Risk Factors Associated With Non-Alcoholic Fatty Liver Disease in Indians: A Case–Control Study

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Background/Aims: NAFLD has today emerged as the leading cause of liver disorder. There is scanty data on risk factors associated with NAFLD emanating from India. The present study was conducted to identify the risk factors associated with NAFLD. **Methods:** 464 consecutive NAFLD patients and 181 control patients were subjected to detailed questionnaire regarding their lifestyle and dietary risk factors. Anthropometric measurements were obtained and biochemical assays were done. Comparison of different variables was made between NAFLD patients and controls using principal component analysis (PCA). **Results:** NAFLD patients had higher BMI [26.25 ± 3.80 vs 21.46 ± 3.08 kg/m², $P = 0.000$], waist-hip ratio [0.96 ± 0.12 vs 0.90 ± 0.08 , $P = 0.000$] and waist-height ratio [0.57 ± 0.09 vs 0.50 ± 0.06 , $P = 0.000$] compared to controls. Fasting blood sugar [101.88 ± 31.57 vs 90.87 ± 10.74 mg/dl] and triglyceride levels [196.16 ± 102.66 vs 133.20 ± 58.37 mg/dl] were significantly higher in NAFLD group. HOMA-IR was also higher in NAFLD group [2.53 ± 2.57 vs 1.16 ± 0.58 , $P = 0.000$]. Majority (90.2%) of NAFLD patients were sedentary. Family history of metabolic syndrome (MS) was positively correlated with NAFLD. Dietary risk factors associated with NAFLD were non-vegetarian diet [35% vs 23%, $P = 0.002$], fried food [35% vs 9%, $P = 0.000$], spicy foods [51% vs 15%, $P = 0.001$] and tea [55% vs 39%, $P = 0.001$]. Diabetes, hypertension, snoring and sleep apnoea syndrome were common factors in NAFLD. On multivariate PCA, waist/height ratio and BMI were significantly higher in the NAFLD patients. **Conclusion:** The risk factors associated with NAFLD are sedentary lifestyle, obesity family history of MS, consumption of meat/fish, spicy foods, fried foods and tea. Other risk factors associated with NAFLD included snoring and MS. (J CLIN EXP HEPATOL 2015;5:295–302)

Non-alcoholic fatty liver disease (NAFLD) is a distinct clinico-pathologic entity characterized histologically by a spectrum ranging from simple steatosis to steatohepatitis (NASH), cirrhosis and even hepatocellular carcinoma (HCC).^{1,2} NAFLD (steatosis of the liver) is highly prevalent in Western countries.¹ With the introduction of westernized lifestyle and the increasing frequency of obesity in the Asia-Pacific region, the prevalence of NAFLD has increased over the past two decades.

Studies from different regions of India have shown that NAFLD is very common in Indians.^{3–5} Risk factors implicated in the development of NAFLD are obesity and metabolic syndrome (MS).^{6,7} However, it is obvious that NAFLD is multifactorial and identifying the various risk factors associated with NAFLD in our population could help us to intervene in order to prevent its progression to more severe forms of the disease.

The few studies identifying the risk factors associated with NAFLD have emanated from the West, where the profiles of NAFLD patients appear to be different.^{8–10} The observed differences in Indian NAFLD patients include a lower frequency of MS,^{9,11} lesser degree of adiposity and histological milder disease at presentation.⁸ A study that compared Indians with matched Caucasians, Hispanics, Blacks and Eastern Asians showed 2- to 3-fold increase in insulin resistance, and 2-fold increase in hepatic triglyceride content in the Indian subgroup.¹²

The aim of the present study was to compare the dietary pattern, and the anthropometric, metabolic and biochemical parameters between NAFLD patients and controls with the objective to find dietary and lifestyle risk factors associated with NAFLD in our population.

Keywords: fatty liver, diet, lifestyle, anthropometry, metabolic syndrome
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Abbreviations: ALT: Alanine Transaminase; AST: Aspartate Transaminase; BMI: Body Mass Index; FBG: fasting blood glucose; HCC: hepatocellular carcinoma; HC: hip circumference; HDL: high-density lipoprotein; HOMA-B: beta-cell function; HOMA: Homeostatic Model Assessment; IR: insulin resistance; MS: Metabolic syndrome; NAFLD: Non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; PCA: Principal Component Analysis; SD: standard deviation; WC: waist circumference
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METHODS

This was an observational, analytical, single-centre study of cases and controls attending a Gastroenterology clinic at Cuttack, Orissa from October 2012 to October 2013. The study was approved by the Kalinga Gastroenterology Foundation (KGF) Ethical Committee. Only those subjects who provided informed consent for the study were included.

Four hundred and sixty-four consecutive NAFLD patients and 181 controls were analyzed in this study.

Patients

These were NAFLD patients ($n = 464$). The diagnosis of NAFLD was made on the basis of ultrasonography and histological confirmation whenever possible. Subjects were considered as cases if they presented with fatty liver defined according to the standard criteria accepted by the American Gastroenterology Association: An increase in hepatic echogenicity taking renal echogenicity as a reference, the presence of enhancement and lack of differentiation in periportal intensity and the vascular wall due to great hyper-echogenicity of the parenchyma.¹³

Liver biopsy was done in 25 patients who gave consent for biopsy. Liver biopsy was done using Bard Biopsy Gun 16 G, through intercostal approach. Grading and staging of liver histopathology was done as per the classification proposed by Kleiner et al. using necro-inflammatory activity for grading of NASH.

Controls

Consecutive age-matched patients who had a normal abdominal ultrasonography, which was performed for various causes, such as abdominal pain and dyspepsia, served as controls.

Exclusion criteria

Patients and controls consuming alcohol >20 g/day, having other known liver diseases (hepatitis viruses A to E, autoimmune disease and Wilson's disease) and those on medications known to induce fatty liver or insulin sensitization, such as estrogens, amiodarone, methotrexate, tamoxifen, glitazones and metformin were excluded.

All patients and controls were questioned about their socio-economic background, occupation, family history of MS and liver diseases, diet pattern and eating habits, smoking and drinking habits, exercise, snoring and symptoms of sleep apnea syndrome in a face-to-face interview. Socio-economic assessment was based on the educational status, occupation and income of the patient as suggested by the modified Kuppuswamy socio-economic scale.¹⁴ The patients were categorized into upper, middle and lower socio-economic status. The average daily tea or coffee use was categorized into 1–3 cups and more than 3 cups/day.

Subjects were asked about the consumption of vegetarian food and frequency of consumption of meat, fruits and aerated drinks. Fried foods were defined as those foods that were prepared by submerging them in hot oil either by using a deep fryer or a chip pan, without using water. For all dietary items, the frequency was categorized as never (reference), 1–2 times per week (infrequent), and >3 times per week (frequent). Subjects were asked about whether they took spices in their diet; they were asked to classify the intensity of spicy diet on a subjective basis as mild, moderate or severe. Moderate exercise for ≥ 30 min each time ≥ 4 times weekly was considered to be regular exercise. A questionnaire addressing all these questions was filled up.

The anthropometric assessment included measurements of weight, stature, and waist circumference (WC) and hip circumference (HC). Body mass index (BMI) was calculated as weight (kg)/stature (m^2). The WC and HC were measured at the level midway between the lowest rib and the iliac crest and at the level of the great trochanter, respectively.

The measurements of fasting glucose, triglycerides, cholesterol and high-density lipoprotein (HDL) cholesterol and liver function tests were performed by standard laboratory methods. Serum insulin level was estimated by electro-chemiluminescence using standard kit (Roche-Diagnostics, USA) with autoanalyser Elecsys 2010 (Roche-Hitachi, Japan). IR was calculated using the homeostatic model assessment (HOMA) method using a mathematical model derived from FBG and plasma insulin. The value of HOMA was calculated by the following equation: (fasting insulin ($\mu U/ml$) $\times$ FBG (mg/dl))/405, and depicted as HOMA-IR value.¹⁵

In order to identify the various risk factors associated with NAFLD, comparison of dietary pattern and lifestyle, anthropometry indices and biochemical and metabolic parameters was done between the cases and healthy controls.

Statistics

Normally distributed continuous variables were expressed as mean $\pm$ SD, and the continuous variables with skewed distribution were expressed as median (range). Student's *t*-test for unpaired data was used to compare groups when variables are normally distributed; otherwise, the Mann-Whitney test was used. Chi-test was used to compare differences in categorical variables. Logistic regression analysis was used for multivariate modelling. Statistical significance was assumed for $P \leq 0.05$.

Power calculation for sample size determination to yield statistically significant results was performed using G*power version 3.1.3.¹⁶ The sample size required for both cases and controls was 55 ($=N$) each in order to attain a power of 0.95 with effect size 0.7 for $\alpha = 0.05$. In the current study, we analyzed data from 460 individuals and 181 controls.

Principal component analysis (PCA)

Data for fasting glucose, post-prandial glucose, serum insulin, HOMA IR and lipid profile were clubbed as metabolic profile. Similarly, data for BMI, weight, height, waist, waist-hip ratio and waist-height ratio were grouped under anthropometric data and AST and ALT levels were analyzed to understand liver biochemical status. PCA was performed on normalized values of liver biochemical, anthropometric and metabolic profiles. Each group was analyzed separately to find the PCA components. Main distribution for all groups was spread across first two principal component axes. Variance, across data within a group along principal component axes, was distinctly different between control and diseased groups. Two-dimensional orthogonal Eigenvalue scores for all variables for each individual in a group were calculated using StatistiXL package (add in to Microsoft Excel) in order to identify the pattern or cluster in the data as a result of the stress condition using serum samples collected from individuals who had consented for this study.

RESULTS

Males outnumbered females and constituted 77.87% of the 461 patients. Both the controls and cases were matched for age. Of the total urban patients in the study, 81.3% had NAFLD compared to 64.75% of rural patients ($P = 0.018$). Only 9.75% of NAFLD patients were hard working people consisting of farmers and labourers. 45.98% persons in NAFLD group had a sedentary lifestyle (those in government service, private sectors and businessman) compared to 14.6% in the control group. Majority of NAFLD patients

belonged to middle class (57%) in contrast to the controls, where majority (59%) were from lower socio-economic status. A family history of MS was present in 31.2% of NAFLD patients compared to 7% in controls ($P < 0.0001$) and the family history of liver disease was seen in 4.57% of NAFLD patients compared to only 0.5% of controls ($P = 0.007$) (Table 1).

There was no difference between the controls and NAFLD patients with regard to predominant cereal consumption, whether one consumes rice or wheat or both. About 90% of both controls and NAFLD patients were non-vegetarians. 35.3% of NAFLD patients consumed non-vegetarian diet frequently compared to 22.9% of controls ($P = 0.002$). Fruit intake was insignificant in both groups. Frequent consumption of fried food [34.9% vs 9.24%, $P < 0.0001$] and spicy foods [50.98% vs 15.2%, $P < 0.0001$] was seen more in NAFLD group compared to controls. Fast food (10.4% vs 7.6%, $P = 0.34$) and aerated drinks (5.2% vs 4.8%, $P = 0.97$) consumption was similar in both the NAFLD and control groups. Medium to very spicy dietary preference was seen in 49.7% in NAFLD compared to 33.2% in controls ($P = 0.004$). Drinking tea was a common feature in NAFLD patients compared to controls (54.9% vs 39.1%, $P < 0.001$) (Table 2). However, on multivariate analysis using a step-wise logistic regression model, only consumption of non-vegetarian food and fried food was associated with NAFLD.

Diabetes and hypertension were more common in NAFLD. There was no difference in the proportion of dental caries, occasional alcohol use and smoking habit between the two groups. Not only snoring (40.8% vs 32%) but also symptoms associated with sleep apnea syndrome, such as daytime sleepiness, impaired concentration, unrefreshing

Table 1 Demographic Profile of Healthy Controls and NAFLD Patients.

	Group A Control	Percentage (%)	Group B NAFLD	Percentage (%)	P value
Total cases (N)	181		464		
Males	120	65.2	359	77.87	0.001
Females	64		102		
Family H/O metabolic syndrome	13	7.1	144	31.23	0.000
Family H/O liver disease	1	0.5	21	4.57	0.007
Background					
Urban	49	26.63	213	46.20	0.000
Rural	135		248		
Occupation					
Labourer/Farmer	33	17.9	44	9.5	0.004
Service/Business	27	14.6	212	45.98	0.000
Others	122	66.3	204	44.25	
Socio-economic status					
Upper	5	2.7	46	9.97	0.001
Middle	68	36.95	263	57.05	0.000
Lower	109	59.23	148	32.10	0.000

Table 2 Dietary Pattern of Healthy Controls and NAFLD Patients.

	Group A Control	%	Group B NAFLD	%	P value
Vegetarians	15	8.1	36	7.8	0.87
Predominant cereal					
Rice	27	14.6	94	20.4	0.09
Wheat	11	5.9	18	3.9	0.29
Both	146	79.3	349	75.7	
Non-vegetarian diet					
Daily/alternate day	41	22.9	150	35.3	0.002
Once/twice weekly	138		275		
Fruits					
Daily/alternate day	13	7.1	52	11.3	0.114
Once/twice weekly	171		409		
Fried food					
Daily/alternate day	17	9.24	161	34.9	0.000
Once/twice weekly	167		300		
Spicy curry					
Daily/alternate day	28	15.2	235	50.98	0.000
Once/twice weekly	156		226		
Fast food					
Daily/alternate day	14	7.6	48	10.4	0.345
Once/twice weekly	170		413		
Aerated drinks					
Daily/alternate day	9	4.8	24	5.2	0.978
Once/twice weekly	175		437		
Diet pattern					
Bland to mild spicy	123	66.8	232	50.3	0.000
Medium to very spicy	61	33.2	229	49.7	

sleep, waking up, breath holding, choking and gasping were more evident in NAFLD compared to controls [17.6% vs 4.4%, $P < 0.001$]. Only 32.8% NAFLD patients and 31.5% of controls undertook regular exercise (Table 3).

Comparison of anthropometric measurements showed significantly higher BMI [26.25 ± 3.80 vs 21.46 ± 3.08 kg/m²], waist-hip ratio [$0.96 \pm .12$ vs $0.90 \pm .08$] and waist-height ratio [$0.57 \pm .09$ vs $0.50 \pm .06$] in NAFLD patients compared to controls. Similarly, fasting blood sugar [101.88 ± 31.57 vs 90.87 ± 10.74 mg/dl], serum triglyceride level [196.16 ± 102.66 vs 133.20 ± 58.37 mg/dl] and serum insulin [9.77 ± 5.47 vs 5.12 ± 2.40] were significantly higher in NAFLD group compared to controls. Insulin resistance as indicated by HOMA IR was also significantly higher in the NAFLD group [2.53 ± 2.57 vs 1.16 ± 0.58] compared to controls (Table 4).

Histopathology was done in 25 NAFLD patients. Biopsy findings revealed fatty change alone in 3 (12%) cases, borderline NASH in 7 (28%) cases and definite NASH in 15 (60%). Fibrosis was noted in 14/25 (56%) in NAFLD patients.

PCA analysis revealed that (a) for metabolic analysis, parameters, such as FBS, triglyceride and HDL levels, contributed significantly in distinguishing two groups (NAFLD and Control), (b) for anthropometric analysis, parameters, such as height, weight, BMI, waist, hip, waist height ratio and waist hip ratio, contributed significantly two groups (NAFLD and Control) and (c) for liver biochemistry analysis parameters, such as liver enzymes like AST and ALT, levels contributed significantly to distinguish two groups (NAFLD and Control) (Figure 1). On multivariate PCA analysis, when NAFLD patients were compared with controls, anthropometric indices like waist height and BMI were significantly higher in the NAFLD group (Figure 2).

DISCUSSION

The present study showed a higher proportion of males in the NAFLD group, which was similar to the earlier studies from India.^{3,4} NAFLD patients had a mean age of 42.15 years, which was similar to the age of the cohort in the

Table 3 Comparison of Known Risk Factors Between Healthy Controls and NAFLD Patients.

	Group A Control	%	Group B NAFLD	%	P value
Tea	72	39.1	253	54.9	0.000
Alcohol	20	10.9	67	14.5	0.27
Smoker	12	6.5	49	10.6	0.14
Chew tobacco	17	9.2	17	3.6	0.007
Known diabetic	1	.5	70	15.2	0.000
Known dyslipidemia	0	0	32	6.9	0.000
Hypertension	7	3.8	80	17.4	0.000
Dental caries	58	31.5	151	32.8	0.834
Exercise					
Regular/3–4 days per week	58	31.5	151	32.8	0.834
1–2 days/week	18	9.8	28	6.1	0.138
Never	106	57.6	282	61.2	0.445
Loud snoring					
Daily or 2–3/week	59	32.1	188	40.8	0.027
<once/wk or never	125		273		
Symptoms of sleep apnea (SOSA)	8	4.4	81	17.6	0.000
Difficulty falling asleep	57	30.1	173	37.5	0.139

Table 4 Comparison of Biochemical and Anthropometric Parameters.

Parameters	Group A Control	Group B NAFLD	P value
Age	39.23 ± 13.16	42.15 ± 10.54	NS
Height	160.89 ± 10.12	163.74 ± 8.03	0.015
Weight	55.5 ± 8.99	70.39 ± 11.02	0.000
BMI	21.46 ± 3.08	26.25 ± 3.80	0.000
Waist	80.44 ± 10.17	94.66 ± 9.44	0.000
Hip	89.74 ± 7.15	97.86 ± 7.60	0.000
Waist/hip ratio	0.90 ± 0.08	0.96 ± 0.12	0.000
Waist/height ratio	0.50 ± 0.06	0.57 ± 0.09	0.000
Sleep hours	6.79 ± 1.32	6.71 ± 1.03	NS
FBS	90.87 ± 10.74	101.88 ± 31.57	0.000
Triglyceride	133.20 ± 58.37	196.16 ± 102.66	0.000
HDL	45.41 ± 8.14	43.23 ± 12.44	NS
AST	30.05 ± 9.17	38.78 ± 17.51	0.000
ALT	35.18 ± 15.23	54.55 ± 32.73	0.000
Sr. Insulin	5.12 ± 2.40	9.77 ± 5.47	0.000
HOMA IR	1.16 ± 0.58	2.53 ± 2.57	0.000
HOMA Beta%	72.92 ± 39.97	123.94 ± 96.54	0.000

NAFLD series of Madan et al.⁸ and Duseja et al.⁹ Similarly, the mean BMI too in our NAFLD patients (26.25 kg/m²) was comparable to the BMI reported in earlier studies from India^{3,4} and was significantly higher than that of controls. Most studies from India had reported male gender, higher BMI, insulin resistance and MS as risk factors associated with NAFLD, which was also evident in our study.^{3,4,10}

Around 30% of our NAFLD patients had a family history of MS. Although this was lower than the figures reported in the study by Loomba et al.,¹⁷ where a considerable proportion of patients had NASH, it was still significantly higher compared to controls (7%).

Data on dietary risk factors from India are lacking. Our study has shown that urban middle class men with a

Figure 1 Principal component analysis of various parameters. Multivariate analysis to compare principal components based on metabolic (a) NAFLD patients and (b) Control groups; anthropometric (c) NAFLD and (d) control groups; liver biochemistry (e) NAFLD and (f) control groups is shown.

sedentary lifestyle had greater risk of NAFLD, which may be due to the dietary pattern, especially high-fat intake in them. Earlier study by Mohan et al.⁴ had shown that a third of the urban adults were NAFLD. Our NAFLD patients consumed meat, spicy food and fried food more often than the controls. Association of higher meat intake and higher fat intake with NAFLD has been shown earlier too in a few studies.^{18,19} Several studies have highlighted the fact that dietary intake rich in saturated fat and

cholesterol and sweet carbohydrates was associated with NAFLD.^{20,21} Fast food and soft drinks contain artificial sweeteners, such as fructose. Results of several recent studies suggest that an increased intake of dietary fructose may be associated with the development of NAFLD.²²⁻²⁴ Assy et al. and Abid et al. demonstrated a positive association between soft drinks consumption and NAFLD.^{23,25} Further, the CARDIA study has shown that fast-food consumption had a strong positive association with weight

Figure 2 Comparison of BMI and Waist/Height values. Significant differences are observed for both male and female individuals between control (ctrl) and NAFLD groups with respect to BMI (upper panel) and waist/height ratio (lower panel). Error bars shown are SD of the data and difference in significance was $P \leq 0.001$ as indicated by *** between the data.

gain and insulin resistance in humans.²⁶ However, aerated drinks or fast-food consumption did not show any association with NAFLD in our study. This may be perhaps because most of our patients studied did not consume aerated drinks or fast food in significant amount to have a bearing on the study. Another novel finding in this study is that drinking tea was significantly associated with development of NAFLD. A recent study from Japan, albeit with a very small number of patients, has shown that drinking green tea without sugar improves liver function in NAFLD patients.²⁷ However, our patients consumed normal tea with milk and sugar and this habit is strongly associated with development of fatty liver in our study. This association could be due to increased calories consumed by frequent drinking of tea laced with significant amounts of sugar and milk.

Number of subjects undergoing regular physical exercise was similar in NAFLD and control group. In the past, other studies have demonstrated that those who undertake less physical activity are more likely to have NAFLD.^{28,29} Besides, dental caries too was not seen to be significantly associated with NAFLD in our study, unlike the study by Masata et al.³⁰ About 30% of NAFLD patients in our study snored regularly and 14% had symptoms of sleep apnea syndrome. Similar observational findings were also evident in a pooled analysis of 18 cross-sectional studies conducted by Musso et al.³¹

There are some limitations in our study. One limitation is the use of ultrasonography to diagnose liver steatosis.

Even if ultrasonography is reasonably accurate as compared with nuclear magnetic resonance spectroscopy and liver biopsy, it cannot identify fatty infiltration of the liver below a threshold of 30%.³² Although liver biopsy is the gold standard to diagnose fatty liver, it is neither feasible nor ethically justified in a condition with low risk of progression and no definite treatment. Besides, dietary and physical activity information was obtained through self-reported questionnaires, which may be subject to both under-reporting and recall bias. Amount of calorie consumption was not done in these patients. However, the present study emphasized on the eating habits and dietary patterns and the quality of food consumed rather than on the total calorie consumed.

CONCLUSION

Urban middle class Indian men with sedentary lifestyle were more likely to have NAFLD. NAFLD patients frequently consumed non-vegetarian food, fried food, spicy foods and tea. In our study, smoking, occasional alcohol consumption, aerated drinks and dental caries did not have any influence on the development of fatty liver. The NAFLD patients had higher prevalence of diabetes, hypertension and problematic snoring. Both obesity and abdominal obesity along with insulin resistance and dyslipidemia were also common in NAFLD patients. With adequate understanding of the aetiology of NAFLD, a multifactorial intervention directed to the risk factors may favour its remission and thereby avoid the development of more severe hepatic complications.

CONFLICTS OF INTEREST

The authors have none to declare.

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