



## Commentary

### Analyzing lipids in the liver & in the red blood cell membrane in liver diseases

Fatty liver is now a commonly encountered finding on ultrasound scan of abdomen during routine health check-up. Histological studies reveal a spectrum of changes in non-alcoholic fatty liver disease (NAFLD). On liver biopsy, the presence of fat droplets in  $\geq 5$  per cent of hepatocytes is considered as pathological, and when it is not accompanied by markers of hepatocellular injury such as ballooning of hepatocytes, it is called simple steatosis. In addition to steatosis, the presence of hepatocellular injury and inflammation with or without fibrosis is categorized as steatohepatitis<sup>1</sup>.

Fat deposits within the hepatocytes assume two distinct histological patterns - macrovesicular and microvesicular steatosis. In macrovesicular steatosis, a single large fat droplet displaces the hepatocyte nucleus to the periphery. In contrast, in microvesicular steatosis, the tiny vesicles of fat are too small to push the nucleus, which thus retains its central position<sup>2</sup>. The presence of numerous tiny vesicles of fat in the hepatocyte gives foamy appearance to the cytoplasm.

The diseases causing hepatic steatosis are of public health importance in India. NAFLD and alcoholic liver diseases are causes of hepatic steatosis which occur in epidemic proportions in India currently<sup>3</sup>. Many of the histological features of NAFLD and alcoholic liver disease are similar. NAFLD typically causes predominantly macrovesicular steatosis in the liver, though at times, mixed macrovesicular and microvesicular steatosis can also occur. However, while isolated/predominant microvesicular steatosis is seen in alcoholic liver disease (termed 'alcoholic foamy degeneration of the liver'), this has not been reported in NAFLD<sup>2</sup>.

Isolated hepatic microvesicular steatosis, though less common, is also of public health importance in India. This histological finding is seen in conditions such as acute fatty liver of pregnancy, Reye's syndrome and valproic acid toxicity<sup>1</sup>. In these uncommon conditions,

fatty acid  $\beta$ -oxidation pathway (located within the cell mitochondria) is affected. Acute fatty liver of pregnancy is an important but under-recognized (and preventable) cause of maternal deaths in India<sup>4</sup>. The latest addition to causes of defective mitochondrial fatty acid oxidation is toxins contained in litchi fruit leading to seasonal outbreaks of an illness similar to Reye's syndrome causing deaths in malnourished children in Bihar and Uttar Pradesh, India<sup>5</sup>.

Lipids such as cholesterol and triglycerides are not soluble in plasma. Lipoproteins are vehicles to transport these (otherwise insoluble) lipids in plasma. Of the five major lipoproteins, very low density lipoproteins (VLDL) are the main transporter of lipid exiting out of the liver. Apolipoproteins are the protein components of lipoproteins.

In NAFLD, there is a block in fat exiting the liver (impaired secretion of VLDL after a fatty meal and reduced synthesis of apolipoprotein B-100, the important apoprotein involved in exporting lipid as VLDL out of the liver)<sup>6</sup>, increased fat inflow into the liver<sup>7</sup> and impaired fatty acid oxidation as well as increased fatty acid synthesis in the liver<sup>8</sup>. In contrast, hepatic microvesicular steatosis syndromes are mainly associated with defective fatty acid oxidation in the mitochondria.

Phospholipids form part of the red blood cell membrane. In a study published in this issue, the authors have raised an interesting question if fatty acids in the red blood cell membrane are altered in NAFLD patients<sup>9</sup>. Some of the limitations of the current study of fatty acids in red cell membrane in NAFLD need to be mentioned. Major classes of membrane fatty acids are saturated and monounsaturated fatty acids, which constitute about 85 per cent of total red blood cell membrane fatty acids, and these are not altered in NAFLD. Moreover, changes in polyunsaturated fatty acids are also minimal. Variables which can affect

red blood cell membrane fatty acids like diet have not been studied. The lack of a control population hampers meaningful interpretation of the study findings. The authors did not find any correlation between the red blood cell membrane fatty acids studied and NAFLD. They noted a weak correlation of the red blood cell membrane fatty acids with cytokines<sup>9</sup>.

The combination of haemolysis in a patient with cirrhosis raises the possibility of autoimmune haemolytic anaemia and autoimmune hepatitis, copper overload causing haemolytic anaemia in Wilson's disease, hyperlipidaemia in alcoholic cirrhosis (Zieve's syndrome) as well as spur cell anaemia. Spur cells (or acanthocytes) are spiculated red blood cells seen in some patients with advanced cirrhosis. Red blood cells from healthy individuals when incubated in the plasma taken from cirrhotic patients with spur cell anaemia undergo transformation from their discoid shape to acanthocytes (with irregular thorn-shaped spikes on the surface). Conversely, when the acanthocytic red blood cells from cirrhotic patients with spur cell anaemia are suspended *in vitro* in the plasma of healthy individuals, these red blood cells regain the normal smooth, discoid shape<sup>10</sup>. These acanthocytes are prone to lysis; this non-immune haemolytic anaemia (spur cell anaemia) in patients with cirrhosis portends poor prognosis. After liver transplantation, the spur cell anaemia subsides by a period of 20 days<sup>11</sup>. It is hypothesized that changes in serum lipids may affect the lipid composition and fluidity of the red blood cell membrane in spur cell anemia<sup>10</sup>.

A previous study analyzed the profile of saturated and unsaturated fats in liver and red blood cell membrane in NAFLD patients<sup>12</sup>. This study showed lower polyunsaturated fats (n-3 and n-6) in liver, without any differences in dietary fatty acid intake, in nonalcoholic steatohepatitis (NASH) individuals compared to those with simple hepatic steatosis. In contrast, saturated and unsaturated fats in the red blood cell membrane were not different in individuals with simple steatosis compared to those with NASH<sup>12</sup>. Whether dietary supplementation of polyunsaturated fatty acids is of benefit in NAFLD patients needs further study<sup>12</sup>.

**Conflicts of Interest:** None.

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