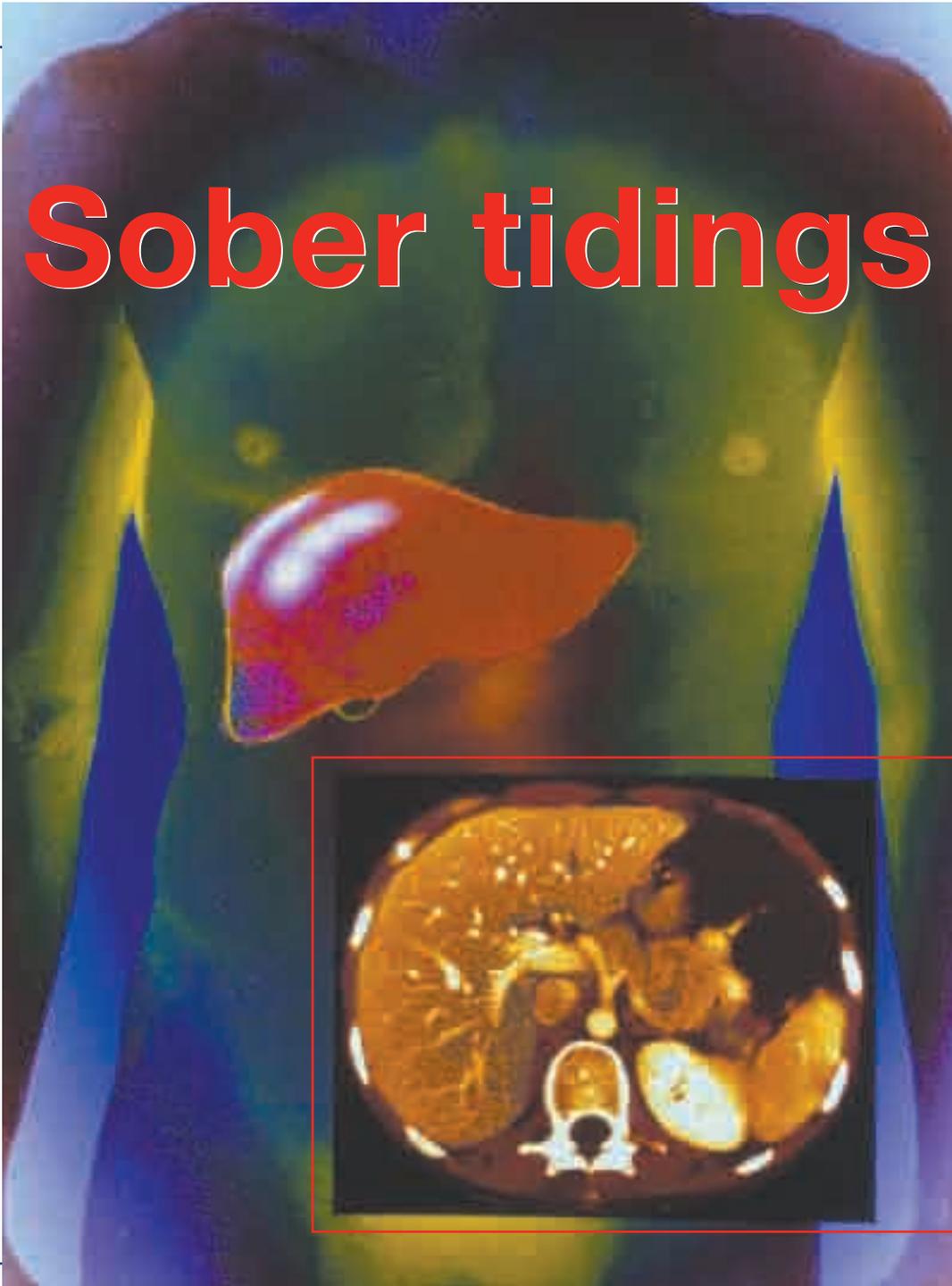




Sober tidings



IF YOU THOUGHT YOUR LIVER WAS VIRTUALLY INDESTRUCTIBLE, THINK AGAIN. **MATT JOHNSON** REPORTS THAT NON-ALCOHOLIC FATTY LIVER DISEASE IS FAST BECOMING A MAJOR CONCERN FOR PATIENTS AND DOCTORS ALIKE.

NAFLD: it's an acronym you can't pronounce and when you spell it out – non-alcoholic fatty liver disease – it doesn't contain a single positive word.

But if you're overweight you should know about it.

The discovery of the link between obesity, NAFLD and cirrhosis is not good news in the middle of an obesity epidemic, but it may provide individuals and their doctors with both the information and motivation they need to

change the way obesity and liver disease are assessed.

Nothing escapes your liver. Not the packet of chips you ate last week, or the bottle of coke you called breakfast the week before. It knows about the choc-chip muffin and coffee you had for morning tea, and it knows about the two aspirins you took last Sunday morning. Lying directly downstream from your intestines, anything absorbed by your gut is carried via your blood to the liver.

“It’s quite stunning, but improve the diet and other factors and liver function improves – and even the cellular changes can reverse: the fat goes away, the inflammation subsides and even the fibrosis can disappear”

– Associate Professor John Dixon

It’s your liver’s job to store what’s good and to detoxify what’s bad, and although you can damage an enormous proportion of your liver before you can no longer ignore the signs and symptoms, it’s not indestructible.

And given the way we’re consuming kilojoules these days, we’re damaging our most resilient organ at an astonishing rate.

It’s estimated up to a third of the adult population may have excessive fat accumulation in their livers – and it’s not just in the morbidly obese and unhealthy Western countries either. One study found the condition in 29% of ‘healthy’ Japanese adults.

Worryingly, NAFLD is present in 2.6% of children, but even that figure can rise to a staggering 53% if the group is obese.

While its effect on the liver is similar to alcoholic liver disease, NAFLD occurs in people who drink little or no alcohol. And aside from its link with obesity, it also has a strong association with diabetes.

The nature of the beast

NAFLD actually describes a spectrum of conditions from mild liver steatosis (fat) through to non-alcoholic steatohepatitis (NASH), where the liver becomes inflamed

and fibrous tissue starts to infiltrate the organ.

Too often, NASH progresses to cirrhosis, which can produce irreversible liver scarring, or lead to liver cancer. At this end of the spectrum, a liver transplant may be the only option – and it’s projected to be the most common transplant in the United States as soon as 2020.

What triggers the early stage of the disease to suddenly progress to NASH is still unknown, and research is hampered by the fact most patients with fatty liver disease feel well and experience few if any symptoms.

For clinicians such as Associate Professor John Dixon, Head of Clinical Studies at the Centre for Obesity Research and Education at Monash University, it’s frustrating that patients present to him in relatively advanced stages of the disease when it could have been identified much earlier.

“Prevention is the key in dealing with the obesity epidemic, but we’re not really doing well there, so we can confidently predict there will be an increase in fatty liver disease – and a proportion of these patients will progress to NASH and some will develop cirrhosis,” he says.

“It’s an almost entirely preventable disease with little more than lifestyle changes.”

Because fat accumulation in the liver is so common among overweight people, the challenges facing clinicians and researchers such as Professor Dixon is to not only identify those patients likely to have NAFLD, but also the biological markers that indicate which of those patients are likely to develop NASH.

And here is where pathology testing plays a role.

Liver function tests offer GPs an opportunity to identify the disease, but there is no definitive blood test for NAFLD.

“Raised ALT (alanine aminotransferase) levels would be the most common abnormality detected in the liver function tests of people with NAFLD,” explains Clinical Professor John Burnett, Head of the Department of Clinical Biochemistry at PathWest at the Royal Perth Hospital.

“But up to 80% of people with NAFLD can have no abnormality in their ALT levels so it’s not a reliable screen for the disease.”

Professor Burnett says ALT levels can even remain normal in the presence of advanced fibrosis and cirrhosis.

“ALT levels can also be raised in other forms of liver disease and although an AST (aspartate aminotransferase) to ALT ratio >1 is associated with NASH and advanced fibrosis, it is not sufficiently diagnostic on its own in an individual patient.”

As a result of the wide range of possible symptoms and the lack of a conclusive test, it’s becoming increasingly recommended that NAFLD be suspected in any overweight or obese person who is found to have even mild elevations in their liver tests during a routine blood testing.

“We need to reinforce that an abnormal result on a liver function test should trigger a clinical suspicion of NAFLD,” Professor Dixon explains.

“It doesn’t necessarily mean the patient has NAFLD, but it does indicate they are at risk – especially if they are also obese – and it should be a trigger to start treating them globally. When you see abnormal liver function don’t dismiss it.”

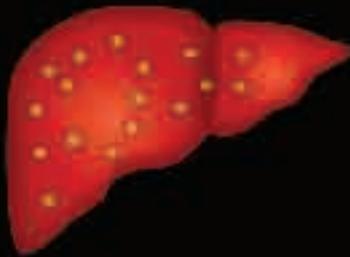
Predicting which patients could progress to NASH has improved in recent years, but it’s still not certain what triggers the exacerbation of the disease.

NAFLD: THE FACTS

- The most common liver disease in the world – it affects 10–24% of the world population
- Can affect any age range – already present in 10% of US children
- Strongly associated with polycystic ovaries and obstructive sleep apnoea

The Spectrum of NAFLD

Fatty Liver



NASH



Cirrhosis



ILLUSTRATION CREDIT: BRETT KITELEY

“There’s always been something of a chicken-and-egg argument: does the fat trigger the inflammatory response in the liver and cause the fibrous deposits, or does the inflammation increase the rate at which the liver accumulates fat?” Professor Dixon says.

“Certainly having a high level of visceral fat has an important role in either case, and 90% of obese people have a fatty liver, but not all of them will progress to NASH.

“Then there is a group who aren’t obese and they do develop NASH. The commonality is that all those who do develop NASH have metabolic syndrome.”

X marks the spot

Metabolic syndrome is a combination of conditions that have been identified to increase the risk of developing cardiovascular disease and diabetes. Professor Dixon was among the researchers who identified the link between metabolic syndrome and NASH.

The exact definition of metabolic syndrome varies slightly between health organisations, but can be summarised as high blood pressure, high blood sugar,

high blood fat and central (or abdominal) obesity. One of the central physiological causes of metabolic syndrome is the decreased sensitivity – or resistance – to insulin, the hormone that controls sugar and fat metabolism.

“As a predictor of NASH, insulin resistance measured by obtaining fasting plasma glucose and fasting insulin levels are very important,” Professor Dixon says.

“Combine that with hypertension, abnormal liver function tests and abdominal fat and we have to say these patients are at high risk.”

He admits it is somewhat frustrating that all the blood tests to determine a patient’s risk of having NAFLD are already relatively routine.

“We just have to interpret them in the right context.”

While existing liver function tests can identify the risk factors and liver dysfunction of NAFLD, a definitive diagnosis of NASH requires liver biopsy.

“The chemistry is very important as it gives you the risk of progressive disease. You can diagnose a fatty liver by ultrasound, CT or MRI, but it doesn’t tell you how much fibrosis and inflammation

1. Fatty liver

The first hit. Obesity or metabolic syndrome cause fat to accumulate in the liver cells. Although not normal, it probably doesn’t permanently damage the liver but it may sensitise it to a “second hit”.

2. NASH

About 10% of people with a fatty liver can develop the serious condition Non-alcoholic Steatohepatitis (NASH). One theory suggests a “second hit” from various inflammatory substances can trigger the onset of NASH in an already fatty liver.

3. Cirrhosis

In NASH, the inflammation causes the destruction of the liver cells and scar tissue to form in its place. The liver may no longer be able to function properly and severe scarring can lead to cirrhosis and liver cancer.



“Fat looks like you would expect fat to look – big white vacuoles – but that doesn’t provide a definitive diagnosis because you can get fatty changes in other conditions such as hepatitis C”

– Dr Adrienne Morey

is present, so a biopsy is essential to arrive at a precise diagnose of NASH.”

After collection under local anaesthetic, the thin sample of liver collected during a biopsy is assessed by pathologists such as Dr Adrienne Morey, Director of Anatomical Pathology at SydPath, at St Vincent’s Hospital in Sydney.

“It’s a narrow core of tissue about 20mm long and a couple of millimetres wide,” she says.

The sample is processed and cut into sections no thicker than three microns.

“We use a panel of stains to highlight the various changes we are looking for.”

The presence of fat cells, fibrosis and inflammation are assessed and graded by the pathologist.

“Fat looks like you would expect fat to look – big white vacuoles – but that doesn’t provide a definitive diagnosis because you can get fatty changes in other conditions such as hepatitis C,” Dr Morey says.

“We also routinely check for micro-organisms and other causes of liver disease because it’s better to optimise the tissue you have. You don’t want to have to go back and collect more tissue.”

The biopsy is usually accompanied by a detailed medical history of the patient to help the pathologist interpret the changes they find, but it remains a subjective skill.

“All of histology is very interpretative and labour intensive,” Dr Morey says.

“It involves multiple different pathologists from preparation to interpretation.”

And this is a situation that is unlikely to change, with no new chemical or molecular tests on the horizon.

“It’s old-time pathology, but without it a diagnosis can’t be made.”

Reversing the damage

While the pathophysiology and diagnosis of NAFLD is complex, the treatment is remarkably simple.

“The primary way of treating this disease is weight loss, exercise, diet and lifestyle,” says Professor Dixon, who points out that despite the seriousness of the condition, it responds well to even moderate weight loss.

“It’s quite stunning, but improve the diet and other factors and liver function improves – and even the cellular changes can reverse: the fat goes away, the inflammation subsides and even the fibrosis can disappear.”

If there is no improvement, the only other treatment to stop progression is weight loss surgery.

It’s an option that Ian Caterson, Boden Professor of Human Nutrition at the University of Sydney, sees as increasingly necessary.

“Ultimately we need to change the behaviour of the population at all levels: we need town planning that provides the opportunity for more activity, and education about better diet, but until then we need to manage the individual,” Professor Caterson says.

“Losing weight by diet and exercise will help patients, but some are genetically unable to get to the point they need or to stay there, so they require surgery to reduce their weight.

“That allows us to then try to control their weight with drugs without the side effects associated with trying to achieve significant weight loss just through medications.”

The failure of any drug to assist in substantial weight loss comes as no surprise to Professor Caterson.

“Drugs are unlikely to provide a magic bullet because there are just so many pathways that affect how we eat and how it is metabolised.”

Professor Dixon does, however, hold hope of an eventual breakthrough in weight-control drugs.

“The pharmaceutical companies have hundreds of prospective drugs in studies because the potential is enormous.”

NAFLD RISK FACTORS

- Obesity, especially abdominal fat
- Hypertension
- Metabolic syndrome
- Diabetes
- Hyperglycaemia
- Abdominal surgery

The breakthrough, he says, is likely to come in the form of drugs that affect the absorption of food through the gut.

“Small changes there can provide big results without the side effects,” he says, referring to the recent release of Byetta (exenatide), a drug that increases the production of insulin when blood sugar levels rise after a large meal, and slows the emptying of the stomach so the pancreas and liver do not become overloaded.

The drug was discovered by researchers looking at how a binge-eating lizard, the Mexican Gila monster, was able to survive between meals. Byetta has been approved by the Therapeutic Goods Administration but is not listed on the Pharmaceutical Benefits Schedule.

Until then, it’s a matter of educating the public to recognise the lifestyle factors that increase their risk, and educating doctors to suspect liver dysfunction.

“GPs play the central role in managing this condition,” says Professor Caterson. “Specialists tend to focus in their own area, but the GPs are in a position to recognise the whole risk profile, and start treating both the lifestyle factors while controlling the specific problems.” 🍷

GPs NOTE: This article is available for patients at <http://pathway.rcpa.edu.au>
