk pool, biochemical screening (measuring aminotransferase levels) and abdominal ultrasound at least once/year.

C. **Secondary prophylaxis:** The purpose of the treatment is improving the hepatic function, solving histologic lesions with an implicit reduction of the risk of evolution to cirrhosis of the liver and it consists of:
   a) nutritional-hygienic regimen:
      a. weight loss (BMI > 25 kg/m^2); with 0.5-0.75 kg/week
      b. hypocaloric diet, reduction of saturated fat foods intake; fats <30% of total calories
      c. high content of dietary fibre
      d. physical exercise
   b) avoiding use of drugs or food supplements with a hepatotoxic potential
   c) treatment of comorbid conditions (diabetes mellitus, dyslipidaemia, etc.)
   d) the hepatoprotective pharmacological therapy should be followed according to evidence-based medical principles, with drugs that have proved their efficacy in clinical

studies. The recommended ones have a proven antioxidant effect (e.g. essential phospholipids, vitamin E, etc.), a hepatocyte membrane stabilising effect (essential phospholipids, silymarin, etc.) and anti fibrotic effect (silibinum, essential phospholipids, etc.).

They have proven their efficacy in improving liver function, reducing the progression of the pathological process, supporting hepatic regeneration, symptomatology control and preventing complications.

The use of hepatoprotective food supplements is not recommended if their composition is not clearly studied and if they have not proven their efficacy in clinical studies.

For this reason, it is important to recommend patients products registered as OTC or prescription drugs.

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Position paper

on the approaching the patients with non-alcoholic fatty liver disease in primary care medicine

This position paper is a set of recommendations in view of providing scientific support and partnership in the management of your patients with non-alcoholic fatty liver disease.

Introduction

- Non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of liver disease worldwide and will probably become as the leading cause of advanced/end-stage liver disease in the coming decades, affecting adults and children alike.[1]
- The epidemiology and demographic characteristics of NAFLD vary across the world, usually in parallel with the prevalence of obesity, although a significant proportion of patients have a normal weight.[1]
- The global prevalence of NAFLD is estimated to be 30%, on average, varying according to the geographical location, age, ethnic group, etc.
- In Romania, the estimated prevalence is about 20%.[1]
- Moreover, NAFLD patients have a high frequency of metabolic comorbidities (diabetes mellitus, cardiovascular conditions, dyslipidaemia, etc.) and could place an increasing pressure on healthcare systems due to their need for management.
- The great number of NAFLD patients and the condition's potential to progress to non-alcoholic steatohepatitis (NASH), cirrhosis and hepatocellular cancer give rise to the need for careful monitoring to detect the condition in its early stages and justify the attention of primary care doctors, specialists and healthcare decision-makers.

NAFLD diagnosis and staging

- Given the high prevalence of NAFLD, the need for a disease diagnosis and severity staging algorithm is a critical medical desideratum.
- While metabolic liver inflammation is the factor leading to the progression of the disease, various studies (including meta-analyses) that have examined histological prognostic features suggest that the fibrosis stage is the parameter best associated with hepatic and extrahepatic mortality, with terminal stages and complications of liver cirrhosis and the need for liver transplants, as well as with extrahepatic conditions (cardiovascular, neurological, etc.).2
- Identifying NAFLD patients in early stages, as well as assessing the potential for evolution to fibrosis are very important, particularly as in over 50% of these patients it has been noticed an absence of specific symptomatology, and up to 80% of them have normal ranges liver function tests.

General Practitioners (GPs) involvement as a first line in detecting/staging NAFLD patients

Identifying NAFLD is required for the following patient subsets:

- apparently healthy adults over the age of 35 and with at least one risk factor;
- overweight or obese persons;
- type II diabetes mellitus patients;
- dyslipidaemia patients;
- metabolic syndrome patients.

Identification method:

A. *Clinical and paraclinical examination:*

a) age, BMI, abdominal circumference;

b) basic set of tests: ALT, AST, complete blood count, triglyceride values, uric acid, gamma-glutamyl transferase.

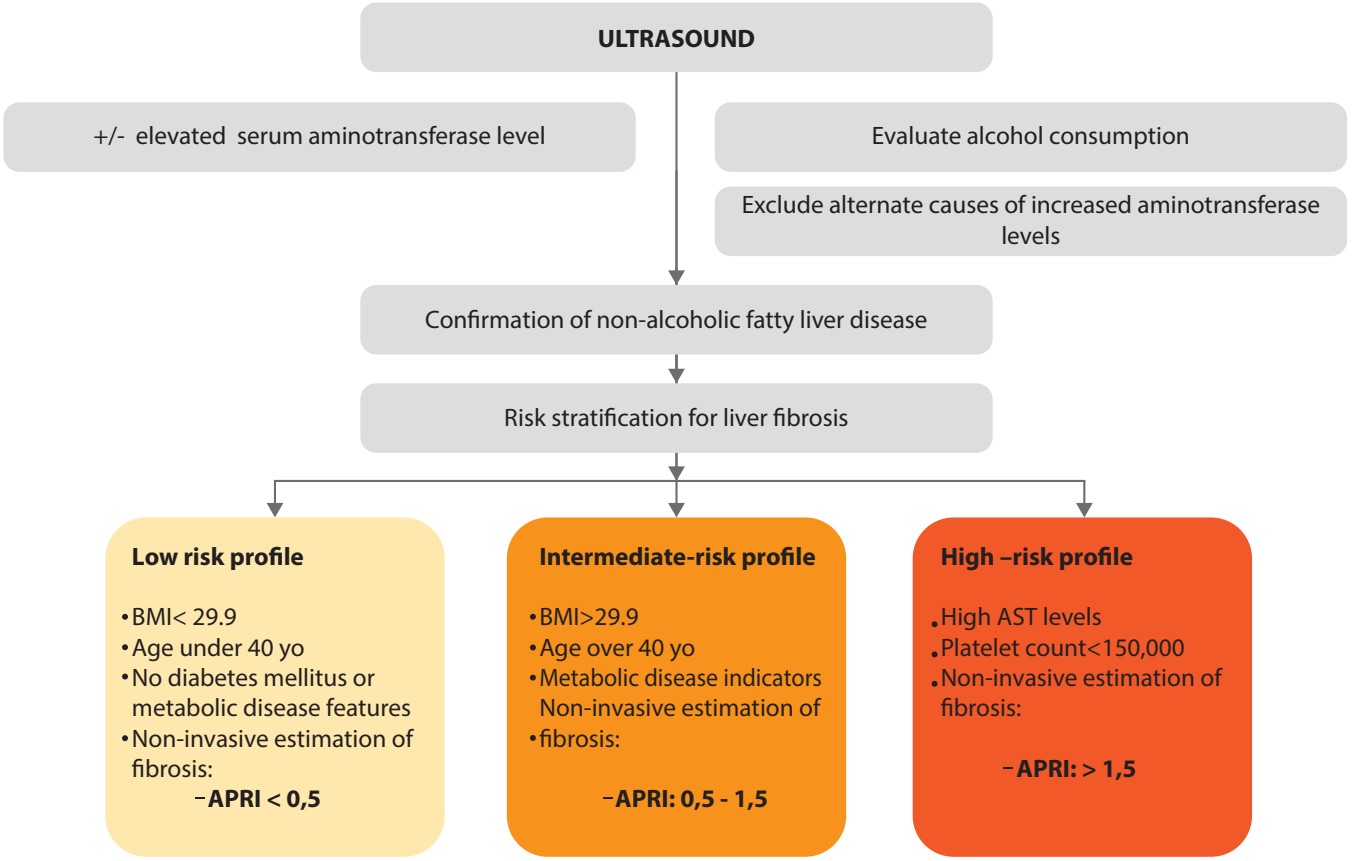
B. *Ultrasound (70-80% sensitivity, 90% specificity – imaging diagnosis)* – remains the most accessible method of identification, as it is known that many NAFLD patients have liver function tests (AST, ALT, GGT) within normal ranges. The ultrasound is recommended for all persons with at least one risk factor, even if they are children.i.

C. *C. Fibrosis risk stratification* using the APRI score to identify patients at risk, with the following recommendations (online calculator):

a) low- (APRI<0.5) or medium-risk categories (>0.5 <1.5), without additional risk factors, will be monitored and treated by the GPs (annually) and referred to a specialist, with a re-examination at least once every 3 years;

b) medium-risk categories (>0.5 <1.5), with other risk factors: metabolic syndrome, diabetes mellitus, other related liver pathologies, will be monitored and treated by the GP (every 6 months) and referred to a specialist, with a re-examination at least once a year;

c) high-risk categories (APRI>1.5) will be monitored and treated by the gastroenterology/ hepatology specialist, with a re-examination every 6 months.



The approach to NAFLD patients involves:

- lifestyle recommendations – a healthy diet;
- changing the lifestyle, avoiding sedentary lifestyle and correcting risk factors;
- treating related medical conditions (dyslipidaemia, diabetes mellitus);
- hepatoprotective pharmacological therapy whose prescription must follow the principles of evidence-based medicine, with drugs whose efficacy has been proven in clinical trials and which are tested regularly;
- avoiding the use of food supplements with a hepatotoxic potential;
- currently, there is no approved etiological therapy for NAFLD/NASH.

In the context of the patients' lack of adherence to diet and physical exercise, associating the hepatoprotective treatment brings benefits to NAFLD patients who have expectations regarding therapy – besides recommendations on the diet, they should have a prescription with a scientifically proven medicine.

For this reason, in the absence of etiological therapy, pathogenic treatment (generically named hepatoprotectives) is the optimal therapeutic option. The patient should know that not any "pill" from the pharmacy is a medicine.

It is recommended to use drugs with a proven antioxidant effect (e.g. essential phospholipids, vitamin E, etc.), which stabilise the hepatocyte membrane (essential phospholipids, silymarin, etc.) and with an antifibrotic effect (silybinum, essential phospholipids, etc.).

These drugs have proven their efficacy in improving the liver function, supporting liver regeneration, controlling the symptomatology and reducing the risk of progression to severe forms.

Liver-protecting food supplements are not recommended unless their composition is clearly studied and unless they have proven their efficacy in clinical trials. According to the legislation in force, they are destined to oral consumption (administration) by healthy people who need a higher exogenous intake, due to specific nutritional requirements related to their physiological state.

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