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RESEARCH ARTICLE
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THE ASSOCIATION OF SERUM URIC ACID WITH NON-ALCOHOLIC FATTY LIVER DISEASE – A CASE CONTROL STUDY IN A TERTIARY HOSPITAL IN NORTH KARNATAKA

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ABSTRACT

BACKGROUND AND OBJECTIVES:

Need for the study:
Non alcoholic fatty liver disease is one of the most prevalent causes of liver cirrhosis in the world. [1]
Cell line studies show - Higher uric acid induces hepatocyte fat accumulation. [2]
Uric acid induces hepatic steatosis by generation of mitochondrial oxidative stress. [3]. This prompts the need for further research.

METHODS:

Source of data: The data is sourced from the patients visiting the department of General medicine in HSK Hospital, SNMC, Bagalkot.
Inclusion criteria:
Adults - aged more than 18 and less than 60 years.
Cases – ultrasonological features of fatty liver.
Controls – Age and gender matched individuals with no ultrasonological liver abnormality.
Exclusion criteria:
1. History of alcohol consumption.
2. Hepatitis B or Hepatitis C reactive patients.
3. Those suffering from viral hepatitis.
4. History of cancer.
5. Those on medications that lead to hyperuricemia.

RESULTS:

1. The mean uric acid levels were 6.4 ± 2.3 in cases compared to 3.9 ± 1.6 in the controls. The difference in between these levels (overall) is statistically significant with a p values of <0.001.
2. The mean uric acid levels among those with normal echogenecity was 3.87 ± 1.63, vs. those with grade 1 fatty liver changes who had levels of 5.96 ± 2.05 and those with grade 2 having values of 8 ± 2.53.

INTERPRETATION:
As per the analysis a higher mean value of Serum uric acid is associated with an increasing grade of fatty liver.
The findings of the study have both diagnostic and therapeutic applicability.

CONCLUSION:
The study performed shows a statistically significant association between the levels of serum uric acid and the presence of non alcoholic fatty liver disease (NAFLD), with elevated levels correlating with the presence of the condition and higher serum levels corresponding with increased grades of NAFLD.

KEYWORDS: NAFLD; Uric acid; Fatty liver; Liver Steatosis.

INTRODUCTION

NAFLD – Non alcoholic fatty liver disease is a metabolic abnormality which mainly involves the hepatic cells with fatty infiltration.
It is mostly associated with metabolic stress related abnormalities. The disorder is seen in the absence of other chronic conditions of liver [4].
This is a condition which is seeing an increased incidence in our modern society due to a combination of dietary factors, lifestyle changes, and is of concern [5, 6]
The disease includes different hepatic disorders, ranging from simple fatty liver disease to non-alcoholic steatohepatitis.
Fatty infiltration is a benign, nonprogressive condition, while steatohepatitis is a complicated condition which is converted to some other chronic conditions like hepatocellular carcinoma, portal hypertension, and may be to hepatic cirrhosis [7]

The presence of NAFLD shows that the person is at risk of progressing to non alcoholic steato-hepatitis (NASH) and is considered to be one of the liver manifestations of metabolic syndromes [8] as it often shows relationship with glucose intolerance, obesity, hypertension and dyslipidaemia.

These are considered to be a group of disorders recognized as metabolic syndrome [8, 9]

The incidence of NAFLD would thus go in tandem with the incidence of metabolic syndrome and both are going along an increasing trend due to lifestyle associated disorders.

Uric acid is a heterocyclic compound of nitrogen, hydrogen, oxygen, and carbon with the formula $C_5H_4N_4O_3$. It is produced in human beings when purine is converted from its nucleosides to uric acid from adenosine and guanosine. It is thus an end product of the metabolism of purine. [10]

Hyperuricemia or increased serum uric acid level causes gout; it is also associated with impaired renal function, hypertension, hypertriglyceridemia and obesity [10], alongside Diabetes Mellitus [11].

As the incidence of NAFLD keeps rising it is imperative that the biochemical profiles in the condition be effectively mapped out to ensure that the condition and its concurrent parameters are identified and appropriately addressed.

During last ten years, relationship between metabolic syndrome and elevated serum uric acid levels has been determined. [12-15]

If a clear link can be pursued between the causative factors and the presence of NAFLD – some form of preventive strategies can be attempted to reduce the incidence of the condition, its early identification and management and the overall prognosis of the condition.

With this, there exists an opportunity and a potential blind spot to identify the role of uric acid and its association with NAFLD and potentially catch the disease in its tracks through a specific targeted therapy to identify and establish its role and allow for potential preventive strategies for the condition.

METHODOLOGY

Study design:
Hospital based case control study

Study area:
The study was conducted in the city of Bagalkot a town situated in the northern part of the state of Karnataka with patients from the district that is named after it and also from the surrounding districts of Bijapur, Koppal, Gadag, and Belgaum.

Study population:
Patients who presented to the Emergency wing or Outpatient department of the hospital – S.N.M.C in Bagalkot either for routine evaluation or for specific abdominal complaints who fit in the inclusion criteria.

Study time:
Research was conducted over a period of 18 months from December 2022 to June of 2024.

Source of the data:
Primary data source:
Patients who presented to the emergency wing and the outpatient department of medicine in S.N.M.C in Bagalkot who fit into the inclusion criteria were included in the study.

Secondary source of data:
To estimate sample size, and the methodology of carrying out the study from multiple journals, academic books, research articles, review articles, newspapers and references from the internet to accredited sources.

Inclusion Criteria:
1. Controls - Age and gender matched healthy individuals with no ultrasonological liver abnormality.
2. Cases – those who have ultrasonological features of fatty liver with NO history of alcohol consumption

Exclusion Criteria:
1.H/O alcohol consumption
2. Viral hepatitis
3. People with H/O Cancers
4. Those on medications that lead to hyperuricemia
5. Age less than 18 years
6. Those on hepatotoxic medications

Sample size:
Sample size estimation was done using open epi software version 2.3.1.
At 95% confidence level, and 80% power of the study - α (two-tailed) = 0.050 and at 95% confidence level.β= 0.200and 80% of power of the study the standard normal deviate for α=Zα=1.960 the standard normal deviate for β=Zβ=0.842

According to the study conducted by Sarwat Abbasi etal Proportion of Study subjects with Raised Uric Acid in NAFLD group = 60%(p1)
Proportion of Study subjects with Raised Uric Acid in Control = 40%(p2); Sample size estimated is 28=30 in each group.i.e 30 In NAFLD and 30 Control group.
Formula used:
n = (Zα/2+Zβ)2 *(p1(1-p1)+p2(1-p2))/(p1-p2)2

Method of data collection:
After obtaining approval and clearance from the institutional ethics committee the individuals fulfilling the inclusion criteria were enrolled for the study after obtaining informed consent.
To collect the required information from the study subjects the "Direct interview method" of Primary source of information technique was used.

The patients were interviewed for collection of necessary information using the pre-tested, semi structured questionnaire method. The questionnaire was prepared by a thorough review of literature.

In order to obtain co-operation of the patient, patient was made comfortable and a positive reinforcement was exerted. No answers were influenced and patient was helped during difficulty.

On admission a detailed history, general and per abdomen specific clinical examination and laboratory investigation like ultrasonography of the abdomen was performed, where a probe was placed over the abdomen and findings will be noted using a Phillips EPIQ 5G ultrasonography machine.

The estimation of the serum uric acid levels in blood was also done where around 2cc of the patient's blood was collected in a plain medical tube for the same and its analysis was done in the Biosystem machine – BA – 400, using the uricase method.

Ethical Consideration
Ethical clearance was taken from Ethical Committee of S. Nijalingappa Medical College and Hanagal Shree Kumareshwar Hospital & ResearchCentre, Bagalkot before conducting the study.

There are four universal ethical principles in biomedical research described in the landmark book-*Principles of biomedical ethics* by Beauchamp and Childress.
a) Respect for autonomy
b) Beneficence
c) Non-malfeasance
d) Justice

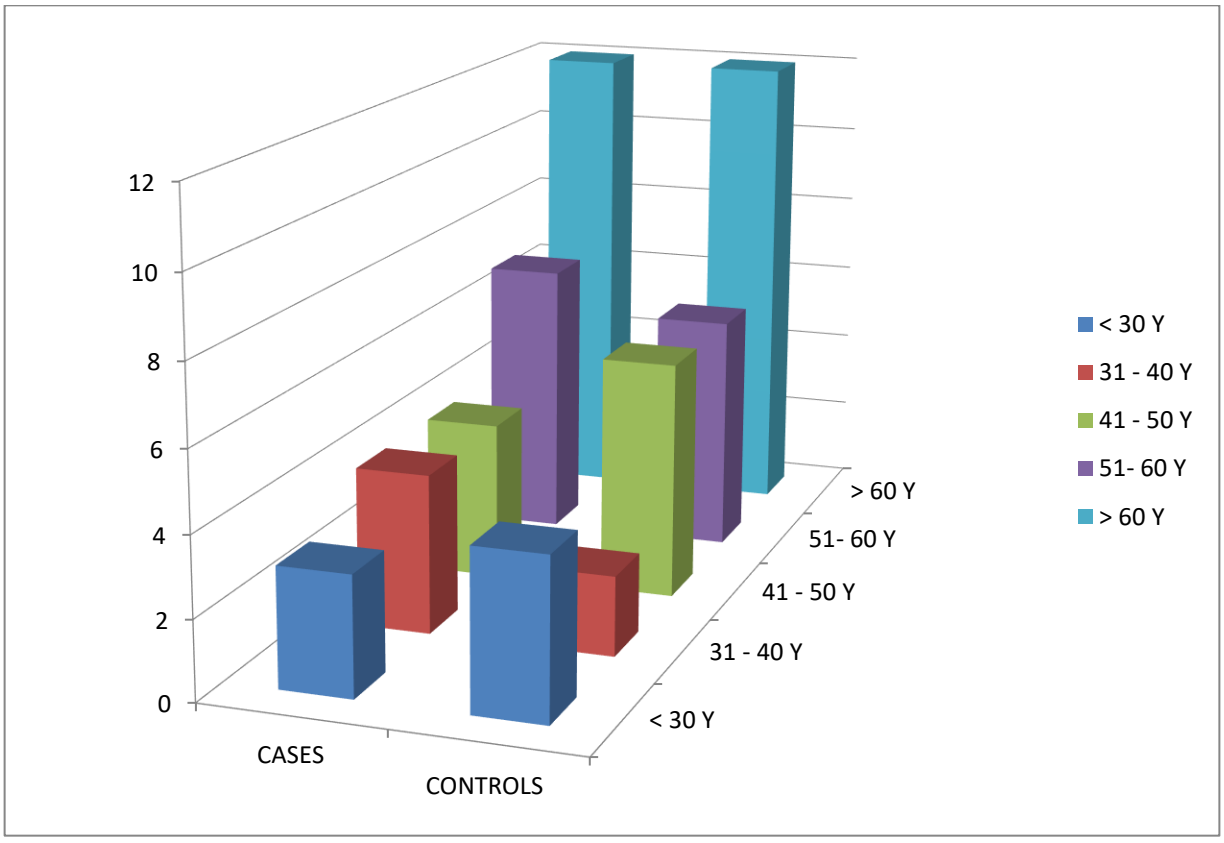
Statistical analysis:
Statistical analysis is done using SPSS software 19.0
Data obtained was tabulated in an excel sheet and analysed.
Quantitative data is expressed as mean ± standard deviation and non parametric data is expressed as median and min max values.
Percentages are used to represent qualitative data.

Chi square test for proportions in qualitative data.
Students unpaired t test for quantitative data.
Other appropriate statistical tests were applied.
P < 0.05 is considered as statistically significant.

RESULTS

Table 1: Comparison of age among cases and controls

Age	Cases	Controls	P value
Mean ± SD	56.23 ± 17.2	55.2±18.3	0.822
<30 years	3 (10%)	4 (13.3%)	0.893
31 to 40 years	4 (13.3%)	2 (6.7%)	0.893
41 to 50 years	4 (13.3%)	6 (20%)	0.893
51 to 60 years	7 (23.3%)	6 (20%)	0.893
>60 years	12 (40%)	12 (40%)	0.893
Total	**30 (100%)**	**30 (100%)**	-



The participants of the study were those who were admitted in S.N.M.C during the study period and the collected samples and participant data reveals that most of the participants (cases and controls) were of a higher age group (>60y).

Nearly 40% of constituent data is from those who are of a higher age group.

There is a progressive decline in the contribution by the other age groups as the age group categories also decline.
The mean age of cases is 56.2 ± 17.2 years and that of the controls id 55.2 ± 18.3 years. As the cases and controls are age and gender matched the presence of a similar span in terms of participants is seen among the 2 groups.

Table 2: Comparison of gender among cases and controls

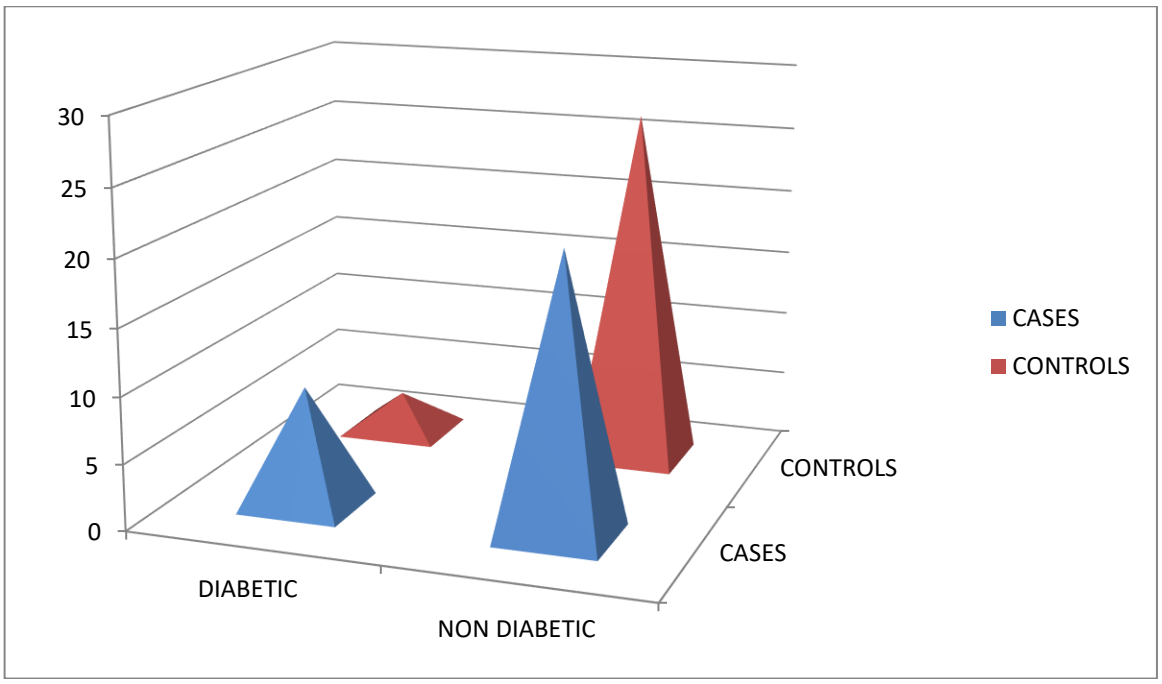
Gender	Cases	Controls	P value
Males	18 (60%)	19 (63.3%)	0.791
Females	12 (40%)	11 (36.7%)	0.791
Total	**30 (100%)**	**30 (100%)**	-

Most of the cases and concurrent controls are of the male gender. Male participants are higher than their female counterparts with a proportion of 60% being contributed by them.

There is no significant difference between the number of participants in terms of gender (male vs. female) in cases vs. controls.

Table 3: Comparison of diabetes among cases and controls

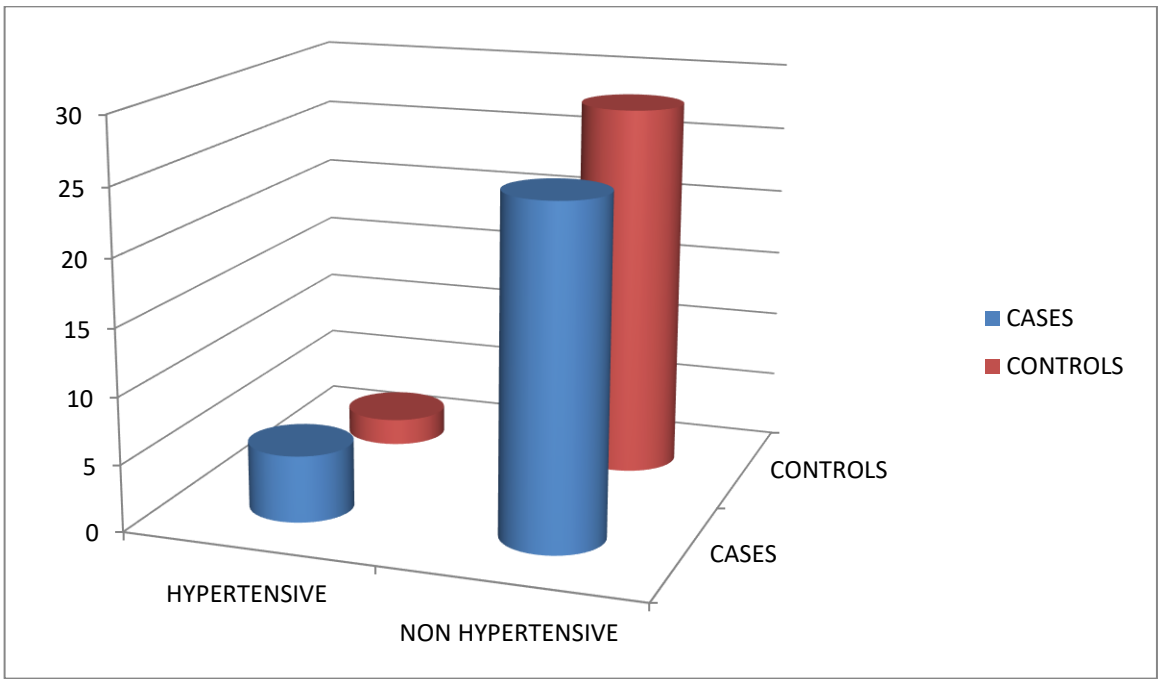
Diabetes	Cases	Controls	P value
Present	9 (30%)	3 (10%)	0.053
Absent	21 (70%)	27 (90%)	0.053
Total	**30 (100%)**	**30 (100%)**	-



The study participants were also evaluated as per the proforma for the presence of diabetes mellitus and the rates were noted down. 30% of the participant cases had diabetes compared to just 10% of the controls.
Although the difference was obvious the statistical significance was not seen with the p value being 0.053.
Most of the cases and controls however (70% and 90% respectively) were not diabetic.

Table 4: Comparison of hypertension among cases and controls

Hypertension	Cases	Controls	P value
Present	5 (16.7%)	2 (6.7%)	0.228
Absent	25 (83.3%)	28 (93.3%)	0.228
Total	**30 (100%)**	**30 (100%)**	-

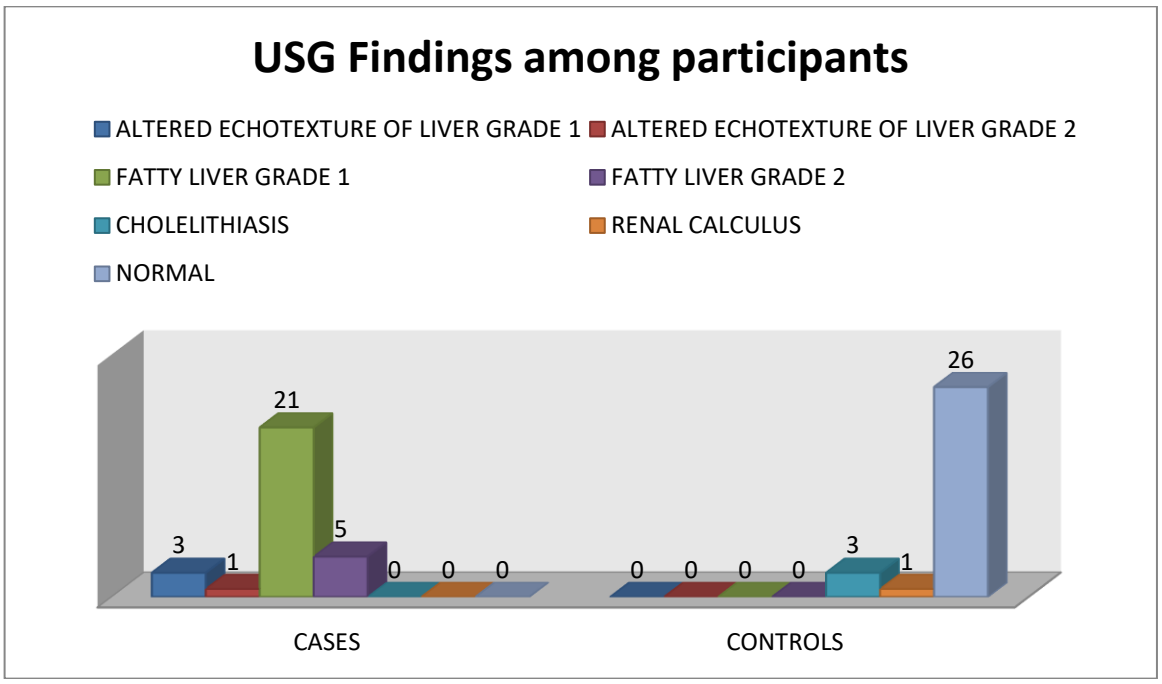


As per the proforma, the presence of hypertension among the participants was also evaluated. Hypertension was present in 16.7% of the study cases vs. 6.7% of controls.
Most of the participants (cases and controls) were not hypertensive.

Although the proportion (and concurrent number) of cases were higher in terms of the presence of hypertension the number is not statistically Significant.

Table 5: Comparison of ultrasound findings among cases and controls

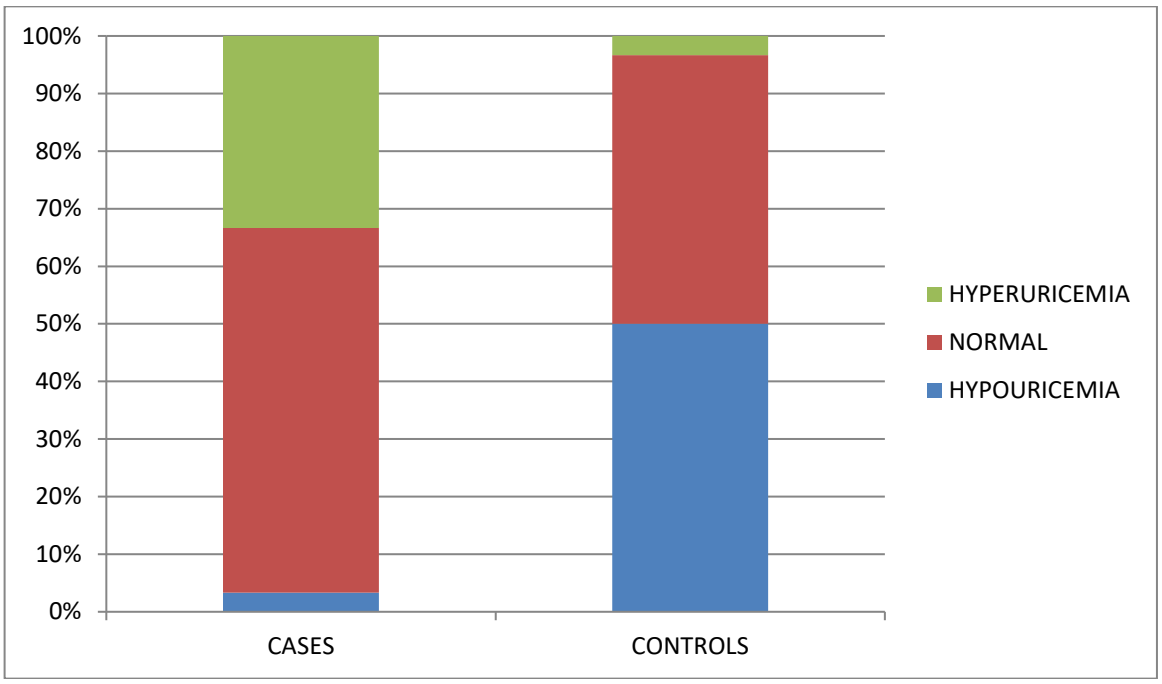
Ultrasound findings	**Cases**	**Controls**	**P value**
Altered echotexture of liver grade 1	3 (10%)	0	**<0.001**
Altered echotexture of liver grade 2	1 (3.3%)	0	**<0.001**
Fatty liver grade 1	21 (70%)	0	**<0.001**
Fatty liver grade 2	5 (16.7%)	0	**<0.001**
Cholelithiasis	0	3 (10%)	**<0.001**
Renal calculus	0	1 (3.3%)	**<0.001**
Normal	0	26 (86.7%)	**<0.001**
Total	**30 (100%)**	**30 (100%)**	-



Ultrasonography was done to evaluate the status of the liver, to look for fatty liver changes.
As per the criteria, none of the cases had normal ultrasonographical findings with some liver pathology being present.
10% of cases had altered echotexture of liver with grade I classification, 3.3% had altered echotexture of the liver with grade II classification, 70% had fatty liver grade 1 and 16.7% had fatty liver grade 2.
The controls were those with normal ultrasonographical liver picture. Normal ultrasonography with no liver or any other ultrasonographically identifiable pathology was present in 86% of the controls.
Among the study controls 10% of the participants had cholelithiasis and 3.3% had renal calculi as the finding in their ultrasonographical evaluation, with no observable pathology of the liver parenchyma.

Table 6: Comparison of uric acid among cases and controls

Uric acid	**Cases**	**Controls**	**P value**
Mean ± SD	6.4±2.3	3.9±1.6	**<0.001**
Hypouricemia Males <3.5mg/dl Females <2.6mg/dl	1 (3.3%)	15 (50%)	**<0.001**
Normal Males 3.5-7.2mg/dl, Females 2.6-6 mg/dl	19 (63.3%)	14 (46.7%)	**<0.001**
Hyperuricemia Males >7.2mg/dl Females >6 mg/dl	10 (33.3%)	1 (3.3%)	**<0.001**
Total	**30 (100%)**	**30 (100%)**	-



Uric acid levels were evaluated among the cases and the controls. In the laboratory which was used to evaluate the study subjects, the cutoff values for normal uric acid levels are 3.5 – 7.2 mg/dl in males and 2.6 to 6 mg/dl in females.

The presence of uric acid levels higher than those cutoffs for the specific genders were counted as hyperuricemia (that is > 6 in females and >7.2 in males) while values below the range was taken as hypo uricemia (<2.6 females and <3.5 in males).

The study shows that the mean uric acid levels were 6.4 ± 2.3 in case of study cases compared to 3.9 ± 1.6 in the study controls. The difference in between these levels (overall) is statistically significant with a p values of <0.001.

50% of the controls were hypouricemic compared with just 3.3% of cases. The proportion of cases with hypouricaemia is much higher in controls than the cases.
The difference between the two is also statistically significant with a p value of <0.001.

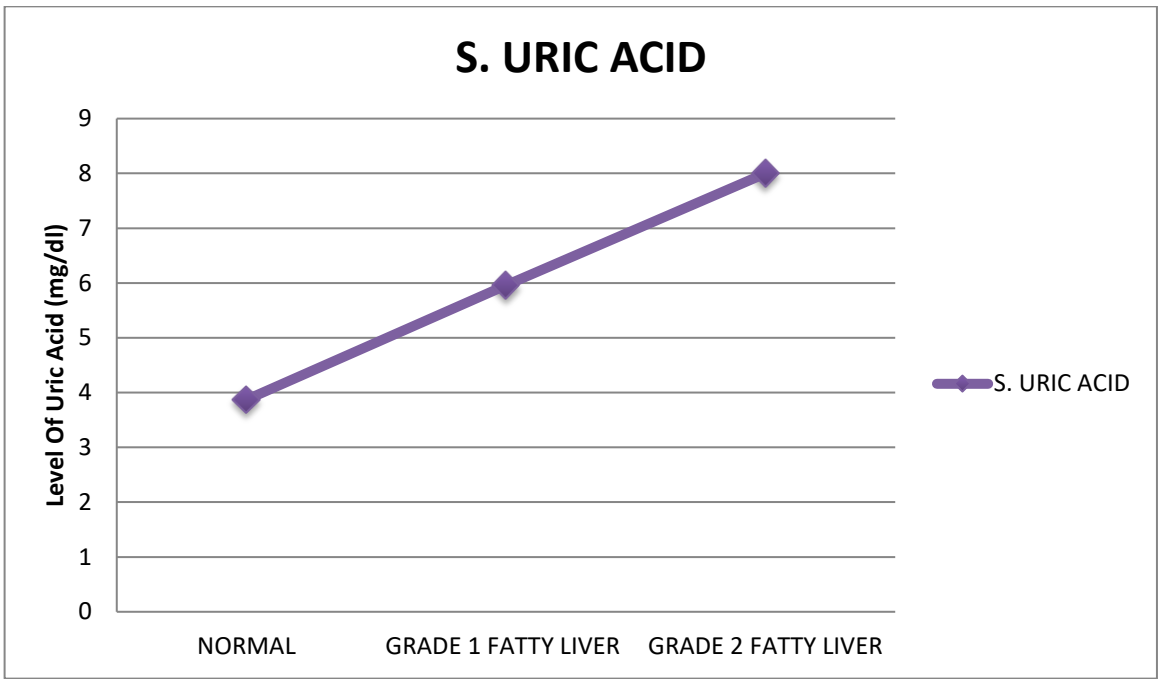
More than half of the cases had uric acid levels in the normal range with 63.3% of the cases having normal uric acid levels. 46.7% of the controls also had uric acid levels within the normal range.

33.3% of the cases had hyperuricemia which is 10 times higher than the controls where only 3.3 % of the study participants had hyperuricemia. The difference between them is statistically significant with a p value of <0.001.

Table 7: Comparison of serum uric acid among fatty liver grades

Fatty liver grades	**S.Uric acid (Mean ± SD)**	**P value**
Normal	3.87±1.63	**<0.001**
Grade 1	5.96±2.05	**<0.001**
Grade 2	8±2.53	**<0.001**

Correlation co-efficient(r) =0.596, P value<0.001



Further analysis was also done to correlate the grades of fatty liver with the levels of serum uric acid.

Among the participants who had a normal liver echogenecity the mean serum uric acid levels was 3.87 ± 1.63, vs. those with grade 1 fatty liver changes who had levels of 5.96 ± 2.05 and those with grade 2 having values of 8 ± 2.53.

There is present as per the analysis a higher mean value of Serum uric acid with an increasing grade of fatty liver

The difference between the same is also statistically significant with a p value of <0.001.
The correlation co efficient between the two has a value of 0.596 as well.

DISCUSSION

The study conducted in S.N.M.C shows that among the participants who were enrolled, evaluated and analyzed, there exists a strong correlation between those who have non alcoholic fatty liver disease and elevated uric acid levels.

There exists a statistically significant difference in the uric acid levels of those with fatty liver compared to those without NAFLD changes, with the mean uric acid levels being 3.87 ± 1.63 in those with normal liver sonography vs. 5.96 ± 2.05 in those with grade I changes and 9 ± 2.53 among those with grade II changes.

This shows that there is indeed a significant correlation between the levels of serum uric acid and the presence of non alcoholic fatty liver disease.
Findings in the above mentioned studies also correlate well with other studies which have been performed over the years.

In a study conducted by sarwat abassi et al [16] the principle study on which the current one is based there exists a strong correlation between NAFLD and the levels of uric acid which showed that uric acid is a good marker for NAFLD.

In our study as well there is a statistically significant correlation between the presence of hyperuricemia and the presence of NAFLD.
The presence of uric acid levels in a lower normal or normal range is seen in a greater proportion of the controls in a statistically significant manner.
This goes on to substantiate similar findings as per studies done across the continent.
In a study conducted in China, sampling over 9000 participants a significant association was found between NAFLD and uric acid levels. Multiple regression analysis also showed that the higher the levels of uric acid the higher the chance of development of NAFLD as well. [15]

Our study also showed that there was also a significant (statistically) difference in the lower range of uric acid levels as well as only 3.3% of the cases had hypouricemia compared with nearly 50% in the control populace.

The probable etiologies for the same are the presence of increased insulin resistance in those with NAFLD.

Recent studies have showed that insulin resistance is not only associated with an increased amount of uric acid production [17], but, is also associated with a decrease in uric acid excretion [18, 19].

This effect of insulin resistance on Uric Acid metabolism may partly explain elevated Serum Uric Acid levels in NAFLD patients.
In our study as well – there is a 3 times higher chance of the patient being diabetic if the participant has NAFLD than those who aren't.

However, in our study it is determined to not be a statistically significant difference.

In tandem with the derangements of metabolic parameters and features of metabolic syndrome being associated with NAFLD, our study showed that study participants with NAFLD had nearly 2.5 times more hypertensives than the controls group.
However this difference is not a statistically significant one.

In addition to the role of insulin resistance, leptin and its role has also been focused on in recent studies [20, 21].

Due to the feature of leptin to induce oxidative stress it may be one of the mechanisms for explaining the elevation in serum uric acid levels [22].

Leptin is also involved in sodium tubular reabsorption, and, may explain the reason for an elevation in uric acid levels due to the same [23]

The association between Serum Uric Acid levels and NAFLD suggests that uric acid could play an important role in the development of NAFLD.

Uric acid has been postulated to act as a natural scavenger of peroxynitrite and peroxynitrite-derived radicals [24, 25].

Animal experiments and clinical studies have shown that there is increased systemic oxidative stress in patients with NAFLD. [26].

The potential of the presence of uric acid as a manifestation of the disease has to be given heed to as recent studies have shown that treatment with uric acid in obese ob/ ob mice resulted in the resolution of fatty liver [27].

Thus, elevated Serum Uric Acid levels may reflect a compensatory mechanism to counteract the increased oxidative stress associated with NAFLD.

On the flip side of the role played by the molecule, uric acid itself becomes a strong oxidant in the background environment of metabolic syndrome [28] causing further stress and cell damage precipitating progression of the disease.

These studies do not clarify how the potentially opposing roles of uric acid in the redox balance is regulated, but the urate redox shuttle may offer an explanation in the paradoxical effects of uric acid on oxidative stress [29], which may further explain why elevated Serum Uric Acid levels is a risk factor for NAFLD, not just in terms of an indicator but as an etiological agent as well.

Uric acid acts as a regent in the oxidative processes and the oxidative stresses which the liver undergoes is produced due to the synthesis of uric acid and reactive oxygen species.
This is catalyzed by xanthine oxidoreductase. This may be one of the primary reasons why high serum uric acid levels act as a risk factor for NAFLD [30, 31].

Metabolic, renal and genetic variations can affect uric acid concentration through its role on the synthesis, excretion and reabsorption of the compound.

Decreasing the concentration of Serum Uric Acid may have beneficial effects to reduce the incidence and prevalence of NAFLD which suggests that serum uric acid is a cause or effect of the disease [32]
Studies done have also shown that higher levels of uric acid are also seen in those with high concentrations of plasma triglycerides [32], further reinforcing the metabolic derangement in those with NAFLD being associated with Uric acid.

There are some elucidations for such relation, and one of them is that during the synthesis of triglycerides there would be an increase in demand for NADPH [32].

Fatty acid synthesis in the liver is also associated with the de novo synthesis of purine which in turn leads to an increase in the production of Uric acid [33].

Chen et al. [34] observed that there is a negative correlation present between the levels of High density lipoprotein – c and uric acid levels.

The likely etiology is the inverse relationship between High density lipoprotein c and insulin sensitivity [35].

Certain studies also revealed that cells which are injured/ undergoing injury also release uric acid which in turn then induces sterile inflammation. [36]

The study conducted by Petta et al also shows that the severity of steatosis was independently associated not only with lobular inflammation, but also with hyperuricemia, furthermore, Lobular inflammation was independently associated with both older age and UA levels. [36]

The study also showed a relation between higher serum uric acid levels and lower adiponectin levels suggesting a possible interference in the expression of adiponectin potentially showing one of the ways in which uric acid is involved in the pathogenesis of NAFLD.

More specifically, a recent mouse model revealed that hyperuricemia may play a role in the pro-inflammatory endocrine imbalance in adipose tissue (increased production of adiponectin and decreased levels of monocyte chemotactic protein-1), which underlies low-grade inflammation and insulin resistance in NAFLD patients. [37]

The proposed mechanisms in Non alcoholic steatohepatitis is the hepatic cell damage/death which is responsible for the release of molecules/ compounds which are not present under normal physiological conditions, into the extracellular environment [38]

Studies have also shown that the release of uric acid in response to tissue injury along with genetic susceptibility to inflammation is something that happens and is seen in NAFLD patients [39]

The same study also shows that there is a relationship wherein there is increased cell death which is associated with a higher level of uric acid. [39]

Depletion of uric acid stimulates a strong protective effect in terms of cell death and reduced inflammation [40].

This suggests that uric acid, at least in the context of NAFLD, may be one of the major triggers of inflammation.

It is conceivable that uric acid levels high enough to trigger endogenous inflammatory reactions would only arise from extensive cell death and would need to be linked to uric acid precipitation; in other words, an antioxidant becomes potent inflammatory stimulant only when it undergoes a phase transition [41].

Hyperinsulinemia which is associated with metabolic syndrome may also explain the high uric acid levels as there is a decrease in the excretion of uric acid [42].

Thus other features of the metabolic syndrome may also cause the disease [36]
Uric acid exerts pro-oxidant and pro-inflammatory effects in adipose tissues [37, 43] and vascular smooth muscle linings [44, 45] furthermore Protein kinase pathway and nuclear factor kB are activated due to intra-cellular pro-oxidant activity of uric acid leading to further damage.

LIMITATIONS:
There are certain limitations in our study, in that there is an inability to attribute elevated uric acid to a causative or consequential role in the development of NAFLD.

Certain factors like life style and diet were not measured during conducting this study which are also contributing factors to increased uric acid levels [46] and NAFLD [47].

The diagnosis of NAFLD was based on ultrasonographic examination, which is not sensitive enough to detect mild steatosis, meaning the patients who are in the initial stages are missed.

Patients on antihypertensive, anti diabetic and lipid-lowering medications, which may influence the natural characteristics of NAFLD, were NOT excluded from this study.

The sample size which was used was a relatively small one and due to the nature of the study it was a single centre study with geographical restriction in terms of participating population, which may have a confounding effect on the results.

Potential future implications from the study:
1. Use of uric acid as a biomarker to identify/ stage NAFLD.
2. Potential therapeutic benefit of uricosuric drugs in reducing the progression of NAFLD or preventing it setting in through the control of the levels of uric acid.
3. Studies of this nature are relatively scarce in India with most of the literature pertaining to the same being from abroad.

4. The prevalence of metabolic syndrome is around 24% in India [48], so the potential future implications of the same and the possibility of increased number of those affected in the future must kept in mind to be addressed.

CONCLUSION

In conclusion the study performed shows a statistically significant association between the levels of serum uric acid and the presence of non alcoholic fatty liver disease (NAFLD), with higher levels correlating with the presence of the condition compared to a reference population.

Furthermore, there is also a statistically significant association between the levels of serum uric acid and the grade of NAFLD, with higher levels of serum uric acid correlating with a higher grade of NAFLD.

A higher proportion of individuals with diabetes mellitus and hypertension have NAFLD compared to a reference population without NAFLD, however in the present study that association is not statistically significant.

The estimation of uric acid in those who have been diagnosed as NAFLD or are suspected to have the disease has a prognostic indication and there also exists the avenue of a potentially therapeutic application of the same, offering a cheap and simple tool for analysis and management.

Contribution: concepts, design, definition of intellectual concept, literature research, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis. Manuscript preparation, manuscript editing and review

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