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Research Article

ASSOCIATIONS BETWEEN HBA1C LEVELS AND LIVER FUNCTION TESTS IN DIABETES: A COMPREHENSIVE ANALYSIS

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ABSTRACT

Objective: Diabetes mellitus (DM) is a chronic multi-system disease characterized by hyperglycemia. The most common type of DM, Type 2 DM (T2DM), is characterized by insulin resistance and insufficient insulin secretory response. T2DM is frequently associated with abnormal liver function tests (LFTs). Our study aims to widen our knowledge of the complex interrelationship between T2DM and LFTs.

Methodology: This study was done in a multi-specialty hospital in Western part of Tamil Nadu among the patients who came for master health check-up between 2017 and 2024. From the laboratory database of 67,000 patients, patients who reported for the 1st time and had their hemoglobin A1c (HbA1c) and LFT values evaluated were selected. They were categorized as normal, pre-diabetic, and diabetic based on HbA1c values. Data were analyzed using SPSS 27. Categorical variables were expressed in the form of frequency and percentages whereas continuous variables were expressed in the form of mean and standard deviation. Analysis of variance (ANOVA) was used to find out any significant difference in lipid profile among the three groups.

Results: Our study had 23,238 participants. Out of them 7168 (30.84%) had normal HbA1c levels, 8347 (35.91%) were pre-diabetics and 7955 (34.23%) were diabetic patients. The mean total protein (TP), serum glutamic-pyruvic transaminase (SGPT), and alkaline phosphatase (ALP) were higher among the diabetic patients. ANOVA showed that there was a significant difference in serum total bilirubin, TP, albumin, serum glutamic-oxaloacetic transaminase (SGOT), SGPT, and ALP between the three groups. Pearson correlation coefficient showed a positive correlation between SGOT, SGPT, ALP, and HbA1c. It showed a negative correlation between TB, albumin, and HbA1c.

Conclusion: From the findings of this study, there is evidence that there exists a significant association between HbA1c levels and LFTs. Elevated HbA1c levels correlate with abnormal LFT results, suggesting a potential link between glycemic control and liver health. These results underscore the need for monitoring both HbA1c and LFTs in patients with diabetes to manage their overall health comprehensively.

Keywords: Hemoglobin A1c; Liver function tests; Master health check-up; Diabetes mellitus; Tamil Nadu.
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INTRODUCTION

Diabetes mellitus (DM) is a chronic multi-system disease characterized by hyperglycemia. The most common type of DM, Type 2 DM (T2DM), is characterized by insulin resistance and insufficient insulin secretory response [1]. Around 422 million individuals globally suffer from diabetes, with the majority residing in low-and middle-income countries. The disease accounts for 1.5 million mortality annually. India, which holds the unpleasant distinction of "the diabetes capital of the world," is experiencing a concerning trend, with an estimated 79.4 million people worldwide expected to have diabetes by 2030 [2]. The liver is essential for glucose homeostasis as it extracts glucose from the blood to use as fuel, it stores glucose as glycogen and synthesizes glucose from non-carbohydrate sources to maintain blood glucose levels during fasting periods [3].

Liver function test (LFT) is one of the most important biochemical tests that clinicians request to learn more about a patient's functional liver state. There have previously been descriptions of liver function in the context of clinical diabetes [4,5]. Serum transaminases, alkaline phosphatase (ALP), bilirubin, total protein (TP), albumin, and prothrombin time are among the most often utilized LFTs. Serum transaminases such as aspartate aminotransferase and alanine aminotransferase can be measured to detect hepatocyte damage. While albumin, prothrombin time, TP, and gamma-glutamyl transpeptidase (GGT) indicate liver synthesis function, bilirubin, ALP, and GGT function as indicators of cholestasis and biliary function [6].

According to more recent research, T2DM frequently has deranged LFTs [7-10]. This has garnered a lot of interest. Indeed, it has been proposed that there exists a high correlation between the blood concentrations of liver enzymes and either insulin resistance or diabetic state [11-13]. An increasing amount of research suggests that, when combined with the more established risk factors, increased liver enzymes may operate as potent risk factors for the onset of T2DM and may even enhance the prediction for diabetes' future development [14-17].

By synthesizing current evidence and clinical insights, this article aims to enhance our knowledge of the complex interrelationship between T2DM and LFTs. By elucidating underlying mechanisms and clinical implications, we strive to empower healthcare professionals with knowledge to optimize management strategies and improve outcomes for individuals affected by this intricate interplay.

METHODS

This study was done in a medical college in Western Tamil Nadu. Our laboratory database contained records of 67000 patients who reported for master health check-up between 2017 and 2024. Ethical committee approval was obtained (EC/AP/1100/12/2023). From this database, we included patients who reported to master health check-up for the 1st time. Among them, those patients who had hemoglobin A1c (HbA1c) values and complete LFT were enrolled in the study. Participants were categorized into three groups based on HbA1c values

Table 1: Mean lipid profile among non-diabetic, pre-diabetic, and diabetic patients

Parameters	Non-diabetic (Mean±SD)	Pre-diabetic (Mean±SD)	Diabetic (Mean±SD)
Total bilirubin	0.55 (0.40–0.77)*	0.48 (0.35–0.67)*	0.50 (0.37–0.70)*
Direct bilirubin	0.18 (0.13–0.24)*	0.16 (0.12–0.21)*	0.17 (0.13–0.23)*
Indirect bilirubin	0.38 (0.26–0.54)*	0.33 (0.23–0.47)*	0.33 (0.23–0.48)*
Total protein	7.29±0.31	7.32±0.41	7.33±0.43
Albumin	0.44±0.31	0.37±0.23	0.38±0.25
SGOT (AST)	21 (18–26)*	22 (19–27)*	20 (16–26)*
SGPT (ALT)	21 (15–31)*	22 (16–32)*	23 (17–34)*
ALP	73.74±26.72	77.39±28.45	83.82±28.58

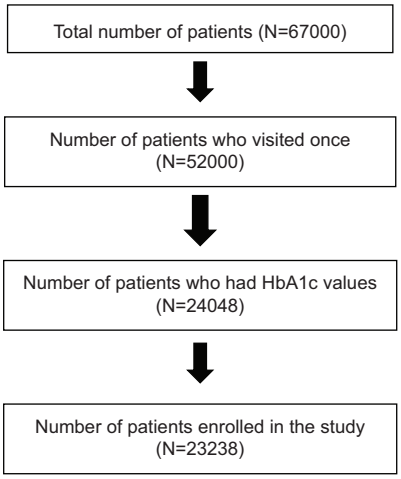
*Median inter-quartile range. The mean TP, SGPT and ALP were higher among the diabetic patients. TP: Total protein, SGOT: Serum glutamic-oxaloacetic transaminase, AST: Aspartate aminotransferase, SGPT: Serum glutamic-pyruvic transaminase, ALT: Alanine transaminase

Table 2: Association between diabetic status and LFT

Parameters	Non-diabetic (Mean±SD)	Pre-diabetic (Mean±SD)	Diabetic (Mean±SD)	F-value	P-value*
Total bilirubin	0.65±0.50	0.55±0.33	0.58±0.46	94.02	<0.05
Direct bilirubin	0.20±0.24	0.18±0.11	0.20±0.28	31.26	<0.05
Indirect bilirubin	0.44±0.31	0.37±0.23	0.38±0.25	144.57	<0.05
Total protein	7.29±0.41	7.32±0.41	7.33±0.43	13.43	<0.05
Albumin	4.47±0.30	4.41±0.28	4.39±0.31	124.99	<0.05
SGOT (AST)	24.44±17.33	24.57±16.99	24.68 ± 20.35	0.32	0.72
SGPT (ALT)	26.34±20.43	27.23±22.60	29.56±28.88	36.31	<0.05
ALP	73.74±26.72	77.39±28.45	83.82±28.58	255.60	<0.05

*ANOVA showed that there was a significant difference in Total Bilirubin, Total Protein, Albumin, SGOT, SGPT, and ALP between the three groups. SGOT: Serum glutamic-oxaloacetic transaminase, AST: Aspartate aminotransferase, SGPT: Serum glutamic-pyruvic transaminase, ALT: Alanine transaminase, LFT: Liver function tests

as normal patients, pre-diabetic patients, and diabetic patients. The cutoff values for HbA1c were based on ADA. As per ADA those who have HbA1c < 5.7% were in the normal group, 5.7–6.4% pre-diabetic and those who had HbA1c more than or equal to 6.5% were considered as diabetic. The data were analyzed using SPSS. Categorical variables were expressed in the form of frequency and percentages and continuous variables were expressed in the form of mean and standard deviation. We used Analysis of variance to find if there was a significant difference in LFT among the three groups. Institute Ethical Committee approval was obtained.



RESULTS

There were 23,238 study participants. Out of them 7168 (30.84%) had normal HbA1c levels, 8347 (35.91%) were pre-diabetics and 7955 (34.23%) were diabetic patients. The serum glutamic-oxaloacetic transaminase (SGOT) values were as follows: Among the non-diabetics, 93.5% had normal levels, among the pre-diabetics 93% had normal levels and among the diabetics, 91% had normal values. The serum glutamic-pyruvic transaminase (SGPT) values were as follows: Among the non-diabetics, 86% had normal levels, among the pre-diabetics 85% had normal levels and among the diabetics, 83% had normal values. The ALP values were as follows: Among the non-diabetics, 95% had normal levels, among the pre-diabetics 95% had normal levels and among the diabetics, 92% had normal values. Table 1 showed the mean total protein, SGPT and ALP were higher for diabetic patients. Table 2 showed a significant difference in Tatal bilirubin, direct bilirubin, Indirect bilirubin, Total protein, Albumin, SGPT and ALP among the three group of patients.

Pearson correlation coefficient showed a positive correlation between SGOT, SGPT, ALP, and HbA1c. It showed a negative correlation between TB, albumin, and HbA1c.

DISCUSSION

The present study had 23,238 participants. Our study was done to know the relation between HbA1c levels and LFT. The present study showed that TP levels were higher for diabetic patients. In his investigation, Nazki *et al.* [18] found that diabetic individuals had increased plasma TP levels. A study by Gul and Rahman [19] showed that diabetes patients had greater levels of plasma TP. A reduction in the fractional synthetic rate of albumin owing to insulin resistance or deficiency may be combined with increased TPs, which could be caused by an increase in acute phase proteins, globulins, and fibrinogen [18].

Our study showed that the mean SGPT levels were higher for diabetics when compared to the other two groups and we found a significant difference between the mean of the three groups. Study by Calanna *et al.* [20] also observed similar findings. Study by Chilay *et al.* [21] observed that SGPT levels were higher among diabetic patients. Jha *et al.* [22] observed that SGPT was elevated in 17% of Bangladeshi population in their study. The cause of these changes in liver enzymes is the oxidative stress brought on by tissue glycation, which is a consequence of long-term diabetes. Due to hepatocellular dysfunction, oxidative stress and cytokine production cause changes in liver enzymes. Fatty alterations may result from hepatic insulin resistance, which can be directly caused by hyperinsulinemia. The buildup of fat in the liver may be harmful to hepatocytes, increasing transaminases

Table 3: Correlation between HbA1c and LFT

LFT	Correlation Co-efficient	p-value
Total bilirubin	−0.05	<0.05
Direct bilirubin	−0.007	0.29
Indirect bilirubin	−0.08	<0.05
Total protein	0.03	<0.05
Albumin	−0.09	<0.05
SGOT (AST)	0.005	0.42
SGPT (ALT)	0.05	<0.05
ALP	0.14	<0.05

SGOT: Serum glutamic-oxaloacetic transaminase, AST: Aspartate aminotransferase, SGPT: Serum glutamic-pyruvic transaminase, ALT: Alanine transaminase, LFT: Liver function tests, HbA1c: Hemoglobin A1c

and decreasing the liver's ability to synthesize new substances [23]. Raised proinflammatory cytokines like tumor necrosis factor, which exacerbates hepatocellular damage, is another feature of the insulin-resistant condition [24]. NAFLD is a significant hepatic manifestation of DM, and as evidenced by numerous research, SGPT has been utilized as a measure of NAFLD [25].

The present study showed that ALP was higher among diabetic patients and a significant difference in ALP levels was observed between the three groups of patients. Study by Zhang *et al.* [26] also showed similar finding. It was noted that ALP contributed to vascular calcification, [27] which was connected to insulin resistance and eventual onset of diabetes [28]. ALP overexpression was shown in the arterial wall of diabetic rat and mouse models of vascular calcification, according to animal experiments [29]. Elevations in serum ALP have been linked to endothelial dysfunction, which is a precursor to insulin resistance and diabetes [30]. It was explained that ALP might lower the bioavailability of nitric oxide (NO) by preventing endothelial cells' tyrosine kinase activity, [31] which would then impede the function of endothelial NO synthase [32].

Our study showed that serum albumin had a negative correlation with HbA1c. Study by Tiwari *et al.* [33] also showed a similar negative correlation between serum albumin and HbA1c. Study by Feng *et al.* [34] also showed similar results. Higher FPG levels cause a patient's albumin to become heavily glycosylated because albumin glycation occurs before hemoglobin glycation. This results in albumin's lysine residues being altered, which reduces albumin's capacity to shield hemoglobin from glycosylation. Glycosylated albumin interacts with the receptor for advanced glycation end products, which can also raise the HbA1c level. Furthermore, individuals with diabetes or other disorders have a higher likelihood of alteration and polymerization due to albumin's facile aggregation and structural changes. Albumin's physiological functions, including its capacity to shield hemoglobin from glycosylation, are impacted by variations in albumin level [34].

Our study showed a negative correlation between bilirubin and HbA1c. Study by Choi *et al.* [35] also showed a similar finding. Hemoglobin glycation is facilitated by bilirubin. Early glycation products are formed due to non-enzymatic reaction between sugars with a variety of proteins [36]. The glycation reaction involves oxidative stress [37]. An early stage of the Maillard reaction called autoxidation of glucose to dicarbonyl intermediates can be aided by oxidative stress [38]. Furthermore, it is believed that the production of malondialdehyde, a byproduct of lipid oxidation, facilitates protein glycation by serving as a bridge between the hemoglobin and sugar moieties [39]. By lowering oxidative stress, bilirubin may prevent hemoglobin from glycating.

CONCLUSION

Our study reveals a significant association between HbA1c levels and LFT, suggesting a potential interplay between glycemic control and hepatic health. Elevated HbA1c levels correlate with abnormalities in LFT parameters, highlighting the importance of comprehensive metabolic monitoring in diabetic patients. Further research is warranted to elucidate the underlying mechanisms and clinical implications of this relationship, with implications for optimizing management strategies aimed at reducing both glycemic and hepatic complications in individuals with diabetes.

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