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THE ASSOCIATION OF RISK FACTORS IN THE DEVELOPMENT OF NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) IN FILIPINO PATIENTS WITH TYPE 2 DIABETES MELLITUS IN A TERTIARY CENTER

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ABSTRACT

Background: Non-alcoholic Fatty Liver Disease (NAFLD) includes a spectrum of liver damage, ranging from simple, bland steatosis, which is usually associated with a benign prognosis, to nonalcoholic steatohepatitis (NASH), which has the potential to progress to cirrhosis and its inherent complications of liver failure and liver cancer. It is reported to be prevalent among patients with Type 2 Diabetes Mellitus.

Objectives: (1) To determine the association of the risk factors in the development of non-alcoholic fatty liver disease, in Filipino patients with Type 2 Diabetes Mellitus; (2) To assess the correlation between the severity of ultrasonographic hepatic steatosis and degree of glucose control, dyslipidemia and obesity; (3) To observe the hepatic markers particularly the transaminases in patients with Type 2 diabetes mellitus with obesity and or dyslipidemia.

Methods: One hundred forty seven diagnosed Type 2 diabetes without history of alcohol intake >30g/week in men and 20g/week in women underwent history and physical examination and anthropometric measurements. BMI was used to estimate overall adiposity. Fasting blood samples were collected for measurement of liver function (GGT, ALT, AST, CHON, Bilirubin, ALP), and hepatitis profile (HBsAg, Anti-HBs, Anti-HCV) to note those with concurrent liver diseases. Lipid profile, were also obtained to identify diabetic patients with dyslipidemia; fasting blood sugar, and HbA1c defined the glycemic control in its relation to the presence of probable NAFLD. All subjects underwent ultrasonography of the liver using one ultrasound machine, performed by one radio-technologist, and read by only one sonologist. Presence of fatty liver was noted and reported as mild, moderate and severe.

Results: Features of NAFLD seen in the subjects in this study include absence of symptoms referable to the liver, elevated transaminases (ALT at 15%, AST at 13%, with ALT/AST > 1at 12%) and with features of metabolic syndrome. Statistatically, there is no association of the ALT/AST >1 (probable NAFLD) among the Type 2 DM subjects with dyslipidemia, obesity and metabolic syndrome. Sonographic NAFLD, however, showed that there is a significant association of fatty liver and obesity at 69% with a p value of <0.001. Elevated ALT is associated with the development of hepatic steatosis. Uncontrolled glycemic status and presence of dyslipidemia did not increase the severity of the fatty liver.

Conclusion: There is a close link of hepatic steatosis to T2DM patients who are obese. Elevated ALT was correlated in the development of fatty liver. Type 2 Diabetes Mellitus associated with NAFLD has the potential to progress to cirrhosis and its inherent complications of liver failure and liver cancer and thus make an important endocrine health problem.

Keywords: Non-alcoholic Fatty Liver Disease, Type 2 Diabetes Mellitus

INTRODUCTION

Non-alcoholic Fatty Liver Disease (NAFLD) comprises the two-thirds of all the cryptogenic causes of chronic liver disease (Hanley et al, 2004). NAFLD includes a spectrum of liver damage, ranging from simple, bland steatosis, which is usually associated with a benign prognosis, to nonalcoholic steatohepatitis (NASH), which has the potential to progress to cirrhosis and its inherent complications of liver failure and liver cancer (Angulo, 2004). NASH is emerging, as common, clinically important chronic liver disease with a prevalence rate estimated to be ~10-20% (Younossi et al, 2002). It is increasingly recognized as a major cause of liver-related morbidity and mortality (Bugianesi et al, 2002). NAFLD is reported to have estimated prevalence ranging from 21 to 78% in Type 2 DM (Kelly et al, 2003). According to Silverman et al (1990), the presence of Type 2 Diabetes Mellitus, regardless of body-mass index, significantly increases the risk and severity of nonalcoholic fatty liver disease. In the studies

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of Adams et al, NAFLD is more frequent among people with diabetes (50%) and obesity (76%), and it is almost universal among diabetic people who are morbidly obese. Obesity, diabetes and dyslipidemia, which are part of the metabolic syndrome are seemed to be closed link in the development of the NAFLD and suggested to be related to insulin resistance (Weston, 2005). Despite being common and potentially serious, the natural history of this condition and the mechanisms leading to disease development remain poorly understood. Furthermore, no medical treatment has proven effective for all patients with NAFLD (Angulo, 2004).

NAFLD is a liver disease with significant lipid deposition in the hepatocytes in patients without history of excessive alcohol ingestion leading to fatty liver (hepatic steatosis). There are no evident clinical symptoms in its initial stage. NAFLD is made up of the unexplained elevation of ALT/AST >1, fatty liver on imaging and importantly hepatic biopsy with the demonstration of lipid deposition of the hepatocytes.

The gold standard in the diagnosis of NASH remains to be the hepatic biopsy. Oftentimes, however, the difficulty arises in getting consent for the procedure among asymptomatic patient. This procedure is an invasive procedure associated with low but important risk of bleeding.

Although the clinical course of NAFLD is usually benign, it can cause elevation of liver enzymes and may indicate the presence of NASH. Serum markers of liver damage, including ALT and AST, may be reasonable noninvasive surrogate measures for use in epidemiological studies (Hanley et al, 2004). Hanley further explained that individuals with NAFLD are known to have 1-4x elevated transaminase concentrations, and, on the basis of analyses of data from the Third National Health and Nutrition Examination Survey (1988-1994), Clark et al, suggested that NAFLD may be the most common cause of chronic elevations of these markers. Elevated GGT is the commonest liver test abnormality in NAFLD/NASH although non-specific. Most often, the ALT is greater than the AST and a slightly elevated ALP $\leq$ 2x the normal.

The features of NAFLD includes (1) absence of symptoms referable to the liver; (2) 1-4x elevation of transaminases; (3) ALT > AST with ALT/AST >1; (4) alkaline phosphatase (ALP) $\leq$ 2x the normal value; (5) may have metabolic syndrome

Sonography is often the first imaging procedure performed in the evaluation of individuals with suspected liver disease. Evaluation for biliary dilatation is always performed, because bile duct obstruction can cause abnormal liver test results, raising the suspicion of liver disease. Ultrasound is a useful but imperfect tool in evaluating diffuse liver disease. Sonography can show hepatomegaly, fatty infiltration of the liver, and cirrhosis, all with good but imperfect sensitivity and specificity. Increased parenchymal echogenicity is a reliable criterion for diagnosing fatty liver. Hepatic imaging may provide clues to the presence of steatosis. Sonographically, the features of hepatic steatosis include the following: (1) diffusely increased parenchymal echogenicity, often associated with unusually fine liver texture; (2) increased attenuation of the ultrasound beam causing poor visualization of the posterior portions of the liver; and (3) decreased visualization of the portal and hepatic veins, probably secondary to compression by the surrounding fat-laden parenchyma as well as increased attenuation of sound and decreased contrast between echogenic fat and the walls of the vessels. Dr McGahan et al proposes the following grading of the degree of fatty infiltration, using a 3.5MHz trasducer: (1) Grade 1(mild), echogenicity is slightly increased, with normal visualization of the diaphragm and the intrahepatic vessel borders; (2) Grade 2 (moderate), echogenicity is moderately increased, with slightly impaired visualization of the diaphragm or intrahepatic vessels; (3) Grade 3 (severe), echogenicity is markedly increased, with poor or no visualization of the diaphragm, the intrahepatic vessels and posterior portion of the right lobe. Compared with CT and liver biopsy, the overall accuracy of sonography in detecting fatty infiltration is 85% to 89%, and the specificity is 56–93% (Mc Gahan) on the hands of competent sonologist. The predictive value for NAFLD approaches 96% if patient is asymptomatic with elevated transaminases and the presence of fatty liver by ultrasound. (Ezur et al). The limitation however is that no imaging method is able to distinguish between simple steatosis and NASH or indicate the stage of fibrosis and the sensitivity of imaging method increases with the degree of fatty infiltration. (Adams, 2005)

The prevalence of NAFLD is likely to increase with the rising incidence of obesity and diabetes. Most people with NAFLD, especially those with simple fatty liver with no inflammation, have little or no problems from the condition. In contrast, about a quarter of people progressing to NASH may have scarring of the liver that gets worse with time. In general, the progression of scarring is slow and can take years and even decades to occur. In some patients the scarring can stabilize and in persons who have lost significant amounts of weight there are cases where scarring has been shown to reverse. In others, the progression continues with scar tissue accumulating in the liver, leading to cirrhosis. NASH is an increasingly common reason for liver transplantation in the United States. (Feldstein et al). In this regard, it is important to identify the diabetic patient

with NAFLD to manage and prevent a possible worst outcome.

OBJECTIVES

The aims of our study are: (1) to determine the associations of the risk factors in the development of non-alcoholic fatty liver disease, in Filipino patients with Type 2 Diabetes Mellitus; (2) to assess the correlation between the severity of ultrasonographic hepatic steatosis and degree of glucose control, dyslipidemia and obesity, and (3) to observe the hepatic markers particularly the transaminases in patients with Type 2 diabetes mellitus with obesity and or dyslipidemia.

Significance of the Study

There is an epidemic rise in Type 2 Diabetes Mellitus in Asian populations. In the global prevalence study, the Philippines is projected to be rank nine among countries with diabetes by year 2030. Type 2 Diabetes Mellitus associated with NAFLD has the potential to progress to cirrhosis and its inherent complications of liver failure and liver cancer and thus make an important health problem in the Philippines. The prevalence of NAFLD in type 2 DM has not been well studied especially in our local setting. To date, this study will be one of the first in our country.

MATERIALS AND METHODS

Design

This is a prospective cross-sectional study of the occurrence of NAFLD in patients with Type 2 Diabetes Mellitus.

Subject Selection Criteria

Those who are diagnosed with Type 2 Diabetes Mellitus, regardless of blood sugar control status were included in the study.

Those with history of alcohol intake >30g/week in men and 20g/week in women (1 glass of wine, 1 can of beer or 1 shot of hard liquor is estimated to have 10-15g alcohol) are excluded in the study. Those with active Hepatitis B and C were also excluded.

Description of the Intervention

All subjects underwent detailed history and physical examination and anthropometric measurements (height, weight, waist circumference and Body Mass Index). Height and weight were measured to the nearest 0.5cm and 0.1kg, respectively. BMI was used to estimate overall adiposity. Fasting blood samples were collected for measurement of liver function (GGT, ALT, AST, CHON, Bilirubin, ALP), and hepatitis profile (HBsAg, Anti-HBs, Anti-HCV) to note those with concurrent liver diseases. Lipid profile, were also obtained to identify diabetic patients with dyslipidemia; fasting blood sugar, and HbA1c defined the glycemic control in its relation to the presence of probable NAFLD. All subjects underwent ultrasonography of the liver using one ultrasound machine, by one radio-technologist, and read by only one radiologist. Presence of fatty liver was noted and reported as mild, moderate and severe.

Definitions of Terms

Body Mass Index (BMI) –
- Obese Class 1 – 25-29.9
- Obese Class 11 - > 30

Waist-Hip- Ratio (WHR)
- Normal Female < 0.80
- Normal Male < 0.90

Waist Circumference
- Normal Female $\leq$ 80cm
- Normal Male $\leq$ 90 cm

Dyslipidemia
- Hypertriglycemidemia $\geq$ 150 mg/dL
- Low HDL < 50 mg/dL in Female
  < 40mg/dL in Male
- High LDL > 100mg/dL

Type 2 DM
- Controlled $\leq$ 7.0 mg/dL
- Uncontrolled > 7.0 mg/dL

Probable NAFLD
- elevated ALT and AST with ALT/AST > 1 without other elevation of other liver profile (except GGT) without hepatitis
- fatty liver by UTZ

Hepatic steatosis – Fatty Liver

Metabolic syndrome

1. Waist circumference - >90 cm (male), >80cm (female)
2. 2 of the following:
   a. Triglycerides $\geq$ 150mg/dL
   b. HDL- < 40mg/d (Male), < 50 mg/dL (Female)
   c. BP $\geq$ 130/85 mmHg
   d. Fasting plasma glucose > 100 mg/dL

Research Setting

Subjects for the study were from the Diabetes Clinic of the Outpatient Department of St. Luke's Medical Center.

Statistical Analysis

The Microsoft Excel software has been utilized for data encoding while the SPSS 14 was used for data analysis. Demographic and clinical profile of patients

were described using descriptive statistics such as means and standard deviations for continuous variables and frequencies and proportions for nominal variables. The t-test or ANOVA, whichever were more appropriate, was used to determine differences in means while the chi square or Fisher's exact test, whichever was more appropriate, was used to determine differences in proportions. All tests were two-tailed and considered significant at $p<0.05$.

RESULTS

Descriptive Statistics

The study has a total of 147 Filipino patients with Type 2 Diabetes Mellitus (Table I). There were 26 (17.7%) of who were male and 121 (82.3%) were female. The ages of the subjects ranged from 19 to 81 years, with a mean age 59 years (SD 9.9). The patients have been diagnosed with DM-2 for a period of one month to 29 years (mean 9.8, SD 6.2). The AiC levels ranged from 4.7 to 13.6, with a mean of 8.2 (SD 2). Ninety-six patients (65.3%) had uncontrolled DM-2 based on AiC levels.

Table 1: Demographic Data

Total no. of patients in the study: 147 (F=121; M=26)

Parameters	Mean	SD (range)
Age (years)	59.2	+/- 9.9 (19-81)
Duration of DM-2 (years)	9.8	+/- 6.2 (0.1 – 29)
HbAic	8.2	+/- 2.0 (4.7- 13.6)
Liver Span (cm)	9.0	+/- 1.8 (6.0 -13.0)

Among the 108 (79.4%) subjects with microvascular complications, neuropathy (68, 50%) was the most common. Other microvascular complications include nephropathy (66, 48.5%), anemia (14, 10.3%), retinopathy (22, 16.2%), and gastropathy (1, 0.7%). There were 43 subjects with macrovascular complications such as PAOD (28, 20.6%), symptomatic CAD (13, 9.6%), and TIA/CVA (6, 4.4%) (Table II).

Table II: Macro- and Micro-vascular Complications of Type 2 DM

DM-2 complications	Freq	%
Microvascular complications	117	79.6
Neuropathy	73	62.4
Nephropathy	73	62.4
Anemia	15	12.8
Retinopathy	24	20.5
Gastropathy	1	0.9
Macrovascular complications	45	30.6
PAOD	30	66.7
CAD	13	28.9
TIA/CVA	6	13.3

Most of the subjects (Table III) were non-obese at 55.8%, with elevated waist circumference at 63%, have dyslipidemia at 96%, and uncontrolled glycemic status at 65.3%.

Table III: Demographic Data

Parameters	Frequency	Percent (%)
BMI (kg/m^2)		
Obese ($\geq$ 25)	65	44.2
Class 1	47	72.3
Class 2	18	27.7
Non-Obese	82	55.8
WC (cm)		
Elevated (M= $\geq$90; F= $\geq$80)	93	63.3
Normal	54	36.7
Dyslipidemia (mg/dL)		
Present (TAG$\geq$150; LDL$\geq$ 100; HDL M= <40, F=<50)	123	83.7
Absent	24	16.3
Glycemic status (HbAiC %)		
Uncontrolled (>7)	96	65.3
Controlled	51	34.7

The result of the liver function test revealed 22 (16.2%) subjects with elevated GGT with a mean of 55.5 (SD 79.7), ranging from 10 to 783. The mean ALT and AST were 43 (SD 29.7) and 32.1 (SD 21.5) respectively, with a range of 13 to 212,. There were 22 (16.2%) and 19 (14%) patients with elevated ALT and AST respectively (Table IV).

Table IV: Liver Profile

Liver Profile	Freq	%
GGT		
Elevated	23	15.6
Normal	124	84.4
ALT		
Elevated (1-4x elevated)	22	15.0
Normal	125	85.0
AST		
Elevated (1-4x elevated)	19	12.9
Normal	128	87.1
Alkaline Phosphatase (ALP)		
Elevated (not >2x elevated)	2	1.5
Normal	145	98.6
ALT/AST		
>1	18	12.2
Not > 1	129	87.8

A significant alkaline phosphatase was seen in one patient (>2x elevated). The mean total bilirubin was 0.7 (SD 1.1), and ranged from 0 to 13.3. Only one patient had elevated value. The mean albumin was 4.1 (SD 0.4) and ranged from 3 to 5.2. Again, only one patient had an elevated albumin.

Concomitant liver disease among all the subjects includes, six (4.4%) subjects with reactive in HBs Ag, 47 (34.6%) were reactive in anti-HBs and only one (0.7%) with positive anti-HCV. Of the six subjects with HBs Ag, one had an ALT/AST > 1, hence excluded in the study. All the other subjects with probable NAFLD had no concomitant liver disease finding.

Among the 18 patients with ALT/AST > 1 (probable NAFLD), 28.6% were Type 2 DM with obesity, 11.1% with dyslipidemia and 11.8% has Type 2 DM, Obesity and Dyslipidemia (Table V). The observed difference however was not statistically significant.

Table V: Probable NAFLD among Type 2 DM Subjects with ALT/AST>1

Subject	ALT/AST >1		ALT/AST not > 1		Total	
	Freq	%	Freq	%	Freq	%
Pure Type 2 DM	0	.0	10	100.0	10	100.0
Type 2 DM + Obese	4	28.6	10	71.4	14	100.0
Type 2 DM + Dyslipidemia	8	11.1	64	88.9	72	100.0
Type 2 DM + Obese + Dyslipidemia (Metabolic Syndrome)	6	11.8	45	88.2	51	100.0
Total	18	12.2	129	87.8	147	100.0

X^2=4.965, p=0.174 Not significant

The subsequent table shows the correlation of obesity and probable NAFLD. (Table VI) Among these obese subjects with ALT/AST > 1, 7 (14.9%) are Class I and in 3 (16.7%) are Class II patients. The observed differences in NAFLD distribution across the BMI groups were not significant (p=0.301) (Table VII)

Table VI: Correlation of Obesity with ALT/AST > 1 (Probable NAFLD)

Parameter	BMI				Total	
	Obese		Normal			
	Freq	%	Freq	%	Freq	%
ALT/AST >1	10	15.4	8	9.8	18	12.2
ALT/ AST not > 1	55	84.6	74	90.2	129	87.8
Total	65	100.0	82	100.0	147	100.0

X^2=1.069, p=0.301. No statistical correlation of obesity and the occurrence of ALT/AST > 1

Table VII: Correlation of the Severity of Obesity with Probable NAFLD

Parameter	BMI			
	Obese I		Obese II	
	Freq	%	Freq	%
ALT/AST >1	7	14.9	3	16.7
ALT/ AST not > 1	40	85.1	15	83.3
Total	47	100.0	18	100.0

Fisher's exact p=1.000. Not significant

Dyslipidemia was noted in 16 of the 18 subjects with ALT/AST > 1 (Probable NAFLD) (Table VIII). There were 16 (12.2%) subjects with dyslipidemia who have ALT/AST > 1 against the 115 (87.8%) subjects with normal transaminases. The observed differences in probable NAFLD distribution across the subjects with dyslipidemia were not significant (p=1.000)

Table VIII: Correlation of Dyslipidemia among Subjects with Probable NAFLD

Parameter	NAFLD (ALT/AST >1)		Non- NAFLD (Normal ALT/AST)		Total	
	Freq	%	Freq	%	Freq	%
Dyslipidemia	16	12.2	115	87.8	131	100.0
Normal	2	12.5	14	87.5	16	100.0
Total 18	12.2	129	87.8	147	100.0	

Fisher's exact p=1.000 Not significant statistical correlation of dyslipidemia with the occurrence of ALT/AST > 1

There were noted incidental findings in the ultrasound of the all subjects mainly non-obstructing stone and mass in the total population. Mass, mostly signed out by the sonologist as hepatic cyst accounted seven subjects, two of which are probable NAFLD however, not statistically significant. (Table IX)

Table IX: Correlation of Incidental Findings Among All the Subjects

Incidental findings by ultrasonography	Diagnosis				Total	
	ALT/AST > 1		ALT/AST not > 1			
	Freq	%	Freq	%	Freq	%
Mass	2	28.6	5	71.4	7	100.0
Non-obstructing stone	1	12.5	7	87.5	8	100.0
None 15	11.4	117	88.6	132	100.0	
Total 18	12.2	129	87.8	147	100.0	

X^2=1.832, p=0.400 Not significant

There were 80 patients (54.4%) who had ultrasonographic findings of fatty liver, while 67 (45.6%)

had normal ultrasound findings. Of the abnormal findings, 56 (70.0%) and 24 (30.0%) had mild and had moderate fatty liver respectively. (Table X)

Table X: Occurrence of Hepatic Steatosis (Fatty Liver) Among All Subjects

Ultrasound	Freq	%
Hepatic steatosis		
Present (Probable NAFLD)	80	54.4
Absent	67	45.6
Hepatic steatosis severity		
Mild	56	70.0
Moderate	24	30.0
Severe	0	0.0

The presence of hepatic steatosis by ultrasonography was observed in 58 (60.4%) and 22 (43.1%) of patients with uncontrolled and controlled DM-2 respectively. The observed difference was not significant (p=0.045). The occurrence of hepatic steatosis was similar between those with dyslipidemia (55.3%) and those without dyslipidemia (50.0%) patients (p=0.634). Abnormal ultrasonographic findings were found in 45 (69.2%) of obese patients and 35 (42.7%) of patients with normal BMI. The observed difference was significant (p=0.001) (Table XI).

Table XI: Correlation of the Sonographic Findings with Glycemic Status, Dyslipidemia and Obesity

Parameter	Ultrasonographic hepatic steatosis				Total		X^2	P value
	Present		Absent					
	Freq	%	Freq	%	Freq	%		
DM-2							4.009	0.045
Uncontrolled	58	60.4	38	39.6	96	100.0		
Controlled	22	43.1	29	56.9	51	100.0		
Total			80	54.4	67	45.6	147	100.0
Dyslipidemia							0.226	0.634
Present	68	55.3	55	44.7	123	100.0		
Absent	12	50.0	12	50.0	24	100.0		
Total			80	54.4	67	45.6	147	100.0
BMI							10.302	0.001
Obese	45	69.2	20	30.8	65	100.0		
Normal	35	42.7	47	57.3	82	100.0		
Total			80	54.4	67	45.6	147	100.0
BMI							16.683	<0.001
Obese I	28	59.6	19	40.4	47	100.0		
Obese II	17	94.4	1	5.6	18	100.0		
Normal	35	42.7	47	57.3	82	100.0		
Total		80	54.4	67	45.6	147	100.0	

Mild hepatic steatosis was seen more common than moderate. No subjects exhibited severe hepatic steatosis. (Table XII).

Table XII: Correlation of the Severity of Hepatic Steatosis with Glycemic Status, Dyslipidemia and Obesity

Parameter	Ultrasonographic hepatic steatosis			
	Mild		Moderate	
	Freq	%	Freq	%
DM-2				
Uncontrolled	40	41.7	18	18.8
Controlled	16	31.4	6	11.8
Total	56	38.1	24	16.3
Dyslipidemia				
Present	47	38.2	21	17.1
Absent	9	37.5	3	12.5
Total	56	38.1	24	16.3
BMI				
Obese	26	40.0	19	29.2
Class I	17	36.2	11	23.4
Class II	9	50.0	8	44.4
Normal	30	36.6	5	6.1
Total	56	38.1	24	16.3

The mean duration of DM-2 in years was 9.8 years (SD 6.3) among those without hepatic steatosis. There is no sufficient evidence to conclude that the ultrasonographic hepatic steatosis is associated with the duration of DM-2 (p=0.897). (Table XIII)

Table XIII: Correlation of the Duration of Type 2 DM with Hepatic Steatosis

Ultrasonographic hepatic steatosis	Duration of DM-2		
	N	Mean	SD (range)
Normal	67	9.8	+/-6.3 (0.329.0)
Mild	56	10.1	+/-6.0 (1.0-26.0)
Moderate	24	9.4	+/-6.5 (0.1-27.0)
Total	147	9.8	+/-6.2 (0.1-29.0)

ANOVA F=0.109, p=0.897

There is no statistical significance for those with ALT/AST > 1 and AST to the presence or absence of hepatic steatosis (fatty liver). However, with statistically significant correlation of elevated ALT with the presence of hepatic steatosis (Table XIV)

Table XIV: Correlation of Hepatic Steatosis with Elevated Transaminases

Parameters	Ultrasonographic hepatic steatosis				Total		X^2	P value
	Present		Absent					
	Freq	%	Freq	%	Freq	%		
ALT							7.829	0.005
Elevated	18	81.8	4	18.2	22	100.0		
Normal	62	49.6	63	50.4	125	100.0		
Total	80	54.4	67	45.6	147	100.0		
AST							5.291	0.021
Elevated	15	78.9	4	21.1	19	100.0		
Normal	65	50.8	63	49.2	128	100.0		
Total	80	54.4	67	45.6	147	100.0		
ALT/AST							4.511	0.034
>1	14	17.5	4	6.0	18	12.2		
Not > 1	66	82.5	63	94.0	129	87.8		
Total	80	100.0	67	100.0	147	100.0		

DISCUSSION

Features of NAFLD seen among the Type 2 diabetic subjects includes elevated ALT at 15%, AST at 13% and ALT/AST >1 at 12%. Only 1.5% showed elevated alkaline phosphatase to not more than 2x the normal limits in the absence of symptoms referable to the liver. Among those with ALT/AST > 1, 3 subjects actually had incidental findings in the ultrasound. This includes a single hepatic cyst with 1.5 cm as the largest diameter for 2 subjects and 1 with non-obstructing gallstone of <1 cm. However, these incidental findings were not statistically significant.

GGT was noted to be significantly elevated among the subjects with ALT/AST >1. This is the commonest abnormality in any non-specific liver disease. In epidemiological studies, it has also a positive association with factors such as alcohol intake, cigarette smoking and coronary heart disease (Harris 2004). In our study, GGT was also elevated even among subjects that are not probable NAFLD at 16%. Its value as a marker for NAFLD has not been evaluated.

The sonographic studies showed a high incidence of hepatic steatosis (fatty liver) at 54% among the Type 2 Diabetes Mellitus subjects. The presence of hepatic steatosis may also indicate a probable NAFLD. There were more subjects noted to be positive in the ultrasound than elevated transaminases.

Interestingly, there were four patients with ALT/AST >1 who had no fatty liver by ultrasound. This was however, not statistically significant.

The predictive value for NAFLD with ALT/AST >1 and sonographic finding of fatty liver approaches 96% as noted by Ezur, and colleagues. This however cannot be noted in the study due to inability to perform the gold standard in the diagnosis of NAFLD which is liver biopsy.

Among the transaminases, the ALT showed statistical significance in the development of hepatic steatosis.

There was no significant relationship of the duration of Type 2 DM, degree of glycemic control and dyslipidemia among those with fatty liver by ultrasound. However, there is a statistical significance in the degree of obesity. The relationship is directly proportional. The higher the BMI, the greater the chances of hepatic steatosis.

There is no significant relationship of metabolic syndrome to the development of hepatic steatosis probably because in our patient population, there were more subjects who were not obese wherein obesity actually showed statistical significance in the development of hepatic steatosis.

There was no significant difference in the elevation of transaminases with the degree of glycemic control, dyslipidemia and obesity.

CONCLUSION

The true prevalence of NAFLD is difficult to ascertain accurately due to lack of effective screening tests that can be applied to the entire population.

Features of NAFLD seen in the study include elevated transaminases (ALT at 15% and AST at 13%), ALT/AST > 1 (12%) in the Type 2 diabetic subjects who are asymptomatic of liver disease. Sonographic NAFLD was observed in 54% of the population.

Elevated ALT showed significant correlation with the development of hepatic steatosis.

As studied by Drs Adams and Hanley, obesity was also noted in this study to be a significant factor in the development of hepatic steatosis.

There is no correlation in the development of hepatic steatosis with the duration of diabetes, glycemic control and dyslipidemia.

RECOMMENDATIONS

There should be an established definitive cut off for the transaminases to improve their utility as surrogate markers in the diagnosis of NAFLD.

We recommend further studies on the utilization of GGT as an early marker to NAFLD since it was seen in the study to be significantly elevated even without rise in the transaminases. These specific subjects may be evaluated later for possible progression to NAFLD.

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APPENDIX 1:

Non-alcoholic Fatty Liver Disease (NAFLD) Study – St Luke's Medical Center

Investigator: Jovie Joy Manuel, MD

Name:_____

Age:_____ Gender:_____ Pin #_____ Contact # _____

Address:_____

Occupation: _____

Hepatitis B ( ) Hepatitis C ( ) Alcoholic: Y/N, ___ ; how much? _____

Drug induced Hepa: Y/N; Hepatocellular CA ( ); Hx of jaundice: Y/N

History:

Duration of Type 2 DM:_____

DM Medications:_____

_____

Family Hx of DM (Y/N): _____

_____

DM Complications:

1. _____
2. _____
3. _____
4. _____
5. _____

Co-morbid condition	Duration	Medication	Frequency

Physical Examination

Liver span: _____

Anthropometric measurement:

Ht: _____ Wt : _____ Waist Circumference: _____ BMI: _____

Blood Exams:

FBS: _____ HBAic: _____

Lipid profile: Total Cholesterol: ____ TAG: ____ HDL: ____ LDL: ____

Hepatitis profile: Hbs Ag: ____ HBsAb:____ Anti HCV: ____

Liver Function test: GGT: ____ ALT:____ AST: ____; ALP: _____

Bilirubin:____ Albumin:____

UTZ, Liver:

Normal: _____ Mild: _____ Moderate: _____ Severe: _____