

# **REPORT of the EASL monothematic conference on NASH**

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The NASH field is burgeoning and seems now in a stage which yields more questions than answers, as C. Day put it in his concluding remarks.

For the definition of NASH there is a consensus (AASLD consensus conference). But there is no perfect consensus yet on the histologic criteria (for instance lobular inflammation is required for 50% pathologists, and hepatocytes ballooning for 60%) (Tiniakos D.).

For the diagnosis, the amount of alcohol consumed should be ascertained by a validated questionnaire or a 7-day diary by a skilled dietician (the upper limit of alcohol for NAFL is now reduced to 20 g/day).

Fifty percent of NASH cases may be missed if ALTs are used as predictors, instead of the "metabolic syndrome" (Bellentani S.).

The prevalence of NASH differs between various studies in different populations and countries, using different methodologies. We need more prospective studies about its epidemiology and natural history, including cryptogenetic cirrhosis and hepatocellular carcinoma (HCC) (Marchesini G., Ratziu V.).

Long-term studies are needed to verify the cardiovascular risk of NAFLD patients (it could be reduced in advanced liver disease thanks to diminished levels of platelets, cholesterol and blood pressure) (Marchesini G.).

On the other hand liver disease is one of the top causes of death of patients with the metabolic syndrome; NASH patients have increased liver-related death compared to those with steatosis but without steatohepatitis ; NASH patients have a higher mortality, mainly liver-related, than the overall mortality in the general population; and the delay of NASH diagnosis in obese or diabetic patients can lead to the development of cirrhosis and of HCC (Ratziu V.)

Cryptogenic cirrhosis can indeed be burned out NASH but there is no definite explanation for the female predominance and the loss of fat in cryptogenic cirrhosis (Caldwell S.).

In children, a distinctive histological feature is the predominance of portal-based chronic inflammation (Tiniakos D.). NASH in children is not rare (mainly in Hispanics and Caucasians) and not benign; prevention is better than cure (Roberts E.).

One thing sure is that NAFLD is now considered as the liver manifestation of the metabolic syndrome.

Insulin resistance (IR) plays a central role in the pathogenesis of NAFLD (Sanyal A.).

For the definition of insulin resistance, the cut-off is arbitrary. For its measure, all methods are good but each measures something different; the euglycemic clamp measures muscular and not liver IR For liver problems, the fasting insulinemia is the most interesting test (Bugianesi E.).

The free fatty acids (FFA) give the stimulus, the substrate and the energy for hepatic glucose production. Elevated levels of FFA decrease the insulin secretion and the muscular glucose utilisation (Bugianesi E.).

IR and fatty liver may happen without an increase in subcutaneous fat; adiponectin deficiency might be involved ; dietary fat content may also influence liver fat; increased liver fat increases the insulin requirements, and liver fat is a cause of IR (Yki-Jarvinen H.).

IR results in increased FFA release from fat stores. Hepatic FFA uptake is largely uncontrolled and therefore directly proportional to plasma FFA concentrations. In the liver, FFA can either be oxidized to generate ATP or esterified to produce triglycerides which can be stored or incorporated into Very Low Density Lipoproteins particles for export. Defects in either of these two pathways could lead to hepatic steatosis. In addition, the liver is able to generate fatty acids from AcetylCoA in the process of lipogenesis, which is stimulated in IR (Kuipers F).

The progression of steatosis to steatohepatitis is associated with increased oxidative stress within hepatocytes. The sources of this oxidative stress include uncoupled oxidation and phosphorylation in the mitochondria, CYP2E1 activation and peroxisomal fatty acid oxidation (Sanyal A., Cortez-Pinto H.). IR can contribute to all of these pathways, and is a pro-inflammatory state (Sanyal A.).

The metabolic syndrome is indeed a chronic inflammatory state, with increased TNF (which induces the generation of ROS and can induce apoptosis) and decreased adiponectin; when TNF is excessive relative to adiponectin, hepatocytes accumulate lipid and are resistant to insulin. Hepatocytes surviving oxidative attack have upregulated NF-kappa B and NF-kB-inducible cytoprotective genes (Diehl A.M.)

Oxidative stress can by itself produce further oxidative stress (vicious circle) by degrading the NF-kB inhibitor, Ikb, allowing the translocation of NF-kB to the nucleus (Cortez-Pinto H.)

PPARa upregulate fatty acid b-oxidation and are predominant in the liver. PPARa stimulation ameliorates steatosis and IR in several animal models but not in NASH patients.

PPARgamma promote lipid storage in mature adipocytes and are abundantly expressed in adipocytes. They also play a critical role in the control of inflammation and in preventing hepatic stellate cells activation (at least at an early stage). A fine tuned or tailored modulation of the activity of the PPARs might be the best strategy to treat hepatic complications of the metabolic syndrome while preventing undesirable consequences (Leclercq I.).

Several cytokines play a major role in various aspects of liver injury and repair. The pro-inflammatory cytokine TNFa has emerged as a key factor in liver diseases. Certain TNFa polymorphisms are associated with susceptibility for IR and TNFa might be involved in the pathogenesis of NASH (Tilg H.).

Apoptosis is important in ASH and NASH. Anti-apoptotic Bcl-2 protein is also up-regulated (as an adaptative response?). Ursodeoxycholic acid inhibits apoptosis, by up-regulating glucocorticoid and mineralocorticoid receptors (Rodrigues C.).

Only a limited amount of information is currently available on the possible role of pro- and anti-fibrogenic factors during NASH. The adipokines, cytokines predominantly secreted by

the adipocytes (i.a. leptin, adiponectin and resistin) represent an area of active research. Inflammation is likely necessary but not sufficient for the development of fibrosis (Marra F.).

While obesity and/or IR are undoubtedly involved in the pathogenesis of NASH some other environmental (diet, exercise, possibly small bowel bacterial overgrowth) and/or combination of genetic factors is required for progression to NASH and fibrosis (Day C.).

Turning pathogenetic mechanisms into treatment is not obvious. Long-term randomized controlled trials with histological endpoints are necessary (Day C.).

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