journal homepage: https://jablm.acclmp.com/

Journal of Applied Biochemistry & Laboratory Medicine (2023) 04 (2):20-29

Original Article

The Importance of Total Iron Binding Capacity Value in Predicting The Tendency of Hyperalbuminemia in Aged Iron-Deficient Patients Without Any Prior History of Chronic Illness

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Keywords:
IDA, Hyperalbuminemia,
TIBC, Insulin resistance

ABSTRACT

Background: Studies on iron deficiency anemia (IDA) have been a popular area of study for several years. It is well established that IDA has a role in malnutrition and hypoalbuminemia in hemodialysis patients with high creatinine levels. However, among individuals with IDA who have no prior history of other chronic diseases, nothing is known regarding the relationship between Total iron binding capacity (TIBC) and various plasma protein levels and their age-related differences.
Methods: 108 individuals having no prior history of chronic illness and having low hemoglobin levels (9.304 ± 2.3 g/dl) were evaluated. Parameters of different serum protein and iron parameters are statistically analyzed on Graph-Pad Prism (v.8.0.2) considering p-value <0.05 to be significant.
Results: TIBC and serum albumin levels are observed to be significantly positively correlated in patients of the aged Group A (P= 0.0022), however, the correlation between TIBC and albumin in the younger Group B is a non-significant positive correlation.
Conclusion: The strongly positive correlation found between serum albumin level and TIBC in our study predicts TIBC's association with increasing albumin can be an early detector of hyperalbuminemia, which may result in various metabolic disorders including type II diabetes.

INTRODUCTION

I Anemia is the most ubiquitous and pervasive public health concern in both developing and non-developing nations. It is a condition marked by a reduction of circulating red blood cells or hemoglobin and an accompanying impairment in the ability to carry oxygen. According to estimates, iron-deficient anemia is the most prevalent type of anemia which affects between one and two billion people globally. More than half of pregnant women in underdeveloped nations and 46-66% of children under 4 are anemic; iron deficiency is the main cause [1-3]. Iron is essential for several important biological processes [4]. However, too much iron also can be harmful; absorption is restricted to 1-2 mg/ day, with macrophages recycling senescent erythrocytes to supply the majority of the daily requirement of 25 mg of iron. The hormone hepcidin regulates the latter two processes thus preventing both iron excess and deficient conditions. Iron-restricted erythropoiesis suggests that there is a problem getting iron to erythroid precursors, this is seen in individuals with autoimmune disorders, cancer, infections, and chronic kidney diseases, stores may be normal or even elevated due to iron sequestration [5-6]. People with chronic kidney illness [7] and elderly people [8] may exhibit both iron deficiency and anemia of prevalent chronic diseases. Nonetheless, it is common in older people where anemia happens even when there is no iron shortage or high hepcidin [9]. On the other hand, an inadequate mobilization of iron from reserves in the face of elevated demands is seen in erythropoiesis-stimulating drug administration [10].

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An important test for the identification of iron-deficient anemia (IDA) and other abnormalities of iron metabolism is the total iron binding capacity (TIBC) [11]. Transferrin levels rise in the blood when iron reserves are reduced. Since only one-third of serum transferrin is saturated with iron, the remaining 67% of serum transferrin has an additional binding capacity. In summary, iron serum level and TIBC are negatively correlated in patients with IDA. Patients with anemia frequently have iron panels performed and TIBC is one of them. Serum albumin is the most dominant protein in blood serum [12-13] and well-studied serum protein. Low serum albumin levels have been strongly correlated with an elevated risk of mortality [14-15]. Given its intricate biochemistry, it makes sense to distinguish serum albumin as a marker of general health state as opposed to just a nutritional indicator, as has been proposed. However, prolonged protein and calorie restriction causes substantial decreases in body weight and somatic protein mass in both healthy individuals and anorexic patients but has little to no effect on blood albumin concentrations [16].

A decrease in albumin synthesis or an increase in albumin breakdown, leading to hypoalbuminemia is strongly related to hepatic inflammatory illness [17-21]. Inflammatory activities may also increase the trans-capillary loss of the protein into the extravascular space, which would lower serum concentrations [22-23]. In addition, a significant predictive factor for people with renal disease is serum albumin. In patients receiving maintenance hemodialysis (MHD), serum albumin levels below 2.5 g/dl have been linked to a 20-fold increased risk of death [24-25].On the other hand, low serum albumin level is highly associated with anemia, and increasing the level of serum albumin may promote the improvement of anemia in hemodialysis patients [26]. However, the only well-recognized cause of hyperalbuminemia in humans is dehydration [27-28]. Several studies were previously done on anemia in chronic kidney disease (CKD) patients related to malnutrition, Protein-losing Enteropathy (PLE), and low serum albumin [29-30]. Our findings demonstrate a significant positive correlation of serum albumin with increasing TIBC, hence stating a higher tendency towards hyperalbuminemia condition in IDA patients with no prior history of any chronic illness.

MATERIALS & METHODS:

Data Collection: This retrospective study was performed at the Biochemistry Department of The Calcutta Medical Research Institute, Kolkata, India. A total of 108 patients were screened and data from the hospital database were collected between January 2017 to October 2023. Patients with no previous history of infections, inflammations, or any sort of chronic disease were selected. Record of parameters like Total Iron Binding Capacity (TIBC), Unsaturated Iron Binding Capacity (UIBC), Transferrin saturation %, Ferritin, Albumin, Globulin, Total Protein (TP), and Haemoglobin were retrieved from the hospital database.

Study Design: Patients of all age groups and both genders were randomly included in this study. The patients were divided into two groups based on their age-aged individuals Group A included patients with the age >50 and the younger individuals Group B included patients with the age of <50. The number of individuals in these groups was 51 & 57 respectively. The prevalence of anemia has been defined among these patients with hemoglobin levels <12 g/dl and ferritin levels <20 (x10-7) g/dl. Patients with albumin levels <3.5 g/dl were considered to be hypoalbuminemia and those with albumin levels>5 g/dl were accepted as confirmed hyperalbuminemia.

Ethical considerations: Since the entire study was conducted on reports of patient samples coming to the lab for routine investigations, hence ethical clearance was obtained for processing and publication of the data.

Study parameter estimations: Blood samples were collected from patients and tests were run for their analysis. Haemoglobin level [biological reference interval 12 g/dl - 15 g/dl] was measured by photometric method in the Horiba Pentra XL 80 Hematology Analyzer. For the remaining study parameters, serum was extracted from the blood samples and run in the Roche Cobas 6000 Analyzer. Iron serum [biological reference interval 37 µg/dl – 170 µg/dl] was measured by the Ferrozine method without de-proteinization. UIBC was measured by the method of direct determination with Ferrozine. With the help of iron serum and UIBC values, TIBC [biological reference interval 2.5-4.5(x10-4) g/dl] and Transferrin Saturation % [biological reference interval 25–50%] were calculated using the established formula [TIBC = (serum iron concentration + UIBC); Transferrin Saturation % = (serum iron concentration ÷ TIBC) x 100]. Ferritin [biological reference interval 20-150 (x10-7) g/dl] was measured by the electrochemiluminescence immunoassay (ECLIA) method. To determine the normal functioning of the liver, the Liver Function Test was performed in the same analyzer. Albumin [biological reference interval 3.4 g/dl – 5 g/dl] was measured by the Bromocresol Green method and the Total Protein [biological reference interval 6.3 g/dl – 8.2 g/dl] was found out by the Biuret method. Globulin levels were calculated with the help of Albumin and TP values (Globulin = Total Protein – Albumin). All these tests were performed maintaining standard laboratory procedures.

Statistical Analyses: The statistical analyses were performed at Graph-Pad Prism Version 8.0.2. We presented descriptive statistics for all the parameters as Mean±S.D. For analyzing the association between various parameters we performed the Welch t-test and Mann-Whitney test respectively for data sets that follow the Gaussian distribution and those that don't follow this distribution. The relationship between TIBC and other parameters was examined with the Pearson correlation test, $p<0.05$ was considered significant.

RESULTS:

1.Comparing the means of the group-wise descriptive analyses revealed that both the groups of populations are anemic due to lower than normal levels of hemoglobin (9.304 ± 2.3). For the elderly aged group (Group A), the ferritin level was below the normal range (18.80 ± 18.25) indicating their iron-deficient condition. The younger aged group (Group B) on the other hand showed near-normal levels of ferritin. Table 1 shows the age and gender-wise distribution analysis of the total population studied. Table 2 represents the characteristics and outputs of all the parameters studied among both age groups. Fig 1 & 2 shows the comparison of TIBC with other parameters for Group A and Group B respectively.

2.Increased TIBC levels were found to be strongly positively correlated with serum albumin levels (Fig 3). Correlation analysis revealed that for Group A individuals TIBC and Albumin are significantly positively correlated (r =0.4189, p-value =0.0022; Fig 4) suggesting hyperalbuminemia with increased total iron binding capacity of the blood which is the case in iron-deficient patients. On the other hand, the younger Group B shows a very less positive correlation which is not significant enough (r =0.1194, p-value =0.3763; Fig 5) to conclude that their TIBC levels affect the albumin levels in their body. Table 3 shows the complete correlation analysis of TIBC and all the other parameters studied.

Table 1: Age and gender-wise distribution

		Age-wise Categories	
	All patients	**Group A**	**Group B**
No. of patients	108	51	57
Woman%	63.88%	54.90%	70.10%
Age (Yr)	48.00± 17.74	63.64± 8.86	34.01± 10.47

± indicates the standard deviation

Table 2: Descriptive statistics and outputs of all the parameters studied among both age groups

Parameters	**All patients**	**Age-wise categories**		**T-test**	
		Group A (>50)	**Group B (<50)**	**P value**	**Summary**
Iron Serum (µg/dl)	47.14 ± 31.38	52.67 ± 30.44	42.19 ± 31.65	*0.0215*	*
TIBC (×10-4 g/dl)	3.434 ± 0.9	3.134 ± 0.8	3.703 ± 0.9	0.0024	**
Ferritin (×10-7g/dl)	20.23 ± 19.28	18.80 ± 18.25	22.46 ± 20.38	*0.1850*	
Transferrin saturation %	17.82 ± 21.91	22.54 ± 28.53	13.60 ± 12.34	*0.0053*	**
Albumin (g/dl)	3.967 ± 0.6	3.805 ± 0.6	4.112 ± 0.5	0.0118	*
Globulin (g/dl)	3.524 ±0.7	3.471 ± 0.8	3.571 ± 0.5	0.4859	
Total protein (g/dl)	7.490 ± 0.7	7.276 ± 0.7	7.682 ± 0.5	0.0032	**
Haemoglobin (g/dl)	9.304 ± 2.3	9.173 ± 2.1	9.421 ± 2.4	0.5783	

*P value significant at P < .05 for 95% confidence interval

Table 3: Correlation of TIBC with various parameters studied:

Parameters	All Patients	Group A (>50)	Group B (<50)
Albumin (g/dl)	r =0.3243 p =0.0006 ***	r =0.4189 p =0.0022 **	r =0.1194 p =0.3763
Globulin (g/dl)	r = -0.02262 p = 0.8163	r = -0.2625 p = 0.0628	r = 0.2230 p = 0.0955
Total Protein (g/dl)	r = 0.2647 p = 0.0056 **	r = 0.07580 p = 0.5970	r = 0.3526 p = 0.0071 **
Haemoglobin (g/dl)	r = -0.2373 p = 0.0163 *	r = 0.06953 p = 0.6278	r = -0.5051 p <0.0001 ****
Iron Seum (µg/dl)	r = -0.3355 p = 0.0004 ***	r = -0.1216 p = 0.3951	r = -0.4576 p = 0.0003 ***
Transferrin Saturation %	r = -0.6189 p <0.0001 ****	r = -0.6242 p = <0.0001 ****	r = -0.6915 p <0.0001 ****
Ferritin (×10-7 g/dl)	r = -0.2938 p = 0.0020 **	r = -0.2919 p = 0.0376	r = -0.3596 p = 0.0060 **

r = correlation coefficient ; P = significance value. P value significant at P <.05 for 95% confidence interval

FIGURES:

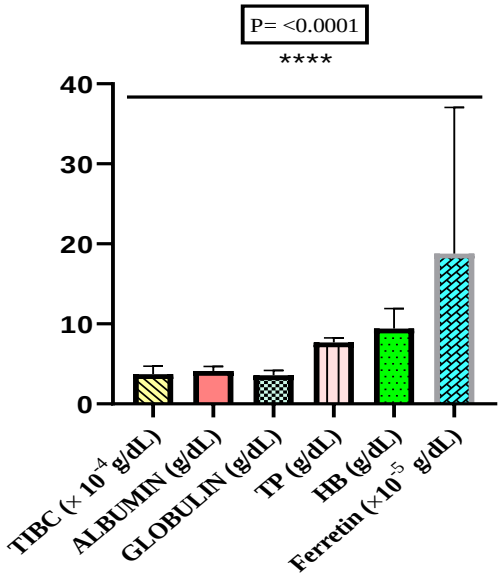

Fig 1: Comparison of serum TIBC levels with various plasma protein fractions & blood hemoglobin & ferritin in individuals > 50 years of age[p-value <0.0001]

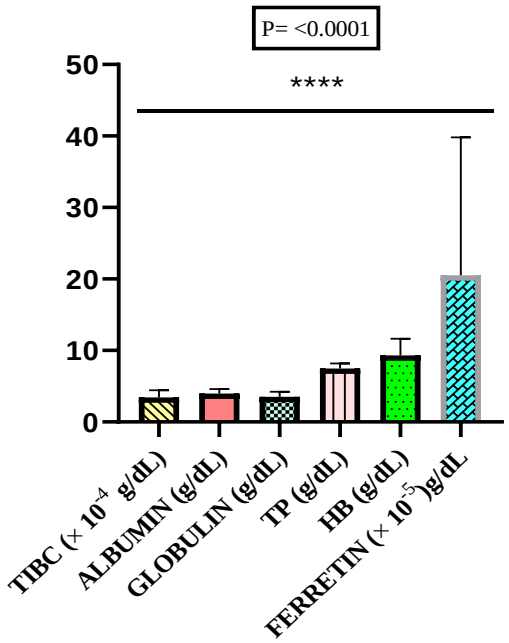

Fig 2: Comparison of serum TIBC levels with various plasma protein fractions & blood hemoglobin & ferritin in individuals ≤ 50 years of age[p-value <0.0001]

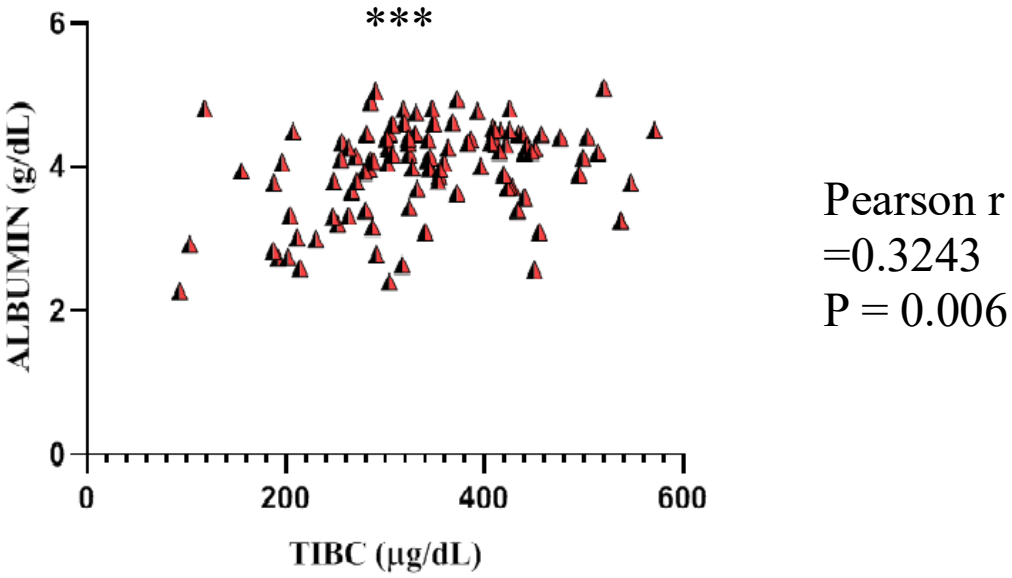

Fig 3: Correlation of serum albumin level with serum TIBC level for all individuals

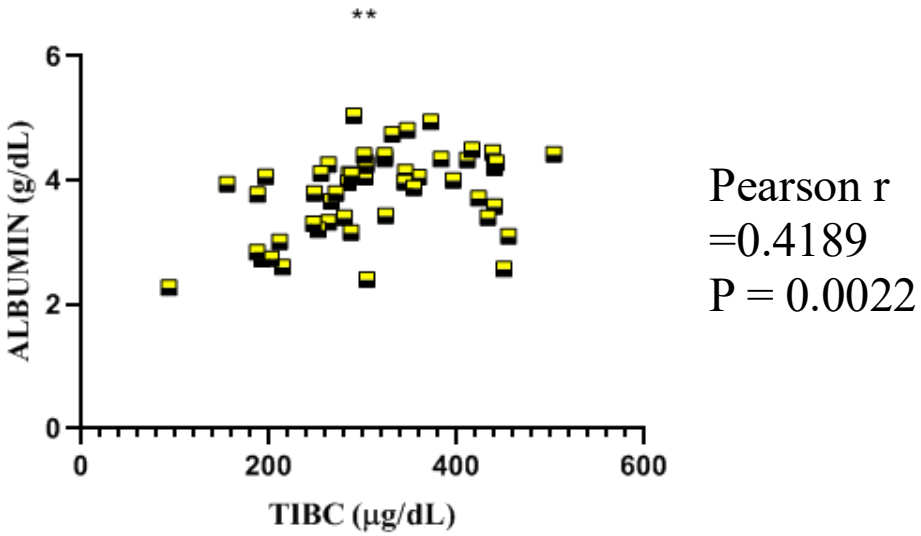

Fig 4: Correlation of serum albumin level with serum TIBC level in individuals > 50 years of age[p-value = 0.0022]

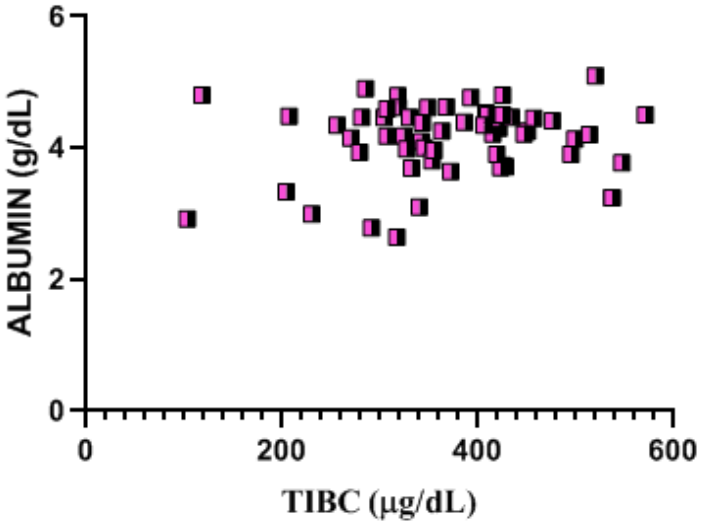

Fig 5: Correlation of serum albumin level with serum TIBC level in individuals ≤ 50 years of age [p-value = 0.3763]

DISCUSSION:

Reduced red blood cells or anemia is characterized by a drop in hemoglobin levels from normal ranges in the blood. Anemia is more likely to strike young women. Previous research indicated that anemia is more common among young women [31]. A total of 63.88% of the patients in this study are female, and 70.10% of the aforementioned women are under 50 years old. This fits into the category of moderate public health issues [32]. Haemoglobin is one of the good standards for diagnosing IDA [33]. However, to predict if they are iron deficient we also took into consideration various parameters like iron serum level, total iron binding capacity, transferrin saturation %, and ferritin levels. Studies showed that among all these parameters ferritin was the most accurate one in determining iron levels in our body [34-36]. Patients with ferritin levels <20 (x10-7) g/dl were considered iron deficient and those >150 (x10-7) g/dl were found to be iron-sufficient individuals. On the other hand, the total number of iron atom binding sites on transferrin, or TIBC, is equal to the protein's capacity. It is widely recognized for its capacity to transport iron [37], and ID is associated with a rise in serum transferrin content. TIBC is intrinsically more stable as a measure of iron status because it is a proxy for transferrin and is not as susceptible to rapid concentration variations as plasma iron concentration, which is influenced by food consumption and significant diurnal variation [38]. As a result, there are few tests and daily changes in TIBC [39]. However, higher TIBC levels only represent severe iron exhaustion and can only identify ID after the onset of anemia owing to the considerable overlap between normal and abnormal values in patients with iron insufficiency [40]. In addition, previous studies have shown that TIBC is not a good marker for the early detection of IDA [41]. Given that every patient who was included in our study fulfilled the requirements for moderate anemia, having <12 g/dl hemoglobin, TIBC ought to fairly represent the degree of iron deficiency in our investigation.

Previous research has comprehensively examined and demonstrated the favorable correlation between TIBC and serum albumin in patients with IDA who have left ventricular modeling. This suggests that TIBC provides appropriate support for its nutritional value [42]. Increased TIBC levels were found to be strongly positively correlated with serum albumin levels. When compared to the younger group (<50 years old), the correlation between TIBC and serum albumin in the older group (>50 years old) was significantly higher **(Fig 4 & 5)**, suggesting that TIBC could be useful in identifying early onset of hyperalbuminemia in IDA patients who have no prior history of chronic illness. Numerous investigations have been conducted in this regard, but the only known factors to cause hyperalbuminemia are metabolic syndromes, including insulin resistance, and dehydration, and treated as an indicator of obesity, and hypernutrition [43-44]. However, a different study found that a lower concentration of serum albumin's cardioprotective effects was linked to a higher risk of cardiovascular death, coronary heart disease, and carotid atherosclerosis [45-46]. Furthermore, glucose metabolism and glucose homeostasis are intimately related to IDA [47]. Studies conducted on animal models have demonstrated that iron deficiency may ultimately lead to changes in insulin signaling, as demonstrated by the presence of hyperglycemia, hyperinsulinemia, and hyperlipidemia. Reduced oxidative capability causes a switch in the preferred fuel used, from fat to glucose, which may ultimately cause insulin resistance and the development of type II diabetes [48-51]. An in vivo rat model demonstrated a dose-dependent increase in albumin mRNA

transcription in response to an increase in insulin levels. Insulin has been identified as a regulator of albumin gene transcription [52-53]. Additionally, our research suggests that insulin resistance and other metabolic dysregulations may be linked to hyperalbuminemia in IDA individuals without a history of chronic illness. The association between TIBC and elevated blood albumin can be evaluated as a potential early indicator of these processes.

CONCLUSION:

Very few studies have been done on patients with no prior history of any chronic illness establishing a possible relationship between TIBC and protein serum levels. Our studies showed that TIBC has a positive correlation with albumin and when compared to the younger group (<50 years old), the aged group (>50 years old) showed a higher significant positive correlation, leading to hyperalbuminemia. Various studies showed that the gradual rise of albumin levels has an impact on metabolic syndrome specifically insulin resistance. Hence, our study predicts that IDA patients with no chronic illness may develop some insulin resistance and in the future type II diabetes and the association of TIBC with increasing levels of serum albumin may have some primary role in its early detection. It is suggested that further research on this context needs to be done.

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ACKNOWLEDGEMENT: Nil

CONFLICT OF INTEREST: Nil