

## Original Research Article

# A study on the prevalence of hypoalbuminemia in the hospitalized type 2 diabetes mellitus patients with acute hyperglycemia and its correlation with the risk to ketosis in these patients

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## ABSTRACT

**Background:** Diabetes mellitus is a chronic metabolic disorder that diminishes the quality and life expectancy of the patients by impacting a significant morbidity and mortality due to its associated complications. Diabetic ketoacidosis is considered as one such acute life-threatening complication of diabetes that is considered a medical emergency.

**Methods:** The study was conducted as a retrospective analysis of 65 patients diagnosed as Type 2 diabetes mellitus as per the criteria of American Diabetes Association 2019 were included in the study. After the ethical clearance, the study was conducted at the Employment State Insurance Corporation Hospital and Post Graduate Institute of Medical Science and Research, Chennai over a period of 6 months from October 2019 to March 2020. A statistical analysis was done and all the calculations were based on two-sided hypothesis with  $p < 0.05$  interpreted as significant.

**Results:** The analysis of the study showed there was a significant prevalence of hypoalbuminemia (37%) among the patients with diabetes admitted with acute hyperglycemia. The occurrence of ketonuria among those patients with hypoalbuminemia were 62.5% [odds ratio (OR): 3.15,  $p$  value: 0.02].

**Conclusions:** From the study, serum albumin levels has an inverse correlation in patients with acute hyperglycemia. Furthermore, low serum albumin harbingers the risk to ketosis in patients admitted with acute hyperglycemia thereby mirroring the relative insulin deficiency in these patients. Serum albumin can be used by the treating physician as a cost-effective tool and a marker for insulin reserve of the beta cell in an individual admitted with acute hyperglycemia, it can be used as a reliable indicator to identify those at risk to ketosis thereby to prevent and treat the dreaded diabetes related complications.

**Keywords:** Diabetic ketoacidosis, Hypoalbuminemia, Ketonuria, Type II diabetes mellitus

## INTRODUCTION

Diabetes mellitus is a heterogeneous group of metabolic disorder characterised by hyperglycaemia resulting from defect in insulin secretion or action or both. India is faced with a galloping epidemic of diabetic. There are about 70 million patients in India with diabetes and it is expected to

exceed beyond 100 million by the year 2030.<sup>1</sup> Type 2 diabetes mellitus is the most common form and is now one of the leading health problems faced by the world. Apart from the chronic complications in diabetes, patients may experience acute life-threatening complications like diabetic ketoacidosis that involves a constellation of acute hyperglycemia with ketoacidosis with a mortality rate of

about 10%.<sup>1,2</sup> Considering the high mortality rate and its associated complication in patients with diabetes, identifying the patients at risk to ketosis and early preventive interventions will improve the outcome in these patients.<sup>3</sup>

Serum albumin is a major plasma protein that constitutes 60% of the total protein synthesised solely by the liver and is now considered as a marker for systemic inflammation.<sup>4</sup> It acts as a negative acute phase reactant and also a prognostic marker in several disease including diabetes.<sup>5</sup> Albumin production is regulated by multiple factors such as the diet, hormonal factors and the oncotic pressure.<sup>6,7</sup>

Chemical studies done previously showed that insulin is required to maintain expression of albumin by stimulating its production in the liver by regulating the genes involved in its transcription.<sup>8</sup> Thus in diabetes, the production of the albumin is impaired and its level decreases.<sup>9-12</sup>

As there is no convenient tool to measure the beta cell function, this study is on serum albumin, an easily available and cost-effective tool to assess the beta cell function indirectly, thereby assessing the insulin secretory reserve that influences both the glycaemic control and the risk to ketone body formation in patients with diabetes.<sup>13</sup>

**Aim and objective**

The aim of the study was to assess the prevalence of hypoalbuminemia in hospitalised diabetic patients with acute hyperglycemia. The objective of this study was to assess the correlation between low serum albumin and ketone body formation and subsequent development of ketosis in hospitalised patients with acute hyperglycemia.

**METHODS**

This study was a retrospective analysis conducted at Employment State Insurance Corporation Hospital and Post Graduate Institute of Medical Science and Research, KK Nagar, Chennai which is a 150 bedded hospital over a period of 6 months from October 2019 to March 2020. This study has been conducted after the ethical clearance from the Institutional Ethical Committee. Patients diagnosed as type-2 diabetes as per the criteria of American Diabetic Association (ADA) 2019 for more than 1-year duration in the department of general medicine and endocrinology during a period of 6 months and for whom blood and urine samples were collected were included in the study. 65 Subjects were selected based on the below formula and their personal information's were concealed.

$$n = \frac{Z^2 \times P \times (1 - P)}{d^2}$$

Sample size (n) =

$$n = \frac{(1.96)^2 \times 0.21 \times (0.79)}{0.01} = 65$$

With an estimated prevalence of ketosis as 21% in type 2 diabetes mellitus (15) with 95% confidence and using a relative precision of 10%.

**Inclusion criteria**

According to the ADA 2019, criteria for diagnosing diabetes: Patients of more than 20 years of age with fasting plasma glucose  $\geq 126$  mg/dl with atleast 8 hours of fasting or 2h postprandial glucose  $\geq 200$  mg/dl during an oral glucose tolerance test (using a glucose load equivalent of 75 g anhydrous glucose dissolved in water as described by WHO) or HbA1c  $\geq 6.5\%$  performed using NGSP Certified method and standardised to the DCCT assay or in a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis and a random plasma glucose  $\geq 200$  mg/dl were diagnosed as diabetes and were selected and in them patients with blood sugar  $>250$  mg/dl were included in the study.<sup>13</sup>

**Exclusion criteria**

Those with acute infections, acute myocardial infarction and acute cerebrovascular accidents that affect the glycaemic control and patients with overt proteinuria, severe malnourishment, liver cirrhosis, malignancy that may alter the serum albumin levels significantly were excluded from the study. Individuals with values of HbA1c of  $>9.0$  are excluded from the study as poor glycaemic control is an independent risk factor for ketosis so as to prevent interference.

Urine ketones were done by a semi-quantitative urine dip stick test. Serum albumin was measured by bromo-cresol, an automatic semi-quantitative method. Subjects with serum albumin  $>3$  g/dl were considered as normoalbuminuric and those with serum albumin  $<3$  g/dl as hypoalbuminemic.<sup>13</sup>

**Statistical analysis**

A statistical analysis was done with the two- sample t test for paired data to compare the continuous variables and one-way ANOVA test for more than 2 groups. Pearson chi-square test was done for categorised variables. Cross tabulation to calculate the odds ratio and 95% confidence Interval were done. All calculations were based on two-sided hypothesis with  $p < 0.05$  interpreted as significant. Statistical analysis done using SPSS software. Microsoft word and excel to generate graphs and tables were used.

**RESULTS**

Of the 65 subjects studied, 40 were males (61.54%) and 25 were females (38.46%). The mean age group of the study

population was 56±6 years similar to both the sex (Figure 1).

The mean blood sugar of the subjects under study was 325±53 mg/dl with the majority of the population in the blood sugar range of 300-350 mg/dl. Of the 65 subjects, 41 (63%) were normoalbuminuric while 24 (36.92%) were hypoalbuminemic (Figure 2).

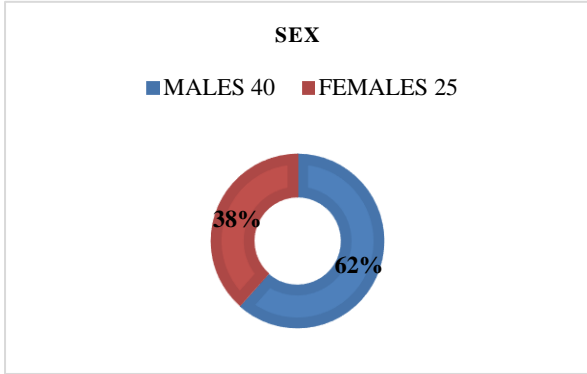


Figure 1: Sex ratio of the study population.

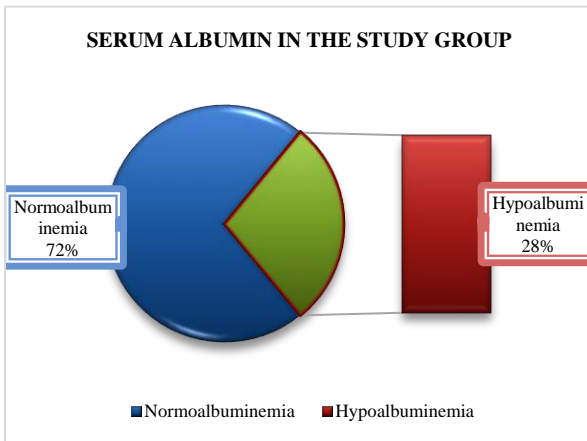


Figure 2: Analysis of serum albumin in the study group.

Majority of the patients with low serum albumin falls under the category of blood sugar >350mg/dl. (Figure 3).

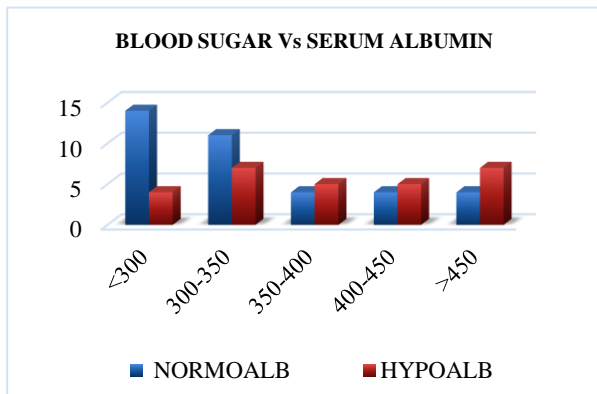


Figure 3: Blood sugar and serum albumin.

Of the 65 patients under study, 28 (43.98%) had ketonuria while 37 (56.92%) had no ketonuria.

The incidence of ketonuria were higher in individuals with blood sugar value >350 mg/dl (Figure 4).

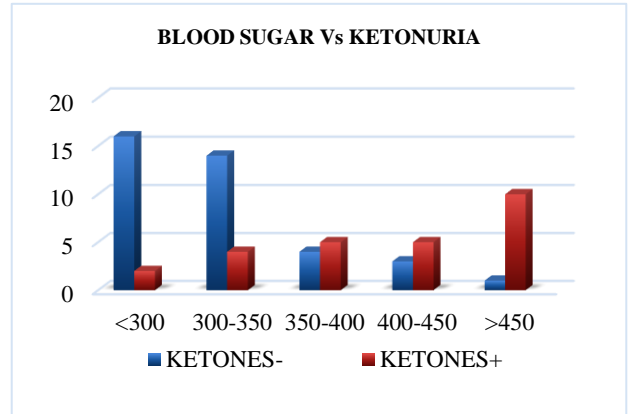


Figure 4: Blood sugar vs ketonuria.

Of the 24 hypoalbuminemic individuals, ketonuria were present in 15 of the patients (62.5%) while 9 had no ketonuria (37.5%) implying the significant association between hypoalbuminemia and ketonuria (Figure 5). Odds ratio for the categorised variable (serum albumin vs ketonuria) was 3.5 with 95% confidence interval being 1.2-10.3 with a p value of 0.02 that was statistically significant (Table 1).

Table 1: Hypoalbuminemia in ketonuria significance.

Urine ketones	Negative	Positive
Low albumin	9	15
Normal albumin	28	13
OR*	3.5*	
95%CI	1.2-10.3	
P value**	0.02**	

\*OR-Odds ratio of 3.5, \*\*significant p value of 0.02 (<0.05), 95% CI- confidence interval

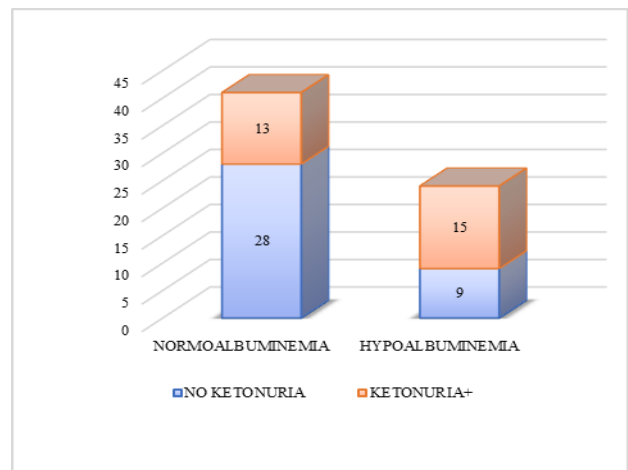


Figure 5: Ketonuria vs serum albumin.

While 28 (68.29%) of the 41 normoalbuminuric individuals (68.29%) had no ketonuria while 13 (31.71%) of the patients had ketonuria (Figure 5).

## DISCUSSION

In the study, majority of the patients with acute hyperglycemia were males as validated by the study done by Nordstorm et al probably due to higher testosterone in males and more visceral deposition of fat in males when compared to females (16). The mean age of the study population was 56±6 years that was consistent with the study by Jayagowri et al with the mean age of diabetes as 58.6±10.4 years.<sup>2</sup>

More than one-third were hypoalbuminemic predicting the greater prevalence of hypoalbuminemia in patients with acute hyperglycaemia. This throws insight on the synthesis of albumin by the liver is dependent on insulin as validated by the study showing 10% daily increment in the albumin production after infusion of insulin in diabetic patients.<sup>17</sup>

In patients with elevated blood sugars, glycation of plasma proteins especially albumin occurs and is preferred over other plasma proteins due to its abundance, longer  $t_{1/2}$  and free amino acid binding residues for glycation.<sup>4</sup> Such glycated albumin are easily degradable resulting in exponential fall in its half-life and fall in its serum levels thereby validating the significant prevalence of hypoalbuminemia in diabetic individual (37%) in this study. Further in patients with acute hyperglycemia with low levels of serum albumin, glycation of other plasma proteins occurs resulting in the formation of the toxic advanced glycation end product (AGE) that is involved in the pathogenesis of complications in Diabetes on a long term.<sup>19-21</sup> Identifying hypoalbuminemic individuals among diabetic patients is therefore crucial to prevent the unwanted glycation of plasma proteins and its associated complications in diabetes.

### *Hypoalbuminemia vs ketonuria*

In this study, one third of the subjects had ketonuria and majority of them had high blood sugars reflecting the relative insulinopenia in those subjects implying an exaggerated beta cell dysfunction and insulin resistance in patients with acute hyperglycemia.<sup>18</sup> More than 2/3<sup>rd</sup> (62.5%) of the ketonuric patients had hypoalbuminemia. These results were consistent with the study by Jayagowri et al were 49.3% of the hypoalbuminemic individuals had ketonuria though the values in this study were slightly higher. The results were also supported by the study by Chung et al that showed 48% prevalence of ketonuria in hypoalbuminemic subjects compared to 30% in normoalbuminuric controls.

This validates the production of albumin is dependent on insulin and low serum albumin mirrors the insulin reserve of the individual thereby on its beta cell functions indirectly.<sup>2,13</sup> Further as per study by Jayagowri et al serum

albumin may also act as a co-regulator along with insulin and glucagon, in the ketogenesis pathway by inhibiting the rate limiting step of mitochondrial carbonyl glutaryl co-synthase enzyme. When the production of the ketone bodies exceeds its destruction, ketosis occur.<sup>2</sup> This may explain the higher proportion of normoalbuminuric individuals with no ketosis. Thus, identifying at-risk individuals to ketosis by the easily accessible tool that also mirrors the insulin reserve will help to prevent the emergency and improve the clinical outcome greatly that will lower the incidence and mortality in diabetic ketoacidosis which is a medical emergency.

### *Limitations*

The major limitation of the study was the study population. The study has to be conducted involving larger group of patients to validate the results.

## CONCLUSION

Serum albumin reflects the insulin reserve of the beta cells and has an inverse correlation to the formation of ketone bodies and the risk to ketosis in patients with type 2 diabetes mellitus admitted with acute hyperglycemia.

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*Ethical approval: The study was approved by the Institutional Ethics Committee*

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