## Fatty Liver

Fatty liver, or fatty infiltration of the liver, is the accumulation of fat in liver cells. Fat accumulates in the liver, replacing cells that have died off, and while it is traditionally associated with heavy use of alcohol, extreme weight gain or diabetes, it can also be associated with poor diet and certain illnesses, such as tuberculosis, intestinal bypass surgery for obesity and certain drugs such as corticosteroids. Fatty liver though is also seen as a chronic inflammatory disease, with linking to IBS and the autonomic nervous system.

"First described in 1980, non-alcoholic fatty liver disease (NAFLD) is now the most common cause of liver disease in industrialised countries. Non-alcoholic fatty liver disease includes both non-alcoholic steato-hepatitis (NASH), involving lobular inflammation and fibrosis, and simple steatosis (non-NASH). This distinction is important, as simple steatosis is unlikely to lead to liver related complications, whereas NASH may lead to increased fibrosis and cirrhosis, and its complications. The difficulty lies in trying to decide whether raised liver functions tests (LFTs) are due to simple steatosis, NASH without fibrosis, NASH with severe fibrosis or cirrhosis, or another cause of hepatitis altogether." (1)

"The prevalence of NAFLD is estimated to be approximately 30% of adults in developed countries such as Australia and the United States, depending on definition and detection methods. However, NAFLD is also becoming increasingly common in Asia (countries previously thought to be at low risk of NAFLD), where a prevalence of up to 15% has been reported in China." (1)

"Simple steatosis appears to be a relatively benign condition, although it may progress to NASH over time. Cardiovascular disease is the major cause of death in patients with NAFLD; NAFLD alone is associated with a slightly higher overall mortality. However, when NAFLD occurs in the presence of other features of the metabolic syndrome, mortality doubles. The Metabolic Syndrome is a clustering of cardiovascular risk factors related to reduced insulin sensitivity. Diagnostic criteria for the syndrome include:

- elevated serum triglycerides (TG)
- lowered serum high-density lipoprotein cholesterol (HDL-C)
- impaired glucose tolerance
- central adiposity
- hypertension.

Although NAFLD is not officially included in the definition of the Metabolic Syndrome, it commonly co-exists with features of this syndrome. In addition to its association with cardiovascular complications, NAFLD can lead to liver related morbidity and mortality. The risk of developing cirrhosis is higher in the presence of NASH, which is more likely in the presence of the following features:

- type 2 diabetes mellitus (T2DM)
- obesity (body mass index [BMI] >30 kg/$m^2$)
- age more than 50 years
- serum aminotransferases (ALT or AST) more than two times the upper limit of normal." (1)

"In the US, NASH is an increasingly common indication for liver transplantation. In the setting of cirrhosis from NASH, the risk of developing hepatocellular carcinoma (HCC) is between 2.4% over7 years, and 12.8% over 3 years, compared to 21% over 10 years for hepatitis C cirrhosis. Hepatocellular carcinoma has also been reported in NASH without cirrhosis, particularly in association with the Metabolic Syndrome." (1)

### Inflammation and fatty liver

"A low-grade chronic inflammation underlies all NAFLD entities/stages and can develop and promote the liver damage. Innate and adaptive immune pathways are activated in

obesity and many findings show that adipose tissue inflammation exacerbates hepatic steatosis and promotes non-alcoholic steatohepatitis (NASH). The adipose tissue has an important role in regulating energy utilization, vascular functions and immune system homeostasis. C-reactive protein (CRP), interleukin (IL)-6, fibrinogen and plasminogen activator inhibitor-1 levels are higher in obese patients compared to healthy subjects." (4)

Cytokines are considered crucial players in inflammatory-associated disorders throughout the body. The pro-inflammatory cytokines Interleukin (IL)-1 (a and b), IL-6 and tumor necrosis factor (TNF) a play a central role in many stages of liver diseases mediating fundamental aspects of those diseases including acute phase protein synthesis, lipid metabolism, cholestasis and degree of fibrosis. (2,3) The importance of TNF-alpha in human and animal fatty liver diseases, both due to genetic manipulation and overnutrition, has been demonstrated. (3) The balance between pro- and anti-inflammatory acting cytokines/adipocytokines appears to play a key role in hepatic and systemic insulin action, and they are supposed to have important functions in the development of NAFLD. (2)

"The role of IL-6 in non-alcoholic fatty liver disease (NAFLD) which is closely associated with obesity and insulin resistance remains controversial. IL-6 is a cytokine with pleiotropic functions and systemic levels are consistently increased in obesity, a state of low grade chronic inflammation. In overweight and obese subjects systemic IL-6, adipose-tissue released IL-6 and monocyte IL-6 synthesis are induced. Systemic concentrations of IL-6 are about 1 pg/ml in resting, healthy controls and are about 2 to 4 fold higher in obesity. The physiological function of IL-6 in metabolic liver disease is still not well understood. Whether its effects are good or evil seems to depend on the site and the time of production, and the metabolic context. (5)

**IBS and fatty liver**

"Non-alcoholic fatty liver disease (NAFLD) and irritable bowel syndrome (IBS) are two very common diseases in the general population. To date, there are no studies that highlight a direct link between NAFLD and IBS, but some recent reports have found an interesting correlation between obesity and IBS. A systematic PubMed database search was conducted highlighting that common mechanisms are involved in many of the local and systemic manifestations of NAFLD, leading to an increased cardiovascular risk, and IBS, leading to microbial dysbiosis, impaired intestinal barrier and altered intestinal motility. It is not known when considering local and systemic inflammation/immune system activation, which one has greater importance in NAFLD and IBS pathogenesis. Also, the nervous system is implicated. In fact, inflammation participates in the development of mood disorders, such as anxiety and depression, characteristics of obesity and consequently of NAFLD and, on the other hand, in intestinal hypersensitivity and dysmotility." (4)

Scalera et al believe that innate immunity is a main pathogenetic component of both NAFLD and IBS. The metabolic syndrome, which often anticipates or is detected in conjunction with NAFLD, leads to a state of chronic inflammation, systemic or local (hepatic), but to date it is still unclear which one of the two types has a greater impact on these patients, even if a lot of evidence favors the former. A very similar scenario, but with partly different participants, is possible in IBS. Although the disease has not been overtly related to an inflammatory systemic disease, as happens for the metabolic syndrome, nevertheless, IBS is characterized by hyper-activation of the immune system and general inflammation. (4)

## Diagnostic assessment of NAFLD

"A definitive diagnosis of NAFLD depends on three factors:

- evidence of fatty infiltration from either imaging (ultrasound, magnetic resonance imaging [MRI]) or histology (liver biopsy)
- exclusion of significant alcohol consumption
- exclusion of other causes of hepatic steatosis (eg. medications, surgery, metabolic disorders).

Confirming hepatic fatty infiltration using ultrasound is important. Specificity is high (95%), but the sensitivity of ultrasound for detecting fatty infiltration is lower (85%). Ultrasound is also useful to look for signs of cirrhosis, such as irregular liver edge, but has a sensitivity of only 43–74% (specificity is slightly higher at 54–89%). Signs of cirrhotic complications are also important, eg. signs of portal hypertension (splenomegaly, increased portal vein size, varices) or other complications such as HCC, portal vein thrombosis, or ascites.

The risk of fibrosis and progressive liver disease in NAFLD increases with severity of insulin resistance. In the absence of simple available clinical measurements of insulin resistance, the number of Metabolic Syndrome features present can be used to estimate risk of insulin resistance. The presence of three or more features of the syndrome, especially if these include central adiposity and type 2 diabetes, are predictive of the presence of NASH rather than simple steatosis. In addition, family history plays a role: an individual with a first degree relative with type 2 diabetes has a 90% chance of developing type 2 diabetes, and therefore NASH. Central adiposity can be assessed using waist circumference measured at the narrowest point mid-way between the lowest rib and the iliac crest at the end of expiration with the patient standing.

Staging liver disease and detecting cirrhosis is the most important aspect of assessing fatty liver disease. However, it is also difficult and error prone. The traditional gold standard in assessing liver disease is liver biopsy. However, biopsy has unfavourable costs, safety, availability, sampling error, inter-observer variability and patient acceptance." (1)

Increasing use of newer scan techniques such as Sheer Wave Elastography has made it possible to have clearer pictures of the level of fibrosis without intrusive testing, and is useful as a simple follow-up scan.

## Management of NAFLD

"The cornerstone to managing NAFLD is achieving weight control and reduction in cardiovascular risk factors such as smoking, diabetes, hypertension and dyslipidaemia. Dietary manipulation, such as the adoption of a Mediterranean- type diet, has shown promising results. The most important feature appears to be caloric reduction. Where diet and exercise are unsuccessful in achieving weight reduction, bariatric surgery may be considered. (1)

"It is not known when considering local and systemic inflammation/immune system activation, which one has greater importance in the cause of fatty liver and IBS. The nervous system is also implicated, while inflammation is involved in the development of mood disorders, such as anxiety and depression, characteristics of obesity and consequently of fatty liver and, on the other hand, in intestinal hypersensitivity and dysmotility." (4) Control of the IBS symptoms is extremely important, as eating food the body sees as a threat causes significant elevation of Interleukins 2,6,8 and 10, indicating that inflammation plays a significant role. (6)

Reference:

1. Iser,D.,Ryan,M. Fatty Liver Disease- A Practical Guide for GPs. Australian Family Physician Vol 42, No 6 June 2013
2. Tilg, H. The role of cytokines in non-alcoholic fatty liver disease. Dig Dis. 2010;28(1):179-85. doi: 10.1159/000282083. Epub 2010 May 7.
3. Niederreiter,L., Tilg,H.: Cytokines and Fatty Liver Disease. Liver Research 2 (2018). https://www.sciencedirect.com/science/article/pii/S254256841800017X

4. Antonella Scalera, Matteo Nicola Dario Di Minno, Giovanni Tarantino. What does irritable bowel syndrome share with non-alcoholic fatty liver disease? *World J Gastroenterol* 2013 September 7; 19(33): 5402-5420
5. Christa Buechler* and Sabrina Bauer. IL-6 in non-alcoholic fatty liver disease – good, evil or both? Endocrinol Metabol Syndrome 2011, 1:1
6. Patel,S., Singh,A., Misra,V., Misra,S., Dwivedi,M., Trivedi,P. Levels of interleukins 2, 6, 8, and 10 in patients with irritable bowel syndrome. Indian J Pathol Microbiol. 2017 Jul-Sep;60(3):385-389. doi: 10.4103/IJPM.IJPM_544_16.