

Association of Non-alcoholic Steatohepatitis and Nonalcoholic Fatty Liver Disease (NAFLD) in Patients of Type 2 Diabetes Mellitus.

Luís Fonseca¹, Helena Sardinha¹

¹College of Medical Pediatrics, University of Lisbon, Lisbon.

Abstract

Background: The most common form of chronic liver disease in children is Non-alcoholic fatty liver disease (NAFLD). It is associated with obesity and a serious public health problem. Non-alcoholic steatohepatitis (NASH) is also commonly associated with type 2 diabetes mellitus (DM). Therefore, this study was carried out to know the Prevalence of NASH and NAFLD in patients of type 2 DM admitted in a tertiary care hospital. **Methods:** This prospective study enrolled T2DM patients in age group of 25-65 years, attending an outpatient Paediatrics department of University of Lisbon, Lisbon, a tertiary care Centre. NAFLD and NASH will be suspected in a patient who is found to have elevations in liver tests such as alanine aminotransferase (ALT) or aspartate aminotransferase (AST). The only means of proving a confirmatory diagnosis of NASH will be done by liver biopsy. **Results:** A total of 225 patients, with more number of female patients 80 (55.38%) than male patients 45 (44.61%) were recruited with the suspicion of Nonalcoholic Fatty Liver Disease (NAFLD) and Non-alcoholic steatohepatitis. Out of 225 patients enrolled in the study, n=78 (54.76%) T2DM patients (n=63 female and n=25 male), was identified as having NAFLD, and n=5 as NASH. **Conclusion:** We conclude that the prevalence of NASH and NAFLD and is high in type 2 DM patients.

Keywords: Nonalcoholic Fatty Liver Disease, Non-alcoholic steatohepatitis, Diabetes.

INTRODUCTION

The term Non-alcoholic steatohepatitis (NASH) was coined by Ludwig and colleagues to describe a form of liver disease observed in middle aged patients with abnormal liver biochemical test results and histologic evidence of alcoholic hepatitis but with no history of alcohol abuse.[1] The spectrum of NAFLD includes, simple steatosis without evidence of cell injury, which tends to be stable over time, to steatohepatitis, which progress to cirrhosis.[2] Non-alcoholic fatty liver disease (NAFLD) has become over the last decade the most common form of chronic liver disease in children and adults. It is tightly associated with obesity and threatens to become a serious public health problem. Epidemiological studies suggest its prevalence in around 9% to 32% of the general population, but with a higher prevalence in overweight / obesity and diabetes.[3]

Non- alcoholic fatty liver disease is commonly associated with obesity, type 2 diabetes, dyslipidemia and insulin resistance – components of the metabolic syndrome. This strongly supports the notion that NAFLD is the hepatic manifestation of the metabolic syndrome.[6]

Non-alcoholic steatohepatitis (NASH) is commonly associated with type 2 diabetes mellitus (DM). Prevalence of NASH in type 2 DM has not been well studied and there is an epidemic rise in type 2 DM in Asian and Western populations. Its association with chronic liver disease in the form of NASH makes it an important health problem. The

Indian population has a higher body fat content and abdominal adiposity: the latter is particularly associated with insulin resistance and hence NAFLD.[3]

Moreover, with increasing incidence and prevalence, the perception of NAFLD being a benign condition of little clinical significance is rapidly changing. The overall prevalence of NAFLD in western countries varies from 15-40% and in Asian countries from 9-40%.[5-7] In India too, NAFLD is emerging as an important cause of liver disease. Epidemiological studies suggest the prevalence of NAFLD to be around 9-32% in general Indian population, with a higher incidence amongst overweight/obese and diabetic/prediabetic patients.[8-10]

So this study is conducted to estimate the prevalence of NAFLD as diagnosed by ultrasound examination of the liver, with type 2 diabetes. Therefore, these patients can be treated earlier and prevented from going into cirrhosis.

MATERIAL AND METHODS

This prospective study was designed to enrol known T2DM patients (duration ≥ 3 years), in the age group of 25-65 years, attending a tertiary care Centre. The study was approved by the ethics committee of the hospital and informed consent was obtained from all the subjects. On the basis of inclusion and exclusion criteria, 325 T2DM patients enrolled over the period of 6 months (December 2011-May 2013) and underwent complete medical and physical examination at the time of enrollment. The history of medication and alcohol consumption and other relevant details were obtained. Data (risk factors and lab values) are collected and are compared between the two subgroups, to know the level of difference between them. NASH will be suspected in a patient who is found to have elevations in liver tests such as alanine aminotransferase (ALT) or aspartate aminotransferase (AST). The only means of proving a confirmatory diagnosis of NASH will be done by liver biopsy. For a liver biopsy, a needle is inserted through the

Address for correspondence*

Dr. Luís Fonseca

College of Medical Pediatrics,
University of Lisbon, Lisbon.

skin to remove a small piece of the liver. NASH will be diagnosed when examination of the tissue with a microscope shows fat along with inflammation and damage to liver cells. If the tissue shows fat without inflammation and damage, simple fatty liver or NAFLD is diagnosed.

We used data of liver enzyme abnormalities to characterize the prevalence, incidence, and risk factors for NAFLD in T2DM patients. The levels of Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) were measured. The elevation (value above normal) in aminotransferase levels was defined as per NHANES III criteria; corresponding to an AST >37IU/L or ALT >40IU/L for men and AST or ALT >31IU/L in women.[11]

The data processing was performed by capturing data into e-Case Report Forms. The Data entered was checked by system design for completeness and integrity. Demographic data is presented as descriptive statistics. Sample studied was characterized by relative (%) and absolute (N) frequencies, for each of the qualitative variable.

RESULTS

A total of 325 patients, with more number of female patients 180 (55.38%) than male patients 145 (44.61%) were recruited with the suspicion of Nonalcoholic Fatty Liver Disease (NAFLD) and Non-alcoholic steatohepatitis in patients of Type 2 Diabetes Mellitus [Table 1].

Out of 325 patients enrolled in the study, n=178 (54.76%) T2DM patients (n=103 female and n=75 male), was identified as having NAFLD, based upon NHANES III criteria as described above [Table 1]. The prevalence of NAFLD was found to be more in females n=103 than males. The majority of the patients were found in 41-55 years age group followed by 25-40 years and least in more than 71 years age group [Table 1].

Table 1: Gender wise distribution in both group

	Cases	Percentage	Control	Percentage
Male	40	68.9%	24	63.1%
Female	18	31.1%	14	36.9%
Total	58	100%	38	100%

Table 2: The mean serum calcium and electrolytes levels in both the groups

Parameters	mean		SD		P value	Significance
	Cases	Control	Cases	Control		
Serum calcium	7.96	9.5	.66	.64	<0.005	Highly significant
Serum potassium	5.33	134.97	5.6	5.44	0.129	Not significant
Serum sodium	136.76	5.27	.89	.99	.78	Not significant

In the current study, elevation in AST and ALT levels, based on NHANES III criteria, were employed to estimate and characterize the prevalence of NAFLD in T2DM patients. The combined AST/ALT levels were more raised than AST and ALT alone [Table 3]. These levels were

highly raised in patients with NASH confirmed by liver biopsy. Around 22 patients were undergone liver biopsy for the suspicion NASH. Out of 22 patients suspected, only 15 patients (n=9 female and n=6 male), were found to be having NASH [Table 2].

DISCUSSION

To the best of our knowledge, there are no pan- India population based studies on prevalence of NAFLD in T2DM population. This is the first cross sectional, multi-centre study to report on the prevalence of NAFLD in Indian T2DM population.

The majority of epidemiological studies on NAFLD in general or in T2DM population in particular, are based on histological evidence of steatosis or fatty infiltration proven by imaging. This study makes the effort to record the prevalence of NAFLD and NASH in T2DM patients on the basis of elevated aminotransferase levels and liver biopsy for the confirmation of NASH.

In our study, the overall prevalence of NAFLD in T2DM Indian population was found to be n=178 (54.76%), which is in line with a prevalence of 54.5% described by Mohan et al,[12] but higher than the prevalence rate of 12.5%[13] and 20%[14] described in other studies. However, in the study by Prashanth et al, showed higher prevalence rate of 87% T2DM patients had NAFLD on histology.[15]

Our study contradicts the previous studies conducted in India showing higher prevalence of NAFLD in males than in the female population.[14] Our results showing higher prevalence of NAFLD in female than male is in accordance with the study conducted by Kalra S et al.[16]

In our study, we have shown that the prevalence of NAFLD increases with age, with the majority of cases occurring between the age of 40 and 60 years. This is in accordance with the previous similar studies.[14,17]

In our study, mean ALT levels were found to be higher than AST levels in identifying T2DM NAFLD cohort as a whole, and in different age group. ALT appears to have a role in gluconeogenesis and seems to be more related to liver fat accumulation than AST.[18] Minor elevation of this enzyme level may be a good predictor of mortality from liver disease as suggested by some authors.[19] Elevation of levels of ALT and AST or both to mild and moderate levels is a very common finding in NAFLD.[20]

Similarly, in T2DM patients, chronic mild elevations of liver enzymes are frequently encountered;[21] emphasizing the already known fact that T2DM has a strong association with NAFLD, including its severe form NASH.

CONCLUSION

The results from this study have established a prevalence pattern of NAFLD and NASH in T2DM population. Beside this, the study has brought to light prevalent aminotransferase levels in the Indian T2DM population. In our consecutively inducted sample, more females were affected by disease and prevalence was found highest in 41-60 year age group.

REFERENCES

1. Andrea E. Reid. Nonalcoholic Fatty Liver Disease. Mark Feldman, Lawrence S. Frieddman, Lawrence J. Brandt, editors. Slesinger and Fordtran's Gastrointestinal and Liver Disease, 9th ed, Philadelphia; 2010. p. 1401-1411.
2. Stephen H. Caldwell, Curtis K. Argo. Non-alcoholic Fatty Liver Disease and Nutrition. James S. Dooley, Anna S.F. Lok, Andrew K. Burroughs, E. Jenny Heathcote, editors. Sherlock's Diseases of the Liver and Biliary System, 12th ed, West Sussex;2011. p. 546-562.
3. Yogesh K Chawla, Sunil Taneja. Non-Alcoholic Fatty Liver Disease. YP Munjal, SK Sharma, editors. API Textbook of Medicine, Ninth ed, Mumbai; 2012. p. 885-887.
4. Agarwal AK, Jain V, Singla S, Baruah BP, Arya V, Yadav R. Prevalence of non-alcoholic fatty liver disease and its correlation with coronary risk factors in patients with type 2 diabetes. JAPI. 2011;59:351-354.
5. Farrell GC, Larter CZ. Nonalcoholic Fatty Liver Disease: from Steatosis to cirrhosis. Hepatology. 2006;43:S00-S112.
6. Lazo M, Clark JM. The epidemiology of nonalcoholic fatty liver disease: a global perspective. Semin Liver Dis. 2008;28:39-50.
7. Bellentani S, Scaglioni F, Marino M, Bedogni G. Epidemiology of non-alcoholic fatty liver disease. Dig Dis. 2010;28:155-61.
8. Duseja A., Nonalcoholic fatty liver disease in India - a lot done, yet more required. Indian J Gastroenterol. 2010;29:217-25.
9. Singh SP, Nayak S, Swain M. Prevalence of non alcoholic fatty liver disease in coastal eastern India: A preliminary ultrasonographic survey. Trop Gastroenterol. 2004;25:76-9.
10. Gupte P, Amarapurkar D, Agal S. Non-alcoholic steatohepatitis in type 2 diabetes mellitus. J Gastroenterol Hepatol. 2004;19:854-858.
11. Uchil D, Pipalia D, Chawla M, Patel R, Maniar S, Narayani, Juneja A. Non-alcoholic fatty liver disease (NAFLD)—the hepatic component of metabolic syndrome. J Assoc Physicians India. 2009;57:201-4.
12. Mohan V, Farooq S, Deepa M, Ravikumar R, Pitchumoni CS. Prevalence of non-alcoholic fatty liver disease in urban south Indians in relation to different grades of glucose intolerance and metabolic syndrome. Diabetes Res Clin Pract. 2009;84:84-91.
13. Gupte P, Amarapurkar D, Agal S. Non-alcoholic steatohepatitis in type 2 diabetes mellitus. J Gastroenterol Hepatol. 2004;19:854-858 9.
14. Amarapurkar D, Kamani P, Patel N, Gupte P, Kumar P, Agal S, et al. Prevalence of non-alcoholic fatty liver disease: population based study. Ann Hepatol. 2007;6:161-3.
15. Prashanth M, Ganesh HK, Vima MV, John M, Bandgar T, Joshi SR, et al. Prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus. J Assoc Physicians India. 2009;57:205-10.
16. Kalra S, Vithalani M, Gulati G, Kulkarni CM, Kadam Y, Pallivathukkal J, et al. Study of Prevalence of Nonalcoholic Fatty Liver Disease (NAFLD) in Type 2 Diabetes Patients in India (SPRINT). Journal of the association of physicians of India. 2013;61:12-17.
17. Williamson RM, Price JF, Glancy S, Perry E, Nee LD, Hayes PC, et al; on behalf of the Edinburgh Type 2 Diabetes Study Investigators. Prevalence of and Risk Factors for Hepatic Steatosis and Nonalcoholic Fatty Liver Disease in People With Type 2 Diabetes: the Edinburgh Type 2 Diabetes Study. Diabetes Care. 2011;34:1139-1144.
18. Westerbacka J, Cornér A, Tiikkainen M, Tamminen M, Vehkavaara S, Häkkinen AM, et al. Women and men have similar amounts of liver and intra-abdominal fat, despite more subcutaneous fat in women: Implications of sex differences in markers of cardiovascular risks. Diabetologia. 2004;47:1360-9.
19. Kim HC, Jee SH, Han KH. Normal serum aminotransferase concentration and risk of mortality from liver disease: Prospective cohort study. Br Med J. 2004;328:983-7.
20. Pratt DS, Kaplan MM, et al. Evaluation of abnormal liver enzymes results in asymptomatic patients. New Eng J Med. 2000;342:1266-1271.
21. Erbey JR, Silberman C, Lydick E. Prevalence of abnormal serum alanine transaminase levels in obese patients and patients with type 2 diabetes. Am J Med. 2000;109:588-590.