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A Case Control Study on Assessment of Serum Gamma-Glutamyl Transferase Levels in Patients with Non-Alcoholic Fatty Liver Disease in Salem, Tamilnadu

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ABSTRACT

Background

The growing incidence of nonalcoholic fatty liver disease (NAFLD), characterized by hepatic lipid deposition, can be attributed to alterations in lifestyle and the prominence of metabolic syndrome. The aim of this study was to determine the association between serum gamma-glutamyl transferase (GGT) levels and the occurrence of NAFLD.

Materials and Methods

The case-control study was conducted in the General Medicine Department of a teaching medical college in Salem, Tamilnadu over the course of one year, encompassing 100 patients aged between 20 and 70 years. A comprehensive study was undertaken, involving 50 NAFLD patients and 50 healthy controls with normal ultrasonographic results. The main areas of focus were the biochemical markers of liver disease and various demographic variables. The analysis of the data was carried out using IBM SPSS version 22.0 software, with tables being generated via Microsoft Excel.

Results

The results of Fisher's exact test showed that there were no statistically significant differences in the age (P value = 0.801) and gender distribution (P value = 0.424) of NAFLD patients and healthy controls. Several parameters exhibit significant differences when comparing the case group to the control group. Significant differences are observed in serum creatinine levels ($p = 0.002$), as well as in triglyceride levels, aspartate aminotransferase, alanine aminotransferase, GGT, low-density lipoprotein, and high-density lipoprotein (all with p values < 0.0001). According to the findings of the Kruskal-Wallis test, there were no statistically significant variations in GGT levels between the different grades of fatty liver (P value = 0.259).

Conclusion

The study findings show that parameters including AST, ALT, GGT, TG, LDL, and HDL might be significant in discerning between control and case groups of NAFLD patients. Serum GGT levels lack the ability to distinguish between the varying degrees of NAFLD severity.

Take-home message

The enzyme gamma-glutamyl transpeptidase (GGT) is found specifically in the plasma membranes of various cell types, primarily in hepatocytes. Circulating GGT is predominantly produced by the liver, with its synthesis being influenced by both genetic and environmental factors. Patients diagnosed with Non-alcoholic Fatty Liver Disease exhibited elevated serum levels of creatinine, triglycerides, aspartate aminotransferase, alanine aminotransferase, Gamma-Glutamyltransferase, low-density lipoprotein, and high-density lipoprotein. However, serum GGT levels

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cannot distinguish between the various degrees of NAFLD severity.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is diagnosed when imaging or histological examination reveals an accumulation of excess fat in the liver. In comparison, other liver diseases, such as alcoholic liver disease, can be adequately eliminated by carefully gathering medical history and conducting basic laboratory tests. The prevalence of metabolic syndrome has been significantly increased because of lifestyle modifications, consequently leading to a higher occurrence of NAFLD. [1,2] The presence of fatty liver alterations is a critical marker for NAFLD, a spectrum of liver disorders encompassing benign simple steatosis or nonalcoholic fatty liver (NAFL) as well as nonalcoholic steatohepatitis (NASH), which is characterized by hepatic inflammation and fibrosis. The progression of NASH can lead to the development of cirrhosis and hepatocellular carcinoma. [2,3]

Among the various cell types, including hepatocytes, bile duct cells, gallbladder cells, pancreatic cells, splenic cells, renal cells, cardiac cells, neural cells, and seminal vesicle cells, the enzyme gamma-glutamyl transpeptidase (GGT) is on the plasma membranes. Genetic and environmental factors play a role in the synthesis of GGT, which is primarily produced in the liver and circulates throughout the body. Previous investigations have established a connection between serum GGT levels and chronic illnesses such as NAFLD, cardiovascular diseases, diabetes, and metabolic syndrome. [4,5] Moreover, a study conducted on a large-scale national population cohort in Korea found GGT to be a novel biomarker for NAFLD among 7,459 patients. [6]

However, studies investigating GGT have primarily been carried out in different regions, with India being overlooked, and have solely focused on assessing serum GGT levels in NAFLD patients. The objective of this case-control study is to evaluate the variations in serum gamma-glutamyltransferase (GGT) levels between patients diagnosed with non-alcoholic fatty liver disease and a group of healthy controls.

MATERIALS AND METHODS

Study settings and duration

In a case-control study conducted at a teaching medical college in Salem, a sample of 100 patients was examined. The study was conducted over a one-year timeframe, specifically from October 2022 to September 2023. In the rural area of Salem, this tertiary care center possesses a capacity of 560 beds. The department of general medicine typically delivers round-the-clock service to a yearly average of more than one lakh outpatients, primarily catering to the populace of Salem and partially extending its reach to the adjacent districts of Erode and Namakkal.

Ethical consideration:

Approval for conducting this study was obtained through the ethical clearance process of the Institutional Ethics Committee on Human Subjects (Approval No. VMKVMC&H/IEC/22/96). Following the approval from the Institutional Ethics Committee, data was gathered from patients who met the inclusion criteria and study protocol, having provided their informed consent through a signed document.

Inclusion criteria for cases:

The study included patients of both sexes who had NAFLD, were between the ages of 20 and 70, and presented with nonspecific abdominal pain and fatigue. Inclusion criteria also required confirmation of NAFLD through ultrasonographic studies.

Selection of controls:

Patients with no known liver disorder or history of alcohol consumption, who attended the outpatient department of General Medicine and exhibited normal ultrasonographic results.

Exclusion criteria:

Individuals who exhibited clinical symptoms of jaundice, viral hepatitis, and those with a history of heavy alcohol consumption. Individuals with a documented medical background of renal, pancreatic, respiratory, cardiac, and neurological conditions, as well as jaundice. Patients who were prescribed medications including anti-epileptics, amiodarone, tamoxifen, synthetic oestrogens, heparin, calcium channel blockers, valproic acid, antiviral agents, and steroids. The study excluded patients who had undergone biliopancreatic surgeries and pregnant women by a comprehensive history, examination, and investigation.

Sample size calculation:

The sample size was determined using OpenEpi software, under the assumption that controls had a 30% exposure rate to fatty liver. With an odds ratio of 4, power of 80%, and a two-sided confidence interval of 95%, the minimum required sample size for each group was calculated to be 41.

Data collection procedure:

Demographic data, including age and gender, laboratory markers, and serum GGT level, were extracted from the patient records.

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Grading of fatty liver using ultrasound:
The assessment of fatty liver is typically accomplished through the utilization of ultrasound characteristics, such as liver brightness, contrast between the liver and kidney, ultrasound visualization of the intrahepatic vessels, liver parenchyma, and diaphragm. [7] The ultrasound findings for grading fatty liver are presented in table 1.

Grade	Findings
Grade 0	Echotexture of the liver is normal
Grade 1	Slight and diffuse increase of liver echogenicity with normal visualization of the diaphragm and of the portal vein wall
Grade 2	Moderate increase of liver echogenicity with slightly impaired appearance of the portal vein wall and the diaphragm
Grade 3	Marked increase of liver echogenicity with poor or no visualization of portal vein wall, diaphragm.

Biochemical analysis
The biochemical measurements were conducted using standard methods through the use of an automated analyzer. Quantification of Alanine Aminotransferase (ALT), Alkaline phosphatase (ALP), Aspartate aminotransferase (AST), and GGT levels were conducted using the Uv-kinetic method. The Diazo method was used to estimate the levels of Total Bilirubin (TB) and Direct Bilirubin (DB). The enzymatic semi-autoanalysis method was employed to calculate the levels of triglycerides (TG), Low Density Lipoprotein (LDL), and High Density Lipoprotein (HDL). Urease and Jaffey's method were employed to estimate the levels of serum urea and creatinine. The Random Blood Sugar (RBS) was estimated using the glucose oxidase-peroxidase coupled method, while the HIV and HBsAg status were determined using the Rapid card method. In case of a positive finding, the subsequent step involved performing the confirmatory ELISA test.

Data processing and analysis
The data analysis was carried out by employing IBM SPSS version 22.0 software (IBM-SPSS Science Inc., Chicago, IL), and tables were generated using Microsoft Excel. Descriptive statistics, such as mean and standard deviation, were used for continuous variables like GGT, ALT, and TG. Frequency and percentage were employed for age group and gender variables. Using the Fisher exact test, we investigated the relationship between the demographic profile and the occurrence of NAFLD. In order to assess the relationship between the percentile values of the blood parameters in the case and control groups, the Mann-Whitney U test was performed. The Kruskal-Wallis test was employed to assess the correlation between GGT levels and the grading of fatty liver in patients diagnosed with NAFLD.

RESULTS
The age distribution remained relatively consistent between the two groups, with the majority of patients falling within the age range of 41-60 years. In both the Control and case groups, females accounted for a larger proportion. The data presented in Table 2 shows that there are no statistically significant differences between the cases and controls in terms of age and gender, as determined by the Fisher exact test.

Table 2: Baseline demographic details of study participants

Variables		Group				P value
		Control (n= 50)		Case (n= 50)		
		Frequency	percent	Frequency	percent	
Age group	<30	3	6.0%	3	6.0%	0.801
	31-40	7	14.0%	4	8.0%	
	41-50	11	22.0%	11	22.0%	
	51-60	21	42.0%	20	40.0%	
	>61	8	16.0%	12	24.0%	
Gender	Female	23	46.0%	27	54.0%	0.424
	Male	27	54.0%	23	46.0%	

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The case and control groups display significant variations in multiple parameters. It is worth mentioning that there are significant variations in serum creatinine levels (p = 0.002) and levels of AST, ALT, GGT, TG, LDL, and HDL (all p< 0.0001). This shows that these parameters might be significant factors in distinguishing between the Control and case groups of NAFLD patients.

Conversely, parameters such as urea, RBS, TB, DB, and ALP do not show statistically significant differences between the two groups, as their p-values surpass the established significance threshold of 0.05 (Table 3).

Table 3: Association between blood parameters among the case and control groups by Mann Whitney U test

Parameters	Group						P value
	Control (n= 50)			Case (n= 50)			
	Median	25th Percentile	75th Percentile	Median	25th Percentile	75th Percentile	
Urea	27.00	22.00	31.00	26.00	19.00	32.00	0.299
Creatinine	0.90	0.80	1.00	0.80	0.70	1.00	0.002*
RBS	112.50	99.00	134.00	111.00	96.00	129.00	0.593
TB	0.80	0.70	0.90	0.80	0.60	0.90	0.509
DB	0.30	0.20	0.40	0.30	0.20	0.40	0.892
AST	29.00	25.00	35.00	57.00	49.00	63.00	<0.0001*
ALT	31.50	25.00	36.00	57.00	53.00	62.00	<0.0001*
ALP	88.00	72.00	102.00	83.00	78.00	90.00	0.182
GGT	20.50	17.00	26.00	78.50	67.00	86.00	<0.0001*
TG	122.50	110.00	136.00	276.50	253.00	298.00	<0.0001*
LDL	87.50	81.00	95.00	133.00	122.00	141.00	<0.0001*
HDL	44.50	41.00	47.00	49.00	45.00	55.00	<0.0001*

* Mann Whitney U test was used and p value of less than 0.05 was considered statistically significant

According to the results of the Kruskal-Wallis test, there were no significant variations in GGT levels across the different grades of fatty liver. Based on the p-value of 0.259, it can be concluded that there was no significant difference in GGT levels across the three grades of fatty liver, as shown in Table 4.

Table 4: Association between GGT levels and grading of fatty liver among NAFLD patients by Kruskal-Wallis test

NAFLD		Fatty Liver			P value
		Median	25th Percentile	75th Percentile	
GGT	**Grade 1**	86.00	67.00	91.00	0.259
	Grade 2	76.00	68.00	85.00	
	Grade 3	78.00	64.00	84.00	

*Kruskal-Wallis test was used and p value of less than 0.05 was considered statistically significant

DISCUSSION

Approximately 50 healthy controls and 50 NAFLD cases were included in the study, with their blood parameters and ultrasound findings being analyzed. The study results showed that there is no statistically significant relationship between urea, RBS, TB, DB, ALP, age, gender, and NAFLD disease. In examining NAFLD patients compared to healthy individuals, we have detected a notable variation in the following parameters. There were significant differences observed between the case and control groups in several indicators, such as serum GGT, ALT, and AST levels. In addition, a noteworthy distinction ($p < 0.001$) was observed in the elevated lipid profiles among these patients with NAFLD. Patients suffering from NAFLD have exhibited a noteworthy contrast in the elevated

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levels of blood triglycerides, LDL, and HDL. According to the results of our investigation, it was observed that NAFLD patients exhibited higher levels of inflammatory markers.

Upon careful examination of these NAFLD patients across different degrees of fatty liver disease, no significant differences were observed. Given the limited sample size in our study, it is imperative to conduct future research with a larger sample size in order to validate the results. Yang et al. conducted a study on the prediction of future stroke risk in Korea by examining the correlation between blood GGT levels and NAFLD. [6] According to a study conducted by Toshikuni N et al., focusing on the relationship between Fatty liver, GGT levels, and their role as risk factors for atherosclerosis, it was established that high GGT levels in patients can be employed as a significant indicator to assess the severity of NAFLD. [8]

The study conducted by Kinoshita K et al. revealed a multitude of important factors associated with the development of atherosclerotic plaque. [9] Among the factors considered were diminished levels of serum HDL cholesterol, a past and present smoking habit, and the simultaneous occurrence of fatty liver and heightened blood GGT levels. Through multivariate analysis, it was determined that the coexistence of fatty liver and a serum GGT level ≥50 U/L emerged as the singular significant risk factor associated with the development of carotid plaque. According to the same study, blood GGT levels have the potential to be employed as a biomarker for the evaluation of NAFLD. The study examined the intricate relationship between serum GGT levels and plaque formation. Patients exhibiting serum GGT levels exceeding 50 U/L show a heightened susceptibility to plaque development and exhibit elevated lipid profiles compared to those with serum GGT levels below 50 U/L. [9]

Our findings are consistent with several cross-sectional studies that have investigated the role of serum GGT in both NAFLD and atherosclerotic diseases. The significance of serum GGT in atherosclerotic and non-alcoholic fatty liver disorders was assessed in studies by Hamabe et al., Shen Z-W et al., and Zein CO et al. [10–12] The research conducted by Zein CO et al. suggests a possible association between blood GGT levels and the initiation of atherosclerotic diseases, chronic renal disorders, and chronic smoking. [12]

According to a study conducted by Tsai E et al., noninvasive techniques such as biomarkers, panel markers, and imaging might aid in the diagnostic assessment of patients with NAFLD. It should be noted that an accurate histopathological diagnosis requires a liver biopsy. Accurate diagnosis and management of NAFLD require the assessment of steatohepatitis and liver fibrosis, with liver biopsy being regarded as the gold standard diagnostic approach, as stated by Tsai et al. [13]

In a study conducted by Saxena T et al., it was observed that SGPT levels were significantly higher in the cases compared to the control group. GGT levels were significantly lower ($p < 0.001$) in the cases compared to the control group in a study on Biomarkers in NAFLD by Saxena T et al. [14]

In another study conducted by Oni ET et al., it was discovered that after adjusting for multiple variables, there was a significant association between current smoking and a 4.65 IU/L increase in GGT levels compared to non-smokers. When divided into groups based on NAFLD, the intensity of this relationship was amplified in individuals with NAFLD. The study investigating the impact of NAFLD on serum GGT levels in cigarette smokers showed a statistically significant correlation between the interaction of NAFLD and smoking, and GGT levels serving as indicators of oxidative stress. [15]

High-performance gel filtration liquid chromatography has the potential to be useful in differentiating between ALD and NAFLD, as observed in a study on GGT fractionalization in NAFLD conducted by Sueyoshi S et al. [16]

The research conducted by Fujji et al. revealed a higher prevalence of fatty liver change in the Abnormal-GGT group compared to the Normal-GGT group. The risk of fatty liver is heightened by consecutive elevated GGT levels, and this risk is further amplified by high TG levels in those individuals, acting independently. [17]

A recent study conducted in China in 2021 examined the relationship between Elevated GGT and NAFLD. Multivariable Cox regression models were employed to determine the hazard ratio for GGT in relation to incident NAFLD, while controlling for demographic and clinical variables. The occurrence of NAFLD in the highest quartile of GGT levels was 3.653 times greater compared to the lowest quartile. [18]

Our study's findings were consistent with a corresponding research conducted in India, examining the predictive value of GGT for high-risk cardiovascular disease among NAFLD patients. The study revealed a positive correlation between GGT, uric acid, ferritin levels, and Framingham cardiovascular score. When considering multivariate analysis, it was determined that high GGT levels exhibited a positive correlation with the presence of high-risk disease, regardless of age and gender. [19]

According to the study conducted by Cho et al., it was observed that elevated serum GGT levels were linked to increased mortality risk, independent of smoking, alcohol consumption, and history of previous CVD and cancer. The measurement of Serum GGT levels could serve as a valuable tool in assessing the risk of both all-cause and disease-specific mortality in the general population.[20]

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Many authors have documented an association between the hormone leptin, produced by adipose tissue, and liver histology. Despite previous findings suggesting elevated leptin levels in patients with steatosis and NASH, there is no conclusive evidence linking leptin levels to steatosis or fibrosis. [21–24]

Limitations

It is important to acknowledge several limitations of our study. First, the restricted size of our sample may affect the generalizability of our findings. The examination of additional variables, such as blood urea nitrogen and smoking history, which could be linked to higher serum GGT levels in NAFLD patients, was not possible. In order to offer a more comprehensive explanation of this relationship, further research with a larger sample size and a thorough analysis of related components is imperative.

CONCLUSION

In this study, it was found that patients with NAFLD had notably higher levels of serum GGT compared to healthy controls. NAFLD patients displayed elevated serum GGT, AST, ALT, and lipid profiles. The findings of these studies show the potential of serum GGT levels as a novel biomarker, which can serve as an indicator of the identification of NAFLD. Serum GGT levels do not provide information on the severity of NAFLD. Further research is required to clarify this association and its clinical implications through larger-scale studies and comprehensive investigations.

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