Significant non-alcoholic fatty liver disease is found in non-diabetic, pre-obese Chinese in Singapore

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ABSTRACT

Introduction: To characterise the anthropometrical and metabolic parameters of a group of non-diabetic and non-obese patients who had histologically-proven non-alcoholic steatohepatitis (NASH).

Methods: During September 1997 to November 1999, consent for liver biopsies were sought from a consecutive series of patients, whose body mass index (BMI) were equal to or less than 30 kg per square metres, and who had persistently elevated serum alanine transaminase (more than 2.5 times upper limit of normal for more than six months), with no associated viral hepatitis, alcohol or drug-induced liver disease, hereditary liver disease and diabetes mellitus. Patients who were found to have steatohepatitis histologically were further studied. Their body weight, height, waist and hip circumferences were taken, and fasting serum lipid and glucose measured. Serum insulin was measured in six patients and insulin resistance (IR) was calculated by homeostasis model assessment. Oral glucose tolerance tests were done if fasting glucose levels were greater than 6 mmol/L. All liver biopsies were reviewed by a single histopathologist. Three age- and sex-matched controls were randomly selected for each patient.

Results: 11 of 12 patients who underwent liver biopsies were found to have NASH. All 11 were Chinese: eight males and three females. 73 percent of them had hepatic fibrosis. Overall, compared to controls, they had significantly higher body weight, BMI, IR and triglyceridaemia. The female patients also had a higher waist-hip ratio than controls. None had diabetes mellitus, and one had impaired glucose tolerance/fasting glycaemia. Nine out of 11 had BMI between 25 and 30 kg per square metres.

Conclusion: Significant histological changes of NASH with hepatic fibrosis were found in Singaporean Chinese non-diabetic patients with BMI of less than 30 kg per square metres.

Keywords: fatty liver disease, hepatic fibrosis, insulin resistance, non-alcoholic steatohepatitis, obesity, transaminases.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is increasingly recognised by many as an important clinical condition, not only because of its growing prevalence,[1] and its potential progression to liver cirrhosis and liver failure, but also its association with serious medical conditions, such as diabetes mellitus (DM). With DM reaching an epidemic scale in Asia, we can anticipate a corresponding increase in the disease burden of NAFLD in our community in the years to come. In some developed countries, NAFLD-associated cirrhosis has become one of the top few indications for liver transplantation.[2-4] It is not uncommon to find that NAFLD is not often recognised till the associated complications have already set in. This is because NAFLD is a clinical phenomenon that consists of a heterogeneous group of patients with conditions that range from simple hepatic steatosis to steatohepatitis, which is associated with grave clinical consequences. Moreover, patients are usually asymptomatic. Quite often, clinical suspicion of the condition is prompted by the incidental and nonspecific finding of an elevation in serum transaminases.[5,6]

As definitive diagnosis of NAFLD and its severity (i.e. hepatic steatosis versus steatohepatitis) can only be made histologically with a liver biopsy, clinical diagnosis of NAFLD is usually made by exclusion of other known causes of liver diseases via various blood tests, supportive imaging, and substantiated by well-known associated clinical features, such as the female gender, obesity and DM[1,7-8] in the absence of significant alcohol intake. While the majority of our patients with NAFLD fit the

above description, we noticed a subset of patients who did not have DM, nor were they obese, as currently defined by the World Health Organisation, but were nonetheless suspicious of having NAFLD clinically. This study was carried out to characterise a consecutive series of non-obese and non-diabetic patients, who had raised serum transaminases with no other clinically-accountable cause except NAFLD, via liver biopsy, anthropometrical and metabolic measurements.

METHODS

During November 1997–September 1999, consecutive patients seen by two hepatologists in the outpatient clinic for persistent elevation of serum transaminases not due to viral hepatitis B or C, alcoholic liver disease, autoimmune or hereditary liver disease, such as Wilson's diseases, were studied. All these patients had normal serum ceruloplasmin and copper levels, and were tested seronegative for HBsAg, anti-HCV IgG. Anti-nuclear antibody (ANA), anti-smooth muscle (SMA) antibody and anti-liver, kidney microsomal antibody (anti-LKM) were also tested for. Patients with features fulfilling the criteria for diagnosis of autoimmune hepatitis[9] were excluded from this cohort and managed separately. Physical examination, serial liver function tests, prothrombin time and routine ultrasonography or computed tomography of the liver were carried out for all the patients. Detailed alcohol and drug history was also taken repeatedly during the course of follow-up to rule out any incriminating agent that could account for the deranged liver function test.

Clinical diagnoses of NAFLD were made after excluding other accountable causes for raised serum transaminases, as detailed above. For those who were obviously obese and/or had DM, advice on weight loss and physical exercise, referrals to the dietician and/or endocrinologist were given. For others who had persistent elevation of serum alanine transaminase (ALT), despite the absence of DM, and had a body mass index (BMI) $\leq$ 30 kg/m^2, consent for liver biopsy was obtained. Persistent elevation of serum ALT was defined as ALT more than 2.5 times upper limit of normal for at least two readings taken $\geq$ six months apart. The usual advice on diet and exercise was, nonetheless, given at the outset, after a clinical diagnosis of NAFLD was made.

Percutaneous aspiration liver biopsies were carried out using Menghini's needles. Those who were reported to have histological evidence of steatohepatitis were referred to the endocrinologist for further evaluation. Subsequent evaluation included taking the patient's weight, height, waist and hip circumferences, and measurement of the patient's serum lipid, glucose and insulin levels after a ten-hour overnight fast. The detailed methodology for these measurements was described previously.[10] Patients whose fasting glucose > 6.0 mmol/L were subjected to 75 g glucose tolerance test to determine if they had normal or impaired glucose tolerance (IGT), impaired fasting glycaemia (IFG) or DM, based on the recommended classification.[11] The patient's insulin resistance (IR) was calculated, whenever possible, by Homeostasis Model Assessment according to the formula (IR = [fasting insulin $\times$ fasting glucose] / 22.5).[12]

For consistency of reporting, a designated histopathologist, who was blinded to the clinical and laboratory parameters, reviewed all the liver biopsy specimens for this group of patients. Non-alcoholic steatohepatitis (NASH) was defined as the presence of steatosis in association with lobular necroinflammatory activity, of mostly lobular distribution, regardless of the presence of Mallory's hyaline or fibrosis.[13] Three age- and sex-matched controls were randomly selected from the 1992 Singapore National Health Survey population[10] for each included study patient. Their anthropometrical parameters and metabolic profiles were compared with those of the matched study patients. The significance of the difference between the study patients and controls for each parameter was calculated by Student's unpaired *t*-test. Fisher's exact test or chi-square test, where appropriate, was used to calculate the significance of association between two variables. All tests were two-tailed and $p < 0.05$ was taken as a statistically significant difference.

RESULTS

During the study period, 12 patients fulfilled our inclusion criteria for liver biopsies and all consented to the procedure. One patient was reported to have moderate hepatic steatosis only, the other 11 were found to have NASH. These 11 NASH patients were further characterised. There were eight males and three females. Their median age was 32 (range 17–51) years. All of them consumed < 20 g alcohol/day. In fact, seven were teetotallers, four only drank occasionally (< 10 g/month) and only one patient consumed 40–90 g of alcohol per week. None had a history of consumption of

Table I. Epidemiological data, anthropometrical parameters and serum transaminases of patients with NASH (n = 11, 8 males and 3 females).

	Mean (SEM)	Median	Range
Age (years)	33 (2.9)	32	17–51
Body weight (kg)	78.2 (1.7)	80.1	71.0–89.8
Body bass index (BMI)	27.8 (0.85)	28.9	21.9–30.0
Waist-hip ratio (WHR)	0.86 (0.18)	0.88	0.78–0.93
Serum ALT (U/L)	128 (9.1)	114	95–195
Serum AST (U/L)	60 (5.4)	55	47–112
Serum alkaline phosphatase (U/L)	61 (4.0)	59	37–83

SEM: standard error of mean

Table II. Anthropometrical parameters of patients with NASH (8 males and 3 females) and age- and sex-matched controls (24 males and 9 females).

		Patients (SEM)	Controls (SEM)	p-value
Mean body weight (kg)	Total	70.2 (1.73)	61.2 (2.36)	< 0.01
	Males	79.6 (2.10)	64.6 (2.07)	< 0.0
	Females	78.1 (3.53)	52.1 (5.89)	0.03
Mean BMI (kg/m^2)	Total	27.8 (0.85)	22.5 (0.76)	< 0.01
	Males	27.4 (1.01)	22.8 (0.68)	< 0.01
	Females	29.4 (0.50)	23.1 (3.11)	N.S.
Mean WHR	Total	0.86 (0.18)	0.80 (0.02)	N.S.
	Males	0.89 (0.01)	0.85 (0.01)	N.S.
	Females	0.80 (0.01)	0.68 (0.01)	< 0.0

SEM: standard error of mean; N.S.: not significant

Table III. Metabolic parameters of patients with NASH (8 males and 3 females) and age- and sex-matched controls (24 males and 9 females).

		Patients (SEM)	Controls (SEM)	p-value
Mean cholesterol (mmol/L)	Total	5.44 (0.11)	5.17 (0.16)	N.S.
Mean HDL (mmol/L)	Total	1.16 (0.06)	1.32 (0.05)	N.S.
Mean LDL (mmol/L)	Total	3.38 (0.10)	3.28 (0.12)	N.S.
Mean cholesterol/HDL ratio	Total	4.82 (0.30)	4.15 (0.23)	N.S.
Mean triglyceride (mmol/L)	Total	1.97 (0.27)	1.26 (0.13)	0.01
	Males	2.14 (0.36)	1.38 (0.17)	0.042
	Females	1.52 (0.07)	0.91 (0.15)	0.048
Mean glucose (mmol/L)	Total	5.07 (0.17)	5.95 (0.44)	N.S.

SEM: standard error of mean; N.S.: not significant

any potentially incriminating drug. All patients' serum ALT/aspartate aminotransferase (AST) ratios were > 1. The median and mean of the average ALT and AST over six months were 114 and 128 (range 95–195) and 60 and 55 (range 47–112) U/L, respectively. The serum alkaline phosphatase was normal (61; range 37–83) U/L (Table I). None had any clinical, laboratory or imaging evidence of liver cirrhosis or portal hypertension. Overall, compared to their sex- and age-matched controls, the patients with NASH had significantly higher body weight and BMI. Two of the patients' BMI were < 25 kg/m^2 (21.9 and 24.4 kg/m^2). The rest had a BMI of range 25–30 kg/m^2. If stratified according to gender, the difference in BMI was only statistically significant among the males. On the other hand, the difference in waist-hip ratio (WHR) was only statistically significant among the females (Table II).

There was no statistically significant difference in the serum fasting total cholesterol, LDL cholesterol and glucose levels between the patients and controls, but the patients with NASH had significantly higher triglyceridaemia than that of the controls (Table III). None of the study patients were diabetic, but one patient was found to have IFG or IGT by the 75 g oral glucose tolerance test. In comparison, two and seven of the controls had DM and IGT, respectively. IR was measured in six patients. They were significantly higher than their matched controls (Table IV). Five out of six patients had IR > 2.5. We managed to retrieve the records of ten out of the 11 patients, including the patient who had IFG/IGT at outset, to look at their latest clinical progress. The patient who had IFG/IGT at baseline developed steroid-induced DM post-bone marrow transplantation for acute myeloid leukaemia subsequently. Over a mean period of follow-up of 47 months, one of the other nine patients whom we managed to follow-up and who did not have IF/IGT initially, developed IGT followed by DM spontaneously over the course of subsequent follow-ups.

Table IV. Insulin resistance of patients with NASH (4 males and 2 females) and age- and sex-matched controls (12 males and 6 females).

		Patients (SEM)	Controls (SEM)	p-value
Mean IR	Total	3.96 (0.73)	2.12 (0.39)	0.03
	Males	3.24 (0.82)	2.39 (0.55)	N.S.
	Females	5.50 (0.76)	1.57 (0.39)	< 0.01

SEM: standard error of mean; N.S.: not significant

Histologically, all except one patient were reported

to have at least a moderate degree of macrovesicular steatosis (i.e. > 33% of hepatocytes were involved), involving zone 3. Six (55%) were noted to have marked and diffuse steatosis (i.e. > 66% of hepatocytes were involved), and two patients had both macrovesicular and microvesicular steatosis. Mixed intraacinar inflammation was noted in all, with predominant monocytic infiltration in seven (64%) patients. Mild portal inflammatory infiltrates were found in seven (64%) patients. While we defined NASH as lobular necroinflammatory activity with steatosis[13] for the purpose of inclusion of patients in this study, more sinister histological features that qualify for a more stringent definition for NASH[14] were found in eight (73%) patients. Hepatocytic ballooning/degenerative changes, Mallory bodies, perivenular/pericellular fibrosis and portal fibrosis were found, in various combinations, in three, two, seven and five patients, respectively. None had microscopical feature of cirrhosis.

While two patients were tested seropositive for ANA (1/400 and 1/800, respectively), none had histological evidence of autoimmune hepatitis. None was seropositive for SMA or anti-LKM. Correlating the clinical variables with histology, we found concurrence between report of routine imaging and histological findings in nine out of 11 patients. Fatty liver was reported by initial imaging in nine patients. However, one patient, whose hepatic ultrasonography was reported as normal, was found to have moderate steatohepatitis with perivenular and portal fibrosis histologically. Another patient, whose hepatic ultrasonography reported hepatic echogenicity suggestive of cirrhosis, was found to have marked steatohepatitis with absence of fibrosis histologically. Also of statistical significance, is the association of perivenular/ pericellular fibrosis histologically with the increasing serum AST levels among patients with NASH (Table V). There was no correlation between serum AST and portal fibrosis, or serum ALT and any form of hepatic fibrosis (perivenular or portal). It is interesting to note that our only patient who consumed any considerable amount of alcohol (≥ 40 g/week) was the only one with IR < 2. No fibrosis was seen in his liver biopsy. His BMI and WHR were 29.6 and 0.89, respectively. Excluding this patient from the statistical analysis did not change the overall conclusion of the study.

DISCUSSION

While BMI of more than 30 kg/m^2 has been used as the definition of obesity in Europe and the USA for a long time, this study illustrated the presence of histologically-proven NASH, which is traditionally associated with obesity, in patients with BMI < 30 kg/m^2. While previous studies have reported NAFLD in Asian patients with relatively "normal" body weight,[15,16] the clinical diagnoses were not substantiated histologically in those studies. Moreover, those studies may have included patients who have only hepatic steatosis, the more benign end of the disease spectrum of NAFLD, which may be of little clinical consequence. However, our study has illustrated the presence of significant histological lesions, which qualify for NASH that are known to be associated with progression of liver disease and liver failure,[17,18] in a group of patients whose BMI were ≤ 30 kg/m^2. Nonetheless, when compared with their matched controls from the general population, these patients had

Table V. Correlation of clinical variables with hepatic fibrosis in patients with NASH.

	Total n	Perivenular/pericellular fibrosis n (%)	Portal fibrosis n (%)	p-value
Serum AST (U/L) (Normal: 7–36)				
< 50	2	0 (0)	0 (0)	
50–55	4	2 (50)	2 (50)	0.03(pvf)
> 55	5	5 (100)	3 (60)	N.S. (pf)^
Gender / BMI				
All males*	8	4 (50)	3 (37)	N.S.*
BMI < 25 kg/m^2 #	2	1 (50)	0 (0)	N.S.**
BMI ≥ 25 kg/m^2 ##	6	3 (50)	2 (33)	
All females*	3	3 (100)	2 (67)	
BMI < 25 kg/m^2 #	0	NA	NA	
BMI ≥ 25 kg/m^2 ##	3	3 (100)	2 (67)	

^ Using chi-square test, increasing AST was found to be significantly associated with perivenular/pericellular fibrosis (pvf), but not with portal fibrosis (pf).

* There was no statistically significant difference in perivenular/pericellular fibrosis, as well as portal fibrosis, between all the males and all the females.

** Comparing all patients (males and females) with BMI < 25 kg/m^2 # to all those with BMI ≥ 25 kg/m^2 ##, there was no statistically significant difference in the perivenular/pericellular fibrosis and portal fibrosis between the two groups.

significantly higher body weight and BMI. Of note too was the presence of two patients with BMI < 25 kg/m^2 in this cohort.

Such findings are, therefore, in support of the latest WHO recommendations, which recognise that the increase in risk of metabolic syndrome is a continuum with increasing BMI and may begin before one's BMI reaches 25 kg/m^2 in many Asian populations.[19] Thus, while retaining the cut-off point for being overweight at 25 kg/m^2 and obesity at ≥ 30 kg/m^2, WHO has recommended additional trigger points for public health action at 23 kg/m^2 or higher. However, we should note that the WHO recommendations were based on observations of complications related primarily to risk factors for cardiovascular disease.[19] Our study not only gives additional substantiation of the WHO recommendation, it also suggests that this lowered threshold is not only applicable to the risk of development of cardiovascular disease in Asians, but also other associated conditions such as NASH. Moreover, although none of our patients had DM at the baseline, they were associated with higher triglyceridaemia and IR, and thus were at risk of developing type 2 DM[20] and cardiovascular complications subsequently. Finally, our study is compatible with the findings of other studies that suggest that NASH is not necessarily a female-predominant disease.[21] Though small in sample size, the differing associated features observed in our patients with NASH are consistent with the proposed gender-differing pathogenesis for NASH.[1,14,17, 22-25]

One of the major limitations of our study is its small sample size, which pose constraints to any meaningful comparison. However, we hope that the findings in our study, which agree with some of the existing concepts in the literature, will draw the attention of many family physicians to the severity of NAFLD, in particular NASH, in some of the asymptomatic patients in our community, and perhaps serve as an impetus to generate more epidemiological studies. Looking forward, from the practical management point of view, it is important to be able to identify patients who are likely to have severe and progressive NAFLD, among those with elevated serum transaminases, in order to allow prognostication and active intervention, whenever possible.[14] Due to the ease of examination, ultrasonography is frequently used for the reporting of fatty liver. While this study was not designed to compare the specificity and sensitivity for this modality of investigation to diagnose NAFLD, it is good to know a good degree of concurrence of histological findings with that of a routine ultrasonographical examination in a tertiary hospital in our day-to-day clinical practice. Nevertheless, we should be mindful of possible diametrically different findings between histology and ultrasonography, as was illustrated in two of the cases in this study. Moreover, ultrasonography will not be able to distinguish mere steatosis from NASH, which has more severe implications and consequences, in patients with NAFLD.

Previous studies have not shown good correlation between biochemistry and the severity of histology for individual patients with NAFLD, and there is no consensus regarding performance of liver biopsies in patients whom we suspect to have NAFLD.[14,24,26,27] It is unfortunate that we did not have histological controls in our study. While we were aware of this deficiency, it would be ethically difficult to justify doing liver biopsies in our control population. Nevertheless, based on the substantial proportion of patients who were found to have NASH in our study, we felt that it would be reasonable to consider performing a liver biopsy for patients diagnosed clinically to have NAFLD and whose ALT were persistently > 2.5 upper limit of normal. This is justifiable, especially after failure of primary intervention, which should include advice on gradual weight losing measures, for patients whose BMI are more than 25 kg/m^2, regardless of their ultrasonographic findings. Finally, as part of the management of patients with NASH, we should be mindful of the emergence of DM and other comorbidities associated with metabolic syndrome. While it is not practical to ascertain the patients' IR at a primary healthcare setting, blood glucose should be checked regularly, even if the initial readings at presentation are normal.

In conclusion, NASH, the more severe end of the spectrum of NAFLD, may be found in nondiabetic Chinese male as well as female patients with BMI < 30 kg/m^2 and whose ALT are persistently > 2.5 U/L. While it was associated with increased body weight and serum triglyceride, females were associated with increased IR and WHR, and males with increased BMI, when compared with controls. Hence, NASH can occur in patients with relatively low BMI, regardless of gender, if other associated risk factors are present. Liver biopsy should be considered for these patients to ascertain the presence of hepatic fibrosis, a feature found in 73% of the study population, in order to better prognosticate them and assess their risk of liver cirrhosis. Finally, NASH can occur in the absence of preexisting DM. Frequent monitoring of metabolic risk factors with the aim of early intervention should continue for these patients beyond the diagnosis of NASH.

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