peer reviewed **ARTICLE OF INTEREST**

Is non-alcoholic fatty liver disease (NAFLD) seen at CT colonography an important extracolonic finding?

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Abstract

This paper describes visualisation of non-alcoholic fatty liver disease (NAFLD) at computer tomographic colonography (CTC). Definitions of NAFLD, NASH, metabolic syndrome, cryptogenic cirrhosis, and their importance in management of patients, are discussed. Images of normal liver, as well as NAFLD, seen at screening CTC, are presented and discussed in terms of their E-classification.

Keywords metabolic syndrome, hepatic steatosis, type 2 diabetes, insulin resistance, cryptogenic cirrhosis

Introduction

Screening computer tomographic colonography (CTC) allows visualisation of the colon as well as extracolonic structures.[1] The examination includes visualisation of the liver as an extracolonic organ, and provides unenhanced images of the liver and spleen. A reader can compare these two organs respective CT attenuation values (Hounsfield units).[2] CT can easily differentiate and quantify visceral and subcutaneous fat. It can also accurately quantify liver fat (steatosis),[3] which is the focus of this paper. It used to be considered a self-limiting and relatively benign condition, but is now recognised as a typical feature of non-alcoholic fatty liver disease (NAFLD) which may lead to non-alcoholic steatohepatitis (NASH), and even cirrhosis.[4] Figures 1a and b are examples of a normal liver and hepatic steatosis. NAFLD is an extracolonic finding (ECF) which needs to be reported in terms of the E-classification.[1,5] The reasons for this are discussed further in this paper.

The incidence of NAFLD has risen considerably over the last few years. Its incidence has been linked to the rapid rise in the prevalence of obesity.[6] It is the most common disease affecting the liver in the United States, and is the leading cause of abnormal liver functions.[7] The worldwide prevalence varies considerably between 20% and 31% in the general population, and up to 70% in patients with type 2 diabetes mellitus.[8,9] It has a strong association with insulin resistance (IR) and hyperglycemia and is thus closely linked to type 2 diabetes.[10] It begins initially with the intracellular accumulation of triglycerides resulting in a condition known as hepatic steatosis.[11] The latter occurs when the fat content exceeds 5% of liver volume and is the first recognisable stage of NAFLD.[10] At this stage a patient is asymptomatic.

At cross-sectional imaging studies, NAFLD in asymptomatic patients is frequently seen as an incidental finding.[2] Within a CTC context this would be an ECF. Literature however shows an interrelated common fat thread between metabolic syndrome, hepatic steatosis, visceral fat, NAFLD, and cardiovascular disease (CVD).[3]

Hepatitis C virus (HCV) is also a common cause of chronic liver disease in North America.[12] It too leads to hepatic steatosis, which is present in ~50% of subjects with HCV. Hepatic steatosis, in most subjects, is related to the metabolic syndrome, often accompanied by NAFLD.

Important acronyms, abbreviations, and terms, used in the literature and this paper, are presented in Table 1.

Importance of reporting NAFLD seen at CTC: E-classification

CTC patients, who are teetotallers or moderate drinkers, should be made aware of the potential risks associated with fatty liver seen at CTC. Zalis et al[5] recommended reporting extracolonic findings (ECFs) in terms of their clinical importance, namely

- low importance: low clinical importance thus no immediate impact on patient management (E2)
- moderate importance: usually benign but may require further work-up (E3)
- significant importance/medically important (E4)

Table 2 shows E1 to E4 classification. Until recently fatty liver was considered a common finding without a potential risk.[4] It is now considered to be of clinical importance. Professor D Kim (personal communication, June 2017) stated that

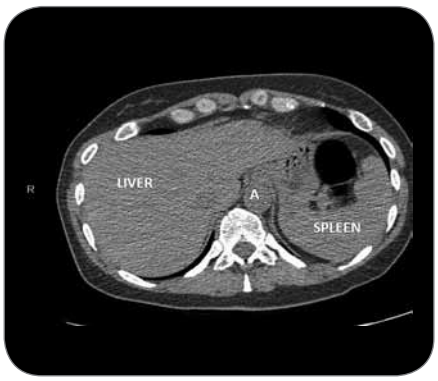

Figure 1a. 2D axial view showing equal density between the liver and the spleen (normal liver HU is 65, spleen HU 55 to 65) [E1]. A = aorta.

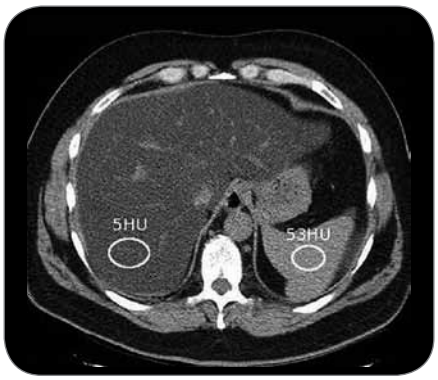

Figure 1b. 2D axial view showing hepatic steatosis in keeping with severe fatty infiltration as liver attenuation is 5 Hounsfield units (HU) whereas the spleen reading is 53HU [E3] *(image courtesy of Prof P Pickhardt, Wisconsin University).*

some radiologists may classify it as E2 (low clinical importance), and others as E3 (moderate clinical importance).

NAFLD and non-alcoholic steatohepatitis (NASH)

NAFLD is the most common cause of chronic liver disease in the general population. It occurs when >5% of hepatocytes are infiltrated by triglycerides in the absence of an alcohol history, as well as without any other causes of liver disease. It is a slowly progressive disease ranging from simple steatosis to inflammation with hepatocyte ballooning and necrosis to variable degrees of fibrosis, ultimately leading to cirrhosis and an increased risk of hepatocellular carcinoma.[13]

Table 1. Important acronyms, abbreviations and terms

NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
IR	insulin resistance
CVD	cardiovascular disease
Metabolic syndrome	risk factor that arises from IR together with abnormal adipose deposition and function
Steatosis	build-up of fats within the liver
Hepatic steatosis	fat content exceeds 5% of liver volume
ALT	alanine aminotransferase
AST	aspartate aminotransferase
GGT	gamma-glutamyltransferase
CC	cryptogenic cirrhosis:end stage of a chronic liver
ECF	extracolonic finding

NASH (non-alcoholic steatohepatitis) is the more advanced form of the disease. It is the combination of fat in the liver associated with inflammatory changes, which in turn cause a higher risk of cardiovascular disease (CVD) and mortality.[14] This is the next stage of NAFLD. It develops when hepatic inflammation occurs, and is defined as the presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis.[8] Its prevalence in the general population is estimated at 3-5%. Patients with NASH are at a much higher risk of developing significant and progressive liver fibrosis, cirrhosis, and hepatocellular carcinoma.[15]

The prevalence of NAFLD is linked to insulin resistance (IR), and is closely associated with the rising incidence of obesity and type 2 diabetes. Up to 95% of obese patients, and 75% of diabetics, are likely to have NAFLD.[16] It is a marker of pathologic ectopic fat accumulation combined with a low-grade inflammatory state.[17]

Metabolic syndrome

A combination of signs and symptoms to-

Table 2. E classification

E1	*Not of clinical importance* Normal examination or anatomic variant	No extracolonic abnormalities visible Anatomic variant, e.g. retroaortic left renal vein
E2	*Low clinical importance* Clinically unimportant findings	No work-up indicated, e.g. • Liver, kidney: simple cysts • Non-obstructing renal stones • Non-obstructing gall stones • Gallbladder: cholelithiasis without cholecystitis • Vertebra: haemangioma • Arterial calcification • Calcified granuloma • Uncomplicated hernias (inguinal, hiatal, femoral, enterocoele) • Various skeletal abnormalities • Adrenal adenomas • Renal calculi • Lipoma • Uterine fibroids
E3	*Moderate clinical importance* Likely unimportant finding and likely to be benign. Incompletely characterized NB (nota bene/note well): In nearly all cases of asymptomatic patients, these lesions prove to be benign	Further work-up may be indicated • Kidney: minimally complex or homogeneously hyper-attenuating cyst • Complicated renal cysts • Prominent adnexal lesions in women • Indeterminate pulmonary nodules • Indeterminate liver lesions • NAFLD (non-alcoholic fatty liver disease) • Pleural effusions • Cardiomegaly • Splenomegaly • Complicated hiatus hernia
E4	*High clinical importance* Potentially important finding. Communicate to referring physician as per accepted practice guidelines NB: Appendicitis, diverticulitis, pancreatitis, irreducible inguinal hernia, pneumothorax, pneumoperitoneum must be communicated to the referring physician/health practitioner	• Kidney: solid renal mass • Liver masses • Lymphadenopathy ≥ 10 mm • Vasculature: aortic aneurysms > 50 mm • Lung: non-uniformly calcified pulmonary nodule ≥ 10mm • Irreducible inguinal hernia containing large bowel

It must be remembered that an extracolonic evaluation is limited by lack of iv contrast and the low-dose CT technique. Adapted from Zalis et al.[5]

Table 3. Metabolic syndrome features

- Waist circumference: >102 cm (40.2 inch) in men or >88 cm (34.6 inch) in women
- Triglyceride level 150 mgm/dL (8.2 mmol/L) or greater
- High density lipoprotein (HDL): <40 mgm/dL (1.036 mmol/L) in men or <50 mgm/dL (1.295 mmol/L) in women
- Blood pressure: systolic 130 mm Hg or greater or diastolic 85 mm Hg or greater
- Fasting blood sugar level 110 mgm/dL (6.1 mmol/L) or greater

Table 4. Amount of beer, spirits and wine in terms of same alcohol content**

TYPE OF DRINK	AMOUNT
Beer (about 5% alcohol)	12 oz (340 mL)
Table wine (about 7% alcohol)	5 oz (147 mL)
Distilled spirits (about 40% alcohol); e.g. a shot of whisky, brandy, etc.	1.5 oz (44 mL)

**Adapted from[24,25]

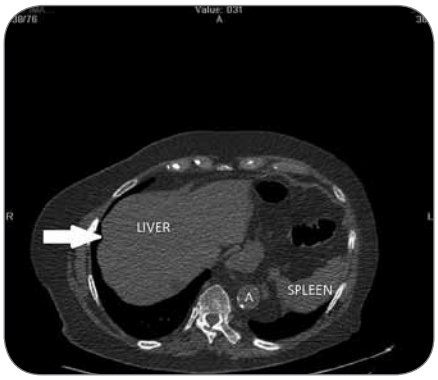

Figure 2. 2D axial view shows cirrhosis of liver [E3]. White arrow shows lobular margin of liver. A = aorta showing calcification.

gether represent a syndrome. Metabolic syndrome is a risk factor that arises from insulin resistance (IR) together with abnormal adipose deposition and function. It increases risk of heart disease, stroke and diabetes.[18] The ATP III (American Treatment Panel) clinical definition of metabolic syndrome[8] requires three or more of the features in Table 3. Patients with this syndrome are four times more likely to have NAFLD than those who do not have the disease. Thirty percent (30%) of those with NAFLD have this syndrome.[9] Those who have it have an approximate doubling of cardiovascular (CV) mortality risk.[19] Patients with NAFLD have also been shown to be at increased risk of cardiovascular disease (CVD), showing that NAFLD per se also contributes to accelerated atherogenesis.[14]

Clinical outcomes of metabolic syndrome

CVD[20] is the primary clinical outcome of this syndrome. Most people with the syndrome have IR. This in turn results in an increased risk of type 2 diabetes. When a patient is diabetic, CVD risk rises sharply. In addition to CVD and type 2 diabetes, patients with the syndrome are susceptible to the following:

- Polycystic ovary syndrome in women
- Fatty liver
- Cholesterol gallstones
- Asthma
- Sleep disturbance

In addition to the ATP III guidelines in Table 3, other organisations include different and additional criteria. The World Health Organisation[21] includes: (i) IR which is required for diagnosis, (ii) risk factors from high blood pressure, and (iii) raised triglycerides, low HDL, increased body mass index (BMI), and microalbuminuria. The WHO underscore that early management of patients may have a significant impact on prevention of both diabetes and cardiovascular disease (CVD). The syndrome can be present for up to 10 years before detection of glycaemic disorders.

Cryptogenic cirrhosis

Cryptogenic cirrhosis (CC) is the end stage of a chronic liver disease in which the cause remains unknown.[22] It has a 5% prevalence rate. Common causes of cirrhosis of the liver include: hepatitis A, B and C; autoimmune hepatitis; toxin exposure; vascular and biliary diseases; and chronic alcohol abuse. However, in recent years the presence of NAFLD/NASH and its progression to fibrosis and cirrhosis has been added as a cause. Metabolic causes (e.g. metabolic syndrome, NAFLD and NASH, type 2 diabetes, and obesity) have also become important. They have been increasingly identified with cryptogenic cirrhosis (CC) compared with other causes.[23] Figure 2 shows cirrhosis of the liver.

NAFLD in terms of alcohol consumption

NAFLD should only be diagnosed in people who consume no alcohol or only modest amounts of alcohol. A history of alcoholism or alcohol abuse refers to a weekly intake of >21 drinks for males , and >14 drinks for females.[11] For the average person, without health problems, modest drinking will cause no harm. If however there are health problems present, alcohol may aggravate these, even in small amounts. It is thus important to define what is meant by a 'standard drink'. It is 14 grams of pure alcohol. Beer contains about 5% alcohol, but this may vary and reach up to 10%. One standard drink of beer is 12oz (340mL). On average there is about 7% alcohol in table wine, but may exceed 17%: a standard drink is 5oz (147mL) and there are five standard drinks in a 25 oz (735mL) bottle. A standard drink of 80-proof spirits (40% alcohol) is 1.5oz (44mL).[24] The bottom line is that one 12 oz (340mL) beer has as much alcohol as 1.5oz (44mL) shot of whisky or 5oz (147mL) glass of wine (see Table 4).[25]

Diagnosis of NAFLD

The diagnosis of NAFLD is made by imaging studies, as well as biochemical testing, and finally by liver biopsy, which is regarded as the 'gold standard'. The latter is however not commonly performed because of its invasive nature with a risk of bleeding and tearing of the liver parenchyma. Of the imaging studies, ultrasound (US), is the commonest screening test. It is cheap and non-invasive. Its disadvantages are being operator dependent, and results are variable. Ultrasound can only detect steatosis when >30% of the liver is affected. Figures 3a and b are examples of a normal liver and a fatty liver US scans. It is however recommended as the first-line investigation to confirm the presence of a fatty liver.[26]

CT scanning is frequently employed in gastroenterology practice for a variety of symptoms and signs. Diagnosis of NAFLD is easily made on CT screening, and screening CTC examinations, by noticing fat within the liver parenchyma. The liver density is 'darker' than normal, and its overall density is less than the spleen (Figures 4a to f).

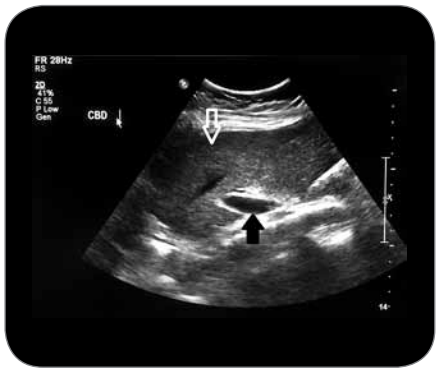

Figure 3a. Normal liver (white arrow) ultrasound scan showing common bile duct (black arrow).

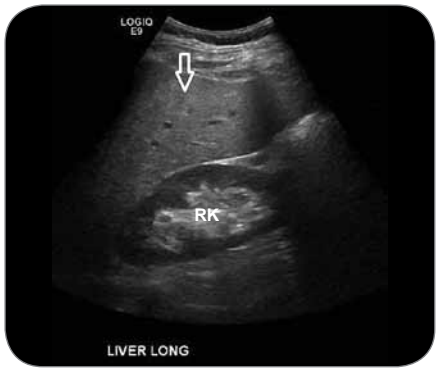

Figure 3b. Bright echo pattern (open white arrow) in keeping with fatty infiltration of the liver. RK = right kidney. *(courtesy of Prof P Pickhardt, Wisconsin University).*

At CT and CTC, measurement of the HU reading of the liver is an accurate method and highly specific for assessing fatty liver infiltration. The HU reading of a healthy liver is between 60-65. Once fatty infiltration occurs the liver becomes 'darker' on the scan and the HU value drops to approximately 45. It is this infiltration that increases in extent when the HU value drops from 45 and often reaches 20-30 HU or less. This indicates moderate-to-severe hepatic steatosis: at least 30% of the liver has been replaced by fat. Pickhart et el[27] proved in their study that the use of unenhanced liver CT attenuation measurements were accurate and precise for quantification of steatosis. An attenuation value of 45 or less was 100% specific for the biopsy proven moderate-to-severe steatosis.[11]

Measuring attenuation values: liver and spleen

When measuring the HU of the liver to assess for fatty filtration, it is useful to also compare the ROI (region of interest) of the spleen. Normal reading of the spleen is usually between 55 to 65, which is very similar to a normal liver reading. With fatty infiltration of the liver, the HU decreases but the splenic HU remains the same (Figures 5 a to c).

Using the ROI tool a HU reading is obtained of the right lobe of the liver, which is far lower than the splenic HU reading. HU reading of 45 or less is diagnostic of fatty liver infiltration of the liver. The lower the reading, the more severe the fatty infiltration. MR spectroscopy (MRS) has excellent sensitivity in detecting and accurately quantifying hepatic steatosis. Inflammation and or NASH can be detected by CT or MRS. Biochemical testing has drawbacks. Up to 70% of NAFLD patients may have normal liver enzymes.[28]

Serum liver enzyme tests

ALT (alanine aminotransferase) and AST (aspartate aminotransferase) are the two performed tests for liver enzymes to assess fatty infiltration. In the early stages of NAFLD, only mildly abnormal liver enzymes are the clue pointing to the disease. ALT is the best single test to correlate with hepatic steatosis. It can however not distinguish between varying stages of NASH. It can be normal in chronic liver disease.[29,30]

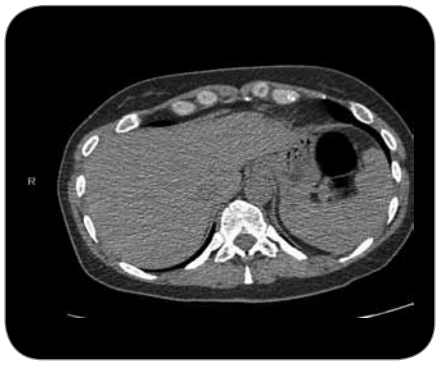

Figure 4a. 2D axial view showing equal density between the liver and the spleen (normal liver HU is 65, spleen HU 55 to 65) [E1].

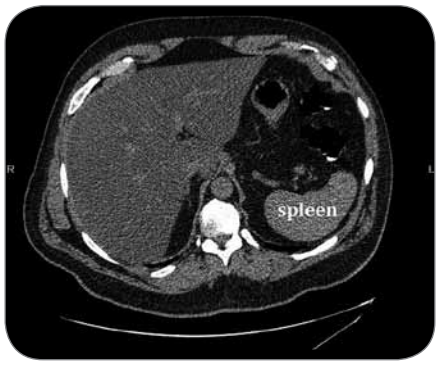

Figure 4b. 2D axial view shows liver is darker then the spleen [E3].

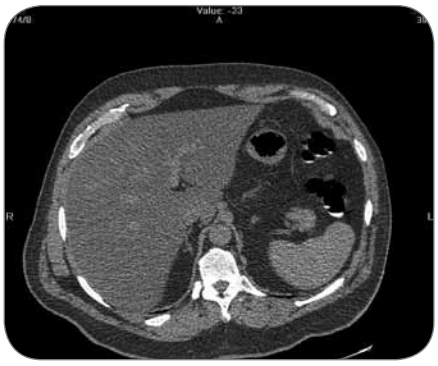

Figure 4c. 2D axial view shows liver is darker than the spleen [E3].

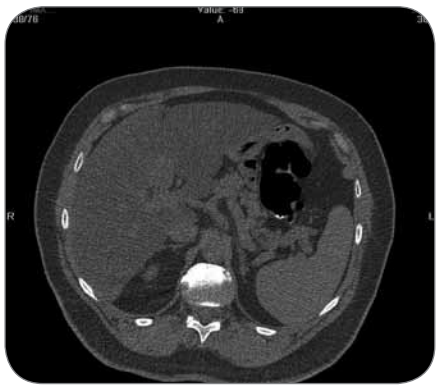

Figure 4d. 2D axial view shows liver darker than spleen [E3].

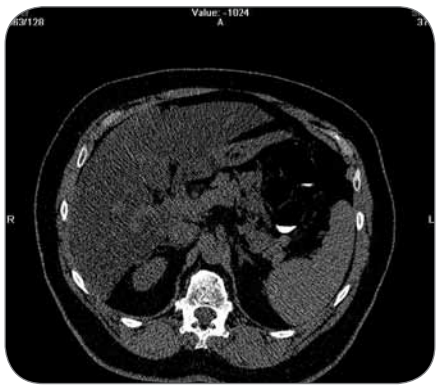

Figure 4e. 2D axial view of the patient in Figure 4d using liver setting [E3].

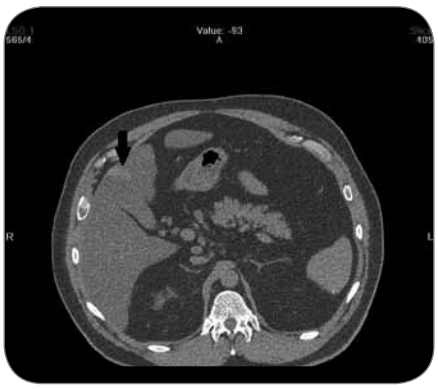

Figure 4f. 2D axial view showing NAFDL with focal liver sparing (black arrow) [E3].

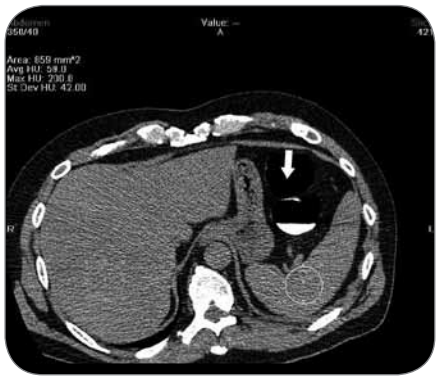

Figure 5a. ROI reading HU 57 for both the liver and the spleen [E1].

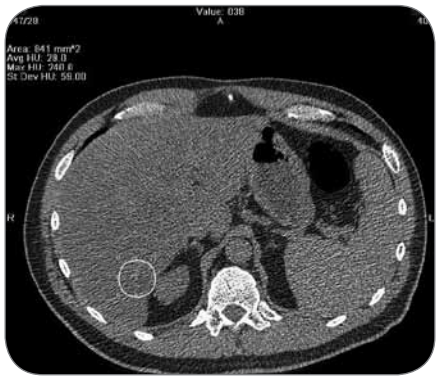

Figure 5b. ROI reading of liver is 38HU [E3].

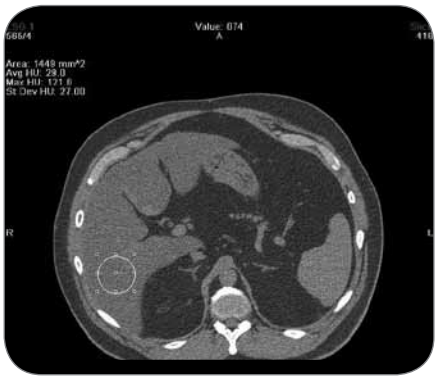

Figure 5c. ROI reading of liver of the patient in Figure 4f is 29HU [E3].

When AST levels are elevated, this is more in favour of an alcohol aetiology

Gamma-glutamyl transferase (GGT) is a blood test, which is also used to determine if there is disease in the liver or bile-ducts. It is usually performed in conjunction with other tests (e.g. AST, ALT and bilirubin). An elevated GGT level suggests there is damage to the liver from a variety of conditions: cardiovascular disease, hypertension, or certain types of drugs, for example. It is especially useful when alcohol may be a factor in liver disease causes as it is usually elevated. It is elevated in 75% of patients who are chronic drinkers. It can be used to monitor patients who are in rehabilitation. There is a significant association between increased GGT and cardiovascular (CV) mortality in a 12 year follow-up period.[31]

How to distinguish NAFLD from alcoholic liver disease

In NAFLD the usual biochemical pattern is that of an increased level of transaminases. Up to 3% of the general population may have elevated ALT.[32] ALT levels are higher than that of AST. When alcohol is the cause of fatty infiltration of the liver, the AST rises higher than ALT, resulting in a ratio of AST: ALT >1.5. Alcohol may also increase the HDL cholesterol as well as the triglycerides.

Main points of NAFLD diagnosis and patient management

NAFLD is now considered a potential risk which could require patient management. As evident in Table 5 there are three recommendations for management of NAFLD.

Who should inform patients with NAFLD of its potential risks?

Studies on patients' perceptions and experiences of CTC examinations underscore the need to provide them with feedback.[33,34] Plumb et al[33] recommend, in their comparative study of patients' experiences of CTC and colonoscopy, that patients should be informed of their CTC results, and whether additional tests may be needed. The author personally informs patients with NAFLD seen at screening CTC of its potential risks so that they can then discuss future management with their physicians.

Key points

- 70% of patients with NAFLD may have normal liver enzymes
- Ultrasound (US) can only detect steatosis when >30% of the liver is affected
- Liver attenuation in steatosis is always lower than the HU of spleen
- Magnetic resonance spectroscopy (MRS) has excellent sensitivity in both detecting and accurately quantifying hepatic steatosis
- Liver biopsy remains the gold standard for diagnosing NAFLD, staging the degree of NASH and assessing histological fibrosis
- Increased incidence of adverse CV events in patients with NAFLD compared to the general population
- NAFLD is characterised by an atherogenic lipid profile, namely
  - High triglyceride (TG) levels
  - Low high-density lipoprotein (HDL) levels
  - An increased level of low density lipoprotein (LDL)
  - Increased very low-density lipoprotein (VLDL) particles
  - Increase levels of lipoprotein B100 concentration
- NAFLD diagnosis includes elevated serum liver enzymes (ALT, AST, GGT)
- Cryptogenic cirrhosis is the end stage of a chronic liver disease

Table 5. NAFLD*

Diagnosis NB: No or minimal alcohol intake, no viral hepatitis, etc.	Elevated liver enzymes: AST, ALT, GGT Imaging study (e.g. US, CT) with evidence of fatty content
Management	There is no established pharmacological treatment for NAFLD. The following are recommended: (i) Increasing exercise (ii) Reducing dietary fat intake (iii) Weight loss

*Adapted from Mercado-Irizarry A, Torres EA.[22]

Conclusion

In recent years the presence of NAFLD in asymptomatic individuals has increased significantly, especially in those who have the metabolic syndrome, are obese or have type 2 diabetes. While most will remain asymptomatic in the presence of NAFLD, a small percentage will progress to non-alcoholic steatohepatitis, and, with inflammatory and necrotic changes will then progress to cirrhosis, and finally hepatocellular carcinoma.

The diagnosis of NAFLD at CTC is easily made on unenhanced abdominal CT scans. The ROI (region of interest) tool is placed over the right lobe of the liver to

measure the HU readings. The liver normally has a HU value of approximately 60. NAFLD is diagnosed when the value drops below 45HU; lower readings mean more fatty infiltration in the liver. NAFLD liver is an extracolonic finding of moderate clinical importance (E3), but some radiologists classify it as E2 (low clinical importance).

Competing interests

The author has no financial or personal relationships which may have inappropriately influenced him in writing this article.

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