Hepatitis C virus-infected patients are 'spared' from the metabolic syndrome but not from insulin resistance. A comparative study of nonalcoholic fatty liver disease and hepatitis C virus-related steatosis

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BACKGROUND: Nonalcoholic fatty liver disease (NAFLD) and chronic hepatitis C feature steatosis and insulin resistance (IR), conditions associated with the metabolic syndrome (MS).
OBJECTIVES: To assess the prevalence of MS and determinants of IR in patients with NAFLD and chronic hepatitis C.
METHODS: Ninety-three consecutive patients with NAFLD, 97 with chronic hepatitis C virus (HCV) genotypes 1 and 2, and 182 'healthy' controls without steatosis were enrolled in the present study. The prevalence of MS was assessed by modified Adult Treatment Panel III criteria and IR by the homeostasis model assessment of insulin resistance (HOMA-IR). IR was defined as the 75th percentile of the HOMA-IR of control subjects.
RESULTS: While the prevalence of IR was similar in NAFLD and HCV-infected subjects (70.0% and 78.7%, respectively), the prevalence of MS was significantly higher in NAFLD patients than in HCV-infected patients (27.9% versus 4.1%) and in controls (5.6%). With multivariate analysis, IR was predicted by body mass index (OR 1.263; 95% CI 1.078 to 1.480) and triglyceridemia (OR 1.011; 95% CI 1.002 to 1.020) in NAFLD and by sex (OR for female sex 0.297; 95% CI 0.094 to 0.940) and fibrosis stage (OR 2.751; 95% CI 1.417 to 5.340) in chronic hepatitis C.
CONCLUSIONS: IR is independently associated with body mass index and triglyceridemia in NAFLD, sex and fibrosis in chronic HCV infection, and has a higher prevalence in NAFLD and chronic hepatitis C than in controls. However, the frequency of MS in HCV-infected patients, similar to that of controls, is significantly lower than that seen in NAFLD patients. The current diagnostic criteria of MS are more likely to 'capture' patients with NAFLD than with chronic hepatitis C, although both groups are insulin resistant.

Key Words: *Body mass index; Fibrosis; HCV; HOMA-IR; Insulin resistance; Metabolic syndrome; Nonalcoholic fatty liver disease; Sex; Steatosis; Triglycerides;*

Des patients infectés par le virus de l'hépatite C sont « épargnés » par le syndrome métabolique mais non par l'insulinorésistance. Une étude comparative de la stéatose hépatique non alcoolique et de la stéatose liée au virus de l'hépatite C

HISTORIQUE : La stéatose hépatique non alcoolique (SHNA) et l'hépatite C chronique comprennent une stéatose et une insulinorésistance (IR), des troubles reliés au syndrome métabolique (SM).
OBJECTIFS : Évaluer la prévalence du SM et les déterminants de l'IR chez les patients atteints d'une SHNA ou d'une hépatite C chronique.
MÉTHODOLOGIE : Quatre-vingt-treize patients consécutifs atteints de SHNA, 97 patients présentant les génotypes 1 et 2 du virus d'hépatite C chronique (VHC) et 182 sujets témoins en santé sans stéatose ont participé à la présente étude. Les auteurs ont évalué la prévalence de SM selon les critères modifiés de l'*Adult Treatment Panel III* et celle de l'IR par l'évaluation du modèle d'homéostasie de l'insulinorésistance (HOMA-IR). L'IR était définie comme le 75e percentile de l'HOMA-IR des sujets témoins.
RÉSULTATS : La prévalence d'IR était similaire chez les sujets atteints de SHNA et chez ceux infectés par le VHC (70,0 % et 78,7 %, respectivement), mais la prévalence de SM était considérablement plus élevée chez les patients atteints de SHNA que chez ceux infectés par le VHC (27,9 % par rapport à 4,1 %) et chez les sujets témoins (5,6 %). À l'analyse multivariée, il était possible de prédire l'IR par l'indice de masse corporelle (RRR 1,263; 95 % IC 1,078 à 1,480) et la triglycéridémie (RRR 1,011; 95 % IC 1,002 à 1,020) en cas de SHNA, et par le sexe (RRR pour les sujets de sexe féminin 0,297; 95 % IC 0,094 à 0,940) et la phase de la fibrose (RRR 2,751; 95 % IC 1,417 à 5,340) en cas d'hépatite C chronique.
CONCLUSIONS : L'IR s'associe de manière indépendante à l'IMC et à la triglycéridémie en cas de SHNA, et au sexe et à la fibrose en cas d'infection par le VHC chronique, et sa prévalence est plus élevée en cas de SHNA et d'hépatite C chronique que chez les sujets témoins. Cependant, la fréquence de SM chez les patients infectés par le VHC, similaire à celle des sujets témoins, est considérablement plus basse que chez les patients atteints de SHNA. Les critères diagnostiques actuels du SM sont plus susceptibles de « repérer » les patients atteints de SHNA que d'hépatite C chronique, même si les deux groupes sont insulinorésistants.

Type 2 diabetes is closely associated with nonalcoholic fatty liver disease (NAFLD) and highly prevalent in hepatitis C virus (HCV) infection (1,2), two liver diseases that share insulin resistance (IR) and hepatic steatosis as their prominent features (3). IR, which spans the gamut of biological adjustments stemming from impaired tissue response to the many insulin actions, represents the precursor of type 2 diabetes in predisposed individuals. IR and/or its histological correlate, steatosis, are common determinants of liver disease progression in both NAFLD (4-6) and HCV infection (7).

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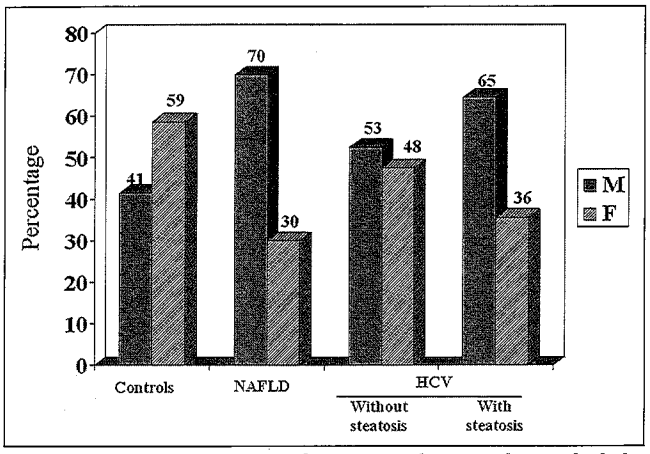

Figure 1) *Proportion of men and women in the control, nonalcoholic fatty liver disease (NAFLD) and hepatitis C virus (HCV)-positive patient groups. Steatosis due to NAFLD appears to be strikingly prevalent in men, as is steatosis associated with HCV infection. In contrast, in patients with HCV infection without steatosis, there is a substantial similarity in the prevalence of men versus women. Overall, the proportion of men is statistically highly significant in the various groups (P<0.001). M Male; F Female*

significant differences between the NAFLD, HCV and control groups in all parameters evaluated (Table 1). In particular, NAFLD patients showed significantly higher BMI, waist girth, serum cholesterol and triglycerides, and steatosis grade than HCV patients. The proportion of men was greater both in NAFLD and in HCV. However, the prevalence of men in those with HCV with steatosis was much higher than in those without steatosis.

The prevalence of MS and related parameters in the three study groups is reported in Table 2. In general, the metabolic disorders are significantly more prevalent in patients with NAFLD than in those with HCV infection (Table 2). However, there was no significant difference between NAFLD and HCV patients in the prevalence of hyperglycemia (19.6% versus 17.5%), and there was a trend for a higher prevalence of hypertension in HCV patients (24% versus 16.9%).

The prevalence of fasting hyperglycemia (fasting glucose of 6.11 mmol/L or higher) in HCV patients (17.5%) was higher than in controls (6.7%), ranking in the same order of magnitude as NAFLD patients (19.6%). The prevalence of hypercholesterolemia and hypertriglyceridemia was significantly higher in patients with NAFLD than in those with HCV infection (59.8% versus 17.5%, respectively; P=0.001) (Table 2). Similarly, the prevalence of obesity (ie, BMI 30 kg/m^2 or higher) was significantly higher in NAFLD patients than in those with HCV infection (34.4% versus 12.4%, respectively; P=0.001) (Table 2). Taken collectively, according to the ATP III modified criteria, the prevalence of MS was significantly higher in NAFLD than in HCV and in healthy controls (27.9% versus 4.1% versus 5.5%, respectively; P=0.001) (Table 2).

To assess the prevalence and independent predictors of IR, a logistic regression analysis was performed for NAFLD and HCV patients. A HOMA-IR value of greater than 2.6659, corresponding to the 75th percentile of the healthy controls value, was used as the dependent variable. All parameters evaluated in the patients and reported in Table 1 were used as independent variables. Age, sex and BMI were entered into the statistical analysis as covariates. As reported in Table 3, the prevalence of IR in NAFLD patients was 70% and the independent factors associated were BMI and triglycerides (Table 3). The prevalence of IR in HCV-infected patients was 78.7% (Table 4). There was no difference in the prevalence of IR among HCV genotype 1 and 2. The univariate analysis for HCV-infected patients revealed that the variables associated with IR were steatosis extent, fibrosis stage, inflammatory grade and HCV viral load. With multivariate analysis, male sex and fibrosis stage were independently associated with IR in this series of HCV-infected patients (Table 4). These same variables predicted IR when the analysis was limited to patients with HCV and steatosis more than 5% alone (data not shown).

DISCUSSION

Our study has three major findings: the low prevalence of MS in HCV, the determinants of IR among NAFLD and HCV patients, and the association of steatosis with the male sex.

MS

A high prevalence of IR, which is a hallmark of MS, was observed in both NALFD and HCV-infected patients (70% and 78.7%, respectively). Despite this, the two liver diseases under scrutiny display a significantly different prevalence of MS, as low in HCV-positive patients as in selected healthy controls – 4.1% versus 5.5%, respectively – versus 27.9% among NAFLD patients. Stated otherwise, the present study demonstrates that, although they are indeed insulin resistant, HCV patients are spared from the development of MS. In contrast, IR observed in the setting of NAFLD has a significant connection with the development of the MS. In the few previously published studies (10-12), the ratio of the prevalence of MS in NASH to the prevalence of MS in HCV has been found to range from 2 to 8 (Table 5). We included all the NAFLD

TABLE 2
Prevalence of metabolic syndrome and its components

Condition*, n (%)	Controls (n=182)	Nonalcoholic fatty liver disease (n=93)	Chronic hepatitis C genotypes 1 and 2 (n=97)	P†	χ^2
Obesity	7 (4.2)	31 (34.4)	12 (12.4)	<0.001	44.046
Hypercholesterolemia	95 (52.2)	55 (59.8)	17 (17.5)	<0.001	41.514
Hypertriglyceridemia	29 (15.9)	44 (47.8)	12 (12.4)	<0.001	43.452
Hyperglycemia	12 (6.7)	18 (19.6)	17 (17.5)	0.003	11.562
Arterial hypertension	34 (47.9)	11 (16.9)	17 (24.0)	<0.001	17.366
Metabolic syndrome	10 (5.5)	26 (27.9)	4 (4.1)	<0.001	21.682

**Diagnostic Criteria: Obesity: Body mass index ≥30 kg/m^2; Hypercholesterolemia: Total cholesterol ≥5.17 mmol/L; Hypertriglyceridemia: Serum triglyceride levels ≥1.7 mmol/L; Hyperglycemia: Taking glucose-lowering drugs or fasting glucose ≥6.1 mmol/L in the absence of any such treatments; Arterial hypertension: Taking antihypertensive drugs or arterial blood pressure ≥130/85 mmHg in the absence of any such treatments.†Refers to multiple comparisons*

TABLE 3
Prevalence and predictors of insulin resistance in nonalcoholic fatty liver disease

Variable	B	SE	P	OR	95% CI	Overall correct, %
Age	0.017	0.026	0.505	1.018	0.967–1.071	
Sex	-1.061	0.687	0.123	0.346	0.090–1.331	
Body mass index	0.233	0.081	0.004	1.263	1.078–1.480	70.0
Triglycerides	0.011	0.004	0.014	1.011	1.002–1.020	
Constant	-8.649	2.640	0.001	0.000	–	

TABLE 4
Prevalence and predictors of insulin resistance in hepatitis C-naive genotype 1 or 2

Variable	B	SE	P	OR	95% CI	Overall correct, %
Age	0.042	0.030	0.154	1.043	0.984–1.105	
Body mass index	0.085	0.071	0.232	1.089	0.947–1.251	
Female	-1.213	0.587	0.039	0.297	0.094–0.940	78.7
Staging	1.012	0.338	0.003	2.751	1.417–5.340	
Constant	-4.607	2.393	0.054	0.010	–	

TABLE 5
Prevalence of the metabolic syndrome assessed through the Adult Treatment Panel III criteria for nonalcoholic fatty liver disease (NAFLD), hepatitis C virus (HCV) and control group in published studies

Author (reference)	Series (NAFLD/HCV)	NAFLD, %	HCV, %	Metabolic syndrome NAFLD/HCV ratio	Controls, %
Targher et al (10)	60/60	52.05*	25.	2.1	0.0
Svegliati-Baroni et al (11)	90/90	22.2	4.4	5.04	NA
Tsochatzis et al (12)	176/95	41.3*	5.1	8.09	NA
Present study†	93/97	27.9	4.1	6.38	5.5

**Only nonalcoholic steatohepatitis patients were included; †The metabolic syndrome was diagnosed through the modified Adult Treatment Panel III criteria; 31% of patients had pure fatty liver. NA Not addressed*

patients rather than those with NASH alone, and we used BMI rather than waist girth to calculate the prevalence of MS. In spite of these methodological differences, the results of the present study found a ratio of 6.38 between the prevalence of MS in NAFLD and in HCV-infected patients (Table 5). This ratio falls within the range reported by other authors (10-12). This finding confirms that HCV is associated with IR rather than with the MS. Hence, the definition of a peculiar HCV-associated dysmetabolic syndrome has been proposed (22). Our findings may be clinically relevant. Patients with chronic hepatitis C rarely manifest fullblown MS as presently defined, although they are insulin resistant. This implies that either specific criteria for MS in patients with HCV infection should be envisaged or, alternatively, importance should be given to the demonstration of IR as a diagnostic criterion of MS.

Determinants of IR

The independent predictors of IR are also different for NALFD and HCV-infected patients. Although previous studies (9,11) reported an independent association between hepatic fibrosis and IR on the one hand, and MS on the other, our study followed a different approach. We addressed the determinants of IR rather than those of fibrosis in both NAFLD (not NASH alone) and HCV. What we found is that BMI and serum levels of triglycerides are independently associated with IR in NAFLD patients, whereas, male sex and histological fibrosis are associated with IR in HCV genotypes 1- or 2-infected patients. It is well known that BMI and triglycerides are independent correlates of NAFLD (23). The data in the present study show that the same determinants that apply to the development of NAFLD are also associated with IR, and support the role of IR in the process of steatogenesis. Little is known about the differential impact of varying HCV genotypes (7). In the present study, we studied HCV genotypes 1 and 2 together. However, a recent paper (24) suggested that for similar analyses, genotype 1 may be grouped with genotype 4, while genotype 2 may be grouped with genotype 3. According to this paper, the analysis of genotype 1 and 2 HCV-infected patients together might therefore not be appropriate for studying the association with IR. However, our study was planned and performed largely before the publication of that study (24) and we believe additional data are needed before any ultimate conclusion can be drawn regarding the role of HCV genotypes in IR. Host (ie, steatosis) (25,26) and viral factors (high viral load and viral genotypes 1 and 4 in IR linked to HCV infection [24,27,28]) have recently been reported to predict IR in HCV infection. Our study demonstrated that fibrosis predicts IR in our HCV patients and is also compatible with these previous reports given that steatosis is a well known precursor of fibrosis (13,26), and that high viral load is a risk factor for histological liver damage (29).

Role of sex

Ancillary findings of our study include that steatosis – metabolic (ie, NAFLD) and HCV-related – is prevalent among men. While the prevalence of male sex in NAFLD is universally accepted (30), data concerning sex prevalence in HCV-related steatosis are more controversial. Poynard et al (31) reported a

male prevalence among those with steatosis. Cammà et al (32) reported that female sex is associated with moderate to severe steatosis. However, the finding that in chronic hepatitis C, the probability of fibrosis F2-F4 was lower for menopausal women receiving hormone replacement therapy, and that steatosis was more frequent and more severe in menopausal women (33), adds further evidence to the specific role of estrogens in the progression of HCV-related liver disease.

The present study may have some limitations related to the modified diagnostic criteria of MS and the choice, as the control group, of healthy nonsteatosic subjects who, by enrollment criteria, encompass a group at low risk for MS. This may have lowered the bar for HOMA-IR in an average-risk general population and thus, the results cannot be universally applied to the general population, but maintain their value in the specific series reported here.

CONCLUSION

Our study shows the prevalence of MS to be significantly higher in patients with NAFLD than that observed in subjects with chronic hepatitis C, although both conditions feature steatosis and a high prevalence of IR. This latter point was related to anthropometric (BMI) and metabolic (triglycerides) derangements in NAFLD but not in chronic hepatitis C patients, in whom other factors (eg, sex and fibrosis score) seem to play a major role. The prevalence of MS in HCV-infected patients was similar to that of healthy nonsteatotic control subjects. Given that the current criteria for the diagnosis of MS are based on anthropometric and metabolic measurements, the results of the present study explain the apparent paradox that chronic hepatitis C patients, although often insulin resistant, are seemingly 'spared' from MS.

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