High prevalence of advanced fibrosis in association with the metabolic syndrome in a Belgian prospective cohort of NAFLD patients with elevated ALT. Results of the Belgian NAFLD registry

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Abstract

Introduction : **Non-alcoholic Fatty Liver Disease (NAFLD) is increasingly recognised as a source of liver related morbidity and mortality. Hard data on epidemiology and natural history are scarce.**

Aim : **To study demographic and metabolic characteristics of the NAFLD patients seen by Belgian hepatologists.**

Methods : **Belgian hepatologists filled in a questionnaire for every newly diagnosed NAFLD patient between January 1st and December 31st 2004. Liver biopsy was advised if ALT > 1.5 × ULN and if 3/5 of the criteria for the metabolic syndrome (MS) (ATPI-II) were present, but was not mandatory. Biopsy was scored using the Brunt classification.**

Results : **230 patients were prospectively included in 9 centres ; 54% were males ; mean age was 49.4 ± 13.9 y ; mean BMI was 30.6 ± 4.6 kg/m². The MS was present in 53%. In 16% formerly undiagnosed diabetes was discovered. 51% had a liver biopsy : 25% met the criteria, 26% did not. Grading did not differ between patients with or without MS. Staging was significantly more severe in patients with MS (2.43 ± 1.25 vs. 1.73 ± 1.18, p < 0.001). A subgroup of patients with GGT > 5 × ULN were significantly older (55.9 vs. 47.64 y, p = 0.02), more frequently diabetic (53% vs. 23%, p = 0.01) and had more advanced fibrosis (3.42 vs. 1.08, p = 0.008). ALT levels were variable.**

Conclusions : **The MS is highly prevalent in Belgian NAFLD patients and is associated with more severe disease. Mild to moderate fibrosis is frequent, and the proposed criteria for liver biopsy are not accurate in selecting these patients. Patients with elevated GGT constitute a subgroup with more advanced disease.** (Acta gastroenterol. belg., **2011**, 74, **9-16**).

Key words : steatosis, fibrosis, overweight, diabetes, GGT.

Introduction

Non-alcoholic Fatty Liver Disease (NAFLD) is defined as the presence of fat accumulation in > 5% of hepatocytes in the absence of significant alcohol use and other causes of secondary steatosis (1). Non-alcoholic Steatohepatitis (NASH) refers to the presence of steatosis, accompanied by inflammation and signs of hepatocellular damage, and hence constitutes a subgroup of NAFLD patients (2). NAFLD and NASH are increasingly recognised as sources of liver-related morbidity and mortality with an important impact in terms of disease burden (3). Exact data on prevalence and natural history are, however, rather scarce and suffer from multiple methodological problems (4).

Patient selection, the absence of accurate non-invasive diagnostic tools and the absence of a reliable method to distinguish alcoholic from non-alcoholic liver disease are the main concerns in interpreting the available epidemiological data (4). It is, however, generally accepted that NAFLD and NASH prevalences in the Western adult population are 20-30% and 2% respectively (3,5-7).

Simple steatosis is usually regarded as a benign condition (1). NASH, however, may lead to progressive fibrosis and ultimately cirrhosis and its complications(8). Liver biopsy remains the best standard for the diagnosis of NASH (1). In view of the disease burden and the obvious limitations of liver biopsy, there is an important need for non-invasive parameters or tools to identify patients at risk for progressive disease.

Epidemiological data also allowed identifying some relevant risk factors such as age and male gender (7,9, 10). Of particular interest is the epidemiological association between NAFLD/NASH and the metabolic syndrome (MS) (11). MS is a clinical entity comprising overweight and obesity (more specifically visceral obesity), dyslipidaemia, arterial hypertension and disturbances in glucose homoeostasis (12). Although not included in the definition, more and more authors consider NAFLD to be the hepatic manifestation of the MS. Even if the exact causal relation remains to be elucidated, the evidence linking NAFLD to the MS seems convincing (6,11).

Because data on NAFLD in the Belgian population are lacking, a study group of the Belgian Association for the Study of the Liver (BASL) initiated a registry, in an attempt to gain epidemiological information on the

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NAFLD patients seen by the Belgian hepatologists in their routine practice, with, besides collecting the classical biochemical, ultrasonographic and (when available) histological data, a special emphasis on the metabolic risk factors. In this paper we present the results of this registry.

Materials and methods

All Belgian gastro-enterologists, member of the BASL, were invited by mail to participate on a voluntary basis. They were asked to fill in, after obtaining written informed consent, a questionnaire on every newly diagnosed NAFLD patient who presented at their practice between January 1st and December 31st 2004.

For inclusion in the registry 4 criteria had to be fulfilled : elevated alanine aminotransferase (ALT) ; hyperechogenic liver on ultrasound ; at least 1 out of 3 risk factors [obesity (Body Mass Index (BMI) > 30 kg/m^2)/overweight (BMI > 25 kg/m^2) (13), hyperglycaemia (fasting glucose > 110 mg/dL), hypertriglyceridaemia (serum triglycerides > 150 mg/dL)] ; exclusion of any other liver disease including alcohol use defined as > 30 g/d in men and > 20 g/d in women was used (14). As liver biopsy was not a prerequisite for the diagnosis of NAFLD, the inclusion criteria were designed to exclude cases in which the diagnosis of NAFLD might have been doubtful (in the absence of histological proof) and were based on the available data on risk factors for NAFLD and NASH (9-11).

The questionnaire included different elements. Patients were identified by initials, age and birth day. Gender was recorded. Criteria for inclusion in the registry were checked. In the metabolic history section a past history of obesity (defined as BMI > 30 kg/m^2) (13), of diabetes (defined as fasting glycaemia ≥ 126 mg/dL) (15,16), of systemic arterial hypertension (defined as blood pressure > 140/90 mm Hg) (16), of hyperlipidaemia (with a distinction between hypercholesterolaemia and hypertriglyceridaemia, without a definition incorporated in the registry) and of treatment for obesity, diabetes, hyperlipidaemia and arterial hypertension were recorded, with the invitation to provide details if any therapy was given in the past.

In the current metabolic status section, the date of examination, body weight (kg), length (cm) and BMI (kg/m^2) were recorded. The investigators had to mention whether the arterial pressure in the supine position was ≤ or > 140/90 mm Hg (16), and whether the waist circumference was ≤ or > to 102 cm in men and 88 cm in women (12). They also had to mention whether there was a current treatment for obesity, diabetes, hyperlipidaemia or arterial hypertension and were asked to provide details when applicable.

In the biochemical profile section, first some metabolic parameters were recorded. The date of examination was noted. Fasting glycaemia was recorded as absolute value (mg/dL) and scored according to 3 categories : ≤ 110 mg/dL, > 110 mg/dL and ≤ 126 mg/dL, or > 126 mg/dL (15). HbA1c was recorded as normal (≤ 6%) or elevated. Absolute values of fasting insulinaemia (μU/mL) and fasting c-peptidaemia (nmol/L) were noted. Total cholesterol was scored : < 200 mg/dL, 200-250 mg/dL or > 250 mg/dL (17). Low Density Lipoprotein (LDL) cholesterol was scored ≤ or > 130 mg/dL. High Density Lipoprotein (HDL) cholesterol was scored ≤ or > 40 mg/dL in men and ≤ or > 50 mg/dL in women (12), and their absolute value was recorded. Triglycerides were scored ≤ or > 150 mg/dL and the absolute value was recorded (17). Homocystein absolute value (mg/dL) was recorded if available. Serum iron (μg/dL), iron saturation (%) and ferritin (ng/mL) were recorded. If genetic testing was performed, the investigator was asked to record if the C282Y mutation was present or not.

The biochemical profile section also comprised a set of liver-related parameters. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (GGT) were scored according to ratio of the absolute value to the upper limit of normal (ULN) set by the investigator's local lab, as absolute values and the reference normal values may vary substantially according to the laboratory tests that were used. AST, ALT and GGT were scored ≤ 1, > 1-2, >2 or >5 × ULN. ALP was scored ≤ 1, > 1-2, > 2 × ULN. Based on the absolute value, albumin was scored ≤ or > 3.5 g/L ; bilirubin ≤ 1.5 mg/dL, > 1.5-3 mg/dL or > 3 mg/dL ; platelet count < 75 × 10^9/L, 75-150 × 10^9/L or > 150 × 10^9/L and International Normalized ratio (INR) < 1.1, 1.1-1.4 or > 1.4.

Liver biopsy was not a prerequisite for inclusion in the registry. A liver biopsy was advised if ALT was ≥ 1.5 × ULN at least 2 times in the previous 6 months, and if at least 3 of the 5 US Third Adult Treatment Panel of the National Cholesterol Education Programme (NCEP-ATP III) criteria for the MS were met (12). These 5 criteria are : visceral obesity based on waist circumference > 102 cm in men or > 88 cm in women ; arterial hypertension (blood pressure > 130/85 mm Hg or treated) ; low HDL cholesterol (< 40 mg/dL in men or < 50 mg/dL in women) ; hypertriglyceridaemia (fasting triglyceridaemia > 150 mg/dL or treated) ; abnormal carbohydrate metabolism (fasting glycaemia > 110 mg/dL or hyperinsulinism or treated diabetes) (12). In 2005 the International Diabetes Federation adapted new criteria for the definition of the MS (18), but as the registry was performed in 2004, the diagnosis of the MS was still based on the ATPIII criteria.

If a biopsy was performed, the date was recorded, and it was asked whether the recommended criteria were met. If a biopsy was not performed, it was asked whether this was the physicians choice or because of patient's refusal or whether there was a specific contraindication to perform a liver biopsy.

To avoid inter-observer variation, there was a centralised reading of the liver biopsies by one single

experienced pathologist, based on a haematoxylin-eosin stain and a Sirius red stain (for connective tissue). Histopathology recording were limited to the grade of steatohepatitis (G) (scored 0-3) and the stage of fibrosis (S) (scored 0-4) according to Brunt et al. (19). Brunt's scoring of fibrosis is identical to the currently used NASH Clinical Network Scoring System (20), that is only in use since its publication in 2005. The grade of steatohepatitis in the Brunt score (0 = no steatohepatitis, 1 = mild, 2 = moderate, 3 = severe) is different from the grading of steatosis in the NASH Clinical Network Scoring System (20), as the latter only scores steatosis and not the overall picture of steatosis, ballooning and inflammation.

In a final section, the investigators were asked if they had prescribed, besides diet and physical exercise, pharmacological treatment (fibrate, statin, metformin, sulfonylurea, sibutramin, orlistat, or other).

Data were pooled in a central database. Results are presented as mean ± standard deviation (SD). Continuous variables were compared with Student T test. Categorical variables were compared with Chi square or Mann Whitney U test. Correlation analysis was performed, as was a binary logistic regression in order to identify independent predictive factors. A p-value of < 0.05 was considered statistically significant.

Results

General and metabolic characteristics

Two hundred thirty patients were prospectively included by 17 physicians in 9 centres. Gender distribution was 126 (54%) male. Mean age was 49.9 ± 13.9 y, range 15-79 y.

Mean BMI was 30.6 ± 4.6 kg/m^2, range 20-45 kg/m^2. Thirty (13%) had a BMI < 25 kg/m^2 meaning that 13% of patients were not overweighed. Patient distribution according to BMI is illustrated in Fig. 1.

Two hundred patients had sufficient data to reliably evaluate the criteria of the MS. The distribution according to the number of criteria present is shown in Fig. 2. The MS could be diagnosed in 105/200 (53%). If every criterion was accorded 1 point, the mean score was 2.6 ± 1.3, with visceral obesity (56%) and hypertriglyceridaemia (55%) being the most prevalent. The presence of each of the criteria is illustrated in Fig. 3.

In 37 patients (16%) formerly undiagnosed diabetes was discovered. Fasting insulinaemia was significantly elevated in patients with the MS (27.02 ± 10.9 μU/mL in patients with the MS vs. 17.65 ± 6.09 μU/mL in patients without the MS, p = 0.004).

Metabolic history

In patients in whom sufficient information was provided (227/230), 14.5% had a history of or an ongoing treatment for obesity, 37.3% for arterial hypertension (10.2% b-blockers, 9.3% angiotensin converting enzyme inhibitors, 8.3% calcium channel blockers, 0.5% miscellaneous or combined treatment), 27.3% for diabetes (20.2% metformin, 5.0% other oral antidiabetics, 2.1% insulin treatment) and 34.4% for dyslipidaemia (17.2% fibrate, 15.8% statin, 1.4% miscellaneous or combined treatment). A combined treatment for at least 2 of these 4 conditions was present in 63.2%.

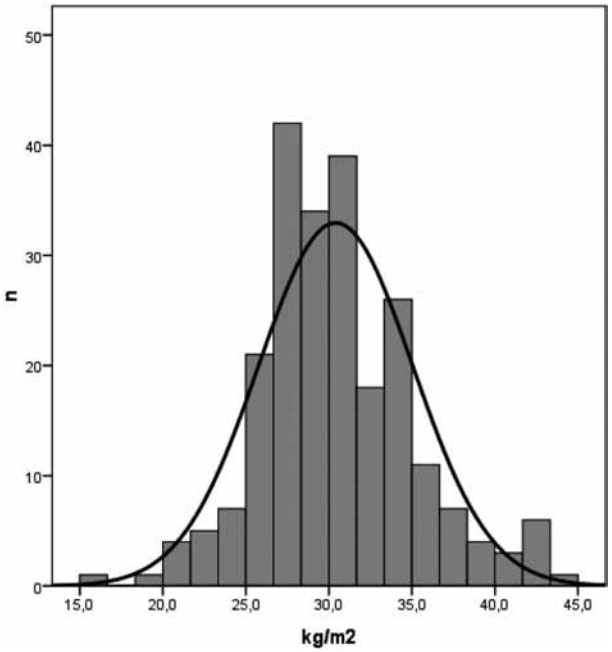

Fig. 1. — BMI distribution of the BASL NAFLD registry patients. n = number of patients, BMI = body mass index (kg/m2).

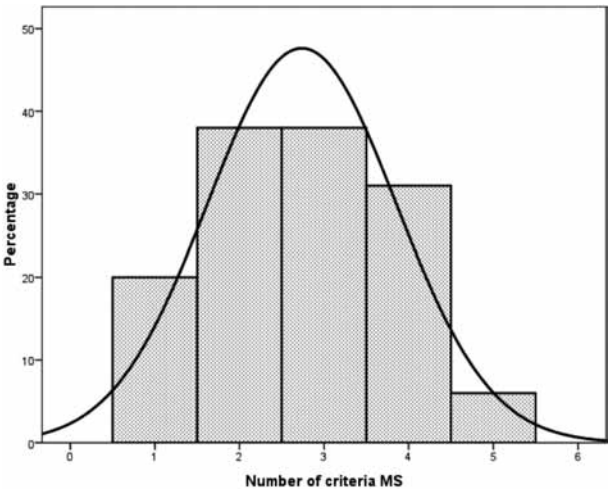

Fig. 2. — Distribution, expressed in percentages, according to the number of criteria of the metabolic syndrome present according to the Adult Treatment Panel III definition.

Liver histology

A liver biopsy was performed in 117/230 (51%) patients. According to the pre-established criteria in

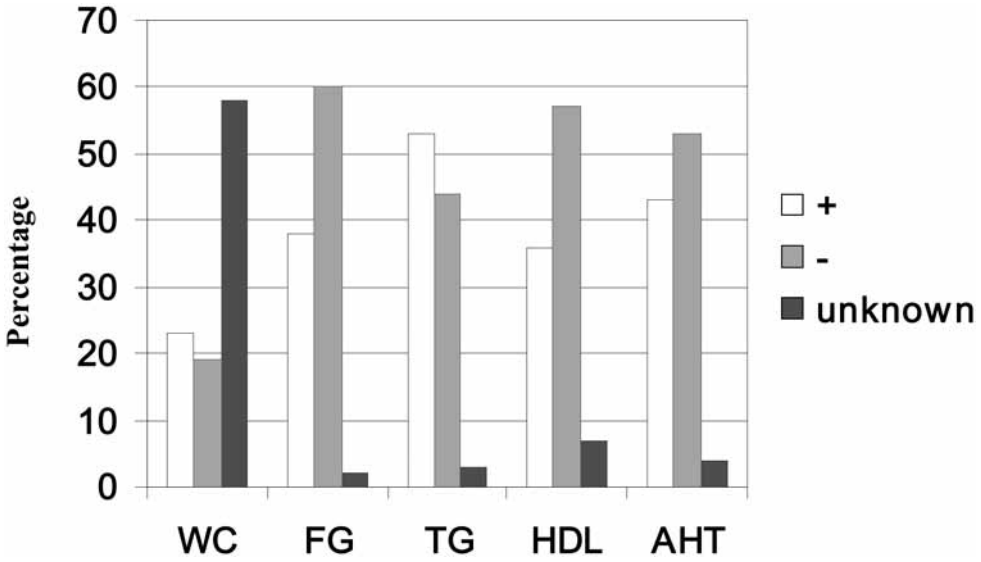

Fig. 3. — Presence of the 5 different criteria of the metabolic syndrome (in %). WC = waist circumference ; FG = fasting glucose ; TG = triglycerides ; HDL = high density lipoprotein ; AHT = arterial hypertension.

which a biopsy was recommended by the registry, 57 of the 117 patients in whom a biopsy was performed met the recommended criteria, 60 did not.

Twenty-five patients (11%) of the overall cohort did not have a biopsy, although they met the recommendations. In 22 cases the latter was based on the physician's decision, in 3 patients because of patient's refusal. Table 1 summarizes the data on biopsy and criteria fulfilment. In 3 patients (1%) it was not clear from the data whether they met the criteria, all 3 did not have a liver biopsy.

The results for grading and staging are summarized in Table 2. Sixteen patients had grade 0. Five of them had minimal steatosis, but besides that also showed significant ballooning, lobular inflammation and/or glucogenated nuclei, confirming the diagnosis of NASH. Thirteen had cirrhosis. It is known that in the cirrhotic stage, steatosis can disappear. The diagnosis was withheld based on clinical, metabolic and biochemical arguments.

If significant fibrosis is defined as stage ≥ F2, 61% had significant fibrosis. Severe fibrosis (F3-4) was present in 34%.

Grading and staging were also compared between patients without and with the MS (Fig. 4 A/B). Grading did not differ between patients with or without MS (1.45 ± 0.94 vs. 1.64 ± 0.77 for patients without and with the MS respectively, $p = 0.483$). Staging, however, was significantly more severe in patients with MS (2.43 ± 1.25) compared to patients without (1.73 ± 1.18) ($p < 0.001$).

Liver biochemistry

As elevated ALT was a prerequisite for inclusion in the registry, patients never had ALT ≤ 1 × ULN. The majority of patients had an ALT > 1 but < 2 × ULN (68%) ; 31% had ALT 2-5 × ULN and 3% had ALT > 3 × ULN. ALT category did not correlate significantly with any metabolic, biochemical or histological parameter. AST did not show any relevant correlation.

The distribution according to GGT was as follows : 20% had a normal GGT level ; 36% 1-2 × ULN ; 34% 2-5x ULN and 10% > 5 × ULN. Only 20% of patients thus had a normal GGT, and almost half of the patients had a GGT > 2 × ULN. A specific correlation between GGT and metabolic, biochemical or histological parameters could not be found. However, the 22 (10%) patients with a GGT > 5x ULN constituted a subgroup of patients who were, compared to the others, significantly older (55.9 ± 13.5 vs. 47.6 ± 14.8 y, $p = 0.02$), who were more frequently diabetic (53% vs. 23%, $p = 0.01$), who had higher levels of triglycerides (215 ± 34 vs. 159 ± 19 mg/dL, $p = 0.003$) and who had more advanced fibrosis (3.42 ± 1.07 vs. 1.08 ± 0.99, $p = 0.008$) (a biopsy was performed in 12/22).

Treatment

Treatment was started by 7/17 physicians in 55 patients. Treatment consisted of fibrates (22 patients), metformin (19 patients), ursodeoxycholic acid (11 patients), statins (6 patients), orlistat (6 patients), thiazolidinedions (2 patients) and vitamin E (1 patient). No specific analysis could be performed on these data.

Discussion

Although NAFLD is presumably the most prevalent liver disease in the Western population, consistent data on the prevalence and natural history of NAFLD and NASH are still scarce. We analysed the data of the registry, conducted in 2004 by the BASL on newly diagnosed NAFLD patients seen by Belgian hepatologists. The

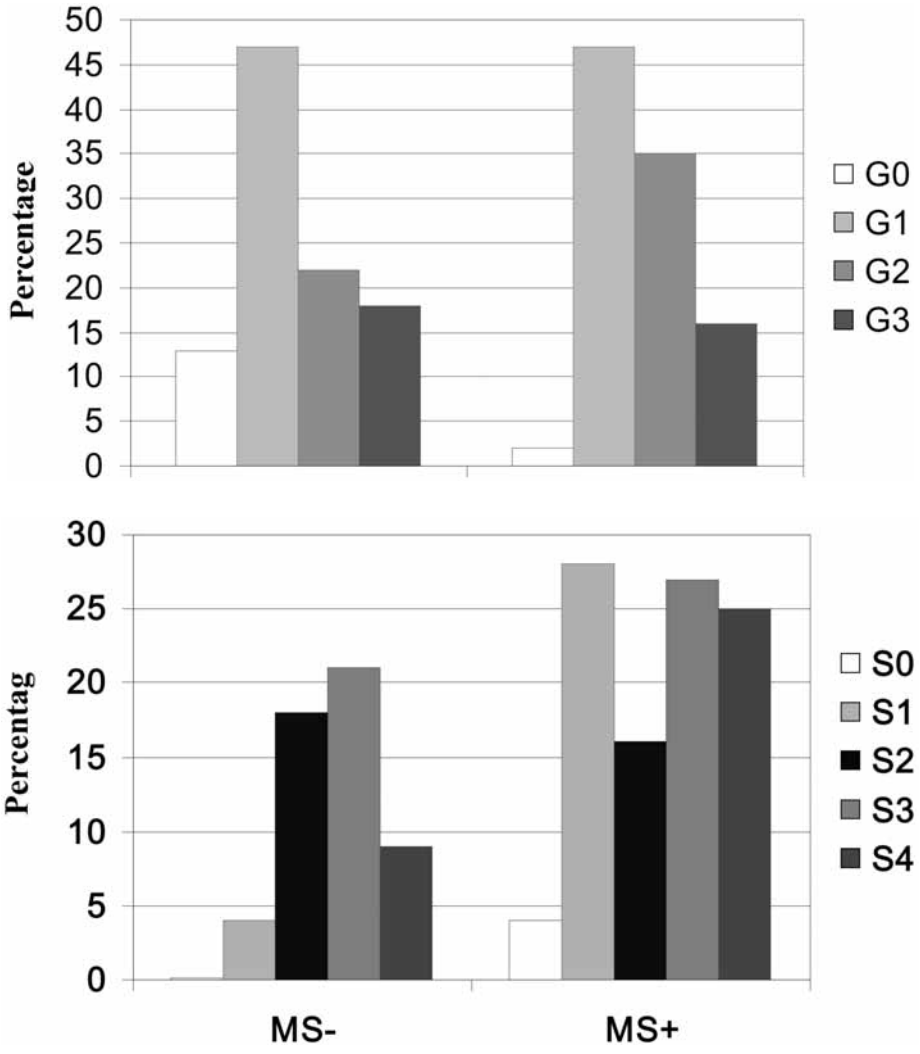

Fig. 4. — Patient distribution, expressed in percentages, according to grading (Fig. 4A) and staging (Fig. 4B) (n = 117). Grading is scored 0-3. Staging is scored 0-4. Y-axis represents percentages. MS = metabolic syndrome ; - = absent ; + = present ; G = grade ; S = stage.

patients in the registry show a high prevalence of advanced liver fibrosis in relation to a high prevalence of features of the MS. Elevated GGT is associated with more advanced disease.

A first conclusion of our registry is indeed a high prevalence of the MS and its features. More than half of the patients are obese, which is strikingly more than in the adult Belgian population, with a prevalence of obesity estimated at 15% (21). This illustrates the role of obesity as a risk factor for NAFLD. Nevertheless, 13 % of patients were not obese or not even overweighed, confirming earlier findings that a normal BMI does not exclude NAFLD (22). The percentage of patients meeting the criteria of the MS is very high : 53%. European data based on the DECODE (Diabetes Epidemiology : Collaborative analysis of Diagnostic criteria in Europe) study showed an overall prevalence of the MS in non-diabetic adult Europeans of 15% according to the modified World Health Organisation criteria (23). Using the NCEP-ATP III criteria, an Italian cohort analysis suggests the presence of the MS in 18% of women and 15% of men (24). In NAFLD patients, a prevalence of 31% was reported by Marchesini *et al*. using the same criteria (11). Also in line with the data presented by Marchesini *et al*. (11), visceral adiposity and hypertriglyceridaemia are amongst the most prevalent features of the MS in our registry. Our results hence confirm the high prevalence of features of the MS in NAFLD patients, underlining the potential causal interplay between these entities.

The role of glucose homoeostasis disturbances merits further attention. Thirty nine % of the patients had a fasting glycaemia of > 110 mg/dL or were treated for diabetes. In the Marchesini series only 12% met this criterion (11). In 16% of these relatively young patients, formerly undiscovered diabetes was diagnosed. Hyperinsulinism was highly prevalent. If the IDF criteria would have been used, data would have been even more striking (18). Diabetes has been identified as a risk factor for inflammation (NASH) and progressive fibrosis in

Table 1. — **The performance of the liver biopsy in relation to the recommended indications. The table summarizes the absolute number and percentage (between brackets) of patients according to whether the recommended criteria were met or not, and whether the biopsy was indeed performed or not. The Table also summarizes the data for both items**

		Criteria for liver biopsy		Total
		absent	present	
Biopsy performed	no	85 (37)	25 (11)	110 (48)
	yes	60 (26)	57 (25)	117 (51)
Total		145 (63)	82 (36)	227 (99)

Table 2. — **Results of grading and staging of 117 liver biopsies. Grading is scored 0-3. Staging is scored 0-4. Absolute numbers (N) and percentages are given**

		N	%
Grade	0	16	13
	1	50	43
	2	23	19
	3	28	25
Stage	0	6	5
	1	40	34
	2	32	27
	3	24	21
	4	15	13

NAFLD (10,25), and liver diseases are now recognised as an important source of disease-specific morbidity and mortality in type 2 diabetics (26), presumably because of NASH. Our data hence stress the important link between disturbances in glucose homoeostasis and NAFLD.

Central reading of over one hundred biopsies shows significant fibrosis in two thirds of the patients and severe or advanced fibrosis in one third. Many patients thus have a significant liver disease. Factors associated with the severity of liver disease were the MS and some of his features. In patients meeting the MS criteria, the mean fibrosis score was significantly higher than in patients without the MS. This is in line with Marchesini *et al*., who found a prevalence of the MS in 14% of patients with simple steatosis, in contrast to 38% in patients with NASH (which is considered to be the more aggressive form of NAFLD, potentially associated with progressive fibrosis) ($p = 0.004$) (11). This is also in line with the known risk factors for fibrosis, as already discussed (27-29). More advanced fibrosis was also seen in the small subgroup of patients with markedly elevated GGT. These patients not only had more advanced fibrosis, but also had significantly more frequently diabetes. This was not unexpected. Diabetes is known to be a major risk factor for NASH : 15% of patients with diabetes have simple steatosis, but 56% have NASH (30). Patients with NAFLD and diabetes develop cirrhosis in 23.9% and experience liver related death in 19% of cases, compared to 10.6% and 2% in NAFLD patients without diabetes respectively (30). We can conclude that in this selected population, advanced liver disease is a frequent finding, with an increased risk in case of diabetes and the MS, again confirming the strong link between NAFLD and the MS.

The pathophysiology of the link between NAFLD and the MS is still incompletely understood. MS-linked hyperinsulinism and a subsequent flux of free fatty acids are believed to be key factors in the pathogenesis of steatosis (31). Adipokines, secreted by visceral adipose tissue are involved in the evolution from steatosis to steatohepatitis, as are oxidative stress generated by lipid peroxidation and some cytokines (e.g. Tumour Necrosis Factor alpha and interleukin-6) (32,33). Many of these factors are leading to recruitment and activation of Kupffer cells and the transformation of stellate cells into myofibroblasts, both of which contribute to progressive liver disease (33). Steatohepatitis might in turn contribute to the severity of glucose and lipid homeostasis disturbances, making NAFLD and NASH a causal element in the development of the MS (8).

ALT elevation, according to local lab limits, was a prerequisite for inclusion. Therefore our conclusions only apply to patients with elevated ALT. It is interesting to see that relatively few patients had ALT > 2 × ULN. In many papers and guidelines, 2 × ULN is frequently used as a cut-off for significant disease or as a criterion in guidelines for further investigation (34). Our results challenge this cut-off, as most of the patients would have been excluded from the registry if this guideline was adopted. We were not able to find any correlation between ALT category and metabolic, biochemical or histological parameters. This confirms that ALT value is of little use in the diagnosis of significant liver disease, and is hardly acceptable as a criterion in guidelines (35). The recent suggestion by Prati *et al*. to lower the cut-off value for normal ALT further questions the relevance of ALT ULN (36,37). We may conclude that ALT value is of little use in assessing disease severity, and that the cut-off level of 2 × ULN should not be used, as it excludes a lot of patients with advanced liver disease.

Finally GGT appeared to be a relevant biochemical marker, as strongly elevated GGT identified a group of older patients, who had more frequently diabetes, and had more advanced fibrosis. GGT is usually regarded as a parameter with poor specificity. It is of notice, however, that GGT appeared to be correlated to fibrosis-score in a large cohort of hepatitis C patients, and that was subsequently included as one of the 5 parameters to calcu-

late an index used to give a non-invasive estimate of liver fibrosis in hepatitis C (38) and in NAFLD (34). GGT is now considered, along with ALT, as one of the most important liver tests related to hepatic steatosis (5,39). A recent analysis of a large cohort of overweighed and obese patients also confirmed the role of GGT as a marker for liver involvement in relation to visceral fat accumulation (40). Elevated GGT should therefore be regarded as an important parameter for the presence of NAFLD.

Some methodological issues should be taken into account to correctly interpret the results. The study was confined to the members of the BASL and participation was on a voluntary basis. As a consequence, most of the patients included will presumably come from physicians with a special interest in hepatology and more specifically in NAFLD. Patients with normal ALT were excluded, based on the assumption that such patients are rarely referred for further diagnostic evaluation and would hence be rare. It is known, however, that ALT can be normal in NAFLD, and that elevation of ALT does not correlate with disease severity (35,37). The presence of a hyperechoic liver parenchyma on ultrasound was another inclusion criterion. Sensitivity and specificity for detection of moderate to severe steatosis are 70-75% and 60-65% respectively (5). For minor degrees of steatosis, ultrasound is, however, less accurate (41). Accuracy also decreases in morbidly obese patients, with a sensitivity of only 40% (42). A third criterion was the presence of at least 1 out of 3 known risk factors for NAFLD, also closely related to the MS. All these criteria were set to have as much certainty as possible on the diagnosis of NAFLD, as a formal histological proof was expected to be missing in a majority of patients, and to avoid including many patients in whom the diagnosis of NAFLD could be seriously questioned. It is, however, evident that these criteria create a certain bias, as patients with mild disease or less typical presentations (e.g. normal ALT, normal appearance of liver parenchyma on ultrasound, absence of classical metabolic features) are excluded. Therefore the registry cannot claim to cover the whole spectrum of NAFLD patients.

A liver biopsy was not mandatory for inclusion in the registry. To date evidence based-guidelines concerning the selection of patients for liver biopsy, are lacking. Biopsy should be restricted to those patients with a risk of more advanced disease, which means, in our actual understanding of NAFLD, progressive fibrosis (27-29). Based on the available data (10,25,27,34), we proposed some criteria. The recommendations were, however, of little influence on the physician's decision, as a lot of biopsies were performed although the recommendations were not met, and a lot of patients who met the criteria did not undergo a biopsy. This seems to reflect the complete absence of clear evidence based-guidelines to select patients for biopsy, leaving the decision to the discretion of the physician.

Conclusion

NAFLD patients with elevated ALT seen by Belgian hepatologists in routine practice are middle-aged men or women, with a particularly high prevalence of the MS and its features. Advanced fibrosis is frequent, and is related to the MS, especially in case of diabetes. These data further underline the intimate, presumably causal relationship between NAFLD and the components of the MS. Our data do not provide clear liver biopsy indication guidelines. They confirm, however, the limited value of ALT in assessing disease severity. Strongly elevated GGT appears to be a marker of more advanced disease in relation to older age and diabetes.

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List of abbreviations

ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
DECODE	Diabetes Epidemiology : Collaborative analysis of Diagnostic criteria in Europe
GGT	Gamma Glutamyl Transpeptidase
HDL	High Density Lipoprotein
IDF	International Diabetes Federation
INR	International Normalized Ratio
LDL	Low Density Lipoprotein
MS	Metabolic Syndrome
NAFLD	Non-alcoholic Fatty liver Disease
NASH	Non-alcoholic Steatohepatitis
NCEP-ATPIII	Third US Adult Treatment Panel of the National Cholesterol Education Program
SEM	Standard Error of the Mean
ULN	Upper Limit of Normal

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