Editorial

NONALCOHOLIC STEATOHEPATITIS AND INSULIN RESISTANCE :

INTERFACE BETWEEN GASTROENTEROLOGISTS AND ENDOCRINOLOGISTS

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ABSTRACT

Nonalcoholic steatohepatitis (NASH), along with other forms of nonalcoholic fatty liver disease, is an increasingly common clinico-pathological syndrome. It is frequently associated with obesity, especially visceral fat, and type 2 diabetes, and is intimately related to 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. The pathophysiology of NASH involves two steps : 1) insulin resistance, which causes steatosis; 2) and oxidative stress, which produces lipid peroxidation and activates inflammatory cytokines. The identification of subjects who may progress from fatty liver to NASH, and from NASH to fibrosis/cirrhosis is an important clinical challenge as well as the finding of appropriate therapy that could prevent such deleterious process. Substantial weight loss is accompanied by a marked attenuation of insulin resistance and related metabolic syndrome and, concomitantly, by an important regression of liver steatosis in most patients, although mild 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.

INTRODUCTION

The spectrum of nonalcoholic fatty liver disease (NAFLD) is broad from steatosis and nonalcoholic 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 and type 2 diabetes appears to be crucial (8,9) so that NASH is now considered as “another disease of affluence” (10). Perhaps of most concern is the recent observations that NAFLD and NASH may also be observed in children and adolescents (11). The increasing prevalence and severity of obesity (12) has heightened concerns about the frequency of the progression of NASH to end-stage liver disease (13). While in patients with fatty liver only, long-term follow-up suggests a benign, non-progressive course, advanced NASH may differ substantially in prognosis and lead to obvious fibrosis and cryptogenic cirrhosis

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(review in 5,9).

The present review aims at discussing the role of insulin resistance and related metabolic abnormalities in the development of NAFLD in general, and NASH in particular. Better understanding of etiopathogenesis and pathophysiology of such liver disease may stimulate new perspectives for successful therapeutic interventions.

ETIOPATHOGENESIS OF NASH

As recently reviewed (14), the etiopathogenesis of NASH appears multifactorial. It has been recently demonstrated that peripheral insulin resistance, increased fatty acid beta-oxidation, and hepatic oxidative stress are present in both fatty liver and NASH, but NASH alone is associated with mitochondrial structural defects (15). A "two hit" hypothesis has been proposed whereby the first "hit", i.e. steatosis, sensitises the liver to a variety of second "hits" which lead to necroinflammation and fibrosis (16) (Figure 1). With regard to the first hit, insulin resistance, compensatory hyperinsulinaemia 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.

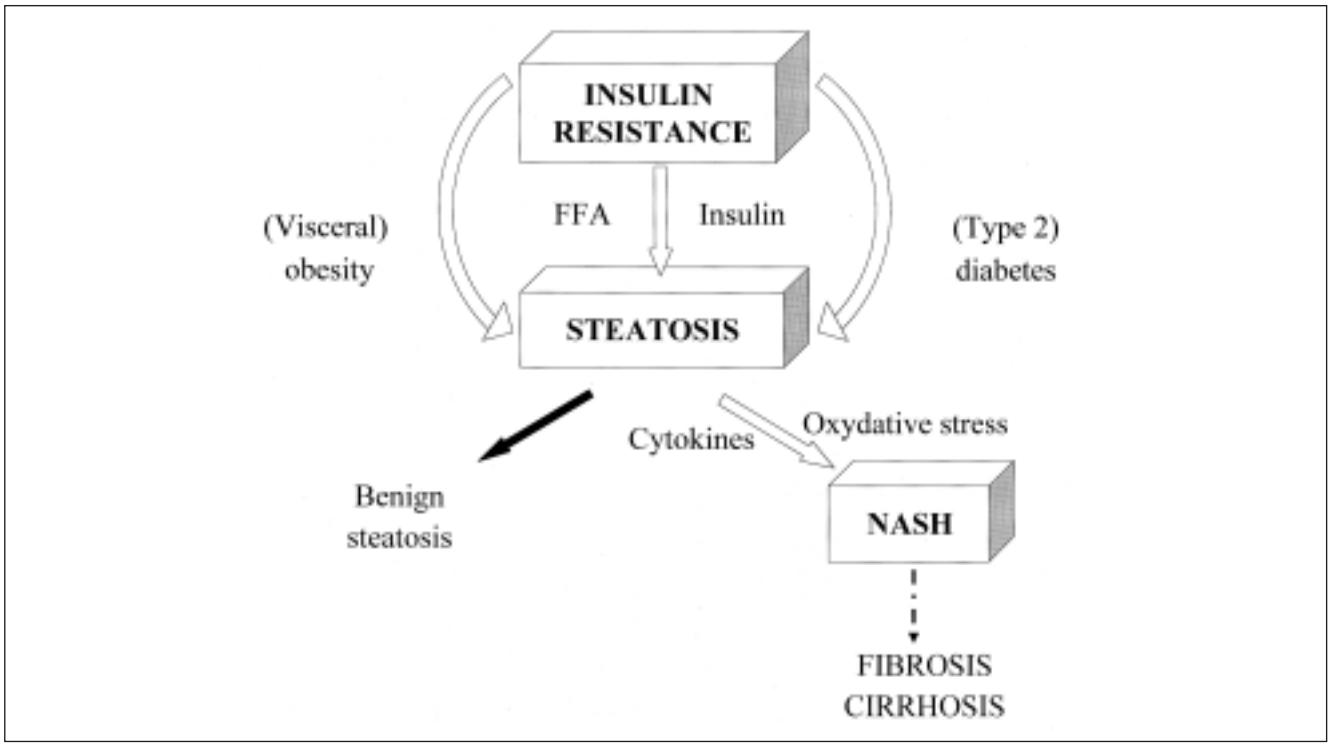

Figure 1 : Insulin resistance initiating the development of steatosis and NASH

a) Role of free fatty acids and insulin resistance

The crucial role of increased FFA levels in the pathogenesis of insulin resistance has been extensively reviewed (17). In addition, 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 (18). Any defect of this multistep process results in accumulation of triglyceride 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 (19).

As already suggested by a pioneer work published as early as 1950 (20), diabetic patients with fatty liver are remarkably insensitive to insulin. Insulin resistance,

together with compensatory hyperinsulinaemia, is a common feature in obesity (21,22). Insulin plays a key role in the regulation of regional FFA metabolism and can inhibit hepatic mitochondrial beta-oxidation of FFA (23). Visceral fat mass is a predictor of both insulin resistance and steatosis (24). Visceral lipolysis is resistant to insulin suppression and is the source of liver fatty acids in insulin resistance and hyperinsulinaemic states such a liver disease (23). Conversely, fatty liver may influence insulin clearance and insulin resistance, a process which can initiate a vicious circle (25). Thus, the conjunction of high FFA and insulin resistance, both directly related to increased (visceral) fat mass (see below), is crucial for the development of liver steatosis.

b) Role of cytokines, leptin and TNF-a

It has been recently suggested that the high circulating leptin levels associated with obesity (26) may contribute to hepatic steatosis (27). Serum leptin levels are significantly higher in patients with NASH (28), and this elevation is out of proportion to BMI (29). 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 nonadipocyte cells (including hepatocytes) from steatosis and lipotoxicity (30). Finally, given the similar intracellular signaling pathways stimulated by leptin and several inflammatory cytokines (27), leptin may also be involved in the progression from hepatic steatosis to steatohepatitis, and possibly fibrosis (31).

Cytokines, especially tumour necrosis factor alpha (TNF-α), have also been incriminated in the pathogenesis of NASH (review in 14,32). As TNF-α is overexpressed in adipose tissue of obese subjects and in overweight patients with type 2 diabetes, resulting in higher circulating TNF-α levels (33), 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 (34). Finally, bacterial overgrowth of the small intestine could also contribute to raised TNF-α in patients with NASH (35). Thus, it has been recently hypothesized that the egress of products from intestinal bacteria into the portal blood, liver, and systemic circulation may trigger a sustained inflammatory cytokine response in genetically susceptible individuals that may contribute to both NASH and insulin resistance (36).

c) Role of oxydative stress and iron accumulation

Oxidative stress may play a prominent role in NASH. An increase in mitochondrial reactive oxygen species production 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 (15). Lipid peroxidation products alter mitochondrial DNA and also react with mitochondrial proteins to inhibit the transfer of electrons along the respiratory chain, further increasing reactive oxygen species production and resulting in a self perpetuating cycle of oxydative stress and lipid peroxidation (37). Other potential sources of oxidative stress that have been suggested to play a role in NASH include an increase in liver iron (14). Recent observations showed that elevated serum ferritin and iron levels are common findings in patients with NASH and insulin resistance, even in absence of haemochromatosis (38,39), and one study reported that increased hepatic iron had the greatest association with the severity of liver fibrosis (40).

ASSOCIATION OF NASH WITH OBESITY AND TYPE 2 DIABETES

As recently reviewed (8,9), obesity is the condition most often associated with NAFLD. In a literature survey of 41 original articles comprising information on liver morphology in 1,515 morbidly obese patients, liver biopsy was considered as normal in only 12 % of the cases (41). 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. Two large series of liver biposies performed in more than 500 severely obese subjects submitted to bariatric surgery have been recentlty 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 (42). In a large personal series of 528 severely obese subjects (BMI 42.6 ± 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 % (43). The severity of steatosis was positively associated with BMI (p = 0.002) (8). Ten % of these patients had signs of steatohepatitis, inflammatory changes being scored as mild in 86 %, moderate in 12 % and severe in 2 % of cases. In contrast, fibrosis and cirrhosis were rather rare (around 3 %).

Besides obesity, elevated blood glucose values have been noted in 34 % to 75 % of patients with NAFLD (review in 1,8,9,36). In type 2 diabetic patients over age 60, the prevalence of fatty liver has been reported to be about 45 % (review in 8,16). The association between type 2 diabetes and NASH seems to be strong, varying from 2 % to 50 % in various studies (14). The role of diabetes in producing more severe liver pathology appears controversial although "diabetic hepatitis" has been recognized as a pathological entity (44). Some (45), but not all (46), studies suggested that diabetes is a strong independent predictor of severe hepatic fibrosis in NASH.

Thus, type 2 diabetes is strongly associated with NAFLD. At present, however, it is not clear if one of these conditions causes the other, or if both are the consequences of another process (review in 36,47).

NASH AS A FEATURE OF THE INSULIN RESISTANCE SYNDROME

Syndromes are clusters of non-chance associations, and the components of a syndrome can generally be related to a common element. In insulin resistance syndrome, central fat accumulation (truncal or abdominal/visceral), impaired glucose metabolism (or overt type 2 diabetes), raised blood pressure (or clinical hypertension), and dyslipidaemia (typically, hypertriglyceridaemia, low HDL cholesterol, high levels of small dense LDL, and postprandial hyperlipidaemia) cluster with insulin resistance, as indicated by a low total-body insulin-mediated glucose disposal (48-50). Because of its simplicity, fasting hyperinsulinaemia is the most commonly used surrogate for insulin resistance. 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 (51,52). Several recent studies 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 (15,53,54). Genetic predisposition that reduces insulin sensitivity and increases serum triglyceride levels may be responsible for its development (53). Besides obesity, hyperlipidaemia has been reported in 20 % to 81 % of patients with NASH (review in 1). Importantly, patients with NASH are more insulin resistant than patients with fatty liver alone (15,34,54-58) and than patients with chronic hepatitis C virus (58). 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 an additional feature of the metabolic syndrome, with specific hepatic insulin resistance (57,59,60).

Viseral fat is strongly associated with insulin resistance and related metabolic disorders characterizing the metabolic syndrome or syndrome X (61,62). It has been shown that abdominal distribution of fat is a predictor of hepatic steatosis, which is independent of body weight and body fat (63). In type 2 diabetic men, liver fat score was highly correlated to visceral/total adipose tissue ratio, insulin resistance and serum triglyceride levels (51). In a series of 48 consecutive patients with NAFLD, most subjects (81 %) were overweight or obese and had increased waist circumference, which closely relates to visceral fat and insulin resistance (60). In NAFLD subjects with normal body weight, a waist-to-hip ratio similar to that of overweight subjects and significantly larger than that of normal subjects has been reported (54). NAFLD was also linked to insulin resistance in normal weight Korean subjects, a population known to have increased visceral adiposity in the presence of normal body weight (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 (11). Again, in this particular population, liver steatosis was more closely related to waist to hip ratio, an index of central obesity, than to BMI. One study reported that surgical removal of visceral fat reverses hepatic insulin resistance (65). Thus, all these observations suggest a key role of visceral adiposity in the development of both insulin resistance and NAFLD. The link between abdominal obesity and liver injury may be explained, especially when resistance to antilipolytic action of insulin is present (23), 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 (61).

Marceau et al (41) reported on the frequent association between the metabolic syndrome observed in se-

vere obesity and liver pathology in 551 liver biopsies performed during anti-obesity surgery. With each addition of 1 of the 4 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 (66), and we attempted to correlate such biological abnormalities with both the presence and the severity of steatosis (42). When compared with patients without fatty liver deposition, those with liver steatosis had significantly higher fasting plasma glucose, insulin, triglyceride and aminoalanine transferase (ALT) levels. The severity of the steatosis was positively correlated, not only to BMI ($p = 0.002$), but also to fasting plasma glucose, insulin and triglyceride concentrations as well as to serum liver enzyme levels (Fig 2). 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 (55). In this study, a raised index of insulin resistance and systemic hypertension, another feature of the metabolic syndrome, were independent predictors 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 (67). In 30 patients with NAFLD, obesity was present in 80 % of patients, hypertension in 50 % and diabetes in 33 %. In addition, glucose metabolism was altered in above two thirds of the patients, with elevated insulin levels in about half (59).

The relationship between insulin resistance, iron overload and liver disease has been recently discussed (37,38). Among 65 patients with a new clinical-pathological syndrome of primary hepatic iron overload (in

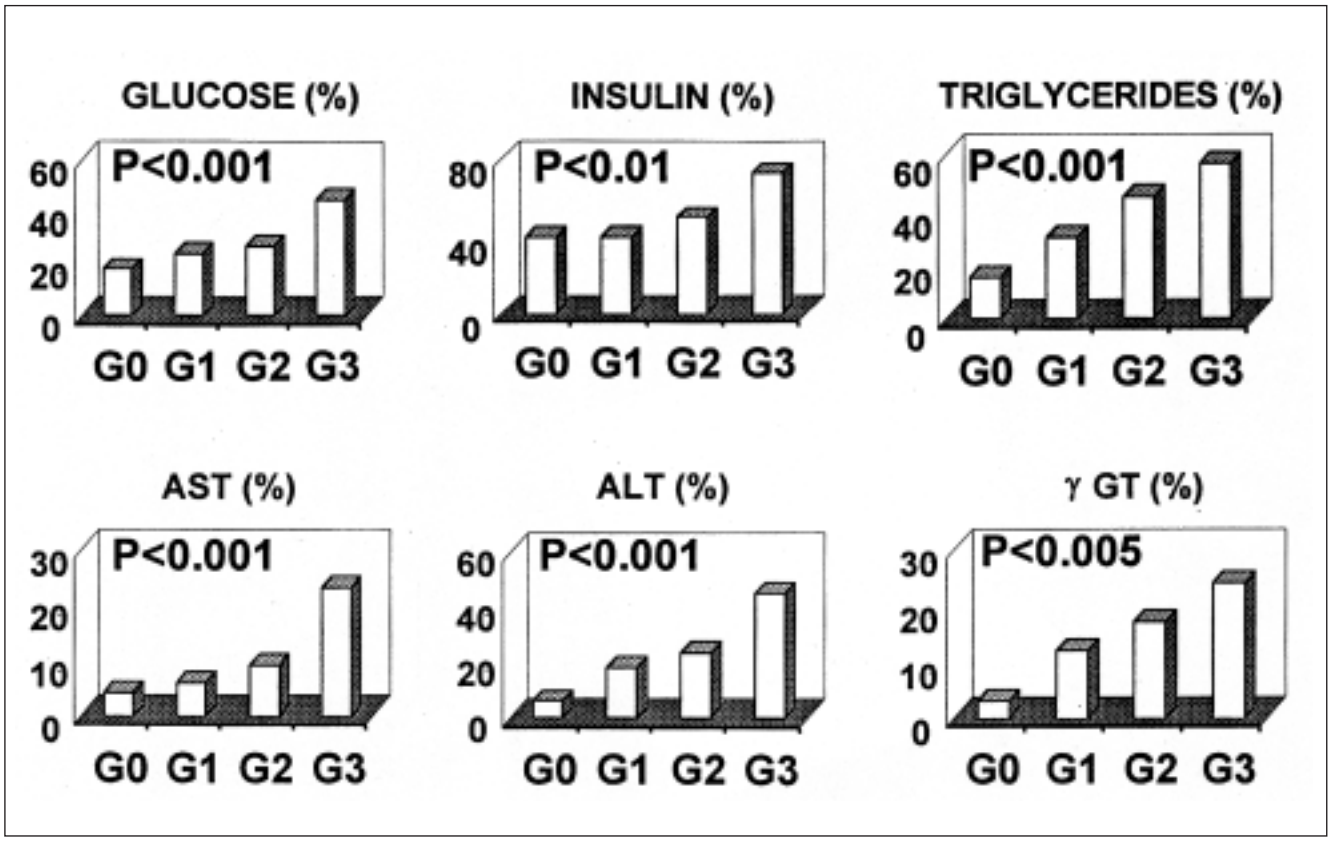

Figure 2 : Relationships between the degree of steatosis (grade 0 : no steatosis; grade 1 : mild steatosis; grade 2 : moderate steatosis; grade 3 : severe steatosis) and the prevalence (%) of high levels of three markers of insulin resistance (fasting plasma glucose, plasma insulin, and serum triglycerides) and of three serum liver enzymes (ALT, AST and gamma-GT) in a large cohort of severely obese subjects (references 8 and 43).

absence of haemochromatosis), 72 % had a BMI greater than 25 kg/m^2, 65 % were dyslipidaemic, and 43 % had abnormal glucose tolearance, i.e. there was a high frequency of some of the features of the insulin resistance syndrome (68). In a subsequent study of 161 patients, the patients with unexplained hepatic iron overload, mostly middle-aged men, had a high rate of insulin resistance syndrome (94 %) (69). In this study, 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. Individuals with high ferritin levels and hepatic iron overload associated with insulin resistance can have symptom relief after venesection (70). 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 aminoalanine transferase (ALT) activity, suggesting a key role of iron and hyperinsulinaemia in the pathogenesis of NAFLD (71).

THERAPEUTIC APPROACHES OF NASH

Besides various specific pharmacological approaches (review in 36,72), 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 (60,73,74). Specific treatment of NASH may be important as NASH is now considered the starting point for most "cryptogenic" cirrhosis (75).

a) Pharmacological interventions targeting insulin resistance

Owing the close relationship between insulin resistance and NAFLD/NASH, it is reasonable to speculate that the use of medications that improve insulin sensitivity may benefit the liver disease, especially in presence of obesity and type 2 diabetes (76). It has been shown that metformin reverses fatty liver disease in obese, leptin-deficient mice (77). In 20 patients with NASH, four 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 (78). These preliminary results should be urgently confirmed in a randomised controlled trial.

Thiazolidinediones are a new class of antidiabetic drugs. They selectively enhance insulin action on glucose metabolism, more in the skeletal muscle than in the liver. The resulting antihyperglycaemic effect is frequently accompanied by a reduction in circulating concentrations of insulin, triglycerides and FFA (79). Normalization of ALT levels was seen in 7 of 10 patients with NASH at the end of a treatment with troglitazone for several months (80). However, this biochemical response was associated with only mild histological improvement, and all follow-up biopsies had still evidence of NASH. It should be noted that troglitazone has been withdrawn because of severe hepatotoxicity. Fortunately, other thiazolidinedione agents, like rosiglitazone and pioglitazone, do not 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 (81). Indeed, poorly controlled patients with type 2 diabetes may have moderate elevations of serum ALT that will decrease with improved glycaemic control during treatment with glitazone (82). These observations deserve further evaluation in NAFLD patients.

b) Reversibility after weight loss

Because obesity is the most common phenotype associated with NASH, it seems paradoxical that more florid forms of the disorder were initially recognized after operations designed to achieve weight reduction, especially jejuno-ileal bypass (JIB) surgery (1,14,71). The spectrum of hepatic disease following JIB includes steatosis, steatohepatitis, progressive fibrosis leading to cirrhosis, and liver failure that may be fatal (83,84). Steatohepatitis often develops during the period of maximum weight loss, but the risk of liver fibrosis increases with the duration of follow-up (85). The pathogenesis of NASH after JIB in morbidly obese patients appears to be multifactorial : potential mechanisms include massive mobilization of FFAs during initial weight loss, severe protein malnutrition and resorption of bacterial toxins from the defunctionalized intestine (14). Thus, after NASH was encountered as a common and severe complication of JIB for morbid obesity during the 1970s, this approach was abandoned (1,14,71) and replaced by

other surgical procedures that do not share such liver complications, i.e. gastroplasty and gastric bypass (86).

Numerous studies showed that weight loss is accompanied by a significant improvement of insulin sensitivity in obese patients. As an example, a full normalization of the abnormalities in insulin secretion, clearance and action on glucose metabolism could be demonstrated in severely obese patients who recovered an ideal body weight after gastroplasty (87). However, the effect of weight loss on liver disease is not consistent as recently reviewed by our group (8,9). Early studies already demonstrated that weight reduction due to fasting or low calorie diets are associated with reduced steatosis, but that a transient increase in the degree of hepatocellular degeneration and focal necrosis may also occur (88).

In most reports, favourable results have been reported after other forms of anti-obesity surgical procedures than JIP. 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 (89). 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 (42). After a mean weight loss of 32 ± 19 kg, a remarkable reduction in liver fatty scores was observed (Table 1). Such regression of steatosis was observed even in absence of weight normalization. Interestingly, it occurred concomitantly with the regression of various features of the insulin resistance syndrome (8,66,90,91). 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 2) (66). Insulin resistance index (87) and hyperleptinaemia (8) were also markedly reduced after weight loss. All these hormonal and metabolic improvements related to weight reduction should favourably influence NAFLD of 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, $p < 0.05$) (42). Our results thus confirm those obtained in another study in which 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 (92). Considering the potential deleterious effect of FFA (16,19), these 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 liver biopsies in a subgroup of 69 obese subjects before and 27 ± 15 months after gastroplasty and a substantial weight loss of 32 ± 19 kg (adapted from reference 43).

Parameters	Before weight loss (%)	After weight loss (%)	p
Liver biopsies (*)			
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

(*) Some liver biopsies may present several abnormalities, especially hepatitis in addition to steatosis

TABLE 2 : Prevalence (%) of abnormal biological values related to the metabolic syndrome in 505 obese subjects before and 26 ± 14 months after gastroplasty and a substantial weight loss of 32 ± 16 kg (adapted from reference 66).

Parameters	Before weight loss (%)	After weight loss (%)	p
Body mass index			
< 30 kg/m^2	0	47.2	0.001
30-40 kg/m^2	41.6	45.7	NS
> 40 kg/m^2	58.4	7.1	0.001
Biological markers			
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

(*) Alanine aminotransferase

CONCLUSIONS

Liver steatosis is a common feature in patients 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. NAFLD and NASH are strongly associated with insulin resistance and classical biological markers of the metabolic syndrome. Drastic weight loss results in a significant improvement of both insulin sensitivity and biological abnormalities of the metabolic syndrome. In a parallel fashion, a marked reduction in both the prevalence and the severity of liver steatosis was observed but, in some cases, at the expense of mild steatohepatitis. Growing evidence leads to the concept that NASH is intimately linked to insulin resistance. Thus, NASH should be considered as being part of the insulin resistance syndrome and, consequently, as an interface for gastroenterologists and endocrinologists.

RÉSUMÉ

La stéatohépatite non alcolique (NASH) est une maladie de mieux en mieux individualisée qui suscite un vif intérêt depuis quelques années. Elle est fréquemment associée à l'obésité, spécialement à l'adiposité viscérale, et au diabète de type 2; elle est intimement liée à la stéatose et à divers marqueurs du syndrome d'insulinorésistance. La prévalence et la sévérité de la stéatose sont corrélées à l'indice de masse corporelle, à la circonférence de la taille, à l'hyperinsulinémie, à l'hypertriglyceridémie et à la diminution de la tolérance au glucose. La physiopathologie de la NASH impliquerait deux processus : 1) l'insulinorésistance, à l'origine de la stéatose; 2) et le stress oxydatif, responsable d'une peroxydation lipidique et d'une activation de cytokines inflammatoires. L'identification des sujets obèses qui vont progresser de la stéatose vers la NASH et de la NASH vers la fibrose ou la cirrhose constitue un défi clinique majeur, tout comme la découverte de traitements susceptibles d'empêcher cette évolution délétère. Une perte de poids importante est accompagnée par une réduction marquée de l'insulinorésistance et du syndrome métabolique associé et, concomitamment, par une régression de la stéatose hépatique chez la plupart des patients, même si une légère inflammation péri-hépatocytaire est observée chez certains sujets. Ainsi, la NASH peut être considérée comme une autre maladie de l'affluence, tout comme le syndrome d'insulinorésistance et, sans doute, fait partie intégrante de celui-ci.

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