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Micro and Macro vascular complications in type 2 diabetic patients with non-alcoholic fatty liver disease

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Abstract
NAFLD is a spectrum of liver lesions ranging from simple hepatic steatosis to NASH with progressive fibrosis leading to cirrhosis and liver failure in some patients and eventually hepatocellular carcinoma. The different parts of this spectrum are probably best regarded as parts of a histological continuum. All patients underwent ultrasound (USG) of the abdomen to detect fatty changes in the liver, performed by aexperienced radiologist, using a high-resolution B-mode ultrasonography system, having an electric linear transducer mid frequency of 3-5 MHz.The scanning was done for an average of 20 minutes.
In our study out of 50 patients,22(44%) patients were having diabetic neuropathy on the basis of clinical examination,out of them 10 (45.45%) patients were males & 12 (54.54%) patients were females. There was higher prevalence of diabetic neuropathy in female patients. 28 (56%) patients were negative for neuropathy. Out of total 50 diabetic patients with NAFLD, 31 (62%) patients were having evidence of CAD, out of 31 patients, 17 (54.8%) were male & 14 (45.2%) were female. 19 (38%) patients having no evidence of CAD.

Keywords: NAFLD, CAD, NASH

Introduction

The prevalence of NAFLD varies considerably depending on the subset of patients being investigated. In obese persons fatty liver affects more than 50% and 100% of severely obese with diabetes. Thus, the prevalence of NAFLD in the general population is linked to the frequency of obesity and diabetes[1].
The technique used to diagnose hepatic steatosis also influences the prevalence reported in different studies (See "Diagnosis"). Large epidemiological studies using liver biopsy in the general population cannot be performed because of the potential severe complications with this procedure. Since 1H-MRS is highly sensitive in detecting fatty infiltration and has the ability to quantitatively assess the amount of fat within the liver, this method is ideal to use in epidemiological studies. Unfortunately, the use of 1H-MRS in large epidemiological studies isheld back by the high cost and the complicated technique. Most epidemiological studies have used ultrasonography or liver function tests to assess the prevalence of NAFLD[2, 3].
NAFLD is a spectrum of liver lesions ranging from simple hepatic steatosis to NASH with progressive fibrosis leading to cirrhosis and liver failure in some patients and eventually hepatocellular carcinoma. The different parts of this spectrum are probably best regarded as parts of a histological continuum.
The clinical features of patients with NAFLD vary considerably between different cohorts of patients. Many reports come from series of NAFLD patients undergoing obesity surgery making results difficult to apply to the typical NAFLD patient of the general population.

Another bias in NAFLD cohorts is that most studies have been conducted in tertiary referral centres. Few studies have explored NAFLD in the general population and none of these has included histopathological evaluation. Studies of NAFLD patients in the general population are probably the best studies to describe the clinical features of the typical NAFLD patient[4].
Most NAFLD patients do not have any symptoms or signs of liver disease unless symptoms of end-stage liver disease are present. If present at all, symptoms in NAFLD patients are constitutional and non-specific. Some patients report fatigue and/or a sensation of fullness on the right side of the upper abdomen. Hepatomegaly is present in 75% of cases, but may be difficult to detect due to the high prevalence of obesity in NAFLD patients. It is evident that overweight/obesity and diabetes are important risk factors for developing NAFLD. With the development of proton magnetic resonance spectroscopy the association between the amounts of fat accumulated within the liver and several risk factors, especially insulin resistance, are being elucidated[5, 6].

Methodology

All patients underwent ultrasound (USG) of the abdomen to detect fatty changes in the liver, performed by experienced radiologist, using a high-resolution B-mode ultrasonography system, having an electric linear transducer mid frequency of 3-5 MHz.The scanning was done for an average of 20 minutes;Fatty liver was defined as the presence of an ultrasonographic pattern consistent with "bright liver", with evident ultrasonographic contrast between hepatic and renal parenchyma, vessel blurring and narrowing of the lumen of the hepatic veins in the absence of findings suggestive of chronic liver disease.
NAFLD was defined as any degree of fatty liver in the absence of alcohol intake. NAFLD, if present, was classified based on standard ultrasonographic criteria as: Grade 1 (mild steatosis): slightly increased liver echogenicity with normal vessels and absent posterior attenuation.
Grade 2 (moderate steatosis): Moderately increased liver echogenicity with partial dimming of vessels and early posterior attenuation.
Grade 3 (severe steatosis): Diffusely increased liver echogenicity with absence of visible vessels and heavy posterior attenuation.

The study group was divided into 2 subgroups:

- **Group A:**Patients with USG evidence of fatty changes in the liver.
- **Group B:**Patients without any USG evidence of fatty changes in the liver.

All the patients and the control subjects underwent a through clinical examination with special emphasis as.
Symptoms: upper abdominal pain Malaise.
Lethargy Jaundice.
Tingling and numbness in feet and hands Blurring of vision.

Polyuria, polydipsia Duration of diabetes:
Treatment received: OHA and/or insulin.

WHO criteria for diagnosis of diabetes mellitus are

1. Symptoms of Diabetes plus Random Blood Sugar > 200 mg/dl[a].
2. Fasting Blood Sugar > 126 mg/dl[b].
3. Two hour plasma glucose >200 mg/dl an oral glucose tolerance test[c].

a) Random is defined as without regard to time since the last meal.
b) Fasting is defined as no calorie intake for at least 8 hours.
c) The test should be performed using a glucose load containing the equivalent of 75 g

anhydrous glucose dissolved in water, not recommended for routine use

- Type 2 diabetes
- Diabetic patients either on oral treatment or insulin therapy.

Exclusion criteria

Age < 35 or >75 years.
Known hepatic disease, HBs antigen or Anti-HCV positivity, History of ingestion of hepatotoxic drug(s).
History of significant alcohol consumption. Significant alcohol consumption define by Ongoing or recent alcohol consumption > 21 drinks on average per week in men and > 14 drinks on average per week in women.

Results

Table 1: Prevalence of hypertension

HT	Male	Female	Total
Present	21	22	43 (86%)
Absent	3	4	7(14%)

Table 2: Comparison of hypertension (HT) between Group A & Group B

HT	Group A (n=50)		Group B (n=30)	
	Male	Female	Male	Female
Present	21	22	4	4
Absent	3	4	14	8

Table 3: Sex distribution of retinopathy

Retinopathy	Male	Female	Total
Present	16	18	34(68%)
Absent	8	8	16(32%)

Out of total 50 patients of type 2 diabetes with fatty liver, 34 (68%) patients were having retinopathy & out of 34 patients 16(47%) were males & 18(53%) were females.

Table 4: Prevalence of diabetic retinopathy

Fundus	Number ofpatients	Percentage
WNL	16	32%
HTN retinopathy	4	8%
NPDR	17	34%
NPDR+HTN retinopathy	5	10%
PDR	8	16%

In our study 17 (34%) patients were having non proliferative diabetic retinopathy, 8 (16%) were having proliferative diabetic retinopathy, while 5 (10%) patients were having mixed

retinopathy include non-proliferative diabetic with hypertensive retinopathy. In addition to that, 4 (8%) diabetic patients were also suffering from hypertension shows only changes of hypertensive retinopathy. While 15 (30%) diabetic patients were having normal fundus.

Table 5: Comparison of diabetic retinopathy between group A & group B

Diabetic retinopathy	Group A (n=50)		Group B (n=30)	
	Male(n=24)	Female(n=26)	Male(n=18)	Female(n=12)
Present	14	16	3	3
Absent	10	10	15	19

Above table suggest prevalence of diabetic retinopathy in group A was 30(60%),while in groupB was 6(20%). Comparison of prevalence of diabetic retinopathy between group A & group Bshowed Chi-square value 12.12thatcorrespondsto p value of 0.0004 at 1 degree of freedom.

Prevalence of non-proliferative diabetic retinopathy (NPDR) was compared between group A &group B, which was showed(x^2 = 5.033, p=0.024)& prevalence of proliferative diabeticretinopathy (PDR) was also compared between group A & group B,which was showed (x^2=0.08, p=0.7646).

Table 6: Prevalence of diabetic neuropathy

Peripheral neuropathy	Male	Female	Total
Present	10	12	22(44%)
Absent	14	14	28(56%)

In our study out of 50 patients,22(44%) patients were having diabetic neuropathy on the basis of clinical examination, out of them 10 (45.45%) patients were males & 12 (54.54%) patients were females. There was higher prevalence of diabetic neuropathy in female patients. 28 (56%) patients were negative for neuropathy.

Table 7: Comparison of diabetic neuropathy between group A & group B

Peripheral neuropathy	Group A (n=50)		Group B (n=30)	
	Male (n=24)	Female (n=26)	Male (n=18)	Female(n=12)
Present	10	12	1	2
Absent	14	14	17	10

To compare the prevalence of diabetic peripheral neuropathy in diabetic patients with NAFLD &without NAFLD, statistical analysis done, which was showed Chi-square value 10.08 thatcorresponds to p value of 0.0014 at 1 degree of freedom. So this showed, in our study higherprevalence of peripheral neuropathy in type 2 diabetic patients was associated with NAFLD.

Table 8: Prevalence of diabetic nephropathy

Sex	Nephropathy	
	Present	Absent
Male	6	18
Female	5	21
Total	11(22%)	39(78%)

In our study out of 50 patients, total 11 (22%) patients were having nephropathy, out of 11patients, 6 (54.54%) patients were males & 5 (45.45%) patients were females.

Table 9: Comparison of prevalence of nephropathy between Group A & Group B

Nephropathy	Group A (n=50)		Group B (n=30)	
	Male (n=24)	Female(n=26)	Male(n=18)	Female(n=12)
Present	6	5	3	4
Absent	18	21	15	8

Prevalence of nephropathy in diabetic patients with NAFLD was higher than patients without NAFLD, but that was statistically not significant. (x^2=0.019 p=0.89) in our study.

Table 10: Prevalence of Coronary artery disease (CAD)

CAD	Male	Female	Total
Patient	17	14	31(62%)
Absent	7	12	19(38%)

Out of total 50 diabetic patients with NAFLD, 31 (62%) patients were having evidence of CAD, out of 31 patients, 17 (54.8%) were male & 14 (45.2%) were female. 19 (38%) patients having no evidence of CAD.

Group B

CAD	Group A (n=50)		Group B (n=30)	
	Male	Female	Male	Female
Present	17	14	4	2
Absent	7	12	14	10

To compare the prevalence of Coronary artery disease (CAD) in diabetic patients with NAFLD& withoutNAFLD,statisticalanalysisdone,whichshowedChi-square value 13.3thatcorresponds to p value of 0.0002 at 1 degree of freedom.

Discussion

Table 11: Prevalence of hypertension (HT) with other studies

Study group	% pt with HT
Yuichirotakeuchi*et al*. (n=1307)[7]	81
Vijayviswanathan*et al*. (n=2161)[8]	64.7
Akagarwal*et al*. (n=124)[9]	71.4
Present study (n=50)	86

To compare prevalence of hypertension, in yuichirotakeuchi*et al*. (n=1307) was 81%, which was comparable to our study.

Retinopathy

Table 12: Comparison of prevalence of diabetic retinopathy with other studies

Study group	% subject with retinopathy
Giovanni targher*et al*. (n=2103)[10]	39
Vijayviswanathan*et al*. (n=2161)[8]	29.4
Present study (n=50)	60

Above table suggest, there was much higher prevalence of diabetic retinopathy as compared to other studies in patients with diabetes with fatty liver, which may because of small sample

size as compared to study done by Giovanni targher*et al*. showed 39% (n=2103),while in vijayviswanathan*et al*. was 29.4% (n=2161).

Table 13: Comparison of prevalence of nephropathy with other studies

Study group	% of patients with nephropathy
Giovanni targher*et al*. (n=2103)[10]	15
Ya-taozhan*et al*. (n=413)[11]	38
Vijayviswanathan*et al*. (n=2161)[8]	32
Present study (n=50)	22

Prevalence of nephropathy in vijayviswanathan*et al*.(n=2161) study was 32%, which was almost comparable to our study[12].

Table 14: Comparison of prevalence of coronary artery disease (CAD) with other studies

Study group	% of diabetic Patients with NAFLD	% of diabeticpatients without NAFLD	P value
Yuichirotakeuchi*et al*. (n=1307)[7]	22	16	0.1
Vijayviswanathan*etal*. (n=2161)[8]	11.5	1.4	0.01
Akagarwal*et al*. (n=124)[9]	60.5	24	0.104
Present study (n=80)	62	20	0.0002

Above table suggest, Prevalence of coronary artery disease (CAD) in Akagarwal et al (n=124) study was 60.5% which was comparable to our study.

Conclusion

NAFLD was also associated with increased prevalence of diabetic macroangiopathy &micro vascular complication. In addition, NAFLD is an independent predictor for diabetic retinopathy & coronary artery disease (CAD) in type 2 diabetic patients. These findings suggest that type 2 diabetic patients with NAFLD should be considered as a high risk group for developing microvascular complication, even if microangiopathy is not clinically detected.So clinicians should look for NAFLD in diabetes, especially in presence of the metabolic syndrome.Once found, aggressive management of diabetes &risk factors should be the primary goal.

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