

Non-alcoholic fatty liver disease in the Philippines: Comparable with other nations?

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Abstract

AIM: To evaluate the prevalence and determined the common characteristics of patients diagnosed with non-alcoholic fatty liver disease (NAFLD) at the Philippine General Hospital, Manila, from January 1999 to December 2004.

METHODS: NAFLD was diagnosed in 134 from a total of 1102 patients, based on clinical, ultrasonographic and/or histopathological findings. Patients with conditions associated with secondary NAFLD were excluded. Chart review was done to note demographics, comorbid illnesses, physical characteristics, hepatomegaly, aspartate/alanine aminotransferase (AST/ALT) levels, albumin, lipid levels, alkaline phosphatase, prothrombin time, and partial thromboplastin time. Data obtained were analyzed using the statistical program SPSS version 10.

RESULTS: Of the 134 patients included, 71% were female and 29% male. Mean patient age was 42.2 years. Sixty percent of patients were obese, 56% had hepatomegaly, and 69% had diabetes. AST levels were elevated in 45% of subjects and ALT levels in 64%.

CONCLUSION: The prevalence of NAFLD at our institution was 12.2%. Patients diagnosed appear to be younger in age in contrast to previous studies. Female sex, obesity, elevated liver enzymes, and diabetes were characteristic features of our NAFLD patients, which is comparable to previous studies from other countries.

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Key words: Fatty liver; Obesity; Non-alcoholic fatty liver disease; Diabetes; Philippines

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is now recognized as one of, if not the most common liver diseases in the United States, with a prevalence of about 5% in the general population, and reaching 25%-75% in patients with obesity and type 2 diabetes mellitus. Data regarding prevalence in the general population of the Philippines have been lacking. NAFLD covers a spectrum of diseases that ranges from simple fatty deposition in the liver to inflammation, fibrosis and cirrhosis. Although the exact etiology is not clear, it may be a part of a metabolic syndrome associated with insulin resistance, diabetes, obesity and hypertension. Patients typically present with asymptomatic serum aminotransferase elevation of 2-3 times the normal level. Symptoms may include fatigue and abdominal pain. Physical examination may show hepatomegaly. Liver biopsy is useful and effective as a prognostic indicator, but it is an invasive and costly tool to diagnose fatty liver, and is mainly used for unexplained cirrhosis. NAFLD can be diagnosed by histology, ultrasonography, CT, and MRI. However, the imaging modalities most often used to identify hepatic steatosis include CT and ultrasonography. Hyperechogenic (bright) liver indicates steatosis, with sensitivity and specificity rates as high as 95%. The prevalence of obesity has been steadily rising in the Philippines, which may be attributed to a change in dietary habits and a sedentary life style.

NAFLD includes a spectrum of liver diseases, including fatty liver, steatohepatitis, and even cirrhosis in the absence of alcohol intake, that are known to be injurious to the liver. It has a benign course in the majority of cases, but up to 20% of these patients with NAFLD have non-alcoholic steatohepatitis NASH^[1,4]. Up to one-third of these NASH cases can progress to cirrhosis, liver failure and even hepatocellular carcinoma^[2]. It is now believed to be a widespread liver disease in Western countries, and most probably, even in Asian countries. Moreover, it may be the leading cause of cryptogenic cirrhosis^[3,5]. Even with its preponderance, NAFLD remains something of a medical mystery. Recent studies have shown an upsurge of

interest in this liver disease and it is becoming increasingly significant^[6].

A lot of work has been done on NAFLD in Western countries^[6-8], but it is relatively new in the Philippines, with only a handful of studies having been done. Recent studies have proposed that obesity and type II diabetes mellitus, which are hyperinsulinemic states with decreased tissue sensitivity to insulin, are the major players in the pathogenesis of NAFLD. This study was conducted to note characteristic features in our NAFLD patients at the Philippine General Hospital, Manila, confirmed by clinical, ultrasonographic and/or histopathological findings, and to establish if these findings were congruent with those of previous studies on NAFLD.

MATERIALS AND METHODS

This study was conducted at the Philippine General Hospital, Manila, Philippines based on case records from January 1999 to December 2004. From a total of 1102 patients with fatty liver, 134 patients were diagnosed with NAFLD, based on clinical and histopathological findings or ultrasound findings suggestive of fatty liver. Fatty liver was diagnosed by ultrasonography using an abdominal probe at 2-5 MHz. Longitudinal, subcostal, ascending, and oblique scans were performed. The ultrasonographic criteria that were used to diagnose fatty liver included liver and kidney echo discrepancy, presence of increased liver echogenicity (bright), echo penetration into the deep portion of the liver, and clarity of liver blood vessel structures. Due to the subjectivity and vagueness of some of the case records reviewed on the amount of alcohol consumption, patients included had absolutely no history of alcohol intake. HCV-antibody-positive patients were excluded. Patients with a history of various surgical procedures that can lead to secondary NAFLD, i.e. gastropexy, jejunioileal bypass, extensive small bowel resection, biliopancreatic diversion, and small bowel diverticulosis, were excluded, as were patients taking drugs or conditions that are known to cause secondary NAFLD.

Chart review was performed to note history, demographics, co-morbid illnesses, physical characteristics, physical examination findings, and laboratory findings. Detailed clinical evaluation of each subject was carried out to note patient characteristics that focused on primary causes of NAFLD. Presence of obesity, hepatomegaly, and diabetes were specifically sought. Body mass index (BMI) of each subject was noted to establish obesity. Patients with BMI < 18, 18-25, 26-29 and \geq 30 were considered under-weight, normal, over-weight and obese, respectively. Fasting serum cholesterol and triglyceride levels of all patients were noted for lipid abnormalities, but a substantial lack of data precluded their inclusion in this study. Fasting blood sugar level in all patients was noted. Diagnosis of diabetes in these patients was made according to standard criteria.

In most patients' medical charts, serum level of alanine/aspartate transaminases (ALT/AST), albumin, prothrombin time, partial thromboplastin time, and alkaline phosphatase were documented. Data from study participants obtained from medical records included

Table 1 Distribution of BMI *n* (%)

Gender	Underweight	Normal	Overweight	Obese
Female	10 (11%)	5 (6%)	8 (9%)	64 (74%)
Male	17 (36%)	10 (21%)	4 (9%)	16 (34%)
Total	27 (20%)	15 (11%)	12 (9%)	80 (60%)

age, gender, nationality, weight, height, BMI, and clinical presentation or presence of hepatomegaly. The results were expressed as means \pm SD. Data obtained was then converted into variables that were analyzed using frequency and cross tabulation functions of computer-based statistical program SPSS version 10. The test was considered to be significant if *P* was < 0.05.

RESULTS

Demographics and physical attributes

Of the 1102 patients diagnosed with fatty liver, 134 (12.2%) met the criteria for review. As expected, a huge proportion of the cases came from metropolitan Manila (69%), with the rest of the cases coming from the southern Luzon regions (21%). Results showed that 71% of the subjects were female and 29% were male. Mean patient age was 42.2 ± 2.1 years. Half of the patients were aged 21-47 years. Mean BMI was 31.8 ± 7.2 , with 60% of patients being obese or having BMI > 30, while 11% had normal BMI, 9% were overweight and 20% were underweight. Most obese patients (80%) were female (Table 1).

Clinical features

Fatigue and right upper quadrant discomfort were the most common symptoms seen in both male (34%) and female (29%) patients. Most however, had no symptoms at all (62%). Overall, a greater proportion of subjects with normal ALT were completely asymptomatic compared with those with abnormal ALT (*P* < 0.04, Fisher's exact test). Approximately 59% of subjects had a relatively unremarkable physical examination, with the exception of their body weight and blood pressure. A large number of NAFLD patients (92; 69%), had diabetes. Hypertensive patients accounted for 22% (29) of the sample population. Twenty-seven patients with NAFLD and normal ALT were obese, as defined by BMI > 30. Twenty-nine patients with NAFLD and normal ALT levels had diabetes, and 14 had hypertension. One patient with normal and one with elevated ALT had hypothyroidism. None of the subjects were taking medication known to be associated with the development of hepatic steatosis.

Laboratory correlation

Based on autopsy, ultrasound or physical examination, 75 (56%) patients had hepatomegaly. A total of seven autopsied patients who met the criteria for NAFLD had an average liver weight of 1722 ± 488 g (normal 1500-1800 g). AST levels were elevated in 60 (45%) of subjects and ALT levels in 86 (64%). AST levels averaged 112 ± 20 U/L for females and 164 ± 27 U/L for males. ALT levels averaged 217 ± 18 U/L for females and 187

Table 2 Laboratory characteristics of NAFLD patients at the Philippine General Hospital

Parameter	Blood chemistry values		
	Total <i>n</i> = 134 (mean)	Male <i>n</i> = 39 (mean)	Female <i>n</i> = 95 (mean)
Liver weight (g)	1722 ± 488	1505 ± 399	1952 ± 512
AST (U/L) <i>n</i> (15-137)	150 ± 19	164 ± 27	112 ± 20
ALT (U/L) <i>n</i> (30-65)	192 ± 17	187 ± 24	217 ± 18
Alkaline phosphatase (g/dL) <i>n</i> (50-136)	89 ± 20	87 ± 30	92 ± 22
Albumin (g/L) <i>n</i> (34-50)	33.5 ± 6	35 ± 8	32 ± 6
Prothrombin time (PT) INR	1.1 ± 1	0.95 ± 1	1.2 ± 1
	Median (range)	Median (range)	Median (range)
PT activity %	88 (79-99)	90 (79-99)	88 (90-97)
Partial thromboplastin time (s)	30.1 (28-49.1)	32 (28-40.3)	34.6 (33-49.1)
Random blood sugar mmol/L <i>n</i> (3.9-6.1)	8.3 (4.9-20.1)	7.6 (5.5-20.1)	8.3(4.9-18.2)

Table 3 Comparison between studies of the characteristic features of NAFLD patients

Study	No. of patients	Age (yr)	Female (%)	Diabetes (%)	Obesity (%)	Hepatomegaly (%)
Ludwig (1988) ³⁸	20	54	65	50	90	67
Diehl (1988) ²⁸	39	52	81	55	71	20
Lee (1989) ²⁵	49	53	78	51	69	-
Powell (1990) ²⁶	42	49	83	36	95	81
Bacon (1994) ²⁷	33	47	42	21	39	21
Matteoni (1999) ²⁹	132	53	53	33	70	92
Khurram (2003) ³¹	50	47	54	44	66	76
Our study (2005)	134	42	71	69	60	56

± 24 U/L for males. Bleeding abnormalities were noted in 26 (19%) patients. Mean blood glucose level for male patients was 6.7 ± 8 mmol/L and 8.1 ± 5 mmol/L for females. Alkaline phosphatase and albumin levels were within the normal range for the whole sample population. Glutamyltransferase levels and lipid profiles were not included due to scarcity of available data from charts reviewed. Details are shown in Table 2.

Risk factors

Female sex, diabetes, hepatomegaly, increased BMI (overweight and obesity) were the main risk factors noted to have a significant relationship with NAFLD ($P < 0.05$). Significant differences ($P < 0.05$) in BMI, liver weight, AST, ALT and blood sugar were also noted between female and male individuals. It was notable that a sizable proportion of our patients (20%) who were underweight also had had NAFLD. No significant relationship was found between the presence of fatty liver and age. A significant number (92; 69%) of our patients had diabetes, 69 (75%) of whom were female. The mean duration of diabetes was 9.9 ± 3.9 years. Mean HbA1C was elevated at 9.1% ± 2.6%. Hepatomegaly with fatty infiltration, as assessed by ultrasound, was reported in 66 patients (49%) with a mean liver size of 17.4 ± 5.2 cm.

DISCUSSION

NAFLD includes a wide spectrum of histological abnormalities that are similar to alcoholic liver disease, but without a prior history of alcoholic intake known to be injurious to the liver. NAFLD is a common problem in the US, Asia-Pacific region, Europe, and the Middle

East. NAFLD can affect any age group but is usually encountered in the 40-60 years age group⁵¹. Prevalence is high even among children, with 2.6% of all children and up to 52.8% of obese children having this disease³. Several investigators have noted that the mean age of patients with NAFLD was 52-54 years^{18,25,28,29}. In other studies mean age varied between 47 and 54 years of age^{26,27,31}. Most of our patients were aged 21-47 years, which is considered a younger age group. This may reflect the changing diet of young Filipinos to caloric rich foods, which has increased the number of people with diabetes in the Philippines, or it may just reflect the limitation of our sample population.

Most of our other results, including the presence of diabetes, hepatomegaly and obesity, correlated with the findings of previous authors^{18,26-30}. Up to 65%-80% of females may have this disease, as shown in our study and in some previous studies, with the exception of that of Bacon *et al*, in which there were only 42% females^{18,26-30}. In our study, females constituted 71% of patients. Different studies have shown a gender-related difference in NAFLD-associated conditions such as hepatomegaly, diabetes and dyslipidemia; these conditions being more common in female NAFLD patients. Our findings were similar in most cases, i.e. 64% patients with obesity were female and 69 females or 51% of the whole population had diabetes. Diabetes mellitus is an independent risk factor for liver-related deaths in NAFLD patients³. In related studies, up to 75% of NAFLD patients had diabetes^{18,26-30}. Our results agreed with these studies, with 60% of our population having diabetes, and there was a significant correlation with NAFLD ($P < 0.05$). It has been noted by Angulo that the prevalence of NAFLD increases by a fraction of 4.6 in patients with obesity, with up to 74%

of such patients having NAFLD^[3]. In previous studies, 30% to 81% of patients diagnosed with NAFLD were found to have obesity^[18,26-30]. Our results correspond with these studies, with a mean BMI of 31.8 ± 7.2 . This was also significantly correlated with the presence of NAFLD ($P < 0.05$). Several studies have shown that truncal obesity is an important risk factor for development of NAFLD, even in patients with normal BMI. Truncal obesity ideally should have been included in the data collection but was not incorporated due to lack of data in case records.

On the other hand, fatty liver is associated with mild to moderate enlargement of the liver. Hepatomegaly is commonly the sole physical finding in most patients with NAFLD, which was also seen in our patients. Similar results have been found in other related studies^[18,26-30]. Hepatomegaly may even be more severe due to the fact that normal values used for comparison come mainly from Caucasian data, and may not reflect true normal values in Filipinos. Hyperlipidemia has also been tagged from previous studies as a risk factor for the development of NAFLD^[18,26-30]. Prevalence of hyperlipidemia in NAFLD patients is quite variable. Diehl *et al* noted it in only 20% of NAFLD patients, contrary to the results of Matteoni *et al* who found it in 92% of patients^[28,29]. Unfortunately, our study was not able to document lipid profiles due to the non-availability of laboratory results. Characteristic features of our NAFLD patients compared with other studies are given in Table 3.

Limitations include the location of our study, which was a large tertiary hospital in the Philippines. This may not be a representative sample population for analysis. Moreover, not all cases of NAFLD were analyzed, because of the lack of data from case records. Results may have differed with inclusion of these patients. Furthermore, normal values used for BMI and hepatomegaly are based mostly on Caucasian data and may not be applicable to the Filipino population. Larger prospective studies with control groups for longer periods of time are needed to firmly establish the validity of our results.

In conclusion, NAFLD was common in our patients, with a mean age of 42 years. In a 5-year period, more females (71%) were diagnosed with NAFLD. Hepatomegaly is the most common physical finding and was noted in 56% of our patients. A younger mean age, obesity (60%), diabetes (69%), hepatomegaly (56%) and female sex (71%) were the most distinct attributes of our patients with NAFLD. Except for a younger age group, the results are comparable to previous studies from other countries.

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