ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 9, Issue, 07, pp.54044-54049, July, 2017

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

NON ALCOHOLIC FATTY LIVER DISEASE IN GENERAL POPULATION- THEIR METABOLIC PROFILE

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ARTICLE INFO

Article History:
Received 03rd April, 2017
Received in revised form
19th May, 2017
Accepted 28th June, 2017
Published online 26th July, 2017

Key words:

Non-alcoholic fatty liver disease,
Diabetic hepatic steatosis,
Atherogenic dyslipidemia and NAFLD,
Insulin resistance.

ABSTRACT

Objective: We aim to study the clinical and metabolic profile with prevalence and clinic-pathological correlates of non-alcoholic fatty liver disease (NAFLD) in routine health check-up.
Method: After ethical clearance, general population presenting for preventive health check-up over a 4-month period was studied. Influence of alcohol was excluded by history and De Ritis ratio. Anthropometric, metabolic parameters and ultrasonography of liver were noted and data was analysed using SPSS 20.0.
Results: Of 412 subjects, 13.6% were diabetic, 22.8% pre-diabetic and 63.6% (n=262) were non-diabetic. One-way ANOVA showed significantly more subjects were either overweight (43%) or obese (38%). On ultrasonography, 143 patients had fatty liver disease majority being males. Subjects with NAFLD had significantly higher levels of BMI, cholesterol, LDL, triglycerides, VLDL, fasting and postprandial blood sugars and lower levels of HDL (all $p<0.01$). Partial correlation of age ($p>.05$), gender ($p=.000$), BMI ($p=.000$), cholesterol ($p=.004$), triglycerides ($p>.05$), HDL ($p>.05$), atherogenic dyslipidemia ($p=.000$) and diabetic status ($p=.002$) with NAFLD revealed several significant correlations controlling for the other factors. Multinomial regression analysis was performed.
Conclusions: Dyslipidemia, diabetes and NAFLD are present in asymptomatic general population. Males and persons with high BMI, atherogenic dyslipidemia and diabetes or prediabetes have greater odds of having hepatic steatosis. Association of atherogenic dyslipidemia with NAFLD provides both a clinical marker and therapeutic target for NAFLD. Significant partial correlations with NAFLD reflect the role of insulin resistance in its pathogenesis.

Citation: Dr. Shimpa Sharma and Dr. Indumathi Soumsundaram, 2017. "Non alcoholic fatty liver disease in general population- their metabolic profile", *International Journal of Current Research*, 9, (07), 54044-54049.

INTRODUCTION

Fatty Liver Disease (FLD) is a spectrum that includes simple fatty liver (steatosis), steatohepatitis, cirrhosis and hepatocellular carcinoma (Oben *et al*., 2008). Hepatic steatosis is reversible, other stages being inexorably progressive in nature. FLD has many causes including excessive alcohol consumption. Non-alcoholic fatty liver disease (NAFLD) has been defined as fatty liver disease in the absence of significant alcohol consumption and is strongly associated with obesity, insulin resistance (IR), metabolic syndrome (MetS) and diabetes mellitus (DM). (Uchil *et al*., 2009; Marchesini *et al*., 2001; Chen *et al*., 2008; Loomis *et al*., 2016; Saponaro *et al*., 2015; Ortiz-Lopez *et al*., 2012). NAFLD has long been postulated to be the hepatic component of MetS (Uchil *et al*., 2009). Marchesini *et al* described it as an additional feature of MetS with specific hepatic insulin resistance (Marchesini *et al*., 2001). Obesity related non-communicable diseases (NCDs) are higher in South Asian population than in the Caucasians (Misra and Khurana, 2011). The former are also known to have higher atherosclerotic and prothrombotic profiles and higher incidence of MetS (Anand *et al*., 2000; Duseja *et al*., 2015). Persons of Indian origin have high incidence of IR and associated conditions of abdominal obesity, hypertension, MetS, DM and their related complications (Duseja *et al*., 2015). The increasing prevalence of IR in India reflects in the prevalence of NAFLD. Worldwide prevalence of NAFLD ranges from 6% to 33% with the median of 20% according to some reports though certain countries report higher numbers (Duseja *et al*., 2015; Lee *et al*., 2007). Indians with NAFLD have differing clinic-pathological profiles compared to the Western subjects (Duseja *et al*., 2007). The two-hit theory of NAFLD states that the primary fatty change reflects hepatic triglycerides accumulation due to several pathogenic mechanisms. The progression to steatohepatitis is conditional to a second insult by

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inflammation, infection or toxic damage. Genetic influences, IR and intestinal microbiota are all postulated to play a role in individual responses to these insults explaining the variations in reporting (Burt *et al*., 1998). Recently a three-hit theory proposed that steatosis and inflammation is followed by the third hit- an inability or failure of hepatocytes to proliferate resulting in progression while others propose a multiple hit theory (Dowman *et al*., 2010; Takaki *et al*., 2013). Ultrasonography (USG) as a diagnostic tool is safe, non-invasive and widely making it a practical choice. Prevalence of NAFLD on USG has been found to vary from 17% to 46% (Vernon *et al*., 2011). We aim to study the clinical and metabolic profile in routine health check and prevalence and clinic-pathological correlates of non-alcoholic fatty liver disease (NAFLD) in the study population.

MATERIALS AND METHODS

Approval of the Institutional Ethics Committee was taken before starting the study. The clinic-pathological profiles of 445 urban patients in South India who opted for a preventive health check-up were examined for prevalence of NAFLD and associated features. Patient identity was kept confidential. Not relying only on history, subjects with De Ritis ratio greater than 1.5 or raised transaminases more than twice normal were excluded from the study (n=33). Data was entered in the Master Chart in Excel sheet. Data analysis was done using SPSS V 20.0. Quantitative data was analysed using mean, standard deviation, student t test, ANOVA and Liner Regression Analysis. Qualitative data was analyzed using Chi Square test and multinomial regression. Partial correlation of data was also done. Statistical significance was taken as $p< 0.05$.

RESULTS

Study Population: Subjects studied were 412 with a male to female ratio of 1.8:1 ($p<0.01$). Continuous variables were assessed as shown in Table 1:

Table 1. Descriptive Statistics

	N	Mean	SD	SEM
Age	412	39.86	13.216	.651
BMI	411	26.54	4.549	.224
FBS	412	106.41	41.631	2.051
PPBS	412	141.95	66.270	3.265
Cholesterol	411	184.30	39.020	1.925
Triglycerides	412	138.75	89.402	4.405
HDL	412	40.73	6.154	.303
LDL	412	124.89	33.176	1.634
VLDL	410	27.00	14.015	.692
AST_ALT_ratio	412	1.00	.277	.014

Body Mass Index (BMI): Applying WHO cut-offs for Asian population, one-way ANOVA showed significantly more subjects were either overweight (43%) or obese (38%) ($F(2,408)$ 571, $p=.000$). Overall the female subjects had significantly higher BMI (27.2 ± 5.5 vs 26.1 ± 3.9; $p=.041$).

Diabetes Mellitus (DM): Of the subjects, 13.6% (n=56) were diabetic, 22.8% (n=94) were pre-diabetic and 63.6% (n=262) were non-diabetic as per the ADA criteria.

Non-alcoholic Fatty Liver Disease (NAFLD): Based on USG, 143 patients had fatty liver disease (34.7%) of which 80% (n=114) were males (conditional OR 0.74). Gender prevalence was 42.7% in males and 20% in female subjects. ($p=.000$). Mean age of subjects with and without NAFLD was not significantly different ($p=.274$)

BMI & NAFLD: BMI was significantly higher in subjects with fatty liver disease (Table 2).

Table 2. BMI and FLD

	FLD_Code	N	Mean	SD	SEM	P value
BMI	Present	142	28.77	4.4	.4	.000
	Absent	269	25.36	4.2	.2	

Females had significantly higher BMI (31.9 ± 5 vs 27.96 ± 3.8) ($p=.000$).

Of NAFLD subjects, majority were obese or overweight revealing strong association of FLD with BMI ($p=.000$; Cramer V .348) (Fig 1).

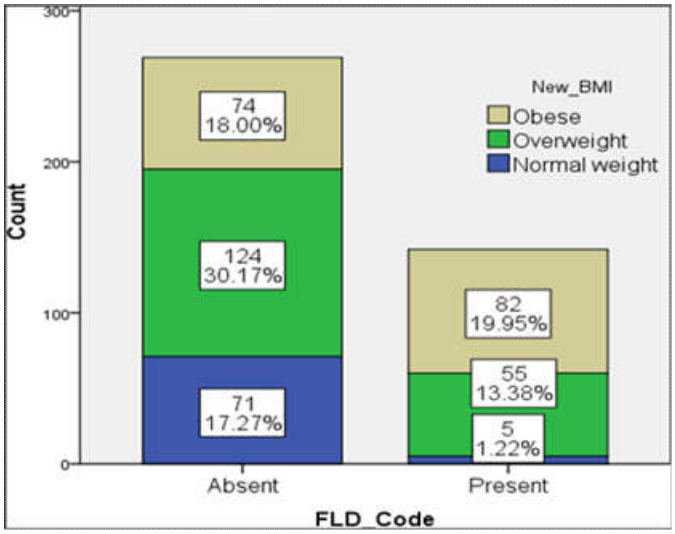

Fig. 1. NAFLD and BMI distribution

Correlation between BMI and NAFLD persisted after controlling for gender, age, diabetes, cholesterol, triglycerides and atherogenic dyslipidemia (all $p=.000$).

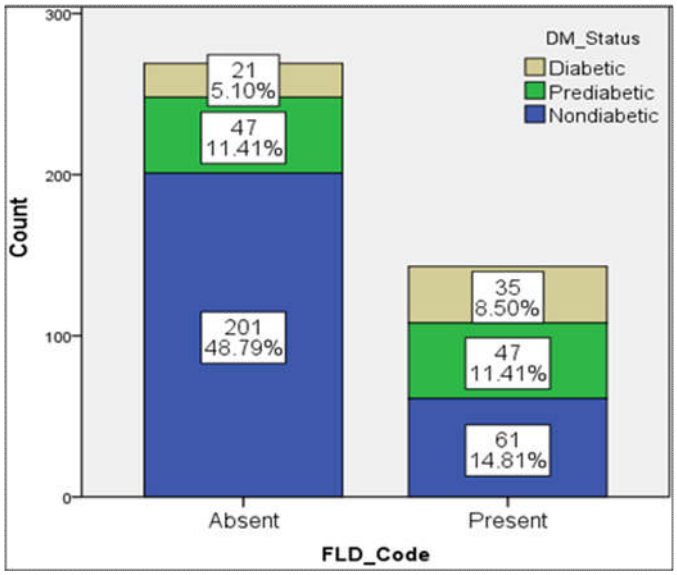

Fig. 2. Diabetes and NAFLD

Diabetic Status: Distribution of diabetic state in subjects is shown in Fig. 2. Significantly 76.7% of non-diabetics (A.R. 6.4) did not display hepatic steatosis while 62.5% of diabetics did (A.R. 4.7, p=.000, Cramer V .326). This association of diabetic status and NAFLD was significant on controlling for BMI (p=.000).

Lipid Profile: Lipid parameters in subjects with and without NAFLD is shown (Table 3).

Table 3. FLD and lipid parameters

	FLD_Code	N	Mean	Std. Deviation	S.E.M	P value
Triglycerides	Present	143	173.59	78.149	6.535	.000
	Absent	269	120.22	89.606	5.463	
HDL	Present	143	39.44	4.980	.416	.001
	Absent	269	41.42	6.601	.402	
LDL	Present	143	133.20	39.397	3.295	.001
	Absent	269	120.47	28.443	1.734	
VLDL	Present	143	34.78	15.639	1.308	.000
	Absent	267	22.83	11.019	.674	
Cholesterol	Present	143	195.16	43.994	3.679	.000
	Absent	268	178.50	34.810	2.126	

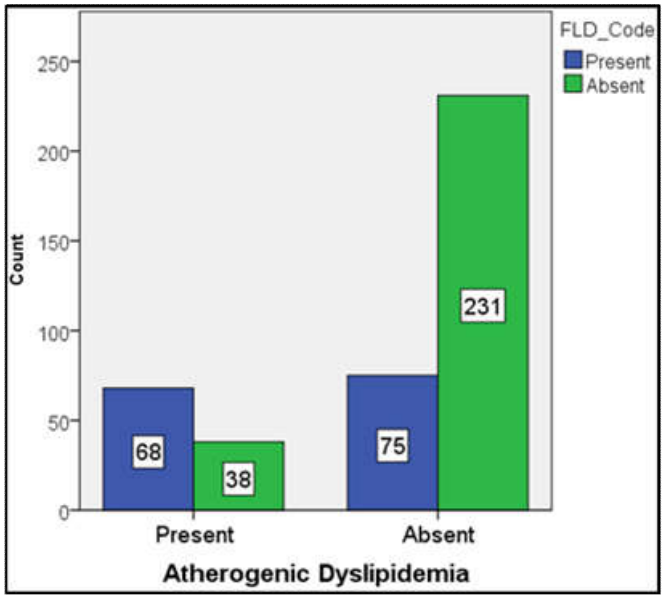

Fig. 3. NAFLD and Atherogenic dyslipidemia

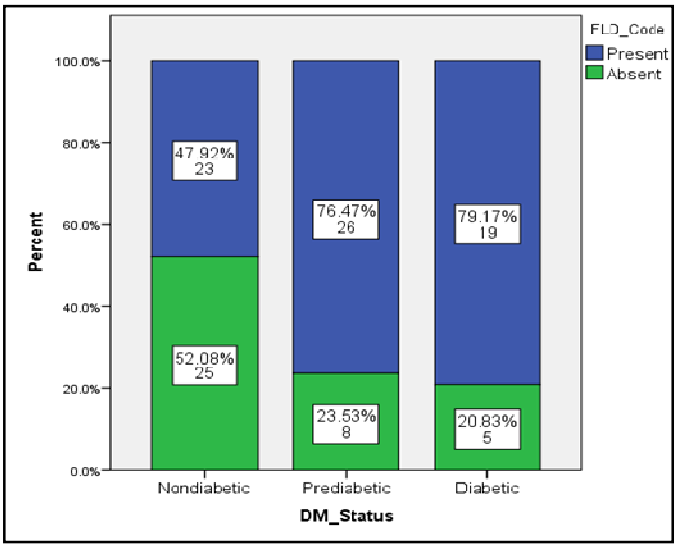

Figure 4. Prevalence of NAFLD as per diabetic status

Triglycerides: Strong association was noted with NAFLD (p=.000, Cramers V .369). NAFLD was present in 57.4% of those with TG over 200 mg/dl (adj. res. 4) and was absent in 77.7% of those with normal TG. A weak but significant correlation persisted after controlling for age, BMI, diabetic status and cholesterol (p=.001; Correlation .172).

Total Cholesterol: NAFLD was weakly associated with serum cholesterol, being present in 45.6% (n=52) of the 114 subjects with levels over 200 mg% (p=.021, Cramer'V .137). Significantly, 69% of subjects with normal cholesterol had no NAFLD (AR 2.6) even after controlling for age, BMI, diabetic status and triglycerides (p=.049).

HDL & LDL: Subjects with NAFLD had significantly higher levels of LDL and lower levels of HDL. LDL levels however remained within the normal range.

Atherogenic dyslipidemia (TG>150, HDL <45)**:** NAFLD strongly correlated with subjects having atherogenic dyslipidemia (n=106) and was present in 64.2% (n=68) (p=.000, Phi = .364) (Figure 3). Partial correlation of NAFLD with atherogenic dyslipidemia was found significant controlling for gender, age, BMI, fasting and postprandial blood sugar (p=.000). In subjects with normal HDL and TG levels (n=60), the prevalence of NAFLD was only 12% (7) (p=.000). Prevalence of FLD in these subjects was also significantly associated with the diabetic status (p=.006).

Multinomial Logistic Regression: A stepwise multinomial logistic regression was performed.

The inclusion of the variables gender, BMI, atherogenic dyslipidemia, and diabetic status statistically improved the predictability of the model ($\chi2(6) = 141.2$, p = .000). The Goodness of Fit showed the model is a good fit (p>.05) predicting the outcome of fatty liver disease in 74% of cases.

- Males were more likely to have hepatic steatosis (OR 3.9, Wald (1)21.175, p=.000).
- Obese subjects were 15 times more likely to have FLD (OR 15.36, Wald (1)26.47; p=.000) while overweight subjects had an odds ratio of 4.6 (Wald (1)8.57; p-.003) compared to normal BMI subjects.
- Diabetics were 3.7 times (Wald (1) 13.5, p=.000) and prediabetics were 2.2 times (Wald (1)6.9, p=.009) more likely to have FLD compared to non-diabetics (Figure 4).
- Subjects with atherogenic dyslipidemia were 4.3 times (Wald (1) 27.8, p=.000) more likely to have hepatic steatosis compared to those with normal lipids

DISCUSSION

Hepatic steatosis vs NAFLD: Excluding subjects with AST/ALT ratios of over 1.5 has definitely reduced the possibility of alcoholic liver disease being an etiological factor. Mean levels of AST (SGOT) and ALT (ASPT) were higher in subjects with FLD but were within normal limits in all subjects. This lends support to the diagnosis of NAFLD on USG. It is however well known that elevated transaminase levels do not correlate with the presence or severity of NAFLD (Duseja *et al*., 2015; Vernon *et al*., 2011).

Prevalence: Prevalence of NAFLD reported by different researchers varies greatly depending on the patient population studied. In 2007 a report by the Asia Pacific Working Party on NAFLD reported varying incidence from 5% to 30%. (Amarapurkar *et al*., 2007). The incidence in India varies from 9% to 35% in various studies (Duseja *et al*., 2015). An Indian study in 2007 reported an incidence of non-alcoholic FLD at 16.6% with a higher incidence of 18.9% in population above age of 20 years while in 2009 an urban study in South India reported a prevalence of 32% (Amarapurkar *et al*., 2007; Mohan *et al*., 2009). This study with 412 patients reports an incidence of NAFLD of 34.7% on ultrasonography the high incidence possibly explained by patient demographics. The trend of increasing prevalence heralds a possible disease burden in future years.

Gender: The multinomial model including gender, BMI, diabetic status and atherogenic dyslipidemia showed that males were more likely (3.9 times) to have NAFLD. This matches other Indian studies that have also reported a preponderance of male subjects though increased prevalence in females has also been reported (Duseja *et al*., 2007; Amarapurkar *et al*., 2007; Kalra *et al*., 2013). Gender difference has been reported in Caucasian studies as well (Loomis *et al*., 2016; JB Moore 2010 Symposium 1, 2010). Risk of NAFLD for males increases over females with increasing BMI being almost 50% higher in a study (Loomis *et al*., 2016). An Indian histopathological study (2008) identified the female gender as a predictor of severity in patients with NASH (Singh *et al*., 2008).

Body Mass Index: Of the subjects only 7% had normal BMI. The high median BMI (Mdn=26, IQR=6) and the higher proportion of overweight and obese subjects could also be explained by patient demographics. This study reveals an increasing prevalence of NAFLD with increasing BMI in both males and female subjects (Figure 1). Lean NAFLD**:** Indian and global researchers have reported a high prevalence of NAFLD in non-obese persons (Das *et al*., 2010; Margariti *et al*., 2012; Pinidiyapathirage *et al*., 2011). In over 18,000 non-obese individuals in China, NAFLD was sonographically diagnosed in 14.3% of general population (Sun *et al*., 2016). In this study, subjects with normal BMI (Asian standards for BMI as per WHO) had only 6% prevalence of NAFLD. Use of the standard global BMI categories earlier used could explain the high proportion of 'lean' NAFLD subjects (Vasudevan *et al*., 2012). It has been reported that over half the subjects with NAFLD have a variant of the adiponutrin/patatin-like phospholipase-3 (PNPLA-3) gene that favors hepatic fat accumulation and these subjects are not necessarily accompanied by features of metabolic syndrome (Yki-Järvinen, 2014). The normal adiponutrin has lipase activity on triglycerides and absence due to the variant PNPLA3 rs 738409 reduces TG hydrolysis in the hepatic cells and thus facilitates steatosis (Alkhouri *et al*., 2011). Obese NAFLD: Obese persons had 15 times the probability of having NAFLD and overweight persons had 4.6 times the probability of having NAFLD compared to lean subjects underlining the association of both NAFLD and obesity with insulin resistance (Chen *et al*., 2008; Loomis *et al*., 2016). Association of obesity with NAFLD has been shown in several studies (Singh *et al*., 2008; Lazo *et al*., 2011). Increasing BMI has been shown to be a predictor of NAFLD (Miyake *et al*., 2013). Obesity was also shown to predict severity of NASH in an Indian study (Singh *et al*., 2008).

Metabolic Profile of Subjects: Subjects with NAFLD have been shown to have significantly higher levels of cholesterol, triglycerides, LDL, VLDL, fasting blood sugar, post-prandial blood sugars and lower levels of HDL compared to non-NAFLD subjects (Amarapurkar *et al*., 2007; Sun *et al*., 2016; Leite *et al*., 2009). Diabetic subjects have a high prevalence of NAFLD diagnosed on sonography and subjects of NAFLD are also shown to have high prevalence of type 2 DM based on a positive association between IR, DM and NAFLD (Uchil *et al*., 2009; Saponaro *et al*., 2015; Ortiz-Lopez *et al*., 2012; Duseja *et al*., 2007; Amarapurkar *et al*., 2007; Faisal *et al*., 2016). This study showed a high prevalence of NAFLD (62.5%) in diabetic patients. This is in agreement with the prevalence of 69.4% found by Leite NC in a Brazilian study (Leite *et al*., 2009). Another Indian researcher reported NAFLD in 68.9% of type 2 DM patients with male patients having higher prevalence (Macherla, 2016). Study of two Electronic Health Record Prospective Studies in the UK and the US earlier this year revealed that the risk for NAFLD in diabetics was nearly double that of nondiabetics in the BMI category over 27 Kg/m2. Risk at BMI of 30-32.5 was between 5 – 9 fold higher in diabetics while higher BMIs had over 10-fold risk of NAFLD compared with BMI of 20-22 g/m2 (Loomis *et al*., 2016). A study by Faisal *et al* found an incidence of 50.7% diabetics amongst 150 NAFLD patients from Egypt (34). Of subjects with NAFLD in this study (n=143), incidence of type 2 DM was 24.5% (n=35) and pre-diabetics was 32.9% (n=47). The common thread of insulin resistance (IR) underlines the need to identify other manifestations of IR such as MetS, DM, polycystic ovarian disease (PCOD) and obesity when NAFLD is noted. We found that overall diabetic and prediabetic persons had higher prevalence of hepatic steatosis compared to nondiabetics and obese diabetics had higher prevalence compared to obese non-diabetics (75% vs 39.5%).

High triglycerides, low HDL and small dense LDL particles define the atherogenic diabetic dyslipidemia. LDL levels are not always elevated and could be normal, even while the presence of small dense particles contribute to morbidity (Sun *et al*., 2016). Atherogenic dyslipidemia seen in diabetic subjects has also been shown to be associated with NAFLD (Alkhouri *et al*., 2011). This study found normal LDL levels in all subjects. Atherogenic dyslipidemia was therefore defined as high TG and low HDL levels for purposes of analysis. This study reveals that subjects with atherogenic dyslipidemia were 4.3 times more likely to have NAFLD in a regression model includinggender, BMI, atherogenic dyslipidemia, and diabetic status. Hypercholesterolemia and high LDL levels have been shown to predict severity in NASH patients in an Indian Study (Singh *et al*., 2008). This study revealed mean cholesterol levels of NAFLD subject being significantly higher with 52 of the 143 NAFLD subjects having elevated cholesterol levels. Individuals with high cholesterol levels should be evaluated and monitored for the progressive stage of NASH. Subjects with NAFLD and NASH have been shown to have higher cardiovascular mortality and morbidity. Considering dyslipidemia as the common link, targeting the lipid levels in these patients may translate into reduced CV mortality in them (Zhang and Lu, 2015). Use of biotin in STZ-induced diabetic mice has been shown to reduced hepatoxicity as manifest by liver enzymes and histopathological examination (Badr Abdullah Aldahmasha *et al*., 2016). These and other studies open avenues to reduce the hepatic morbidity and mortality in subjects with NAFLD, a likely major clinical challenge of the near future.

Conclusion

The presence of NAFLD is significantly associated with male gender, overweight and obese subjects, diabetic status, elevated levels of fasting and post prandial blood sugar, cholesterol, triglycerides, VLDL and LDL and low levels of HDL. Males, subjects with higher BMIs, atherogenic dyslipidemia and diabetes or prediabetes have higher probability of having hepatic steatosis. A model with predictability of 74% has been presented including routinely performed assessments. The Odds Ratio of NAFLD in subjects with atherogenic dyslipidemia indicates a need to perform an abdominal ultrasound examination in such patients. Since NAFLD is seen in otherwise healthy subjects and is often associated with dysmetabolic states routine health check-ups must include abdominal sonography in high risk persons. Targeting levels of triglyceride, LDL and HDL for optimization could contribute to reducing cardiovascular morbidity in patients of NAFLD. Elevated cholesterol levels in subjects with NAFLD should instigate investigations to identify NASH and institute aggressive measures to reduce progression. The financial burden of diagnosis and management of chronic liver disease in a country minimally covered by insurance will be staggering. Obesity, insulin resistance and dyslipidemia must be viewed not simply as reflection of CV risk or an end by themselves but as a call to investigate the patient for hepatic complications.

Conflict of Interest: None

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors contribution

- 1st author has contributed to the study concept and design, data analysis, preparation of manuscript and submission
- 2nd author has contributed to study concept, data collection, editing of manuscript

Acknowledgement: Sincere thanks to Dr Arvind Gulbake for his helpful suggestions in preparation of final manuscript.

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