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**Original Research Article**

# Evaluation of liver function in acute complications of type 2 diabetes mellitus

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## ABSTRACT

**Background:** Diabetic ketoacidosis (DKA) and Hyperosmolar Hyperglycaemic state (HHS) are the acute complications of Type 2 Diabetes Mellitus (T2DM). The aim was to evaluate the role of liver function parameters in T2DM patients with DKA and HHS.
**Methods:** This descriptive study included 50 subjects in each of the following four groups: non-T2DM, T2DM without acute complications, T2DM with DKA, T2DM with HHS. Data on demography, clinical and lab diagnosis, as well as liver function parameters were collected from May 2017 to October 2017. The baseline data and liver function parameters were compared across the study groups.
**Results:** There was significant hyperglycemia and associated baseline electrolyte, Arterial Blood Gas (ABG) analysis changes in acute complications of T2DM. Besides GGT, the serum total and direct bilirubin levels were also higher in T2DM cases with DKA. Significant levels of hypoalbuminemia and hyperglobulinemia along with raised SGPT and ALP levels were seen in acute complications of T2DM, especially in HHS complicating T2DM.
**Conclusions:** Decreased serum albumin levels, along with elevated liver enzymes-SGPT, ALP, and GGT characterized the acute complications of T2DM, with specific alterations of liver function parameters seen in DKA and HHS cases.

**Keywords:** Acute complications of type 2 diabetes mellitus, Diabetic ketoacidosis, Hyperosmolar hyperglycaemic state, Liver function

## INTRODUCTION

Diabetes mellitus comprises of a group of metabolic disorders characterized by long-term hyperglycemia. Of the several types of diabetes mellitus, Type 2 Diabetes Mellitus (T2DM) is the commonest form, affecting about 415million of people around the world. India is in the second lead position with 69million diabetic adults and a prevalence rate of 8.7%.[1] With the increasing incidence of T2DM, the occurrence of complications associated with T2DM are also on a surge.

The chronic complications such as diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, cardiovascular disease tend to increase the long-term morbidity and mortality of T2DM patients.[2] Diabetic ketoacidosis

(DKA) and Hyperosmolar Hyperglycemic State (HHS) are the two commonly occurring acute complications of T2DM causing sudden mortality in diabetic patients.[3]

T2DM with DKA is characterized by the triad of hyperglycemia, ketosis and acidosis, while T2DM with HHS is characterized by hyperglycemia and dehydration without any significant ketosis. So, conventionally several biochemical parameters are used to diagnose the acute complications of T2DM, like plasma glucose, serum electrolytes, Arterial Blood Gas (ABG) analysis parameters, serum and urine ketones.[4]

Elevated liver enzymes are independent risk factors for the development of T2DM.[5] T2DM cases with DKA showed alterations in hepatic enzyme levels.[6,7] Serum albumin levels of T2DM patients showed a negative relationship with their HbA1C levels and were also altered in DKA complicating T2DM.[8,9]

Due to the conflicting findings of the previous studies done in T2DM cases with DKA and the lack of information among HHS cases of T2DM, this study aimed at evaluating the role of liver function parameters in acute complications of T2DM.

## METHODS

This was a descriptive study conducted between May 2017 and October 2017. The study was approved by the Institute Ethics Committee. The study population comprised of the following four groups which was non-T2DM, T2DM without acute complications, T2DM with DKA, T2DM with HHS, with at least 46 cases in each group. The sample size of 46 was determined using the sample size calculation tool, with the formula $N=[(Z\alpha+Z\beta)/C]2+3$.[7]

The clinical diagnosis of T2DM, DKA and HHS were made based on the American Diabetic Association (ADA) criteria.[3,10] Cases with incomplete clinical data as well as cases of cirrhosis, hepatitis, any other liver disease, chronic kidney disease, malignancy, hemorrhage, alcoholics, starvation, drug poisoning, acute myocardial infarction were excluded.

Demographic data, clinical data and data on laboratory diagnosis were collected from the medical case records of the study population. Data on liver function parameters were also collected in all the four groups. The routine biochemical investigations were done in Roche Cobas C311 autoanalyzer, electrolytes were assayed in Roche 9180 electrolyte analyzer and ABG analyses were done in Roche Cobas b121 analyzer.

Anion gap was calculated from the formula: anion gap= [serum sodium (mEq/L)]- [serum chloride (mEq/L) +serum bicarbonate (mEq/L)].[11] Plasma osmolality was calculated from the following formula: Plasma osmolality=1.86 [serum sodium (mEq/L)]+plasma glucose (mg/dL)/18+plasma urea (mg/dL)/2.8+9.[12] The data were expressed as mean, median, standard deviation (SD) and interquartile range.

One-way ANOVA test and Kruskal Wallis test were used to compare the baseline and liver function parameters across the study groups. Independent t test and Mann Whitney U test were used to compare the ABG analyses between DKA and HHS cases of T2DM. p-value <0.05 was considered statistically significant. SPSS 16 was the software used for statistical analysis.

## RESULTS

Gender-wise distribution of the study population is illustrated in the Figure 1.

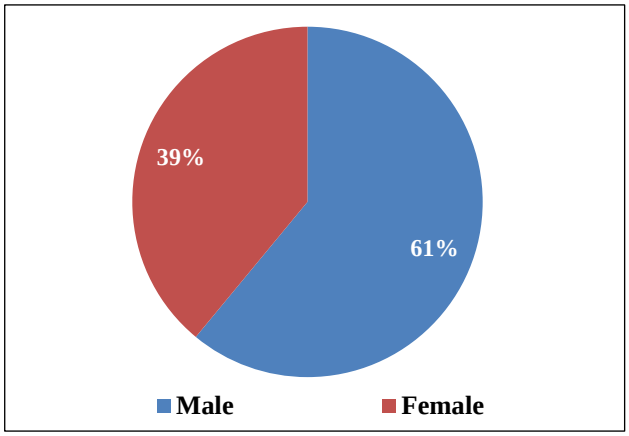


**Figure 1: Gender distribution in the study population.**

On the whole, 61% male and 39% female subjects participated in this study. The study subjects were categorized into four study groups namely non-T2DM, T2DM without acute complications, T2DM with DKA and T2DM with HHS. The gender-wise distribution amongst the four study groups is depicted in Figure 2.

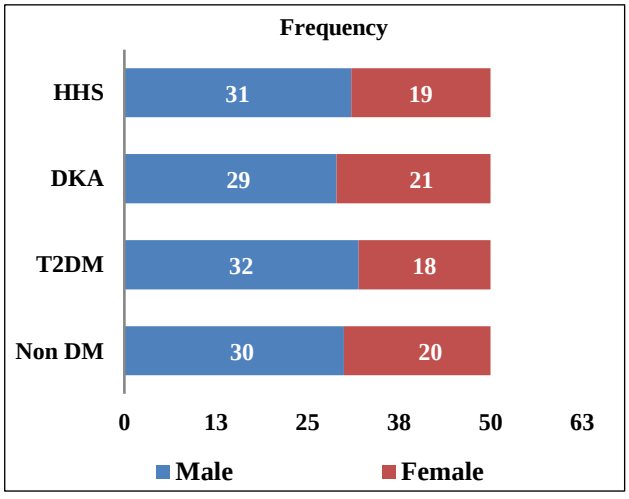


**Figure 2: Gender distribution amongst the four study groups.**

The four study groups had similar gender distributions of about 60% males and 40% females. This was in concurrence with the current national statistics showing higher prevalence of T2DM in Indian males than the females.[1] When compared to the non-T2DM cases, the mean age was significantly higher in uncomplicated as well as DKA and HHS cases of T2DM. Random plasma glucose (RPG) and HbA1C levels were significantly elevated in the three T2DM groups compared to the non T2DM group (p <0.001*), the maximal elevations were seen in T2DM cases with HHS.

The assayed renal function parameters-serum urea and creatinine were within normal limits and unaltered between non-T2DM and uncomplicated T2DM but were significantly raised in DKA and HHS groups (p <0.001*).

Serum electrolytes showed significant hyponatremia, bicarbonate depletions, high anion gap and delta gap, hyperosmolality in the T2DM cases with DKA and HHS. These alterations in baseline parameters were extreme in T2DM cases with HHS (Table 1).

ABG analysis estimating the arterial pH, pO2, pCO2 and bicarbonate levels were performed in acute complications of T2DM, which revealed underlying metabolic acidosis with compensatory respiratory alkalosis in both DKA and HHS groups, without any significant variations across the two groups (Table 2).

Amongst the measured liver function parameters, serum albumin, globulin, SGPT, ALP and GGT showed significant changes in T2DM compared to non-T2DM group.

While the serum globulin, SGPT and ALP levels were elevated, the serum albumin levels were decreased considerably in the acute complications of T2DM than the uncomplicated T2DM cases, with the HHS group showing substantial alterations.

Serum total and direct bilirubin, together with serum GGT levels were significantly higher in the T2DM cases with acute complications, with the DKA group showing maximum deviations (Table 3).

**Table 1: Comparison of demographic data and baseline biochemical parameters across the study groups.**

| Parameter | Non-T2DM (n=50) | T2DM without acute complications (n=50) | T2DM with DKA (n=50) | T2DM with HHS (n=50) | Table value | p value |
|---|---|---|---|---|---|---|
| Age (years) | 43.68±12.56 | 52.06±10.33 | 51.60±13.42 | 56.72±9.984 | 10.76 | <0.001[a]* |
| RPG (mg/dL) | 96 (83.75, 105.75) | 262 (223, 322) | 351.5 (293, 480.25) | 630.5 (609.75,683.75) | 170.89 | <0.001[b]* |
| Serum urea (mg/dL) | 19 (16, 22) | 18 (15, 24.25) | 30 (21, 54) | 47 (33.5, 73.5) | 82.33 | <0.001[b]* |
| Serum creatinine (mg/dL) | 0.7 (0.5, 0.8) | 0.7 (0.6, 0.8) | 0.9 (0.7, 1.2) | 1.15 (0.9, 1.6) | 61.64 | <0.001[b]* |
| HbA1C (%) | 5.76±0.34 | 8.03±1.37 | 8.45±1.78 | 9.95±1.59 | 77.94 | <0.001[a]* |
| Serum $Na^+$ (mEq/L) | 137.9±2.88 | 136.10±3.38 | 132.12±6.41 | 132.56±5.62 | 16.89 | <0.001[a]* |
| Serum $K^+$ (mEq/L) | 4.27±0.46 | 4.24±0.42 | 4.38±0.87 | 4.27±0.85 | 0.43 | 0.73[a] |
| Serum $Cl^-$ (mEq/L) | 99.76±6.84 | 100.62±4.70 | 99.34±6.69 | 97.19±14.93 | 1.26 | 0.29[a] |
| Serum $HCO_3^-$ (mEq/L) | 24.84±3.58 | 23.9±2.41 | 17.89±4.24 | 18.58±4.34 | 46.16 | <0.001[a]* |
| Anion gap | 16 (11.75, 24.25) | 15.5 (10.75, 15.5) | 19 (16, 22.25) | 18 (14, 23) | 10.02 | 0.018[b]* |
| Delta gap | 4 (1, 12.25) | 3.5 (1.25, 8) | 7 (4, 10.25) | 6 (2, 11) | 9.99 | 0.019[b]* |
| Plasma osmolality (mOsm/kg) | 286.80±6.19 | 294.30±8.79 | 299.46±17.85 | 321.36±12.29 | 75.44 | <0.001[a]* |
| a- One-way Anova test, b- Kruskal Wallis test, *Significant p value <0.05 | | | | | | |

**Table 2: Comparison of arterial blood gas (ABG) analysis parameters across the study groups.**

| Parameter | T2DM with DKA (n=50) | T2DM with HHS (n=50) | Table value | p value |
|---|---|---|---|---|
| Arterial pH | 7.38±0.8 | 7.35±0.59 | 3.62 | 0.60[a] |
| Arterial $pCO_2$ (mm Hg) | 28.58±7.21 | 29.38±6.47 | 0.73 | 0.39[a] |
| Arterial $pO_2$ (mm Hg) | 88(74,98.25) | 93 (84,102.25) | 2.11 | 0.035[b]* |
| Arterial $HCO_3^-$ (mEq/L) | 17.88±4.24 | 18.58±4.34 | 0.005 | 0.945[a] |
| a- Independent t test, b- Mann Whitney U test, *Significant p value <0.05 | | | | |

**Table 3: Comparison of liver function parameter across the study groups.**

| Parameter | Non-T2DM (n=50) | T2DM without acute complications (n=50) | T2DM with DKA (n=50) | T2DM with HHS (n=50) | Table value | p value |
|---|---|---|---|---|---|---|
| Serum total bilirubin (mg/dL) | 0.5 (0.4,0.73) | 0.5 (0.4,0.725) | 0.8 (0.5,1.2) | 0.6 (0.4,0.9) | 15.37 | 0.002[b]* |
| Serum direct bilirubin (mg/dL) | 0.2 (0.1, 0.2) | 0.2 (0.1, 0.2) | 0.3 (0.2,0.3) | 0.2 (0.1, 0.2) | 29.20 | <0.001[b]* |
| Serum indirect bilirubin (mg/dL) | 0.4 (0.2,0.5) | 0.4 (0.2,0.6) | 0.3 (0.2,0.3) | 0.2(0.1, 0.2) | 4.92 | 0.18[b] |
| Serum total protein (g/dL) | 7.40±0.43 | 7.46±0.53 | 7.13±0.98 | 7.18±0.91 | 2.41 | 0.68[a] |
| Serum albumin (g/dL) | 4.39±0.32 | 4.14±0.48 | 3.32±0.57 | 3.27±0.54 | 67.30 | <0.001[a]* |
| Serum globulin (g/dL) | 3.01±0.49 | 3.33±0.67 | 3.81±0.83 | 3.91±0.68 | 19.09 | <0.001[a]* |
| Serum SGOT (U/L) | 19 (15.75,25.25) | 19 (15,26.25) | 25.5 (15, 45.5) | 20(16,24) | 6.41 | 0.09[b] |
| Serum SGPT (U/L) | 17 (15,22.25) | 19 (16,30.25) | 19 (12.75,26.25) | 21(18,35.5) | 10.35 | 0.016[b]* |
| Serum ALP (U/L) | 73 (58,86.25) | 79.5 (65.75,102.25) | 105.5(74.25,118.25) | 109(93,144) | 40.87 | <0.001[b]* |
| Serum GGT (U/L) | 22.5(15.75,35) | 27.5 (19.75,50) | 43.5 (21.75,80.5) | 38(26.75,47) | 20.27 | <0.001[b]* |
| a- One-way Anova test, b- Kruskal Wallis test, *Significant p value <0.05 | | | | | | |

## DISCUSSION

The findings of demographic and baseline parameters in the present study were in accordance with most of the published clinical data and guidelines. Elderly age group is as such a risk factor for acute T2DM complications, especially HHS.[3] This attribute to the significantly high mean age group of the HHS group in the study population (Table 1). Uncontrolled hyperglycemia in T2DM was the bottom-line of both DKA and HHS, thus explaining the higher RPG and HbA1C levels in the DKA and HHS groups. Prerenal azotemia is an associated feature of acute diabetic complications, which corresponds to the findings of elevated renal function parameters (serum urea, creatinine) in DKA and HHS groups. Hyponatremia and hyperosmolality in these conditions are caused by the underlying dehydration.

The guidelines for laboratory diagnosis of HHS mandates RPG levels more than 600mg/dL and plasma osmolality above 320mOsm/kg, which were adhered to by the HHS study group. High anion gap metabolic acidosis (anion gap >12, serum bicarbonate <18mEq/L) and ketosis are important distinctive features of DKA, which were similarly represented by the study's DKA group in their ABG and electrolyte analyses values (Tables 1 and 2). Hence, the baseline study parameters were corresponding to the established diagnostic guidelines of acute T2DM complications.[4]

Amongst the liver function parameters, serum total bilirubin, direct bilirubin, GGT levels were significantly increased in T2DM cases with DKA, while serum SGPT, ALP levels were significantly higher in the HHS group. In agreement with the present findings, Takaike H et al, revealed transient elevations of hepatic aminotransferases in DKA cases shortly after initiating insulin therapy, due to unknown reasons.[6] On the contrary, Bai F et al, demonstrated decreased levels of bilirubin and GGT in DKA, which is discordant with the present findings.[7] DKA patients frequently show gastrointestinal symptoms besides abnormal liver profile, which may be due to some underlying reversible hepatocellular damage like fatty infiltration or hypoperfusion induced by the ketoacidosis.[13] The reason for specific patterns of hepatic enzymes in DKA and HHS remains unknown.

Lipid peroxidation, cellular apoptosis and decreased antioxidant levels are the pathologic consequences of hyperketonemia in DKA.[14] Heme oxygenase system and its related products like carbon monoxide, bilirubin, biliverdin are important biological antioxidants. Several studies depicted negative relationships between serum bilirubin levels and T2DM as well as the diabetic complications. Farasat T et al, deduced significant negative correlations of serum bilirubin levels with fasting glucose as well as HbA1C levels in T2DM subjects.[15] The paradoxical increase in bilirubin levels in the DKA subjects could be a protective mechanism against the underlying oxidative damage.

Serum albumin levels were drastically reduced below the normal range in acute diabetic complications, along with a compensatory rise in the globulins and this was more pronounced in the HHS group. Analogous results were produced by DKA cases with T2DM in a study by Bai F et al.[7] Similarly Cheng PC et al, showed inverse

association between serum albumin and β-hydroxybutyrate levels in T2DM patients with DKA.[9]

Accordingly, low serum albumin and albumin: globulin ratio, along with high serum total protein and globulin levels were seen in several studies conducted on T2DM cases due to the associated chronic inflammation.[16,17] Hypoalbuminemia as such increased the risk of T2DM in the high-risk subjects and is also an indicator of chronicity of T2DM.[8,18] Serum albumin levels had prognostic role in acute severe illnesses. Knaus WA et al, validated the inclusion of serum albumin and bilirubin levels besides other physiological and biochemical parameters in the APACHE III scoring system used to assess the prognosis of critically ill patients.[19,20] Oxidative damage to cells is the eventual outcome of chronic hyperglycemic state of T2DM, which could also damage the hepatocytes, thereby resulting in elevated liver enzymes and decreased hepatic protein synthesizing capacity. The thiol groups in albumin have antioxidant property, which will be used up in scavenging the generated free radicals. The study by Hilsarkar PJ et al, ascertained lower antioxidant levels in T2DM patients, which also included reduced serum albumin levels.[21]

Moreover, the acute complications of T2DM are accompanied by increased inflammatory cytokines and interleukins which down-regulate the hepatic albumin synthesis, since albumin is a negative acute phase protein. The primary pathogenic mechanism of T2DM and DKA is relative insulin deficiency. The insulin deficiency in turn leads to decreased hepatic albumin production and accelerated proteolysis, all of which lead to hypoalbuminemia in DKA. HHS is often precipitated by prolonged deprivation of water and nutrition in elderly T2DM patients.[3] The profound hypoalbuminemia noticed in HHS group could be owed to the poor nutritional status of the subjects.

## CONCLUSION

Decreased serum albumin levels and elevated liver enzymes- SGPT, ALP, GGT characterized the acute complications of T2DM with specific alterations of liver function parameters in DKA and HHS cases.

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