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Original Research Article

Comparison of non-invasive scores predictive of development of metabolic dysfunction associated liver disease in patients of type 2 diabetes mellitus and evaluation of additive effect of smoking in these patients

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ABSTRACT

Background: Metabolic dysfunction associated liver disease (MASLD) has been found to be at alarming increase in Indian population. Prevalence of metabolic syndrome including Type 2 Diabetes Mellitus is also increasing which may be attributed to certain lifestyle changes. In the present study, we compared the likelihood of liver fibrosis by measurement of non-invasive scores among Type 2 diabetics and smokers, Type 2 diabetics but non-smokers and healthy controls. Our study will provide useful insights to evaluate the association between Type 2 diabetes, smoking and development of MASLD.
Methods: The study was done at a tertiary care hospital. Participants were divided into 3 groups (each of 40 participants) which included those with type 2 diabetes mellitus and smokers, those with type 2 diabetes mellitus but non-smokers and healthy controls. Parameters included in the database were age, sex, body mass index, history of diabetes, history of hypertension, any medication, tobacco use and alcohol consumption. Venous blood samples were taken in the morning after a 12-h overnight fasting and investigations were done. Results were recorded.
Results: FIB-4 score and AST/ALT ratio was significantly higher in diabetics and smoker patients, in comparison to diabetics but non-smokers and healthy controls.
Conclusions: Smoking and underlying type 2 diabetes mellitus have a synergistic effect on the severity of fibrosis, as compared to nonsmokers with type 2 diabetes mellitus. Hence smoking cessation, in addition to glycemic control with regular medication, may be beneficial in reducing the severity of MASLD among patients with type 2 diabetes mellitus.

Keywords: Type 2 diabetes mellitus, Smoking, Metabolic dysfunction associated liver disease, FIB-4 score

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) contributes to a large proportion of chronic liver disease burden with rising prevalence. in Indian population, estimated prevalence among adults is around 38.6%. prevalence of NAFLD in average-risk and high-risk subgroups has estimated to be 28.1% and 52.8% respectively. available data suggest that approximately one in three adults have NAFLD in india.[1] non-alcoholic fatty liver disease can eventually progress to fibrosis, cirrhosis and even to hepatocellular carcinoma.[2]

Insulin resistance and type 2 diabetes mellitus have been linked to the incidence and progression of metabolic syndrome associated liver disease (MASLD).[3,4] Many

studies have found their multicausal role in development of NAFLD and consequent progression to fibrosis.[3,5] Persistent hyperglycemia, secondary to uncontrolled or poorly controlled type 2 diabetes mellitus, promotes chronic glucotoxicity. By extension, hyperglycemia fosters the progression of hepatic steatosis, necrosis, inflammation and hepatocellular dysfunction.[6] Many studies have demonstrated that tobacco consumption has been independently implicated in the incidence and progression of MASLD (Metabolic dysfunction associated Steatotic Liver dysfunction) formerly known as NAFLD.[7-9] The enhancing effect of tobacco use on MASH-associated and MASLD-associated fibrosis has been linked to insulin resistance and the release of pro-inflammatory cytokines. Conversely, other studies have shown no clear relationship between tobacco use and MASLD.[10,11] Some previous studies have shown conflicting interactions between cigarette smoking, type 2 diabetes mellitus and MASLD.[7,8,12] Timely identification of modifiable risk factors is crucial for prevention and management of MASLD. So major objective of our study was to find out whether type 2 diabetes mellitus and tobacco use act synergistically to increase the risk of fibrosis in MASLD. In this study, we evaluated the association between tobacco use and type 2 diabetes mellitus in causation of MASLD liver fibrosis which was assessed by measurement of Fibrosis-4 (FIB-4) scores.[13]

Aim and objectives

This study was planned to observe the effect of interaction between tobacco consumption and type 2 diabetes mellitus on liver function tests and non-invasive scores predictive of liver fibrosis.

METHODS

Study type, location and duration

It was a case-control study. The study was conducted at Guru Gobind Singh medical college and hospital, Faridkot, Punjab, India. The study was done in the period from June 2012 to September 2013. Informed written consent was taken from the participants before enrolling them for participation in the study. Participants were divided into 3 groups (each of 40 participants) which included those with type 2 diabetes mellitus and smokers (primary exposure group), those with type 2 diabetes mellitus but non-smokers (secondary exposure group) and healthy controls. The likelihood of liver fibrosis was determined using a defined fibrosis-4 index cutoff value of 1.3.

Inclusion criteria

Inclusion criteria for diabetes patients was according to American diabetes association (ADA) criteria for diagnosis of diabetes, i.e., fasting plasma glucose ≥126 mg/dl, random plasma glucose or post 2-hour oral glucose tolerance test ≥200 mg/dl, glycosylated haemoglobin (HbA1c) ≥6.5%, or documented use of anti-diabetic medications for management of hyperglycemia.[14]

Exclusion criteria

Patients suffering from all other causes of liver damage were excluded from the study. These were the patients with history of excessive alcohol consumption, viral hepatitis or HIV, autoimmune hepatitis, or patients on hepatotoxic drugs.

Parameters included in the database were age, sex, body mass index (BMI), history of diabetes, history of hypertension, medication use (statin, aspirin, oral hypoglycemics, anti-cancer drugs), tobacco use, alcohol consumption. Tobacco use was categorized into "never smoker" and "ever-smoker" (comprised of both former and current smokers). Venous blood samples were taken in the morning after a 12-h overnight fast from all patients and healthy controls. Following investigations were performed: complete blood count which was done on Beckman cell counter, fasting plasma glucose, renal function tests (blood urea, serum creatinine), liver function tests (total bilirubin, conjugated bilirubin, ALT, AST and ALP), lipid profile and glycosylated haemoglobin (HbA1c) which was done on i-chroma reader based on immunoturbidimetric method. All other biochemistry investigations were done on fully automated Beckman Coulter AU 480 Analyser.

Anthropometric evaluation

For all participants, weight (kg) and height (metre) was measured. BMI was calculated by the formula:

$$Weight\ (kg)/Height\ (meter)$$

Obesity was defined as BMI >25 kg/m^2, according to the criteria of the Japan society for the study of obesity.[2,15] A reliable, inexpensive and non-invasive marker of hepatic fibrosis is required in patients with non-alcoholic fatty liver disease (NAFLD). For this purpose, FIB-4 score was chosen because liver fibrosis often progresses non-linearly. So it is important to be able to re-assess fibrosis trends in individual patients over time, and invasive re-assessments carry significant risk to patients. FIB-4 allows for non-invasive liver fibrosis assessment. Following scores were calculated for each patient for determining non-invasive marker panels for detection of liver fibrosis:

$$FIB4\ score = Age\ (years)\ X\ AST\ (U/l) / Platelet(10\ 9/l)\ X\ \sqrt{ALT}$$

$$ALT\ to\ AST\ Ratio = ALT\ (U/l)/AST\ (U/l)$$

$$AST\ to\ platelet\ ratio\ index\ (APRI) = AST\ (U/l)/Platelet\ (10\ 9/l)\ X\ 100$$

FIB4 index cut-off values proposed by Sterling et al.[9,16-19] Low cut-off point (<1.45), Intermediate (1.45-3.25), High cut-off point (>3.25). The cut-off adopted for APRI (Aspartate transaminase to platelet ratio index) according to the cited studies was as follows: APRI <0.5 to identify a fibrosis-free liver, APRI >0.5 for liver fibrosis and APRI >1.5 for probable cirrhosis.[19,20]

Statistical analysis

All the baseline parameters were recorded in a tabulated form. Continuous data was presented as mean and the corresponding SD (mean±SD). Categorical variables were expressed in counts and percentages. Descriptive statistics were computed to observe the effect of smoking and type 2 diabetes mellitus on liver functions outcome. Statistical analysis was performed to compare the means of FIB-4 score (as continuous numerical variable) and to determine the difference between the two exposure groups and reference group, p value ≤0.05 was considered statistically significant.

RESULTS

As seen in (Table 1), all the three groups showed no significant difference in age and sex distribution.

Table 1: Distribution of patients based on different parameters.

Parameter	Type 2 DM + smoker (N=40)	Type 2 DM but non-smoker (N=40)	Non- diabetic, non-smoker (Healthy controls) (N=40)	P value
Age (years)	52.3±4.7	52.4±4.5	51.1±3.3	>0.05
Sex distribution (%Males, Females)	50.5, 49.5	49.8, 50.2	50.1, 49.9	>0.05
%Rural, urban	49.8, 50.2	50.1%, 49.9	49.9%, 50.1%	>0.05
BMI (kg/m^2)	29.8±3.5	29.1±3.2	26.3±2.4	<0.05
FPG (mg%)	276.48 ±32.66	266.55 ±31.9	78.70±21.56	< 0.001
HbA1c (%)	7.8±0.9	7.6±0.9	5.2±0.6	<0.001
Platelet count (10^9/l)	158.6±35.1	211.9±41.6	216.1±42.9	<0.001
TBI (mg%)	0.61±0.12	0.60±0.11	0.58±0.09	>0.05
ALT (U/l)	38.7±11.4	38.3±10.7	37.1±10.9	>0.05
AST(U/l)	89.1±21.8	41.6±10.2	35.8±10.4	<0.001
ALP(U/l)	72.3± 25.1	73.1±24.3	71.9±23.9	>0.05

Table 2: Results of non-invasive scores predictive of liver fibrosis.

Parameter	Type 2 DM + smoker (n=40)	Type 2 DM but non-smoker (n=40)	No DM, non-smoker (n=40)	P value
FIB-4 score	6.06±1.86	2.06±0.61	1.02±0.17	<0.001
AST/ALT ratio (AAR)	2.93±0.58	1.25±0.30	1.10±0.29	<0.001
AST/platelet ratio	0.61±0.13	0.21±0.04	0.17±0.03	<0.001

Fasting plasma glucose and HbA1c were significantly higher in Type 2 diabetic patients (both smokers and non-smokers) in comparison with healthy controls. Also, values of both the parameters were higher in Type 2 diabetic smokers as compared to Type 2 diabetic non-smokers(p<0.001). Platelet count was significantly lower in Type 2 diabetic smokers as compared to Type 2 diabetic non-smokers and healthy controls (p<0.001). Among the liver function tests, AST showed very significant difference among the three groups. The values of AST were much higher in Type 2 diabetic smokers in comparison with Type 2 diabetic non-smokers, who further had high AST values when compared to healthy controls (p<0.001).

As demonstrated in (Table 2), FIB-4 Score and the values of AST/ALT Ratio and AST/Platelet ratio were significantly higher in Type 2 diabetic smoker group, as compared to Type 2 diabetic non-smoker group. And the values of all the three parameters were further significantly higher in Type 2 diabetic non-smokers when compared to healthy controls (p<0.001).

DISCUSSION

In the present study, we found that smoking and underlying type 2 diabetes mellitus have a synergistic effect on the severity of fibrosis, as compared to nonsmokers with type 2 diabetes mellitus. Our study revealed that individuals diagnosed with type 2 diabetes mellitus had a greater prevalence of MASLD-associated hepatic fibrosis. Barb et al similarly reported a 2-fold increase in prevalent MASLD-related fibrosis with type 2 diabetes mellitus, though the study was limited to overweight and obese individuals.[21,22] As seen in (Table 2) in our study, results of non-invasive scores predictive of MASLD-associated hepatic fibrosis clear cut

demonstrate the additive effect of both the risk factors of smoking and type 2 diabetes mellitus. Our study also showed that tobacco use and type 2 diabetes mellitus are independent risk factors for MASLD severity. We explored this concept to delineate the cumulative effects of tobacco use in the background of type 2 diabetes mellitus in comparison to healthy controls and nonsmokers with type 2 diabetes mellitus.

Two pathophysiological mechanisms can be possible for the observed additive effect of combined type 2 diabetes mellitus and tobacco use on causation of hepatic fibrosis. Firstly, evidence supports the independent and direct effect of tobacco use on insulin resistance.[23] This association may be mediated by adiponectin, a secretory adipokine produced by the adipocytes. Adiponectin has also been shown to negatively correlate with insulin resistance, with lower levels observed among tobacco users.[15] In addition to the adiponectin effect, smoking has also been indirectly linked to insulin resistance through visceral adiposity. Canoy et al revealed in their study a significant association between cigarette smoking and visceral abdominal adiposity.[24]

A higher measure of central obesity was significantly observed among tobacco users. This association suggests a stronger link between insulin resistance and hepatic fibrosis among patients with MASLD. The second possible explanation for our findings could be that tobacco use creates direct hepatotoxic effects on the liver. For example, there is a known increase in specific pro-inflammatory cytokines (IL-1, IL-6, IL-8, and TNF- α) associated with tobacco use.[17,25] These cytokines promote oxidative stress which in turn causes increased lipid peroxidation, and subsequently result in liver fibrosis.[17] In a higher-risk population with already increased production of free radicals, such as patients with Type 2 Diabetes Mellitus, the inflammatory damage tobacco causes may serve as a catalyst for accelerated fibrosis. A study by Chalasani et al found that subjects with NASH have significantly higher systemic levels of lipid peroxidation products and this could indicate an increased risk of MASLD.[26]

Limitations

The study enrolled only those participants (patients as well as healthy controls) who visited the institute.

CONCLUSION

In conclusion, the findings of our study provided concrete risk estimates for clinicians working to counsel patients with Metabolic dysfunction associated liver dysfunction disease on smoking cessation and optimizing diabetes control. Based on our findings, we believe that smoking cessation, in addition to glycemic control with regular medication, may be beneficial in reducing the severity of MASLD among patients with type 2 diabetes mellitus.

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