Exploring the Relationship of Drugs/Dietary Factors/Obesity in Occurrence of Nonalcoholic Fatty Liver Disease

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Abstract
Nonalcoholic fatty liver disease is one of the common liver diseases worldwide, with a high prevalence in the obese, with faulty dietary habits & persons taking frequent medications & it is probably underestimated as a cause of life threatening complications like, cirrhosis, hepatocellular Carcinoma etc.79 patients of either sex between 10-65yrs of age, incidentally found to have fatty liver by ultrasonography, referred to Radiology and Gastroenterology departments were the study population. The lifestyle pattern. Biochemical tests, like liver function test, serum lipid profile & fasting blood sugar (FBS) were checked for all patients. Anthropometric data including weight & height were recorded. The BMI value>25kg/m^2 was considered as risk factor. History about the diet & use of medications including alternative medicines known to cause fatty liver disease were recorded. The degree of steatosis was graded ultrasonographically by a single Radiologist from 0-3. This study of two months duration concluded that is often asymptomatic and is an incidental finding during ultrasonography of liver on routine screening. In the absence of established therapies it can be treated by modifying the risk factors. We identified the modifiable risk factors like BMI, dietary pattern associated with Non-alcoholic Fatty Liver Disease. Standard diet therapy, lifestyle modification could be used as an effective treatment for NAFLD patients. Minimising intake of fast food, soft drinks and non-vegetarian spicy diet will also help to maintain a healthy lifestyle.

Key Words: Non Alcoholic Fatty Liver Disease, Obesity, Ultrasonography.

Introduction
Non-alcoholic fatty liver disease (NAFLD) has been recognized as a major health burden, characterized by excess of fat in liver which may lead to simple steatosis, steatohepatitis, cirrhosis and hepatocellular carcinoma (HCC) in the absence of excessive alcohol intake(1). The exact pathogenesis of NAFLD is not yet clearly understood. The existing hypothesis by experts in this field is that several insults may be involved in causing progressive liver injury (2). There are reports about obesity, faulty lifestyle & unhealthy dietary pattern associated with fatty liver disease (3). Various drugs & toxins are reported to be the potential causes of NAFLD(4). However such data, particularly association of diet & drugs behind NAFLD is still limited. Unbalanced nutrition is not only strongly associated with NAFLD, but is also a risk factor that a large portion of the population is exposed to(3). It remains uncertain
whether diets that are enriched with certain types of food or, nutrients are more likely to cause fatty liver than other types of diets. Increasing incidence of NAFLD has been well documented from Asian Countries like Japan and China (5). There is increase in incidence of diabetes mellitus, obesity and faulty lifestyle as predisposing factors for NAFLD in India in last 2 decades (6). Hence it is logical to expect increase in incidence of NAFLD in India. There is limited data about the predisposing factors associated with NAFLD. Therefore it is necessary to estimate the prevalence of NAFLD in general population and to identify the modifiable risk factors. Fatty liver disease is also found in our setup in persons with normal body weight, without history of diabetes mellitus or, high fat diet or alcohol consumption. Considering the risk of serious complications (like, non-alcoholic steatohepatitis, cirrhosis& hepatocellular carcinoma etc.) in association with NAFLD, it is essential to find out possible modifiable risk factors, behind causation of NAFLD. Most patients with fatty liver disease are asymptomatic. They usually come for medical attention by incidental finding of increased liver echogenecity during ultrasonography performed for other reasons. Though liver biopsy is the gold standard for diagnosis of fatty liver, ultrasonography could be used as a non-invasive predictor of liver histology in both moderate & severe steatosis, & advanced fibrosis with acceptable sensitivity & specificity (6).

Objective
NAFLD is a cause of chronic liver disease and has also been suggested to be associated with many complications. As there is lack of a universally accepted medical treatment for NAFLD, this study has been planned to estimate the prevalence of NAFLD in association with the above mentioned modifiable risk factors.

Patients & Methods
This was an observational, retrospective study conducted in the Department of Pharmacology in collaboration with the Department of Gastroenterology and Radiology, S.C.B Medical College & Hospital, Cuttack, Odisha, from 1st May 2012 to 30th June 2012. Total 79 patients of either sex between 10-65 yrs of age, incidentally found to have fatty liver by ultrasonography, referred to Radiology and Gastroenterology Departments were the study population, depending upon the exclusion & inclusion criteria. Written consent was taken from all patients. All patients underwent complete history evaluation, anthropometric measurements & physical examination. Detailed history including history of alcohol consumption, usage of medication including alternative medication & food pattern, food supplement was taken. All patients were asked about their lifestyle pattern like leisure time activity. Biochemical tests, like liver function test, serum lipid profile & fasting blood sugar (FBS) were checked for all patients. Anthropometric data including weight & height were recorded & the body mass index (BMI) of each patient was calculated by applying formula, weight (kg)/height (m²). The BMI value > 25 kg/m² was considered as risk factor (5). Detailed history about the diet & use of medications including alternative medicines known to cause fatty liver disease during. The degree of steatosis was graded ultrasonographically by a single Radiologist from 0-3 according to table given below (54).

| GRADE | LIVER PICTURE |
|-------|---------------|
| 0     | Normal parenchymal liver echogenecity |
| 1     | Increased liver echogenecity without haziness of blood vessel |
| 2     | Increased liver echogenecity with haziness of blood vessel |
| 3     | Increased liver echogenecity leading to loss of normal contrast between liver and diaphragm. |

Inclusion criteria
- Patients of the Gastroenterology Dept with a radiological/provisional diagnosis
- Patients willing for follow up.

Exclusion Criteria
- Alcohol consumption > 40gr/week
- Overt diabetes (FBS > 125mg/dl)
- Chronic medical condition (e.g., renal/cardiac disease.)
Not consenting to the study or not able to refer for regular follow-up.

This study protocol has been approved by the Institutional Ethics Committee. All the data were taken as mean ± sd and were analysed by percentage (%) values.

Observation & Results

Observation Table-1 Demographic criteria of NAFLD patients.

| n' | 79 |
|---|---|
| SEX | Male=57, Female=22 | Male=71.79%, Female=28.21% |
| AGE in years | 44.3±11.2 |
| B.M.I (kg/m²) | 28.9±6.37 |
| Duration of disease (days) | 237.7±322.06 |
| Lifestyle | Sedentary-13, Active-6 | Sedentary-92.4%, Active-7.6% |

Out of 79 NAFLD diagnosed patients, 57 were male and 22 were female with mean age 44.3±11.2 years. Their mean body mass index was 28.9±6.37 kg/m². Mean duration of their complaints was 237.7±322.06 days. Majority of them sedentary lifestyle (73), 92.4% and 6 of them were active 7.6%.

Observation Table-2 Ultrasonographic Fatty Liver Grades

| Fatty Change | 'N' | % |
|---|---|---|
| Mild (Grade I) | 67 | 84.8 |
| Moderate (Grade II) | 11 | 13.9 |
| Gross (Grade III) | 1 | 1.2 |

Majority of patients (84.8%) had mild fatty changes as seen in USG. 13.9% had moderate fatty change. 1.2% showed gross fatty change in USG.

Observation Table-3 Biochemical parameters of NAFLD Patients

| Parameters | Value (mean±sd) | n' |
|---|---|---|
| AST (IU/L) | 35.9±14.2 | 66 |
| ALT (IU/L) | 47.9±25.8 | 67 |
| ALP (IU/L) | 149.0±46.3 | 64 |
| TOTAL BILIRUBIN (mg/dl) | 0.78±0.23 | 68 |
| DIRECT BILIRUBIN (mg/dl) | 0.29±0.21 | 68 |
| Cholesterol (mg/dl) | 200.7±38.003 | 69 |
| TRIGLYCERIDE (mg/dl) | 164.6±79.06 | 60 |
| HDL (mg/dl) | 45.6±7.98 | 65 |
| LDL (mg/dl) | 127.3±4.9 | 64 |
| VLDL (mg/dl) | 36.1±3.23 | 61 |
| PBS (mg/dl) | 87±17.9 | 35 |

Observation Table-4: Dietary habits of NAFLD Patients

| PATTERN | No. of Patients | n | % |
|---|---|---|---|
| Vegetarian | 11 | 79 | 13.9 |
| Non-Vegetarian | 68 | 79 | 86.07 |
| Vegetarian (spicy) | 5 | 61 | 45.45 |
| Non-Vegetarian (spicy) | 33 | 68 | 51.4 |
| Soft Drinks | 13 | 79 | 16.4 |
| Fast Food | 30 | 79 | 37.9 |
| Soft Drinks + Fast Food | 24 | 79 | 30.3 |
| Neither | 12 | 79 | 15.18 |

Majority of patients were non-vegetarian (86.07%) while 13.9% were vegetarian. Out of vegetarian patients, 45.45% were spicy eaters and out of the non-vegetarian, 51.4% were spicy eaters. 16.4% of patients took soft drinks, 37.9% of patients took fast food while 30.3% took both.

Observation Table-5 (Chief complaints of NAFLD patients)

| Complain | 'N' | % |
|---|---|---|
| Pain Abdomen | 55 | 69.6% |
| Vomiting, Indigestion (Dyspepsia) | 18 | 22.78% |
| G.E.R.D. | 3 | 3.7% |
| Constipation | 2 | 2.5% |
| Blood In Stool | 1 | 1.2% |

Most of the patients had the chief complaint of pain abdomen (69.6%) while 22.78% had complained of vomiting & indigestion. 3.7% patients had chief complaint of G.E.R.D, while 2.5% had chief complaint of constipation. One patient (1.2%) had complained of blood in stool.

Observation Table-6 (Drugs taken by NAFLD patients during last 3 months)

| Drugs | No. Of Patients | % |
|---|---|---|
| OCP | 11 Out Of 22 Females | 50 |
| Ppi | 13 | 15.4 |
| Ppi + Anti-Hypertensives | 5 | 6.3 |
| Ppi + Anti-Depressants | 5 | 6.3 |
| Ppi + Anti-Spasmodics | 16 | 20.5 |
| Librax (Chlordiazepoxide) | 4 | 5.06 |
| Piomed + Glycinorn | 1 | 1.2 |
| Statins | 1 | 1.2 |
| None | 23 | 29 |

Out of 22 female patients 11 used OCPs. Out of total 79 patients, 13 (15.4%) took only PPIs while 26 patients took PPIs in combination with either anti-hypertensives (6.3%) anti-spasmodics 16 (20.5%) anti-depressants 5 (6.3%). 4 (5.06%) patients took Librax (chlordiazepoxide) while one patient took either Piomed with Glycinorn or Statin.
Result
In this study, 79 (57 males, 22 females) patients were enrolled with the mean age of 44.3±11.2 years. Most patients with fatty liver disease were asymptomatic. However with meticulous questioning more than half (55) mentioned upper abdominal pain. Their mean body mass index was found to be 28.9±6.37 kg/m². They suffered from the disease for 237.7±322.06 days. Regular physical activities was significantly less in our study population, majority 73 (92.4%) of the patients were leading sedentary lifestyle & only 6 (7.6%) were active in their life style.
As per Observation Table II, 67 patients (84.8%) had USG Grade 1 i.e. mild steatosis. 11 patients (13.9%) had USG Grade II (moderate) steatosis where as only 1 patient (1.2%) had USG Grade III (gross) steatosis.

The laboratory test values of liver enzymes, serum bilirubin, lipid profiles, fasting blood sugar etc. are given in observation table III. In total 66 patients the mean AST value was found to be 35.9±14.2 IU/L, the mean value of ALT & ALP in 67 & 64 patients respectively was found to be 47.9±25.8 U/L & 149.6±46.3 U/L. Total & direct serum bilirubin value was 0.78±0.23 & 0.29±0.21 mg/dl respectively. Serum cholesterol 200.7±38.003 mg/dl, triglyceride 164.6±79.06 mg/dl, HDL (45.6±7.98 mg/dl), LDL (127.3±34.9 mg/dl), VLDL (36.1±13.23 mg/dl), FBS (87.1±17.9 mg/dl).

As per observation table IV, out of total 79 patients 68 (86.07%) were non vegetarian & 11 (13.9%) patients were vegetarians. Out of 68 non vegetarians 35 (51.4%) patients are nonveg spicy eater. 5 out of 11 vegetarian patients (45.45%) were spicy eaters. 30 (37.9%) patients of the study population took fast food regularly, 13 (16.4%) patients used to take soft drinks while 24 (30.3%) patients used to take both.

As shown in observation table V, 55 (69.6%) patients had chief complaint of pain abdomen. 18 (22.78%) patients complained of vomiting, indigestion and dyspepsia. 3 (3.7%) patients had gastro esophageal reflux disease(GERD). 2 (2.5%) patients had the chief complaint of constipation & 1 (1.2%) complained of blood in stool.

As shown in observation table VI, 23 (29%) patients had no drug history. Out of 22 female patients in our study 11 (50%) patients had a history of using Oral Contraceptive Pills. Piomed & glycinorneach used by only 1 (1.2%) patients. Other drugs like proton pump inhibitors, antispasmodics, anti depressants & statins used could be before the treatment of the signs & symptoms of the disease.

Discussion
NAFLD is a cause of chronic liver disease & a component of metabolic syndrome, it has tendency to develop metabolic complications (9). The treatment of NAFLD is controversial. No effective treatment is there to treat NAFLD. In the absence of therapeutic modalities of proven efficacy, care is taken towards correction of the risk factors for the disease. Identification of modifiable risk factors for prevention & treatment of NAFLD is therefore important. This study discussed the correlation of risk factors like dietary composition, medications & BMI in association with NAFLD. NAFLD was diagnosed in patients who initially came to medical attention by the incidental findings of increased liver echogenicity during ultrasonography done for master health checkup & other reasons. Ultrasonography could be used as a economical, non-invasive predictor of liver histology in mild, moderate and severe steatosis with acceptable sensitivity and specificity (10, 11). 67 (84.8%) patients of our study population shown to have Grade I (mild) fatty changes of liver in ultrasonography. The mean age of our study population was found to be 44.3 ±11.2 years. This is in accordance to a study carried out by Dr. D.Amarapurkar et al (10) where it was observed that more cases of NAFLD were reported in patients of the age group of 40-49 who were obese with a sedentary lifestyle. Majority of our study population were obese having mean BMI value 28.9±6.37 kg/m², a characteristic feature and risk
factor associated with NAFLD (13).73(92.4%) patients of the study population were leading sedentary lifestyle which is again an important risk factor associated with NAFLD. This is in accordance with the report of Shiria Zelber-Sagi et al (3).More than half of the patients in our study were non-vegetarian and spicy eaters and took fast food and soft drinks regularly. These findings are in accordance with the findings of Shiria Zelber-Sagi et al (3).Nutrition has been demonstrated to be associated with NAFLD in both animal and human study(8). 50% of the females in our study population had a history of taking OCPs. This might be the cause of fatty liver in female patients. Estimation of serum lipid profile and liver function test also served as a diagnostic tool of NAFLD(4).Mild to moderate elevation of serum aminotransferases (ALT,AST) is the most common and often the only laboratory abnormality found in patients with NAFLD(7).But our study showed that though there is rise in levels of serum ALT( 47.9±25.8 IU/L), there is no rise in AST, ALP, total and direct bilirubin. Values of lipid profile and FBS of our study population were found to be within the normal range and this differs from the study done by Sheth S.G. et al (14) which showed that elevated serum lipid profile and FBS concentration are also common findings in NAFLD patients.

Summary
This study of 2 months duration was an observational retrospective analysis of causal association of certain factors like drugs, diet & BMI, associated with NAFLD occurrence, was conducted in the department of Pharmacology in collaboration with the Radiology & Gastroenterology dept. of S.C.B Medical College & Hospital, Cuttack, Odisha. Total 79 patients were enrolled who were diagnosed to be of NAFLD, the degree of fatty changes was graded by ultrasound. Majority of the study population sought medical attention after incidental ultrasonographic finding of fatty changes. Majority of patients were of grade -1(mild steatosis). Upper abdominal pain & discomfort was the chief complain among maximum patients. The mean body mass index (BMI) of the study population was >25kg/m².taken as risk factor. Majority of our study population were leading sedentary life style with unhealthy dietary patterns. 50% of female population gave h/o taking o.c pills. Other drugs known to cause fatty changes in liver were not properly studied

Conclusion
This study of two months duration with 79 study population concluded that NAFLD is often asymptomatic and is a incidental finding during ultrasonography of liver on routine screening. In the absence of established therapies it can be treated by modifying the risk factors. We identified the modifiable risk factors like BMI,leisure period activity, dietary pattern associated with NAFLD. Standard diet therapy, lifestyle modification could be used as an effective treatment for NAFLD patients. Minimising intake of fast food, soft drinks and non-vegetarian spicy diet will also help to maintain a healthy lifestyle. Furthermore, all NAFLD patients, whether obese or of normal weight should be informed that a healthy diet has benefits beyond weight reduction. Ultrasonography can be used as a cost effective and non-invasive method of diagnosis of NAFLD. This was a preliminary, observational, retrospective study of two months duration only. We got only limited inference about causal association. So large, long term, case controlled prospective studies may provide much information about the natural history, treatment and prognosis of this poorly understood disorder.

References
1. Farrel GC, LarterCZ. Nonalcoholic Fatty Liver disease from steatosis to cirrhosis. Hepatology 2006; 43:S00-S112
2. Day CP, ZamesOF !steato hepatitis : a tale of two “ Hits “ ? Gastroenterology 114(4): 842-845, 1998
3. Shira Zelber-Sagi, Vlad Ratziu, and Ran Oren. Nutrition and physical activity in NAFLD: An overview of the epidemiological evidence. World J Gastroenterol. 2011 August; 17(29):3377-3389.

4. David A. Sass, MD, Parke Chang, MD, and Kapil B. Chopra, MD. Nonalcoholic Fatty Liver Disease: A Clinical Review. Digestive Diseases and Sciences, Vol. 50, No. 1 (January 2005), pp. 171-180.

5. Mohan V, Deepa R. Adipocytokines and the expanding << Asian Indian Phenotype >>. J Assoc Physic Ind. 2006; 54: 685-6.

6. Joseph AE, Saverymuttu SH, al-sam S, Cook MG, Maxwell JD. Comparison of liver histology with ultrasonography in assessing diffuse parenchymal liver disease. Clin Radiol 1991; 43:26-31.

7. Itoh S, Tsukada Y, Motomura Y, Ichinoe A. Five patients with nonalcoholic diabetic cirrhosis. Acta Hepatogastroenterol Stuttg 1979; 26:90-97.

8. Angulo P, Lindor KD: Non-alcoholic fatty liver disease. J Gastroenterol Hepatol 17 (Suppl):S186–S190, 2002.

9. Vozarova B, Stefan N, Lindsay RS, Saremi A, Pratley RE, Bogardus C, Tataranni PA. High alanine aminotransferase is associated with decreased hepatic insulin sensitivity and predicts the development of type 2 diabetes. Diabetes 2002; 51: 1889-1895.

10. Gupte P, Amarapurkar D, Agal S, Baijal R, Kulshrestha P, Pramanik S, Patel N, Madan A, Amarapurkar A, Hafeezunnisa. Non-alcoholic steatohepatitis in type 2 diabetes mellitus. Gastroenterol Hepatol 2004; 19: 854-858.

11. DelGaudio A, Boschi L, Del Gaudio GA, Mastrangelo L, Munari D. Liver damage in obese patients. Obes Surg 2002; 12: 802-804.

12. Hamaguchi M, Kojima T, Takeda N, Nakagawa T, Taniguchi H, Fujii K, Omatsu T, Nakajima T, Sarui H, Shimazaki M, Kato T, Okuda J, Ida K. The metabolic syndrome as a predictor of nonalcoholic fatty liver disease. Ann Intern Med 2005; 143: 722-728.

13. Bogin E, Avidar Y, Merom M. Biochemical changes in liver and blood during liver fattening in rats. J Clin Chem Clin Biochem 1986; 24: 621-626.

14. Sheth SG, Gordon FD, Chopra S: Non-alcoholic steatohepatitis. Ann Intern Med 126(2):137-145, 1997.