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Obesity and liver disease

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Abstract: Non-alcoholic steatohepatitis (NASH) is a disease of emerging identity and importance. It is frequently associated with obesity, especially visceral fat, and is intimately related to fatty liver and markers of the insulin resistance syndrome. Both the prevalence and the severity of liver steatosis are related to body mass index, waist circumference, hyperinsulinaemia, hypertriglyceridaemia and impaired glucose tolerance or type 2 diabetes. The identification of obese patients who may progress from steatosis to NASH and from NASH to fibrosis/cirrhosis is an important clinical challenge. Substantial weight loss is accompanied by a marked attenuation of insulin resistance and related metabolic syndrome and, concomitantly, by a remarkable regression of liver steatosis in most patients, although increased inflammation may be detected in some subjects. Thus, NASH may be considered as another disease of affluence, as is the insulin resistance syndrome, and perhaps being part of it, especially in obese patients.

Key words: insulin resistance; liver; NASH; obesity; type 2 diabetes; weight loss.

Although non-alcoholic fatty liver disease (NAFLD) was considered relatively uncommon until recently[1], over the past 3 years there has been an explosion of studies on various aspects of this disease and NAFLD has come a long way in a relatively short space of time.[2] By strict definition, NAFLD is a liver disease defined by both clinical (non-alcoholic) and histopathological characteristics.[3] The spectrum of this disease is broad - from steatosis and non-alcoholic steatohepatitis (NASH) through to cirrhosis and liver failure.[1-6] The term NASH was coined in 1980 to describe 'the pathological and clinical features of nonalcoholic disease of the liver associated with the pathological features most commonly seen in alcoholic liver disease itself'.[7] The role of obesity appears to be crucial so that NASH is now considered as 'another disease of affluence'.[8] Thus, with the epidemic of overweight and obesity[9], the clinician is increasingly confronted with the problems and dilemnas associated with NAFLD and NASH.[1-6] Perhaps of most concern is the recent observation that NAFLD and NASH could also be observed in children and adolescents[10,11], a population in which the prevalence of obesity is growing very fast.[9]

The present review aims at discussing the role of obesity and metabolic abnormalities associated with insulin resistance, especially diabetes mellitus and dyslipidaemias, in the development of NAFLD in general, and NASH in particular. Possible regression of liver abnormalities after weight loss and treatment targeted at insulin resistance will also be considered.

DIAGNOSIS

Most patients with NAFLD are asymptomatic, and patients are typically found incidentally to have abnormal liver function tests or hepatomegaly when being evaluated for another condition.[1,3,5,6]

The most common abnormality in liver function tests is a two-to threefold elevation in the alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. The AST/ALT ratio is usually < 1, which can help distinguish NAFLD from alcoholic-related liverdisease. When it is > 1 in NAFLD, it suggests an advanced fibrotic stage of disease. In a recent large survey on 12 808 men, ALT-dominant liver disorders were related to obesity, lack of physical exercise, and hyperlipidaemia, whereas AST-dominant liver disorders were related to alcohol consumption and diabetes mellitus.[12]

Analysis of liver biopsy specimens is the cornerstone of diagnosis: hepatic morphological findings range from mild fatty degeneration and inflammation to cell degeneration, fibrosis and cirrhosis with or without the presence of Mallory hyaline bodies. The principal aim of biopsy investigation is to identify patients who can progress to cirrhosis as they will require monitoring and possible treatment. Fortunately, several clinical and laboratory features could predict the presence of NASH and/or fibrosis.[13-16] According to Day[2], liver biopsy should be restricted to patients with some, if not all, of the following: (a) ALT greater than twice normal; (b) AST > ALT; (c) at least moderate 'central' obesity; (d) impaired glucose tolerance or type 2 diabetes; (e) hypertension; and (f) hypertriglyceridaemia. A standardized scoring system, as recently described[3], should lead to more consistency in

the reporting of histological features.[2]

AETIOPATHOGENESIS OF NASH

As recently reviewed[17], the aetiopathogenesis of NASH appears multifactorial. In 1998, the 'two hit' hypothesis was proposed whereby the first 'hit', i.e. steatosis, sensitizes the liver to a variety of second 'hits' which lead to necroinflammation and fibrosis.[18] With regard to the first hit, insulin resistance and increased free fatty acid (FFA) supply to the liver seem to play a major role. In most subjects, it is related to obesity and abdominal fat distribution, various features of the metabolic syndrome, and sometimes overt type 2 diabetes mellitus (see below). The principal candidates for the second hit are abnormal cytokine production and oxidative stress.

Role of free fatty acids and insulin resistance

Increased influx of FFA to the liver combined with potential alterations in their hepatic metabolism (including increased triglyceride synthesis, decreased triglyceride export, or decreased fatty acid oxidation) may result in hepatic steatosis.[19] Any defect of this multistep process results in an accumulation of triglycerides within the hepatocyte. Whether this process is responsible for the subsequent inflammatory cell infiltration characteristic of NASH or whether an inflammatory response in the liver evoked by some other stimulus causes sufficient hepatocyte dysfunction to result in steatosis has not been established yet.[20]

Insulin resistance and hyperinsulinaemia are common features in obesity.[21] Insulin plays a key role in the regulation of regional FFA metabolism and can inhibit hepatic mitochondrial beta-oxidation of FFA.[22] Visceral fat mass is a predictor not only of steatosis but also of hyperinsulinaemia and insulin resistance.[23] Visceral lipolysis is resistant to insulin suppression and is the source of liver fatty acids in insulin resistance and hyperinsulinaemic states such as a liver disease.[22] Furthermore, fatty liver may influence insulin clearance and insulin resistance, which can initiate a vicious circle.[24] Thus, the conjunction of high FFA and insulin resistance, both directly related to increased (visceral) fat mass, is crucial for the development of liver steatosis.

The role of cytokines, leptin and TNF-α

It has been recently suggested that the high circulating leptin levels associated with obesity may contribute to hepatic steatosis.[25] Recent data suggested that serum leptin levels were significantly higher in patients with NASH[26], and this elevation was out of proportion to BMI.[27] These observations led to the hypothesis that elevated serum leptin levels may promote hepatic steatosis and steatohepatitis. However, the precise role of leptin remains to be elucidated as animal studies suggested that a physiological role of hyperleptinaemia resulting from caloric excess may be to protect non-adipocyte cells (including hepatocytes) from steatosis and lipotoxicity.[28] Finally, given the similar intracellular signalling pathways stimulated by leptin and several inflammatory cytokines[25], leptin could also be involved in the progression from hepatic steatosis to steatohepatitis, and possibly fibrosis.[29]

Cytokines, especially tumour necrosis factor-alpha (TNF-α), have also been incriminated in the pathogenesis of NASH (reviewed in refs 17 and 30). As TNF-α is overexpressed in the adipose tissue of obese subjects and in overweight patients with type 2 diabetes, resulting in higher circulating TNF-α levels[31], its role should be further investigated in the pathogenesis of NASH associated with obesity and/or diabetes. In favour of this hypothesis, a recent study suggested that TNF-α polymorphisms could represent a susceptibility genotype for insulin resistance, NAFLD and NASH.[32]

The intriguing possibility that NASH could also arise because of gut-derived endotoxins (or other bacterial toxins) in obese individuals (even in the absence of previous jejuno-ileal bypass) has been recently reviewed.[17] It has been proposed that bacterial overgrowth of the small intestine could contribute to raised TNF-α in patients with NASH, particularly those with diabetes.[33] Finally, such bacterial overgrowth may also increase endogenous ethanol production. A recent study demonstrated a positive correlation between breath ethanol concentration and BMI, an observation which may have potential implications for the pathogenesis of NASH in obese subjects.[34]

The role of oxidative stress and iron accumulation

Oxidative stress may play a prominent role in NASH. An increase in the production of mitochondrial reactive oxygen species seems likely to be a response to an increased hepatic supply of FFA, resulting in a compensatory increase in the rate of mitochondrial beta oxidation.[35] Lipid peroxidation products alter mitochondrial DNA and also react with mitochondrial proteins to inhibit the transfer of electrons along the respiratory chain, further

increasing the production of reactive oxygen species and resulting in a self-perpetuating cycle of oxidative stress and lipid peroxidation.[36] Other potential sources of oxidative stress that have been suggested to play a role in NASH include the cytochrome P450 enzymes CYP2E1 and CYP3A4 and an increase in liver iron.[17]

Recent observations showed that elevated serum ferritin and iron levels are common findings in patients with NASH and insulin resistance, even in the absence of haemochromatosis.[37,38] One study reported that increased hepatic iron had the greatest association with the severity of fibrosis.[39] Hyperferritinaemic individuals with insulin-resistance-associated hepatic iron overload can have symptom relief after venesection.[40] In 17 patients with moderate obesity, impaired glucose tolerance and clinical evidence of NAFLD, iron depletion by phlebotomy was associated with significant reduction of fasting and stimulated insulin levels (in agreement with a reduction of insulin resistance) and, concomitantly, a near-normalization of serum ALT activity, suggesting a key role of iron and hyperinsulinaemia in the pathogenesis of NAFLD.[41]

THE ASSOCIATION OF NASH WITH OBESITY

Fat people have fat liver. Obesity is the condition most often associated with NAFLD. In most studies, 69-100% of patients with NASH were also obese (reviewed in ref. 1). Steatosis is a common observation in obesity and may be associated with inflammatory signs of non-specific hepatitis. The observation that some obese individuals presented a liver disease histologically indistinguishable from alcoholic liver disease itself had long been recognized.[42-49] Interestingly, it has been recently demonstrated that obesity also increases the risk of liver disease induced by either alcohol[50] or chronic hepatitis C.[51-53]

In a literature survey of 41 original articles comprising information on liver morphology in 1515 morbidly obese patients, liver biopsy was considered as normal in only 12% of the cases.[54] The most frequent abnormality reported was fatty changes present in 80% of the biopsies; portal inflammation was also common (33%) while portal or periportal fibrosis was observed in 29%. Cirrhosis, however, involved only 3% of the biopsies. As recently reviewed[55], these findings were confirmed in further studies.[44,56,57] In an autopsy study, steatohepatitis was found in 18.5% of markedly obese patients in contrast to only 2.7% of lean patients, while severe fibrosis was found in 13.8% versus 6.6% respectively.[58]

Large series of liver biposies performed in severely obese subjects submitted to bariatric surgery have been recently published. In 551 liver biopsies, steatosis was found in 86%, fibrosis in 74%, mild inflammation or steatohepatitis in 24%, and unexpected cirrhosis in 2% of the patients.[59] In a large personal series of 528 severely obese subjects (BMI 42.6 $\pm$ 6.8 kg/m^2), 74% of the biopsies showed fatty deposition, estimated as mild in 41% of cases, moderate in 32% and severe in 27%.[60] The severity of steatosis was positively associated with BMI ($P = 0.002$), but not with the known duration of obesity.[55] Ten percent of these patients had signs of steatohepatitis, inflammatory changes being scored as mild in 86%, moderate in 12% and severe in 2% of cases. A recent study in 105 unselected consecutive, severely obese patients undergoing laparoscopic obesity surgery reported a 71% incidence of steatosis and 25% incidence of NASH (42% of patients with NASH had advanced fibrosis).[16]

The role of BMI and fat distribution on liver abnormalities has been considered in several studies. In a series of 144 patients with NASH, BMI was the only independent predictor of the degree of fat infiltration ($P = 0.003$)[13] and histological examination in 33 potential living liver donors showed that BMI is a strong predictor of hepatic steatosis.[61] However, it has been shown that the abdominal distribution of fat is a predictor of hepatic steatosis, which is independent of body weight and body fat.[62] In a study on 221 biopsy-proven chronic hepatitis C patients, visceral fat distribution rather than BMI proved to be associated with steatosis ($P < 0.001$).[53] In type 2 diabetic men, liver fat score was highly correlated to visceral/total adipose tissue ratio, insulin resistance and serum triglycerides levels.[63] In a series of 48 consecutive patients referred to their gastroenterology unit for NAFLD confirmed by biopsy, most subjects (81%) were overweight or obese and had an increased waist circumference, which closely relates to visceral fat and insulin resistance.[64] In a recent paediatric study on 375 obese children and adolescents, liver steatosis was present in 33% to 47% of the subjects according to the Tanner pubertal stages.[10] Again, in this particular population, liver steatosis was more closely related to waist-to-hip ratio, an index of central obesity ($P < 0.001$), than to BMI ($P < 0.05$). The link between abdominal obesity and liver injury may be explained, especially when resistance to antilipolytic action of insulin is present[22], by the fact that fatty acids are mobilized more rapidly from visceral (central) than from subcutaneous (peripheral) fat and drained directly to the liver via the portal vein.[65] A recent study reported that surgical removal of visceral fat reverses hepatic insulin resistance.[66]

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THE ASSOCIATION OF NASH WITH TYPE 2 DIABETES

Liver abnormalities are common in diabetic patients, the majority being attributable to fatty liver.[67] Besides obesity, elevated blood glucose values have been noted in 34-75% of patients with NAFLD (reviewed in ref. 1). In type 2 diabetic patients over age 60, the prevalence of fatty liver has been reported to be about 45%, whereas fatty liver is rare in subjects with type I diabetes (reviewed in refs 19 and 55). In the above personal series of 528 severely obese subjects, the prevalence of steatosis was higher in patients with impaired glucose tolerance or type 2 diabetes compared to non-diabetic subjects (89 versus 69%, $P < 0.001$).[60] In 48 consecutive NAFLD patients, type 2 diabetes was found in 44% of the subjects, 29% had impaired glucose tolerance, and 17% were hyperinsulinaemic.[64] According to several studies, no clear correlation seems to exist between the degree of glucose control or the duration of the disease and the fatty liver infiltration (reviewed in refs 19 and 55).

The role of diabetes in producing more severe liver pathology has been controversial although 'diabetic hepatitis' has been recognized as a pathological entity.[68] The association between type 2 diabetes and NASH seems to be strong, varying from 2 to 50% in various studies.[17] Up to one-third of patients may have diabetes or fasting hyperglycaemia at the time of diagnosis of NASH. An autopsy study noted a trend toward a higher prevalence of NASH in patients with type 2 diabetes requiring insulin.[58] The distribution of fatty metamorphosis and fibrosis in the morbidly obese patient may correlate in severity with the degree of impaired glucose tolerance.[69] In the large series of Marceau et al[59], patients with impaired glucose tolerance or diabetes had a sevenfold increased risk of fibrosis ($P < 0.0001$). Apart from age, diabetes appears to be a strong independent predictor of severe hepatic fibrosis in NASH.[13] However, in a recent series, the presence of diabetes mellitus did not differ among patients with either simple fatty liver or more severe lesions such as steatohepatitis, steatonecrosis or fibrosis.[70] Thus, the precise role of diabetes in the occurrence of NASH and fibrosis remains uncertain.

THE ASSOCIATION OF NASH WITH INSULIN RESISTANCE SYNDROME

Several recent studies have reported that both peripheral and hepatic insulin resistance are present in almost all patients with NAFLD, irrespective of the coexistence of obesity or impaired glucose tolerance.[35,71,72] Importantly, patients with NASH are more insulin-resistant than patients with fatty liver alone.[16,32,35,72] NAFLD, in the presence of normoglycaemia and normal or moderately increased body weight, is characterized by clinical and laboratory data similar to those found in diabetes and obesity. Thus, NAFLD may be considered as an additional feature of the metabolic syndrome, with specific hepatic insulin resistance.[72,73]

Insulin resistance is associated with various metabolic abnormalities, especially dyslipidaemia (hypertriglyceridaemia, low HDL cholesterol, high levels of small dense LDL, post-prandial hyperlipidaemia), leading to the concept of'metabolic syndrome'.[74] Hyperinsulinaemia has been long recognized in hepatic steatosis, irrespective of weight excess, and fatty liver has been considered to be associated with relative insulin resistance to which elevated FFA may contribute.[63,75] Besides obesity, hyperlipidaemia has been reported in 20-81% of patients with NASH (reviewed in ref. I).

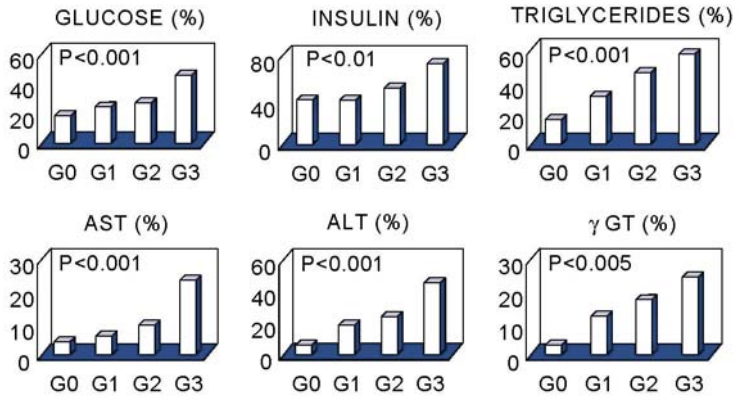
Marceau et al[59] reported on the frequent association between the metabolic syndrome observed in severe obesity and liver pathology in 551 liver biopsies performed during antiobesity surgery. With each addition of one of the four following components of the metabolic syndrome (elevated waist/hip ratio, impaired glucose tolerance, hypertension, and dyslipidaemia), the risk of steatosis increased exponentially from 1- to 99-fold ($P < 0.001$).

In a large series of 505 severely obese subjects evaluated before gastroplasty, we estimated various biological parameters classically associated with the insulin-resistance syndrome[76], and we attempted to correlate biological abnormalities with both the presence and the severity of steatosis.[60] When compared with patients without fatty liver deposition, those with liver steatosis had significantly higher fasting plasma glucose, insulin, triglycerides and ALT levels. The severity of the steatosis was positively correlated not only with BMI ($P = 0.002$), but also with fasting plasma glucose, insulin and triglycerides concentrations and serum liver enzyme levels (Figure 1).

Similar observations, suggesting a close relationship between NAFLD and NASH in obese subjects with various features of the insulin resistance syndrome, were reported in smaller series. Among 105 consecutive patients submitted to laparoscopic obesity surgery, 26 patients were found to have NASH and 11 of these advanced fibrosis.[16] A raised index of insulin resistance and systemic hypertension, another feature of the metabolic syndrome, was an independent predictor of NASH. In a retrospective review of 90 patients with NASH, insulin resistance was present in almost all subjects (85%), as well as various components of the metabolic syndrome such as diabetes, hyperlipidaemia, hypertension and atherosclerotic disease.[77] Interestingly, familial clustering was common, with 18% of patients having a similarly affected first-degree relative. Hepatic steatosis was found

in 50% of patients with unexplained hepatic iron overload plus at least one of the components of the insulin-resistance syndrome, including truncal obesity, type 2 diabetes mellitus and hypertriglyceridaemia.[37] NAFLD is associated with insulin resistance and hyperinsulinaemia even in lean subjects with normal glucose tolerance. Genetic factors that reduce insulin sensitivity and increase serum triglyceride levels may be responsible for its development.[71]

Figure 1: *Relationships between the degree of steatosis (grade 0: no steatosis; grade 1: mild steatosis; grade 2: moderate steatosis; grade 3: severe steatosis) and the prevalence (%) of high levels of three markers of insulin resistance (fasting plasma glucose, plasma insulin, and serum triglycerides) and of three serum liver enzymes (ALT, AST and gamma-GT) in a large cohort of severely obese subjects (references 55 and 60).*



THE PROGNOSTIC VALUE OF NASH IN OBESE SUBJECTS

The natural history of NAFLD varies according to its histological type.[3] A study retrospectively determined the histological and/or clinical outcome of 98 patients with the whole range of NAFLD from simple steatosis through NASH to fatty cirrhosis. After a median 8-year follow-up, 25% of individuals with NASH progressed to cirrhosis compared with only 3.4% of patients with simple steatosis.[70] The observation that NAFLD patients without NASH have a benign prognosis confirmed results from a previous study confined to patients with non-alcoholic fatty liver only, followed for up to 19 years.[78] Older age, obesity, and the presence of diabetes mellitus help to identify those NASH patients who might have severe liver fibrosis.[13]

Two studies reported a high prevalence of obesity and diabetes in patients with cryptogenic cirrhosis compared with patients of known aetiology and suggested that NASH may account for most, if not all, cases of cryptogenic cirrhosis.[79,80] A recent report of NASH and cryptogenic cirrhosis occurring within kindreds suggested that genetic factors may be important.[81] Polymorphisms in genes encoding proteins involved in hepatic lipid metabolism and storage may be important, as illustrated by the association between a low-activity promoter polymorphism in the gene encoding microsomal triglyceride transfer protein and NASH in patients with type 2 diabetes.[82] Finally, a recent study suggested that hyperglycaemia and insulin are key factors in the progresson of fibrosis in patients with NASH through the upregulation of connective tissue growth factor.[83]

Three recent studies including obese patients have identified several clinical and laboratory features that predict the presence of NASH and/or fibrosis, and thus the possible progression to cirrhosis. The first study included 93 mildly obese patients (BMI > 25 kg/m^2) being investigated for abnormal liver blood tests.[14] Age > 50 years, BMI > 28 kg/m^2, ALT more than twice normal, and serum triglycerides > 1.7 mmol/l were independent predictors of septal fibrosis. The second study was performed in 105 severely obese patients undergoing obesity surgery.[16] Independent predictors of NASH and advanced pericellular fibrosis were an ALT greater than normal, hypertension, and either insulin resistance index (NASH) or fasting C-peptide (fibrosis), but not age. Half of the patients with NASH had overt type 2 diabetes compared with only 6% of those without NASH, and the waist/hip ratio was significantly higher in the NASH patients. A third study in 144 patients selected on the basis of biopsy-proven NASH reported that age > 45 years, obesity, type 2 diabetes, and an AST/ALT ratio > I were independent predictors of fibrosis.[13]

The increasing prevalence and severity of obesity has heightened concerns about the frequency of progression of NASH to end-stage liver disease. Of 1207 patients evaluated for liver transplantation, 31 patients (2.6%) had NASH as the primary cause of liver disease.[84] These observations demonstrate that NASH can progress to end-stage liver disease in a minority of affected patients. In a series of 90 patients with NASH, 28% of subjects had

cirrhosis and almost half of those had complications of portal hypertension, necessitating liver transplantation.[77] Obesity was common in affected patients and cirrhosis was more common in the morbidly obese subjects. In 125 patients in whom unsuspected cirrhosis was discovered during gastric bariatric operations, cirrhosis may be attributed to severe obesity in three-quarters of the patients.[85]

Thus, while in patients with fatty liver only, long-term follow-up suggests a benign, non-progressive course[78], advanced NASH may differ substantially in prognosis and lead to obvious fibrosis and cryptogenic cirrhosis.[79]

THERAPEUTIC APPROACHES TO NASH

The decision whether to treat an individual with NAFLD should be primarily dictated by knowing the potential risk of progression to end-stage liver disease. However, because no prospective, longitudinal clinical studies, especially with liver biopsies, have been performed, treatment recommendations remain speculative. Besides various specific pharmacological approaches (reviewed in ref. 86), treatment of patients with NASH has typically been focused on the management of associated conditions such as obesity, diabetes mellitus and hyperlipidaemia, although it is not always effective in reversing NASH.[87,88] In a series of 48 NAFLD patients, dietary intervention resulting in a moderate weight loss (only 3.7 kg), supplemented by oral hypoglycaemic or lipid-lowering drugs as needed, decreased fasting blood glucose and improved serum lipid profile after a median 24-month follow-up. A substantial reduction in serum liver enzymes was observed in almost all patients (96%) with normalization of liver profile in more than half of the patients.[64]

Drugs improving insulin sensitivity

Owing to the close relationship between insulin resistance and NAFLD/NASH[16,32,35,71,72], it is reasonable to speculate that increasing insulin sensitivity may benefit liver disease, especially in the presence of obesity and type 2 diabetes.[89] It has been shown that metformin reverses fatty liver disease in obese, leptin-deficient mice.[90] In 20 patients with NASH, 4 months of metformin treatment led to a reduction in serum transaminase (which were normalized in 50% of cases) and liver volume compared with no changes in non-compliant patients.[91] Clearly, a randomized controlled trial is urgently required to confirm these results.

Thiazolidinediones are a new class of antidiabetic drugs that selectively enhance certain actions of insulin, causing an antihyperglycaemic effect frequently accompanied by a reduction in circulating concentrations of insulin, triglycerides and FFA.[92] Normalization of ALT levels was seen in seven of 10 patients with NASH at the end of a treatment with troglitazone for several months.[93] However, this biochemical response was associated with only mild histological improvement, and all follow-up biopsies still had evidence of NASH. It should be noted that troglitazone has been withdrawn because of severe hepatotoxicity. Fortunately, other thiazolidinedione agents, such as rosiglitazone and pioglitazone, seem not to share this hepatotoxicity, and anecdotal reductions of ALT levels in patients with initial elevation of liver enzymes have been reported in clinical trials with type 2 diabetic patients.[94] These observations deserve further evaluation in NAFLD patients.

Reversibility after weight loss

The effect of weight loss on liver disease is not consistent, as was recently reviewed by our group.[55] Early studies demonstrated that weight reduction due to fasting or low-calorie diets is associated with reduced steatosis, but that a transient increase in the degree of hepatocellular degeneration and focal necrosis may also occur.[95] In a more recent study, a rapid weight loss of 34 ± 9 kg with a very-low-calorie formula diet resulted in a significant improvement of fatty change, but 24% of the patients developed slight portal inflammation or fibrosis.[96] While improvement generally occurs after gradual weight reduction, histological lesions of steatohepatitis may deteriorate after rapid weight loss.[55]

During the 1970s, NASH was encountered as a common complication of jejunoileal bypass surgery for morbid obesity (reviewed in refs 1, 17, 88 and 97). In fact, the pathogenesis of NASH after jejunal bypass in morbidly obese patients appears to be multifactorial: potential mechanisms include absorption of bacterial products or bile acids from the blind loop, severe protein malnutrition and massive mobilization of FFAs during weight loss.[17] In contrast, gastric bypass does not seem to be associated with such a high incidence of liver abnormalities, and reduction of fatty liver is common. In a series of 91 patients followed from 2 to 61 months after gastric bypass with gastrojejunostomy, liver biopsies showed that 65 patients had reduced steatosis; pre-gastric bypass biopsies showed perisinusoidal fibrosis in 13 patients which disappeared afterwards in 10 patients.[98]

Of our large cohort of severely obese subjects submitted to a gastroplasty (vertical-ring gastroplasty or adjustable

banding), 69 patients had a second liver biopsy 27±15 months after initial surgery.[60] After a mean weight loss of 32 ± 19 kg, a remarkable decrement in liver fatty scores was observed (Table I, lower part). Such regression of steatosis occurred even in the absence of weight normalization. Interestingly, it occurred concomitantly with the regression of various features of the insulin-resistance syndrome.[55,99] Indeed, a remarkable improvement in the biological markers of the metabolic syndrome was observed in 505 obese patients after a mean follow-up of 26 ± 14 months and a mean weight loss of 32 ± 16 kg after gastroplasty (Table 1, upper part).[76] Hyperleptinaemia was also markedly reduced after weight loss[55], and a full normalization of the abnormalities in insulin secretion, clearance and action on glucose metabolism could be demonstrated in patients who recovered an ideal body weight after surgery.[100] All of these hormonal and metabolic improvements related to weight reduction should favourably influence NAFLD in obese subjects. However, a slight but significant increase in the prevalence of hepatitis was observed after pronounced weight reduction (26% of the biopsies after gastroplasty versus 14% before, $P < 0.05$).[60] Considering the potential deleterious effect of FFA[18,20], our data may suggest that the rapid mobilization of lipid stores induced by drastic weight loss may be toxic for the liver and result in mild lobular hepatitis in some patients.

Table 1: *Prevalence (%) of abnormal biological values related to the metabolic syndrome in 505 obese subjects and of abnormal liver biopsies in a subgroup of 69 obese subjects before and about 2 years after gastroplasty and a substantial weight loss of about 30 kg (adapted from references 60 and 76).*

Parameters	Before weight loss (%)	After weight loss (%)	*P*
Biological markers (*n* = 505)			
Hyperinsulinaemia	58	32	0.004
Hyperglycaemia	35	21	0.004
Hypertriglyceridaemia	44	24	0.005
Low HDL cholesterol	44	35	0.05
Hyperfibrinogenaemia	43	20	0.003
Hyperuricaemia	15	9	0.04
Elevated serum ALT	35	21	0.01
Liver biopsies[a] (*n* = 69)			
Normal	13	45	0.001
Steatosis	83	38	0.001
mild	21	62	0.001
moderate	37	23	0.001
severe	42	15	0.001
Hepatitis	14	26	0.05
Fibrosis or cirrhosis	1.5	1.5	NS

[a]Some liver biopsies may present several abnormalities, especially hepatitis in addition to steatosis.

CONCLUSIONS

Liver steatosis is a common feature in severely obese subjects and is especially associated with visceral adiposity and diabetic status. Although it is often considered as a benign disease, it may progress in some patients to steatohepatitis and cryptogenic cirrhosis. A positive relationship of NAFLD is observed with classical biological markers of the metabolic syndrome, such as hyperinsulinaemia and hypertriglycer-iidaemia. Drastic weight loss results in a significant improvement of both insulin sensitivity and biological abnormalities of the metabolic syndrome and, in a parallel fashion, is associated with a marked reduction in both prevalence and severity of liver steatosis, but in some cases, at the expense of mild steatohepatitis. Recent data from the literature and personal observations led to the concept that NASH should be considered as being part of the insulin-resistance syndrome. Thus, both NASH and metabolic syndrome associated with severe obesity are common markers of a so-called disease of affluence.

Practice points

• most patients with non alcoholic fatty liver disease (NAFLD) are asymptomatic, and typically patients are found incidentally to have abnormal liver function tests or hepatomegaly when being evaluated for another condition

• nonalcoholic steatohepatitis (NASH) is frequently associated with obesity, especially visceral fat that increases efflux of free fatty acids to the liver

• NASH is intimately related to markers of the insulin resistance syndrome, especially impaired glucose tolerance or type 2 diabetes and dyslipidaemia

• marked weight loss is accompanied by a remarkable regression of liver steatosis in most patients, which parallels the improvement of markers of the metabolic syndrome

• NASH may be considered as another disease of affluence, as is the insulin resistance syndrome, and perhaps being part of it

Research agenda

• the identification of obese patients who may progress from simple steatosis to NASH and from NASH to fibrosis/cirrhosis is an important clinical challenge

• despite recent progress in the understanding of the aetiopathogenesis of NASH in the last few years, further research should assess the precise trigger and role of oxidative stress and cytokine production

• the causes and consequences of inflammation observed after drastic weight loss in some obese patients require further fundamental and clinical investigations

• the effect of old (metformin) or new (thiazolidinediones,...) insulin sensitizers on fatty liver and NASH should be better evaluated

• considering the increasing prevalence of NASH, other specific therapeutic approaches should be developed and evaluated in controlled clinical trials

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