Fatty Liver—Seat of Insulin Resistance

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I
n the 60th year of publication of JAPI (Journal of Association of Physicians of India), as I take the mantle of Editorship of JAPI, it would only be appropriate to place on records the hard work put in by the editors S.S. Misra, G. Coelho, N.J. Mody, K.G. Nair, G.S. Sainani, V.R. Joshi, P.J. Mehta, S.K. Bichile and Shashank R. Joshi who have put in their selfless service to bring JAPI to international standards. In the last six years JAPI is full text free on the web and also has a rapid publication section. I would appeal to all the members of API to extend their support in furthering the advancement of scientific knowledge for the medical community.

LIVER is the largest metabolic organ of human and is the factory of fuel homeostasis. Its role in the pathogenesis of Type 2 Diabetes, Metabolic Syndrome is being well recognized. Liver is a classic site for ectopic lipid deposition. Traditionally, fatty liver, also known as Steatohepatitis, steatorrhoeic hepatitis, or steatosis hepatitis, which is a reversible condition where large triglyceride vacuoles of fat accumulate in hepatocytes via the process of steatosis. Fatty liver can be considered a single entity (despite multiple etiologies) that occurs worldwide in those with excessive ethanol intake and those who are obese (with or without effects of insulin resistance and metabolic syndrome). The condition is also associated with other diseases that influence fat and fuel metabolism. Histologically it is difficult to distinguish alcoholic fatty liver from non-alcoholic fatty liver and both show microvesicular and macrovesicular fatty changes at different stages.

Fatty change represents the intra-cytoplasmic accumulation of neutral fats namely the Triglycerides. At the beginning, the hepatocytes present small fat liposomal vacuoles around the nucleus—microvesicular fat. In this stage liver cells are filled with multiple fat droplets that do not displace centrally located nucleus. In the late stages, the size of the vacuoles increases pushing the nucleus to the periphery of the cell giving characteristic signet ring appearance—macrovesicular fat. These vesicles are well delineated and optically "empty" because fats dissolve during tissue processing. Large vacuoles may coalesce, producing fat cysts which are irreversible lesions. Macrovesicular fatty process is the most common form and is typically associated with Type 2 Diabetes, Obesity, Metabolic Syndrome as well as ethanol and steroid use. Microvesicular changes are typically seen in Acute Pregnancy Fatty Liver and Reye's Syndrome, where often severe liver disease caused by microvesicular fatty change. The diagnosis of steatosis is made when fat in the liver exceeds 5–10% by weight.¹

Multiple defects in fuel and fat metabolism are implicated in the genesis of Fatty Liver Syndromes which may be due to imbalance in energy consumption and its combustion resulting in lipid storage or can be a consequence of peripheral resistance to insulin, whereby the transport of fatty acids from adipocytes to the liver is increased. Impairment or inhibition of receptor molecules (PPAR-α, PPAR-γ and SREBP1) that control the enzymes responsible for the oxidation and synthesis of fatty acids appears to contribute to fat accumulation. In addition, alcoholism is known to damage mitochondria and other cellular structure further impairing cellular energy mechanism. On the other hand, a non-alcoholic fatty liver may begin as excess of unmetabolised energy in liver cells. Hepatic steatosis is considered reversible and to some extent nonprogressive if there is cessation or removal of underlying cause. However currently the underlying metabolic abnormalities persist making it a front runner for chronic liver disease and cirrhosis.²

When severe fatty liver is sometimes accompanied by inflammation, a situation that is referred to as steatohepatitis. Progression to alcoholic steatohepatitis (ASH) or non-alcoholic steatohepatitis (NASH) depend on persistence or severity of inciting cause. Histopathological lesions in both conditions are similar. However, the extent of inflammatory response varies widely and does not always correlate with degree of fat accumulation. Steatosis (retention of lipid) and onset of steatohepatitis may represent successive stages in Fatty liver disease progression. Liver with extensive inflammation and high degree of steatosis often progresses to more severe forms of the disease.

Non-alcoholic fatty liver disease (NAFLD) is fatty inflammation of the liver when this is not due to excessive alcohol use. Primary NAFLD is predominantly metabolic in etiology. It is related to insulin resistance and the metabolic syndrome, and may respond to treatments originally developed for other insulin resistant states (e.g. diabetes mellitus type 2), such as weight loss, metformin and thiazolidinedione. Non-alcoholic steatohepatitis (NASH) is the most extreme form of NAFLD, which is regarded as a major cause of cirrhosis of the liver of unknown cause.³ One debated mechanism promotes a “second hit”, or further injury, enough to cause change that leads from hepatic steatosis to hepatic inflammation. Oxidative stress, hormonal imbalances and mitochondrial abnormalities are potential causes for this “second hit” phenomenon.¹ NASH was first described in 1980 in a series of patients of the Mayo Clinic.³ Its relevance and high prevalence were recognized mainly in the 1990s. Some feel that NASH is a diagnosis of exclusion, and that many cases may be in fact be due to other causes. NAFLD can also be caused by the following medications (termed secondary NAFLD): Amiodarone, Antiviral drugs (nucleoside analogues),

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Aspirin / NSAIDs, Corticosteroids, Methotrexate, Nifedipine, Perhexiline, Tamoxifen, Tetracycline, Valproic acid.

NAFLD is considered to cover a spectrum of disease activity. This spectrum begins as fatty accumulation in the liver (hepatic steatosis). A liver can remain fatty without disturbing liver function, but by varying mechanisms and possible insults to the liver may also progress to outright inflammation of the liver. When inflammation occurs in this setting, the condition is then called NASH. Over time up to 20 percent of patients with NASH may develop cirrhosis. The exact cause of NAFLD is still unknown. However, both obesity and insulin resistance probably play a strong role in the disease process. The exact reasons and mechanisms by which the disease progresses from one stage to the next are the subject of much research and debate.

Several reports of NAFLD and NASH have been described from India in the past decade. They are predominantly urban from all major cities and closely follow the epidemic of diabetes and metabolic syndrome. In fact initially sonography with biochemistry and later histology was used. Even chemical shift imaging with MR has also been used. Gupta et al. were one of the early investigators from India which found that the prevalence of NASH is high in type 2 DM patients and liver biopsy is the only investigation to differentiate between non-alcoholic fatty liver and steatohepatitis. Singh et al found Female gender, BMI, waist:hip ratio, hypercholesterolemia and LDL levels are independent predictors of disease severity in patients with NASH and may influence the decision to biopsy. Duseja et al. found that the clinicopathological profile of Indian patients with NAFLD may be different from that of Western patients. Banerjee et al. reported fatty liver as a seat of insulin resistance from Eastern India recently.

In this issue of JAPI there is a single city reportage of NASH from two distinct public and private settings. Also the public setting is from a cohort of Diabetes while the private setting is from a gastrointesinal cohort. Both the studies are a continuum of the early work from across India highlighting the need to identify Fatty Liver-NASH as a early marker for Metabolic Syndrome. In both Pre diabetes and Diabetes it will have long term impact. The high prevalence of NASH and Diabetes has not only clinical practice implications but also serious public health policy ramifications. This Ectopic Liver Fat is back on the spotlight in Diabetes and Fuel Metabolism and will need urgent attention amongst the vulnerable Asian Indians. Lifestyle as well as medications like Metformin and glitazones hold the key to both therapy as well as prevention of NASH in Metabolic Syndrome.

References

Announcement
Research Grant Announcements 2008

Research proposals are invited from Indian scientists, interested in conducting research in the field of diabetes mellitus, for funding by RSSDI. These proposals may fall into one of the following two categories: Projects involving funding up to Rs 40,000 per project (preference will be given to young scientists < 40 yrs) Projects involving funding up to Rs 3-4 lakhs (preferably multicentric). For Details contact: Prof. S.V. Madhu, Chairman, Research Committee, RSSDI; Department of Medicine, Division of Endocrinology & Metabolism; University College of Medical Sciences (UCMS); Dilshad Garden, Delhi – 110 095; Phone: +91-22586262; e-mail: rssdihq@gmail.com

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