Original Article

Study of Prevalence of Nonalcoholic Fatty Liver Disease (NAFLD) in Type 2 Diabetes Patients in India (SPRINT)

Sanjay Kalra[1], Manoj Vithalani[2], Gurjeet Gulati[3], CM Kulkarni[4], Yogesh Kadam[5], James Pallivathukkal[6], Brahmananda Das[7], Rakesh Sahay[8], KD Modi[9]

Abstract

Non-alcoholic fatty liver disease (NAFLD) is a distinct hepatic condition and one of the most common causes of chronic liver disease globally. Prevalence of the disease is estimated to be around 9-32% in the general Indian population, with a higher incidence rate amongst obese and diabetic patients. We conducted this study to determine frequency and risk factors of NAFLD in nonalcoholic Indian type 2 diabetic (T2DM) patients, based on elevated aminotransferase levels, defined as per NHANES III criteria.

Out of 924 patients (355 female/569 male), in age group of 25-84 years, enrolled at 189 centers across 101 cities in India, a cohort of 522(56.5%) T2DM patients were identified as having NAFLD. Prevalence of the disease was found to be higher in females (60%) than in males (54.3%) T2DM patients; with prevalence of NAFLD varying from 44.1% in western India to 72.4% in northern states. In our study the prevalence of NAFLD increased with increasing age, with 239(45.8%) identified patients in age group of 25-50 years and 283(54.2%) among those aged 51 years (OR:0.71, 95%CI: 0.54–0.92, p=0.005); with highest prevalence recorded in 61-70 year age group, at 61.8%. The results from the study reinforced the well established clinical association of NAFLD with elements of metabolic syndrome (MetS) including dyslipidemia, hypertension and obesity; as T2DM population with these co-morbid conditions had 38%, 17% and 14% higher risk respectively, for NAFLD.

The mean AST and ALT levels were 54.8±36.1 IU/L and 55.6±39.8 IU/L, respectively in NAFLD population and highest in age group of 25-40 years and lowest in 71-84 years age group. Mean ALT levels were found to be higher than mean AST levels across all age groups in identified T2DM NAFLD cohort, with 340(65.3%) patients having elevation of both AST and ALT levels.

The results from this study besides demonstrating the prevalence pattern of NAFLD and associated risk factors in Indian T2DM patients, also point out that even mild elevation in aminotransferase levels warrants attention, since it might more often than not point to previously unsuspected liver disease.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a distinct hepatic condition characterized by abnormal fat accumulation in liver cells; histologically resembling alcohol induced liver damage. The term NAFLD is used to describe a wide array of fatty liver changes from simple steatosis to steatohepatitis, cirrhosis and hepatocellular carcinoma (HCC), in the absence of excessive alcohol intake.[1] A disease practically unheard of 3 decades ago, is now considered as one of the most common causes of chronic liver disease in industrialized world.[2] 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%.[3-5] 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.[6-12]

Metabolic syndrome and associated comorbidities like type 2 diabetes (T2DM), obesity and dyslipidemia are predisposing factors of NAFLD; and prevalence of NAFLD has increased parallel to these epidemics.[13-15] The association of T2DM with microvascular and macrovascular complications is well established, but the association of T2DM with NAFLD as a major complication has been recently recognised. The prevalence of NAFLD amongst T2DM patients is described to be higher than in non-diabetic patients. Approximately 70% of T2DM patients have a fatty liver and they also appear to have more severe forms of the disease including Nonalcoholic steatohepatitis (NASH) and fibrosis,[4,16] with standardized mortality rate for death greater than that for cardiovascular disease(CVD).[17] There is evidence that T2DM patients with NAFLD are at higher risk of developing cirrhosis compared to non-diabetic patients.[18-19] The prevalence of NAFLD in T2DM patients in India is reported to be in range of 12.5-87.5%.[8-10,12]

Chronic liver disease is often identified by asymptomatic elevations of two serum transaminases; alanine transaminase (ALT) and aspartate transaminase (AST) during routine

[1]Consultant Endocrinologist, Bharti Hospital, Kunjpura Road, Karnal, Haryana-132001; [2]Consulting Physician, Medisurge Hospital, Ahmedabad; [3]Consultant Gastroenterologist, Paras Hospitals, C-1 Sushant Lok- 1, Sector-43, Gurgaon, Haryana-122002; [4]Shrey Nursing Home, Baroda Dairy Char Rasta, Opp ONGC, Manakpura, Baroda, Gujarat; [5]M.N.A.M.S., Diplomat National Board of Medicine, Honorary Associate Professor of Medicine, BJ Medical College, Pune - 411001; [6]M.B.B.M. Hospital, Kothamangalam, Cochin, Kerala; [7]Retired Professor, Cuttack Medical College, CDA Sector-6, Plot No - B/1512, Cuttack-753014; [8]Professor-Department of Endocrinology, Osmania Medical College and General Hospital, Hyderabad; [9]Sr. Endocrinologist, Modi Diabetic Centre, Humayun Nagar, Mehdipatnam, Hyderabad
Received: 11.07.2011; Re-revised: 24.05.2012; Accepted: 24.05.2012

Table 1: Demographic characteristics of T2DM patient enrolled in study and patients identified as NAFLD patients

	Patients enrolled (n=924)	NAFLD patients (n=522)
Mean Age (years)	52.16 ± 10.76	52.57 ± 10.70
Gender n (%)	Males: 569 (61.6%) Females: 355 (38.4%)	Males: 309 (59.2%) Females: 213 (40.8%)
Pre existing Conditions n (%)		
Dyslipidemia	485 (52.5%)	311 (59.6%)
Hypertension	557 (60.3%)	336 (64.4%)
Obesity	469 (50.8%)	280 (53.6%)
Mean AST levels (IU/L)	41.0 ± 31.7	54.8 ± 36.1
Mean ALT levels (IU/L)	42.0 ± 34.1	55.6 ± 39.8

Table 2: All India and Zonal Prevalence rate of NAFLD in T2DM patients

	Total	NAFLD Patients n (%)	Male n (%)	Female n (%)
All India	924	522 (56.5%)	309 (59.2%)	213 (40.8%)
North	192	139 (72.4%)	77 (55.4%)	62 (44.6%)
South	298	180 (60.4%)	115 (63.9%)	65 (36.1%)
East	105	58 (55.2%)	37 (63.8%)	21 (36.2%)
West	329	145 (44.1%)	80 (55.2%)	65 (44.8%)

North: Delhi, Haryana, Himachal Pradesh, Punjab, Uttar Pradesh, Uttarakhand; South: Andhra Pradesh, Karnataka, Kerala, Tamil Nadu; East: Bihar, Jharkhand, Orissa, West Bengal; West: Chhattisgarh, Gujarat, Madhya Pradesh, Maharashtra, Rajasthan

serum chemistry; but more often slight increase in levels are overlooked. Nonetheless, there is evidence to suggest that apparently mild elevation in levels of these enzymes, may be a marker for significant liver disease (i.e. bridging fibrosis and cirrhosis).[20] Elevation of the levels of any of the two enzymes (AST or ALT) has been found to be in range of 2.8%-13.3% in the general population[4,21] and 7.8%-31.5%[22-27] in T2DM patients. The studies have found that liver enzyme abnormalities plus T2DM constitutes a greater risk of CVD[28-30] and renal disease.[31] This makes diagnosis of NAFLD in T2DM patients not only essential for the prevention of hepatic complications but also important for the prevention of CVD and renal impairment.

The extent of elevated levels of liver transaminases in the Indian T2DM population is currently not clear. In the studies conducted in Indian T2DM patients the diagnosis of NAFLD is based on histological evidence of steatosis or fatty infiltration proven by imaging tests.[8-10,12] We conducted a prospective, cross-sectional, multi-center study, to estimate and characterize the prevalence, incidence and risk factors for NAFLD in Indian T2DM patients, on the basis of elevated liver transaminase levels.

Material and Method

The study was designed to include known T2DM patients (duration ≥3 years), in age group of 25-84 years, a total of 924 T2DM patients were consecutively included in study. Patients enrolled in the study underwent complete medical and physical examination at the time of enrollment. The history of medication and alcohol consumption and other relevant details were obtained via direct patient interview by 189 diabetologists and physicians at routine diabetic clinics, across 101 cities in India, over the period of 4 months (December 2010-March 2011). All the subjects with daily alcohol consumption of more than 20gm/day (two 30ml drinks) and known history of chronic viral hepatitis were not included in this study. Consequently, we used data of liver enzyme abnormalities to characterize the prevalence, incidence, and risk factors for NAFLD in a cohort of in Indian T2DM patients.

Table 3: Gender based prevalence and risk estimation of NAFLD in T2DM patients

		NAFLD Population	Non-NAFLD Population	RR (95% CI)
All India (n=924)	Females	213 (60%)	142 (35.3%)	1.10 (0.99-1.24, p=.051)
	Males*	309 (54.3%)	260 (64.7%)	
North (n=192)	Females	62 (79.5%)	16 (20.5%)	1.18 (0.99-1.40, p=.048)
	Males*	77 (67.5%)	37 (32.5%)	
South (n=298)	Females	65 (58%)	47 (42%)	0.94 (0.77-1.14, p=.299)
	Males*	115 (61.8%)	71 (38.2%)	
East (n=105)	Females	21 (53.9%)	18 (46.2%)	0.96 (0.67-1.38, p=.492)
	Males*	37 (56.1%)	29 (43.9%)	
West (n=329)	Females	65 (51.6%)	61 (48.4%)	1.31 (1.03-1.66, p=.020)
	Males*	80 (39.4%)	123 (60.6%)	

*Reference Value

The levels of Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) were evaluated by collection of venous blood samples and serum biochemistry performed at one designated laboratory at each site. Internal quality control was maintained at each laboratory. 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.[32]

Data Management and Statistical analysis

The data processing was performed by capturing data into e-Case Report Forms. 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. The patient characteristics of NAFLD patients and the risk estimates for association with each characteristic were verified using Pearson Chi-square test or the Fisher's Exact Test. Mean values, standard deviations, minimums and maximums were used to indicate the quantitative variables of the data and 95% CI was used to define statistical significance.

Results

A total of 924 (355 female/ 569 male) T2DM patients, with mean age of 52.16 ±10.76 years (ranging from 25-84 years), were enrolled in the study. Out of this, a cohort of 522(56.5%) T2DM patients (213 female/ 309 male), was identified as having NAFLD, based upon NHANES III criteria as described above. Data of these patients was analyzed further. Table 1 shows the characteristics of T2DM patients studied.

Amid all India prevalence of 56.5%, the prevalence of NAFLD varied from 44.1% in western India to 72.4% in northern states (Table 2). Prevalence rate of disease was found to be higher in female (60%) than in male (54.3%) T2DM patients, with similar trends reported from northern and western India (Table 3).

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 mean AST and ALT levels were 54.8±36.1 IU/L and 55.6±39.8 IU/L, respectively in NAFLD population.

There was significant difference in aminotransferase levels of NAFLD (n=522) vs. Non-NAFLD (n=402) T2DM population, amid difference in AST level of 31.7 IU/L (54.8 IU/L vs. 23.1 IU/L; p=.000;95%CI) and ALT level of 31.3 IU/L (55.6 IU/L vs.

Table 4 : Prevalence of elevated aminotransferase levels in NAFLD population

	NAFLD Population (n=522)	Male (n=309)	Female (n=213)
Elevated AST	99 (19%)	73 (23.6%)	26 (12.2%)
Elevated ALT	83 (15.9%)	40 (12.9%)	43 (20.2%)
Elevated AST and ALT	340 (65.1%)	196 (63.4%)	144 (67.6%)

24.3 IU/L; p=.000;95%Cl). Mean (SD) AST levels were highest in 25-40 years at 60.2 (53.1) IU/L, followed by 61-70, 41-50, 51-60, and 71-84 years age groups at 56.4 (44.0), 53.8 (32.2), 53.3 (26.5) and 47.5 (14.5) IU/L respectively. Similar trends were also observed in mean (SD) ALT levels at, 62.9 (70.4), 59.3(43.5), 54.1(33.7), 52.6(20.9) and 50.3 (26.6) IU/L, in 25-40, 61-70, 41-50, 51-60 and 71-84 years age groups respectively. Although relationship between age and AST and ALT levels was negative, it was not significant (r=-0.048, p=0.137 and r=-0.051, p=0.125, respectively).

On the other hand there was a significant positive correlation between AST and ALT levels (r=0.720, n=522, p=.000), which is clearly illustrated in results presented above. Out of 522 identified patients, 182 (34.9%) had at least one abnormal aminotransferase (AST or ALT) level, while 340 (65.1%) patients had elevation of both AST and ALT levels. Out of this, higher number of female patients had elevated ALT and AST+ALT levels (Table 4).

The prevalence of NAFLD was found to be highest at 61.8% in 61-70 year age group, followed by 41-50 year, 51-60 year and 25-40 year age groups, at 57.7%, 54.9% and 54.7% respectively. The prevalence of NAFLD was found to be lowest in 71-84 year age group at 50%. Result from the study also demonstrated that T2DM population with co-morbid conditions like obesity, hypertension and dyslipidemia had 14%, 17% and 38% higher risk respectively, for NAFLD. The results of risk estimates for association with each characteristic are presented in Table 5.

Table 5 : Risk estimation for NAFLD with associated pre existing conditions:

		NAFLD Population (n=522)	Non-NAFLD Population (n=402)	RR (95% Cl)
Obesity	No*	242 (46.4%)	213 (53%)	1.14 (1-1.3;p=.027)
	Yes	280 (53.6%)	189 (47%)	
Hypertension	No*	186 (35.6%)	181 (45%)	1.17 (1.05-1.31;p=.002)
	Yes	336 (64.4%)	221 (55%)	
Dyslipidemia	No*	211 (40.4%)	228 (56.7%)	1.38 (1.21-1.57;p=000)
	Yes	311 (59.6%)	174 (43.3%)	

*Reference Value

Discussion

To 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-center study to report on 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 first effort to record the prevalence of NAFLD in T2DM patients on the basis of elevated aminotransferase levels.

In our study, overall prevalence of NAFLD in T2DM Indian population was found to be 56.5%, which is in line with prevalence of 54.5% described by Mohan et al,[10] but higher than the prevalence rate of 12.5%[8] and 20%[9] described in other studies. However in the study by Prashanth et al,[12] 87% T2DM patients had NAFLD on histology. Most of the studies in India have shown higher prevalence of NAFLD in males than in female population (M:F ratio of 2:1 approx.),[7,9,11,33] but our study revealed higher prevalence rate of disease in female (60%) than in male (54.3%) population, with same pattern reported from north and west part of the country.

Obesity has been recognised as important risk factor for NAFLD in T2DM patients in our study. The National Family Health Survey (NFHS-3) India 2005-06, has revealed that more number of females (13%) than males (9%) in India are overweight/obese. Concurrently, the survey also reveals that one-third of females in Punjab and Delhi are overweight/obese.[34] These findings may complement higher prevalence of NAFLD in female patients across India, especially in northern states in our study 54.9% of all female NAFLD patients in our study were obese with similar trends from north (53.2%) and western (63.1%) India. However, a detailed study will be required to confirm these findings.

NAFLD is probably the most common cause of liver disease in the preadolescent and adolescent age groups; studies in India have also revealed the mean age of general Indian NAFLD patients to be between 35 and 50yrs.[7,33,35] However previous studies have also shown that the prevalence of NAFLD increases with age,[9,36] with the majority of cases occurring between the age of 40 and 60 years. In our study too, the prevalence of NAFLD increased with increasing age. There were 239 (45.8%) identified patients in the age group of 25-50 years, and 283 (54.2%) among those aged ≥51 years (OR:0.71, 95%CI: 0.54–0.92, p=0.005); with highest prevalence recorded in the 61-70 year age group, at 61.8%.

There is important and well-established clinical association of NAFLD with element of MetS, including dyslipidemia, hypertension and obesity. Several studies have suggested relationship of disease with these features of the MetS.[37-38] Since majority of patients in study NAFLD cohort were obese (53.6%), dyslipidemic (59.6%) or hypertensive (64.4%), it makes it possible to arrive at a conclusion that T2DM patients with these co-morbid conditions, definitely have a higher risk of NAFLD. The results from our study confirm these observations, as it depicts 14%, 17% and 38% higher risk for NAFLD in obese, hypertensive and dyslipidemic Indian T2DM population, respectively. However the predictability of these risk factors has not been determined and the effect of gender on such relationships has not been fully elucidated.

In our study, mean ALT levels were found to be higher than AST levels in identified T2DM NAFLD cohort as a whole, and also in different age group. ALT appears to have a role in gluconeogenesis[39] and seems to be more related to liver fat accumulation than AST.[40] Minor elevation of this enzyme level may be a good predictor of mortality from liver disease as suggested by some authors.[41] Elevation of levels of ALT and AST or both to mild and moderate levels is a very common finding in NAFLD.[42] Similarly, in T2DM patients, chronic mild elevations of liver enzymes are frequently encountered;[43] emphasizing the already known fact that T2DM has a strong association with NAFLD, including its severe form NASH.[44] Though the pathogenesis and sequence of event leading to NAFLD and ultimately to NASH is not entirely understood, we can assume that liver fat accumulation and progression of steatosis to NASH to be two significant mechanisms.[45]

Some evidence points towards the fact that NAFLD may be the hepatic component of MetS.[8,46-47] Different stages of NAFLD are now believed to be due to obesity. Obesity is commonly associated with insulin resistance and might have high concentration of hepatic triglycerides which might in turn lead to NAFLD.[48] Studies have also shown beneficial effect of dietary modification, weight loss and exercise in reducing insulin resistance and in normalization of ALT in patients with NAFLD.[49] But in patients not responding to dietary and life style modification, medical interventions like anti-obesity drugs (orlistat) and insulin sensitizers (metformin and pioglitazone), can prove to be effective treatment.

Orlistat reduces the absorption of long chain fatty acids and cholesterol by approximately 30%[50] and studies have revealed the beneficial effect of adding orlistat in obese NAFLD patients.[51-54] Drug has shown to significantly reduce serum ALT levels and reverse fatty liver as studied by ultrasound.[54] Clinical trials have also shown insulin sensitizers to be a promising treatment for NAFLD. In open label studies, metformin was effective in improving liver biochemical tests, but did not result in improvement of fibrosis in patients with NASH.[55-56] A significant increase in plasma adiponectin concentration associated with improvement of insulin resistance and decrease in hepatic fat content, was seen in T2DM patients treated with pioglitazone.[57] In a placebo-controlled pioglitazone trial, pioglitazone was associated with significant declines in serum aminotransferase levels increased hepatic insulin sensitivity, and significant improvement in NASH histology.[58]

Though discussed treatment modalities appears to be a reasonable alternative for treatment of NASH particularly in patients with T2DM, but serious and persistent efforts should be made to modify potential risk factors such as obesity, hyperlipidemia and poor diabetes control in all patients with NAFLD/NASH.

Conclusion

The results from this study have established a prevalence pattern of NAFLD in Indian T2DM population. Beside this, the study has brought to light prevalent aminotransferase levels in Indian T2DM population. In our consecutively inducted sample, more females [60%] were affected by disease and prevalence was found highest in 61-70 year age group. Also in our study we demonstrated risk for NAFLD with associated elements of MetS, age groups and gender.

One of the limitations of our study is that we used elevation in aminotransferase levels as a surrogate without a proof of fatty liver; keeping in mind that NAFLD may exist without elevation of liver enzymes. However we did apply sex-specific cutoffs of aminotransferase levels, to do away any potential draw back in estimation of NAFLD in female population. Moreover it has became imperative to find markers to diagnose NAFLD in diabetics apart from the conventionally used methods like imaging and histological tests, since NAFLD may represent an independent risk factor which augments further total cardiovascular and renal risk in the T2DM patients.

Results from this study should sensitize doctors to the need for frequent evaluation of aminotransferase levels in T2DM patients, as even mild elevation of these liver enzymes may be a sign of unanticipated hepatic disorder. We sincerely wish this study will be an important step in understanding prevalence of NAFLD in Indian T2DM patients and designing preventive strategies as well as future studies on this condition.

Acknowledgement

This study was sponsored by USV Limited, Mumbai, India. Data management, statistical and editorial support was provided by medONE, Pharma solutions, New Delhi, India.

The SPRINT Study participants are : Dr. A. Banerjee, Dr. A.D. Ghosh, Dr. A.K. Bhatt, Dr. A.K. Raman, Dr. A.N. Vyas, Dr. A.R. Chavan, Dr. A.V. Girisimha Rao, Dr. Abhijit Jadhav, Dr. Abhishek Agarwal, Dr. Afroz Khan, Dr. Ahaji, Dr. Ajay Aditya, Dr. Ajay Kaduskar, Dr. Ajay Pratap, Dr. Ajeet Nalavade, Dr. Akshay R., Dr. Alka Gandhi, Dr. Amalaselvam, Dr. Ambita Garg, Dr. Amol Pathak, Dr. Aneesh Ghosh, Dr. Anil Rajgire, Dr. Arvind Kumar, Dr. Ashok K. Taneja, Dr. Ashok Sharma, Dr. Ashok Shukla, Dr. Ashwini Joshi, Dr. Atul Gupta, Dr. B. Padma Kumar, Dr. B.B. Aggarwal, Dr. B.B. Aggrawal, Dr. Balwinder Singh, Dr. Bidyutprava Das, Dr. Biren Roy Chaohan, Dr. C.M. Kulkarni, Dr. C.T. Tindwani, Dr. Chaitanya Kumar, Dr. Chakradhar, Dr. D J Dass Gupta, Dr. D. Dhanamithiran, Dr. D. Murlidhar, Dr. D.R. Karunanidhi, Dr. D.S Raudach Saheb, Dr. D.S. Goel, Dr. Darshan C. Shah, Dr. Deepak P. Munshi, Dr. Deepak Raichura, Dr. Deepak Raisinghani, Dr. Dilip Wadhwani, Dr. G. Ray Chowdhury, Dr. G.S. Baba Yunus, Dr. Ganesh Rote, Dr. Garwindejat Singh, Dr. Gira Svinivasan, Dr. Goutam Dhar, Dr. Gurvinder Singh, Dr. H. Takkar, Dr. H.P. Agrawal, Dr. Harish Takkar, Dr. Harsha B.S., Dr. Imtiaz Pasha, Dr. Indraneel Basu, Dr. Janes. P, Dr. Jeet Singh, Dr. Jitendra Jadwani, Dr. Jitesh Chaure, Dr. Jobhy Jrphy, Dr. Jothi Palakshi, Dr. K. Gopalal Krishana, Dr. K.K. Vishwani. Dr. K. Saraladevi, Dr. K.D. Modi, Dr. K.Khare, Dr. K.O. Joseph, Dr. K.V. Mallikarjuna Rao, Dr. Kailash Sharma, Dr. Karimbhai, Dr. Karuna Ramteke, Dr. Kms Jagadeesan, Dr. M. Sree Kanth Reddy, Dr. M.M. Ganguly, Dr. M.Muralikrishna, Dr. M.R. Passi, Dr. M.V. Pansuria Seheb, Dr. M.V. Vaishnav, Dr. Mahadevan, Dr. Mandar Anant Arekar, Dr. Manjit Rai, Dr. Manoj Vithalani, Dr. Meera, Dr. Minesh Agarwal, Dr. N. Narendra Prasad, N.R. Bhattacharya, Dr. Narendra Prasad, Dr. Nirau B. Shah, Dr. Nirav Mehta, Dr. Noopur Vani, Dr. Onkar Nath Rai, Dr. P. Durai, Dr. P. Nitnavare, P. Sarkar, Dr. P. V. Ajit Kumar, Dr. P. Vijaykumar, Dr. P.C. Jha, Dr. P.C. Trivedi, Dr. P.S. Grover, Dr. Pankaj Anant Patil, Dr. Pinaki Dey, Dr. Pradeep Jain, Dr. Pradip K. Shinghal, Dr. Prakash Bhagade, Dr. Prakash K Gandhi, Dr. Pranat Kumar Thatoi, Dr. Prasanna Kumar, Dr. Prasanna Kumar Ratha, Dr. Praveeh Kumar, Dr. Praveen K, Dr. Prince Sodhi, Dr. R. Das, Dr. R. Ganeshmoorthy , Dr. R. Govindan Nayar, Dr. R. Kumar, Dr. R.K.P. Shahi, Dr. R.S. Ratra, Dr. Raghavendra M.S, Dr. Rajendra Solanki, Dr. Rajesh Parvaliya, Dr. Ravi Kumar, Dr. Ravindra K. Joshi, Dr. Ravishankar A.G., Dr. Renuka Sriram, Dr. Ripaben Vaishnav, Dr. S. Barthan, Dr. S. Kiran Kumar, Dr. S. Mohan Kumar, Dr. S. Purushotham, Dr. S. Suneetha, Dr. S.A. Abzalpakar, Dr. S.A. Nellopher Naaz, Dr. S.Dandapani, Dr. S.K. Chauhan, Dr. S.K. Chauhan, Dr. S.K. Kalra, Dr. S.K. Mukherjee, Dr. S.L. Mehta, Dr. S.N. Bentoor, Dr. S.N. Saha, Dr. S.R. Baheti, Dr. Sajith V. S., Dr. Samant Jain, Dr. Samant Jain, Dr. Samir Swami, Dr. Samrat D. Shah, Dr. Sandeep Kansara, Dr. Sandeep Sarawne, Dr. Sandeep Sonavane, Dr. Sandhya Nema, Dr. Sanjay Jain, Dr. Sanjay Lyer, Dr. Sanjay Tiwari, Dr. Sanket Sorate, Dr. Satish Patil, Dr. Satish Sharma, Dr. Satyendra Sharma, Dr. Seema Bagari, Dr. Shashikiran Umakanth, Dr. Shekhar Shah, Dr. Shriniva Parabhakarra. Kulkarni, Dr. Sonali. A. Patange, Dr. Srikantan .S, Dr. Sudheesh.T, Dr. Sundeep Sircar, Dr. Sunil Singhvi, Dr. Sunil Ukani, Dr. Susanta Kumar Nayak, Dr. T. Ghosh, Dr. T.K. Gopinathan, Dr. Thomas Sebastain, Dr. Tushar Patil, Dr. U.V. Mohan, Dr. Ubed Khan, Dr. Uipeth K. Kenan, Dr. V. Lakshminarayan, Dr. V.K. Saivastava, Dr. V.K.R. Narasimman, Dr. V.M. Manikandan, Dr. Veeranna Gowda, Dr.

Vijay D Karahde, Dr. Vinit C. Dandawate, Dr. Virender Singh, Dr. Vishal Chopra, Dr. Vivek Deshpande, Dr. V K Agrawal.

References

1. Farrell GC, Larter CZ. Nonalcoholic Fatty Liver Disease: from Steatosis to cirrhosis. *Hepatology* 2006;43:S00-S112.
2. Suzuki A, Angulo P, Lymp J, St Sauver J, Muto A, Okada T, Lindor K.; Chronological development of elevated aminotransferases in a nonalcoholic population. *Hepatology* 2005;41:64–71.
3. Farrell GC, Larter CZ. Nonalcoholic Fatty Liver Disease: from Steatosis to cirrhosis. *Hepatology* 2006;43:S00-S112.
4. Lazo M, Clark JM., The epidemiology of nonalcoholic fatty liver disease: a global perspective. *Semin Liver Dis* 2008;28:39-50.
5. Bellentani S, Scaglioni F, Marino M, Bedogni G., Epidemiology of non-alcoholic fatty liver disease. *Dig Dis* 2010;28:155-61.
6. Duseja A., Nonalcoholic fatty liver disease in India - a lot done, yet more required. *Indian J Gastroenterol* 2010;29:217-25.
7. Singh SP, Nayak S, Swain M, et al. Prevalence of non alcoholic fatty liver disease in coastal eastern India: A preliminary ultrsonographic survey. *Trop Gastroenterol* 2004;25:76-9.
8. Gupte P, Amarapurkar D, Agal S, et al. Non-alcoholic steatohepatitis in type 2 diabetes mellitus. *J Gastroenterol Hepatol* 2004;19:854–858
9. 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.
10. 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.
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. 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.
13. McCullough AJ. Thiazolidinediones for nonalcoholic steatohepatitis—promising but not ready for prime time. *N Engl J Med* 2006;355:2361-3.
14. Bugianesi E, Vanni E, Marchesini G, NASH and the risk of cirrhosis and hepatocellular carcinoma in type 2 diabetes, Current Diabetes Reports 2007;7:175–80.
15. Collantes R, Ong JP, Younossi ZM, Nonalcoholic fatty liver disease and the epidemic of obesity, Cleveland. *Clin J Med* 2004;71:657–64.
16. Cusi K., Nonalcoholic fatty liver disease in type 2 diabetes mellitus. *Curr Opin Endocrinol Diabetes Obes* 2009;16:141-9.
17. Tolman KG, Fonseca V, Tan MH, Dalpiaz A., Narrative review: hepatobiliary disease in type 2 diabetes mellitus. *Ann Intern Med* 2004;141:946-56.
18. Angulo P, Keach JC, Batts KP, Lindor KD, Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. *Hepatology* 1999;30:1356–62.
19. Younossi ZM, Gramlich T, Matteoni CA, et al., Nonalcoholic fatty liver disease in patients with type 2 diabetes. *Clin Gastroenterol Hepatol* 2004;2:262–5.
20. Ferreira VS, Pernambuco RB, Lopes EP, Morais CN, Rodrigues MC, Arruda MJ, et al., Frequency and risk factors associated with non-alcoholic fatty liver disease in patients with type 2 diabetes mellitus. *Arq Bras Endocrinol Metabol* 2010;54:362-8
21. Clark JM, Brancati FL, Diehl AM. The prevalence and etiology of elevated aminotransferase levels in the United States. *Am J Gastroenterol* 2003;98:960–967.
22. Yildirim B, Ozugurlu F, Sahin S, Ozyurt H, Atis O, Akbas A, et al., Association between elevated aminotransferase levels and the metabolic syndrome in Northern Turkey. *Ann Hepatol* 2010;9:161-5
23. Elizabeth H Harris. Elevated liver function tests in Type 2 Diabetes. *Clinical Diabetes* 2005;23:115-9.
24. West J, Brousil J, Gazis A, Jackson L, Mansell P, Bennett A. et al., Elevated serum alanine transaminase in patients with type 1 or type 2 diabetes mellitus. *QJM* 2006;99:871-6.
25. Meybodi MA, Afkhami-Ardekani M, Rashidi M., Prevalence of abnormal serum alanine aminotransferase levels in type 2 diabetic patients in Iran. *Pak J Biol Sci* 2008;11:2274-7.
26. Judi L, Toukan A, Khader Y, Ajlouni K, Khatib MA., Prevalence of elevated hepatic transaminases among Jordanian patients with type 2 diabetes mellitus. *Ann Saudi Med* 2010;30:25-32.
27. Esteghamati A, Jamali A, Khalilzadeh O, Noshad S, Khalili M, Zandieh A. et al., Metabolic syndrome is linked to a mild elevation in liver aminotransferases in diabetic patients with undetectable non-alcoholic fatty liver disease by ultrasound. *Diabetol Metab Syndr* 2010;2:65.
28. Ioannou GN, Weiss NS, Boyko EJ, Mozaffarian D, Lee SP. Elevated serum alanine aminotransferase activity and calculated risk of coronary heart disease in the United States. *Hepatology* 2006;43:1145–51.
29. Targher G, Bertolini L, Padovani R, Rodella S, Tessari R, Zenari L, et al. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. *Diabetes Care* 2007;30:1212-8.
30. Lautämaki R, Borra R, Iozzo P, Komu M, Lehtimaki T, Salmi M, et al. Liver steatosis coexists with myocardial insulin resistance and coronary dysfunction in patients with type 2 diabetes. *Am J Physiol Enddocrinol Metab* 2006;291:E282-90.
31. Targher G, Bertolini L, Rodella S, Zoppin G, Lippi G, Day C, Muggeo M. Non-alcoholic fatty liver disease is independently associated with an increased prevalence of chronic kidney disease and proliferative/laser-treated retinopathy in type 2 diabetic patients. *Diabetologia* 2008;51:444-50.
32. Gunter, EW, Lewis, BG, Koncikowski, SM. Laboratory procedures used for the Third National Health and Nutrition Examination Survey (NHANES III), 1988-1994. US Department of Health and Human Services, Center for Disease Control and Prevention, National Center for Environmental Health, National Center for Health Statistics: Atlanta, GA, 1996
33. Amrapukar DN, Amrapukar A. Non-alcoholic steatohepatitis clinicopathological profile. *JAPI* 2000;48:311-3.
34. http://www.nfhsindia.org/nutrition_report_for_website_18sep09.pdf
35. Duseja A, Das A, Das R, et al. The clinicopathological profile of Indian patients with nonalcoholic fatty liver disease (NAFLD) is different from that in the west. *Dig Dis Sci* 2007;52:2368–74.
36. 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.
37. Marchesini G, Brizi M, Bianchi G, et al. Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. *Diabetes* 2001;50:1844–50.
38. Angelico F, Del Ben M, Conti R, et al. Non-alcoholic fatty liver syndrome: a hepatic consequence of common metabolic diseases. *J Gastroenterol Hepatol* 2003;18:588–94.
39. Rosen F, Roberts NR, Nichol CA. Glucocorticosteroids and transaminase activity: Increased activity of glutamic pyruvic transaminase in four conditions associated with gluconeogenesis. *J Biol Chem* 1959;476:80.
40. Westerbacka J, Cornér A, Tiikkainen M, Tamminen M, Vehkavaara S, Häkkinen AM, et al. Women and men have similar amounts of liver and intraabdominal fat, despite more subcutaneous fat in women:

Implications of sex differences in markers of cardiovascular risks. *Diabetologia* 2004;47:1360–9

41. 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
42. Pratt DS, Kaplan MM,et al.Evaluation of abnormal liver enzymes results in asymptomatic patients. *New England Journal of Medicine* 2000;342:1266-1271.
43. 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.
44. Marchesini G, Brizi M, Morselli-Labate A, Blanchi G, Bugianesi E, McCullogh A, Forlani G, Melachionda N. Association of non-alcoholic fatty liver disease and insulin resistance. *Am J Med* 1999;107:450–5.
45. Petta S, Muratore C, Craxì A. Non-alcoholic fatty liver disease pathogenesis: the present and the future. *Dig Liver Dis* 2009;41:615-25.
46. Bedogni G, Miglioli L, Masutti F, et al. Prevalence of and risk factors for nonalcoholic fatty liver disease: the Dionysos nutrition and liver study. *Hepatology* 2005;42:44–52.
47. Donati G, Stagni B, Piscaglia F, et al. Increased prevalence of fatty liver in arterial hypertensive patients with normal liver enzymes: role of insulin resistance. *Gut* 2004;53:1020–1023.
48. Hsiao P, Kuo K, Shin S, et al. Significant correlations between severe fatty liver and risk factors for metabolic syndrome. *J Gastroenterol Hepatol* 2007;22:2118–2123.
49. Day CP, James OF. Steatohepatitis: a tale of two 'hits'? Gastroenterology 1998;114:842–845.
50. Naniwadekar AS, Nutritional Recommendations for Patients with Non-Alcoholic Fatty Liver Disease:An Evidence Based Review. *Pract Gastroenterol* 2010;34:8-16.
51. Harrison SA, Fincke C, Helinski D, et al: A pilot study of orlistat treatment in obese, non-alcoholic steatohepatitis patients. *Aliment Pharmacol Ther* 2004;20:623–628.
52. Hatzitolios A, Savopoulos C, Lazaraki G, et al: Efficacy of omega-3 fatty acids, atorvastatin and orlistat in non-alcoholic fatty liver disease with dyslipidemia. *Indian J Gastroenterol* 2004;23:131–134.
53. Sabuncu T, Nazligul Y, Karaoglanoglu M, et al: The effects of sibutramine and orlistat on the ultrasonographic findings, insulin resistance and liver enzyme levels in obese patients with nonalcoholic steatohepatitis. *Rom J Gastroenterol* 2003;12:189–192.
54. Zelber-Sagi S, Kessler A, Brazowsky E, et al: A double-blind randomized placebo-controlled trial of orlistat for the treatment of nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol* 2006;4:639-4.
55. Uygun A, Kadayifci A, Isik AT, et al. Metformin in the treatment of patients with non-alcoholic steatohepatitis. *Aliment Pharmacol* Ther 2004;19:537-44.
56. Marchesini G, Brizi M, Bianchi G, Tomassetti S, Zoli M, Melchionda N. Metformin in non-alcoholic steatohepatitis. *Lancet* 2001;358:893-4
57. Bajaj M, Suraamornkul S, Piper P, et al. Decreased plasma adiponectin concentrations are closely related to hepatic fat content and hepatic insulin resistance in pioglitazone-treated type 2 diabetic patients. *J Clin Endocrinol Metab* 2004;89:200-6.
58. Belfort R, Harrison SA, Brown K, Darland C, Finch J, Hardies J, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl J Med* 2006;355:2297-307.