CASE REPORT

hs-CRP A NOVEL PROGNOSTIC MARKER FOR NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) ASSOCIATED WITH STABLE TYPE 2 DIABETES MELLITUS

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ABSTRACT

Introduction: The term Non alcoholic fatty liver disease (NAFLD) is used to describe fatty liver changes from simple steatosis to steatohepatitis, cirrhosis and hepatocellular carcinoma in the absence of excessive alcohol intake.
High serum level of hs-CRP is an independent risk factor of short-term progression to NASH in NAFLD patients associated with stable Type 2 Diabetes Mellitus.
Aims & Objectives: To determine the levels of hs-CRP in patients of Non- alcoholic fatty liver disease with stable Type 2 Diabetes Mellitus and its correlation with age and sex matched healthy controls and different grades of NAFLD according to ultrasound findings.
Materials and Methods: The present study included 80 cases of ultrasonographically verified Non-alcoholic fatty liver disease patients with stable Type II Diabetes Mellitus aged between 30 to 60 years reported in Medicine IPD and OPD of Maharaja Yashwant Rao Hospital, Indore and 80 age and sex matched apparently healthy controls. **Exclusion criteria**: Patients with past history of autoimmune hepatitis, hepatic dysfunction, or cirrhosis, alcoholism, gestational DM, hepatotoxic drugs, pregnancy, smoking, known renal disease, medication with herbal medicine or supplements for body building and incomplete medical records were excluded from the study. 5 ml overnight fasting blood sample was collected from each subject and analyzed for FBS, serum cholesterol, serum triglycerides, hs-CRP and HbA1c in fully automated analyzer and their anthropometric measurements like head circumference, neck circumference, hip circumference, height, weight, BMI, waist to hip ratio were measured and recorded.
All data were analyzed using SPSS statistical software. Results were expressed as mean±standard deviation. Student t-test was used to compare between the groups and P value<0.05 was considered as significant and < 0.001 as highly significant.
Results and Observations: Results revealed that significant increase was observed in BMI, Neck circumference, Waist Hip Ratio, hs-CRP, fasting blood sugar, HbA1c, Total cholesterol and Triglycerides.
Conclusion: hsCRP may be used as prognostic marker for progression to hepatic complications like progressive changes in grades of fatty liver and NASH in patients of Nonalcoholic fatty liver disease with stable Type 2 Diabetes Mellitus.

INTRODUCTION

The term Non alcoholic fatty liver disease(NAFLD) is used to describe fatty liver changes from simple steatosis to steatohepatitis, cirrhosis and hepatocellular carcinoma in the absence of excessive alcohol intake *(Farrel GC)*[1]. Non-alcoholic fatty liver disease (NAFLD) is a distinct hepatic condition characterized by abnormal accumulation of fat in liver cells and resembling histologically with alcoholic induced liver damage.

At the present, global prevalence of NAFLD is estimated at about 9% in the developing countries and 30% in the developed countries. Indeed, NAFLD is the most common cause of chronic liver disease in the industrialised world. The overall prevalence of NAFLD in western countries varies from 15-40% and in Asian countries from 9-40% *(Farrel GC et al., Lazo M et al. & Bellentani S et al.)*[1, 2, 3].

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/ pre-diabetic patients *(Duseja A et al., Singh SP et al.& Agal S, et al.)*[4, 5, 6].

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 recognized. The prevalence of NAFLD

amongst T2DM patients is described to be higher than in non-diabetic patients. There is evidence that T2DM patients with NAFLD are at higher risk of developing cirrhosis compared to non-diabetic patients *(Angulo P &Younossi ZM et al.)*[7,8]. It is seen that cardiovascular events have always been considered to be the major causes for excess mortality among the patients with NIDDM, the threat of hepatic failure and encephalopathy should not be underestimated. High serum level of hs-CRP is an independent risk factor of short-term progression to NASH in patients of Nonalcoholic fatty liver disease with Type 2 Diabetes Mellitus. Those NAFLD patients with Type 2 Diabetes Mellitus that present with high serum level of hs-CRP should be subjected to regular monitoring, lifestyle intervention and medication.

MATERIALS AND METHODS

The present study was conducted in the Departments of Biochemistry and Medicine of the Mahatma Gandhi Memorial Medical College, Indore, Madhya Pradesh, after it was approved and permitted by the institutional scientific and ethical committee. The period of study was from May 2016 to April 2017. The present study included 80 cases of ultrasonographically verified Non-alcoholic fatty liver disease patients with stable Type II Diabetes Mellitus aged between 30 to 60 years reported in Medicine IPD and OPD of Maharaja Yashwant Rao Hospital, Indore and 80 age and sex matched apparently healthy controls. Informed written consent was taken from all the subjects.

Exclusion criteria: Patients with past history of autoimmune hepatitis, hepatic dysfunction, or cirrhosis, alcoholism, gestational DM, hepatotoxic drugs, pregnancy, smoking, known renal disease, medication with herbal medicine or supplements for body building and incomplete medical records were excluded from the study. 5 ml overnight fasting blood sample was collected from each subject and analyzed for FBS, serum cholesterol, serum triglycerides, hs-CRP and HbA1c in fully automated analyzer and their anthropometric measurements like head circumference, neck circumference, hip circumference, height, weight, BMI, waist to hip ratio were measured and recorded.

All data were analyzed using SPSS statistical software. Results were expressed as mean±standard deviation. Student t-test was used to compare between the groups and P value<0.05 was considered as significant and < 0.001 as highly significant.

OBSERVATION AND RESULTS

Table 1 Baseline Data of NAFLD patients with Stable Type 2 Diabetes Mellitus

Parameter	Cases(Mean±SD)(n=80)	Controls(Mean±SD)(n=80)	p-value
Age	50.40±7.96	49.61±8.04	>0.534
BMI	28.78±4.59	22.16±1.11	<0.001
Neck Circumference	35.92±3.66	31.54±1.50	< 0.001
Waist Hip Ratio	0.940	0.790	<0.001
Fasting Blood Sugar	151.5±22.5	90.19±4.80	< 0.001
HbA1C	6.69±0.129	5.10±0.345	< 0.05
Cholesterol	183.5±27.2	147.2±16.1	< 0.001
Ttiglycerides	192.4±67.5	112.5±13.6	< 0.001

Table 2 Comparison of Serum hs-Crp Levels between Case And Control

| Group	Mean±S.D	P value
Case(n=80)	5.91±4.16	<0.001
Control(n=80)	1.80±1.29	

Table 2 shows significant increase in hs-CRP in cases as compared to controls
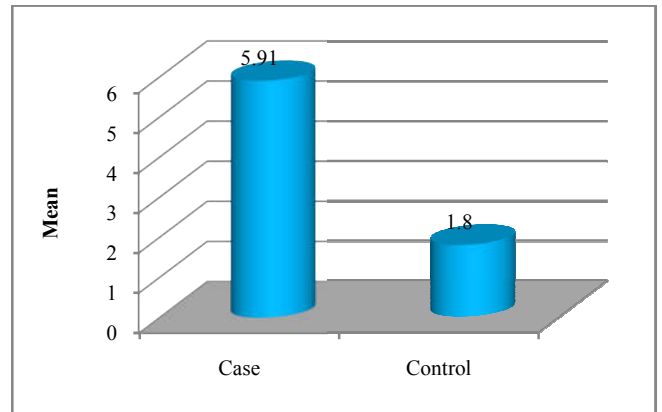
Fig 1 Comparison of serum hs-crp levels between case and control

Table 3 Intragroup Comparison of Serum hs-Crp Levels With Different Grades of Fatty Liver

Grade of NAFLD	hs-CRP (mg/L) (Mean±SD)	P-value
Grade I	3.3494±2.1283	<0.001
Grade II	9.4405±1.6307	
Grade I	3.3494±2.1283	<0.001
Grade III	13.6950±1.0228	
Grade II	9.4405±1.6307	<0.05
Grade III	13.6950±1.0228	
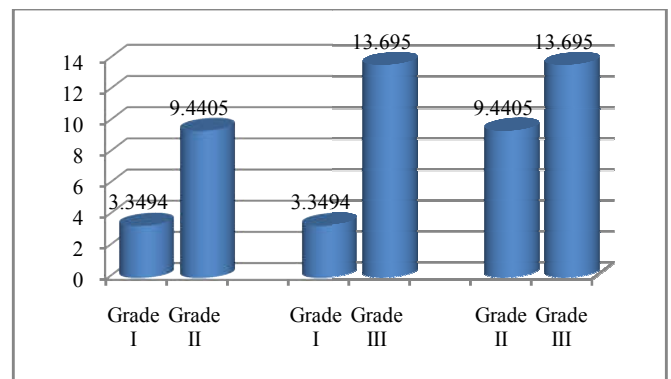
Fig 2 shows significant rise in hs-CRP levels with increase in grades of fatty liver

DISCUSSION

NAFLD is a pathological condition associated with obesity, Type 2 Diabetes Mellitus and metabolic syndrome.

The correlation between diabetes mellitus and NAFLD is robust as shown by a study in Japanese adults where it was found that 27% with normal fasting glucose, 43% with impaired fasting glucose and 62% with newly diagnosed diabetes had NAFLD. Hence, NAFLD rises in proportion to blood glucose level. Our study shows that Type 2 Diabetes Mellitus significantly increases the severity of NAFLD compared to non-diabetics confirming that diabetes is a major risk factor for NAFLD in our population. Bruce *et al.,* (2003)[9] have revealed that a low-grade inflammation precedes and predicts the onset of diabetes in adults.

Our study shows a significantly higher hsCRP value in patients of NAFLD with Type 2 Diabetes Mellitus as compared to normal healthy controls and hence hsCRP may indicate that NAFLD with Type 2 Diabetes Mellitus are at a greater risk of NASH or have already developed it.

Obesity in particular central obesity has been described as one of the strongest risk factors for NAFLD and fibrosis. In our study, 60% of the total cases were found to have BMI > 30 Kg/m2.

As per the study done by Hingorio *et al*.[10]and Roli Agrawal *et al*.[11] the maximum no of the patients are obese, have neck circumference and waist hip ratio above their cut off value both in male and female.

Studies done by Villanova *et al*.[12], Ling S *et al*.[13], and Agarwal *et al*.[14] also showed higher values of waist circumference and BMI in NAFLD group than in non NAFLD group.

In our study too we found that 48 patients ie 60% are obese and maximum number of the patients ie 96.96% males and 80.85% females have their waist hip ratio above the cut off value and 69.69% male and 74.46% female have neck circumference more than the cut off value. Dyslipidaemias are associated with NAFLD. In present study higher values of total cholesterol and TG were associated with NAFLD (p=0.000 and 0.000 respectively). In study done by Hamaguchi M *et al*.[15], and Agarwal *et al*.[16] similar results were found.

This is the case-control study in which comprehensive analysis of hs-CRP, anthropometric and metabolic co-variates has been researched among Asian Indians in central India. In this study, the NAFLD in T2DM was associated with increased hs-CRP level. *Priyanka Nigam et.al* [17] stated that presence of NAFLD showed independent relationships with subsequent inflammation. This study showed higher hs-CRP levels as compared to those without NAFLD.

Yeniova AO et.al.[18] stated that hs-CRP can be used as a non-invasive marker of NAFLD as it was found to be a strong predictor of NAFLD in this study. In our study, mean hsCRP levels were found to be higher in patients of NAFLD with T2DM.

In our study, out of 80 patients of NAFLD with T2DM, 43 patients had higher hs-CRP level i.e, 53.75% patients had elevated hs-CRP level and remaining 37 patients i.e, 46.25% were having normal hs-CRP level. Our study shows significant increase in hs-CRP levels with increase in grades of fatty liver in NAFLD patients with stable Type 2 Diabetes Mellitus and hence hs-CRP may be used as prognostic marker for progression to hepatic complications like progressive changes in grades of fatty liver and NASH in patients of NAFLD with Type 2 Diabetes Mellitus.

CONCLUSION

hsCRP may be used as a prognostic marker for progression to hepatic complications like progressive changes in grades of fatty liver and NASH in patients of Nonalcoholic fatty liver disease with stable Type 2 Diabetes Mellitus. For the perspective of long-term prognosis, the serum level of CRP is also a potential predictive factor of cirrhosis, hepatic failure and malignant tumors.

Those NIDDM patients with NAFLD that present with high serum level of hs-CRP and should be subjected to regular monitoring, lifestyle modification and medication.

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