

Original Research Article

Role of total calcium and corrected calcium in comparisons with computed tomography to predict severity of acute pancreatitis

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ABSTRACT

Background: The objective of the study was to evaluate corrected calcium levels in patient of acute pancreatitis and to evaluate role of corrected calcium as predictor of severity in acute pancreatitis in comparison to computed tomography (CT) scan.

Methods: The study was conducted in Department of Biochemistry of G.G.S Medical College in collaboration with the Department of Surgery and Department of Radio diagnosis. 50 patients, with clinical diagnosis of acute pancreatitis, attending the Inpatient Department of Department of Surgery, were taken. 50 patients, of either sex of 18 to 70 age groups suffering from acute pancreatitis were enrolled for the study.

Results: On exploring the data, highly significant negative correlation found between CT severity index (CTSI) and serum calcium ($p \leq 0.001$; r value = -0.520) whereas the non-significant correlation found between CTSI and amylase ($p = 0.778$; r value = -0.041). The corrected calcium and CTSI shows highly negative significant correlation ($p \leq 0.001$; r value = -0.654). Serum albumin with CTSI also shows significant correlation ($p = 0.006$; r value = 0.385). But no significant association with lipase ($p \geq 0.05$).

Conclusions: We observed that corrected calcium and calcium is better and alternative marker for predicating the severity of disease because corrected calcium and calcium is having good positive predictive value to indicate progression of damage and also a highly significant negative predictive value to rule out severity of acute pancreatitis.

Keywords: Acute pancreatitis, Albumin corrected calcium, Computed tomography severity index, Sensitivity, Specificity

INTRODUCTION

Acute pancreatitis (AP) is defined as an acute condition presenting with abdominal pain and is usually associated with raised pancreatic enzyme levels in the blood or urine as a result of pancreatic inflammation.¹ The diagnosis of AP is usually based on a combination of clinical findings, laboratory investigations, and imaging techniques. There is no gold standard test available to diagnose AP at present.^{2,3} Calcium plays a central role in the pathogenesis of pancreatitis and our understanding in this

field is still evolving. Calcium is required for normal secretory function of the pancreatic acinar cells, but these signals are transient and mainly confined to apical pole. It has been shown that sustained global increase in cytosolic Ca^{++} is responsible for premature trypsinogen activation, vacuolization, and acinar cell death.⁴ Recent insight into calcium-mediated acinar cell injury suggests that hypocalcemia of severe acute pancreatitis (SAP) might play a protective role by depleting the acinar cells of extracellular supply of calcium.⁵

Calcium binds to albumin and only the unbound (free or ionized) calcium is biologically active, the serum level must be adjusted for abnormal albumin levels. For every 1 g/dl drop in serum albumin below 4 g/dl, measured serum calcium decreases by 0.8 mg/dl. The previous study shows that most common cause of the low serum calcium often found in patients with this disease is a low serum albumin; when correction of serum calcium is made for hypo-albuminaemia, most patients are found to be normocalcaemic. The occasional hypocalcaemia as shown by the 'corrected' serum calcium or by serum ionized calcium measurement is usually mild and transient, indicating that the normal homeostatic mechanisms of the body can efficiently maintain the physiologically active fraction of the serum calcium within, or close to, the normal range.⁶

Serum calcium and albumin-corrected calcium (ACC) obtained within the first 24h of hospital admission are useful predictors of severity in AP and have sensitivity (S), specificity (Sp), and predictive values that are comparable with those of the traditional prognostic scales. With an adequate interpretation of their cut-off points, they are valuable for identifying the patients that require intensive care support, even in primary and secondary care hospitals. The aim of study to evaluate corrected calcium levels in patient of AP and to evaluate role of corrected calcium as predictor of severity in AP in comparison to computed tomography (CT) scan.

METHODS

The study was conducted in Department of Biochemistry of G.G.S Medical College in collaboration with the Department of Surgery and Department of Radio diagnosis with the time frame of April 2016 to April 2017, 50 patients, with clinical diagnosis of AP, attending the Inpatient Department of Department of Surgery, were taken. 50 patients, of either sex of 18 to 70 age groups suffering from AP were enrolled for the study. Excluded patients with history of any acute or chronic illness which can affect the concerned parameters like, diabetes mellitus, pregnant females, impaired renal function, allergy to contrast, hyperparathyroidism, malnourished,

calcium supplements. After the 24 hours of admission serum calcium, corrected calcium, serum albumin, amylase, lipase, contrast-enhanced computed tomography scan was done for AP patients. In order to evaluate the TC and ACC as severity the lowest TC value were collected within first 24 Hours of admission. These values were then corrected according to the serum albumin level to obtain albumin corrected calcium. Albumin corrected calcium (mg/dl) = total calcium (mg/dl) + 0.8 × [4-serum albumin (g/dl)].⁷

The modified CT severity index (CTSI) or Balthazar score was determined at admission and 48 hours at some time and any point of time during admission as per the need of the patient.⁸ Ethical clearance was obtained from the institution review board. Informed consent was obtained from each patient.

Data analysis

One-way ANOVA and the chi-square test were employed to establish the statistical significance of the different groups, based on the characteristics of the analyzed variables. Statistical significance determines with $p < 0.05$. ROC curve was used in order to establish possible cutoff value for TC and ACC. The maximum cutoff value was utilized to calculate the S, Sp, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR) and negative likelihood ratio (NLR) of each criterion by means of contingency tables. All the statistical analyses were done using statistical package for the social sciences programme v.21 (IBM SPSS0029).

RESULTS

During the study period, 50 patients were included in study. The age of the patients ranged from 18 to 70 years. AP was common in the age group of 36 to 50 year (42%) followed by 24% in the age group of 18-35 years. There were 36 males and 14 females giving a ratio of 2.5:1. Among all age groups 60% cases of alcoholic pancreatitis and gall stone account for 28% of AP were present.

Table 1: Mean value of routine parameters in patients.

Parameters	Mean±SD	Range	Acceptable normal range
Fasting plasma glucose (mg/dl)	122.58±41.49	71.00-259.00	70-110
Blood urea (mg/dl)	37.70±28.99	10.00-136.00	15-45
Creatinine (mg/dl)	1.15±2.00	0.50-1.5	0.8-1.3
ALT (IU/l)	72.88±48.17	11.00-255.00	5-35 (F) 30-65 (M)
AST (IU/l)	83.12±87.11	11.00-608.00	5-40
ALP(IU/l)	243.64±268.26	66.00-1360.00	>15 yrs (60-150)
Total Bilirubin(mg/dl)	1.37±1.93	0.50-14.30	0.3-1.1
Direct Bilirubin(mg/dl)	0.50±1.30	0.10-9.50	0.1-0.4
Serum Sodium(mEq/l)	134.32±3.87	128.00-142.00	135-155
Serum potassium (mEq/l)	3.80±0.61	3.00-5.70	3.5-5.5
Serum chloride(mEq/l)	94.60±3.20	90.00-106.00	98-107

Table 2: Mean value of special parameters in patients.

Parameters	Mean±SD	Range	Acceptable normal range
Serum amylase (U/l)	746.34±816.53	75.00-4408.00	Up to 90
Serum lipase (U/l)	889.27±1343.94	90.00-8263.00	Up to 190
Serum calcium (mg/dl)	7.65±0.77	5.20-8.70	9-11
Serum albumin (g/dl)	3.71±0.44	2.40-4.20	3.5-5.5
Corrected calcium (mg/dl)	7.88±0.76	5.60-9.32	8.4-9.5

Table 3: Correlation of CTSI with calcium, corrected calcium, amylase, lipase and serum albumin.

	Parameter	P value	Correlation coefficient	Significance
CTSI	Calcium (mg/dl)	<0.001	-0.520	HS
	Albumin (g/dl)	0.006	0.385	S
	Corrected calcium (mg/dl)	<0.001	-0.654	HS
	Amylase (IU/l)	0.778	-0.041	NS
	Lipase (IU/l)	0.310	0.146	NS

Table 4: ROC showing sensitivity, specificity, predictive values and likelihood ratios of the calcium and corrected calcium predicting progression to severe acute pancreatitis.

Parameter	AUC	S (%)	Sp (%)	PPV (%)	NPV (%)	LR+	LR-
Serum calcium	0.762	82.6	66.7	82.14	100	1.23	0.80
Corrected calcium	0.853	82.6	77.8	88.46	100	1.06	0.94

The data of patients group according the severity of pancreatitis on the basis of CTSI scoring system. Out of 50 patients 27 were comes under moderate pancreatitis and 23 under severe pancreatitis. In this study, no patients were enrolled with mild pancreatitis.

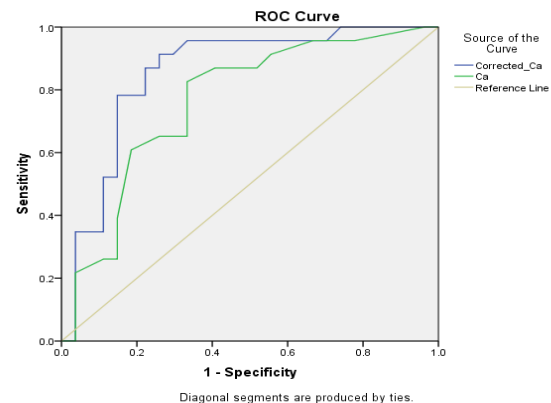
Table 1 shows fasting plasma glucose (FPG), AST, ALT, ALP was deranged with mean value of 122.58±41.49 mg/dl, 83.12±87.11 IU/l, 72.88±48.17 IU/l, 243.64±268.26 u/l respectively in AP patients.

Raised level of serum amylase and lipase early marker of AP. The above table shows the mean values of serum amylase, lipase, calcium, corrected calcium, albumin in AP patients. The mean value of serum calcium 7.65±0.77 mg/dl showing hypocalcemia.

Corrected calcium was calculated from serum calcium and serum albumin by applying respective formula,

Corrected calcium (mg/dl) = total calcium (mg/dl) + 0.8 × [4-serum albumin (g/dl)].

On exploring the data, highly significant negative correlation found between CTSI and Serum calcium ($p \leq 0.001$; r value=-0.520) whereas the non-significant correlation found between CTSI and amylase ($p=0.778$; r value=-0.041). The corrected calcium and CTSI shows highly negative significant correlation ($p \leq 0.001$; r value=-0.654). Serum albumin with CTSI also shows significant correlation ($p=0.006$; r value=0.385). But no significant association with lipase ($p \geq 0.05$)

**Figure 1: ROC curve of sensitivity, specificity, predictive values and likelihood ratios of the calcium and corrected calcium predicting progression to severe acute pancreatitis.**

The results of the analysis with ROC curves shows that maximum cut off value for total calcium is 7.85 mg/dl and for corrected calcium it is 7.81 mg/dl. The curve analysis shows serum calcium having sensitivity (S) 82.6%, specificity (Sp) 66.7%, PPV 82.14%, NPV 100%, LR+ 1.23, LR-0.80. And for corrected calcium the curve shows the sensitivity (S) 82.6%, specificity (Sp) 77.8%, PPV 88.46%, NPV 100%, LR+ 1.06, LR-0.94.

DISCUSSION

Amylase is a glycoside hydrolase enzyme primarily produced by the pancreas and salivary glands. In AP, the level of amylase increases rapidly within six hours of

onset of disease, with half-life of 10 to 12 hours, remains elevated for 3 to 5 days.⁹⁻¹¹ Clinical symptoms of AP does not correlate even if amylase levels falls to its normal levels from the peak value which indicates that amylase level does not show significant statistic correlation with disease severity and ultimate prognosis.¹²

Our study, shows the mean value of serum amylase is 746.34 ± 816.53 also did not indicate correlation with severity of pancreatitis as illustrated in Table 3 ($p=0.778$, r value= -0.041).

The serum concentration of lipase increases within 3 to 6 hours of onset of disease and peaks value reaches within 24 hours and remains constant for 7 to 14 days before it falls to the normal level. Lipase is reabsorbed in renal tubules and stays for long at higher concentration, thereby giving greater sensitivity in patients with delayed presentation. Increased serum level of lipase can also be seen in intra-abdominal pathologies including acute cholecystitis, appendicitis, inflammatory bowel disease, intestinal ischemia, obstruction, perforation, and renal insufficiency suggesting a poor correlation between lipase activity and disease severity.¹³

Earlier study also concluded that amylase and lipase concentration did not predict the severity of AP as assessed by imaging techniques.¹⁴

Lankisch et al also concluded that severity of AP is independent of the elevation in serum amylase and lipase level ($\leq 3n$ or $>3n$) on admission. Patients with slight increased levels can also develop severe AP.¹⁵

Present study also observed the mean value of lipase 889.27 ± 1343.94 having no significant correlation with CTSI ($p=0.310$, r value= 0.146).

Table 2 and 3 concluded highly negative statistically significant correlation found between CTSI and serum calcium with mean value 7.65 ± 0.77 ($p \leq 0.001$; r value= -0.520). The corrected calcium with mean value 7.88 ± 0.76 and CTSI shows highly negative significant correlation ($p \leq 0.001$; r value= -0.654). Serum albumin with mean value 3.71 ± 0.44 ($p=0.006$; r value= 0.385) CTSI also shows significant correlation.

In a study conducted in 2017 on patients of AP showed mean calcium value 6.9 mg/dl and 7.84 mg/dl with developed complication and without complication respectively. While the mean adjusted values were 7.38 mg/dl and 7.39 mg/dl in respective categories. Calcium levels ≤ 7.5 mg/dl (hypocalcemia) is good predictor for diagnosing the severity of AP.¹⁶

In Table 3 and 4 our study concluded that the cutoff value of total calcium and corrected calcium ≤ 7.85 mg/dl and ≤ 7.81 mg/dl respectively were also similar to that of the CTSI scores. The sensitivity (S) 82.6%, specificity (Sp) 66.7%, PPV 82.14%, NPV 100%, LR+1.23, LR-0.80 for

total calcium was observed while for corrected calcium the sensitivity (S) 82.6%, specificity (Sp) 77.8%, PPV 88.46%, NPV 100%, LR+1.06, LR-0.94 was seen. The total calcium and corrected calcium lower than cutoff value would be ample to identify patient with severity of AP.

Edakkepuram concluded that hypocalcaemia and low ACC can predict severity of AP, as with BISAP score, but it is not superior to BISAP score.¹⁶

Albumin is a major immune protein in the human body. A low serum albumin level can lead to decreased immunity, hence reducing the anti-infection ability of patients.¹⁷ Therefore, the level of serum albumin is also good indicator of AP. Our study shows significant correlation of hypoalbuminemia with CTSI (3.71 ± 0.44 , $p=0.006$; r value= 0.385) (Table 3).

On exploring the data of Table 4 showed highly significant correlation of serum calcium, corrected calcium with CTSI. The mean value of serum calcium in moderate and severe pancreatitis were 7.91 ± 0.75 mg/dl and 7.32 ± 0.69 mg/dl respectively. And the corrected calcium with the mean value of 8.25 ± 0.71 and 7.41 ± 0.56 mg/dl in moderate and severe pancreatitis respectively. The statistical analysis shows that the level of calcium and corrected calcium decrease with increase in disease severity ($p \leq 0.00$).

In regard to ACC, with the 7.5mg/dl cut-off point, its S was the same as that of the rest of the criteria analyzed, but its PPV and LR+ were the highest. With the 6.5 mg/dl cut-off point, its PPV reached 83% and its diagnostic accuracy was approximately 82% (calculated with the Fagan nomogram method and an estimated AP prevalence of 9.4%). These high prediction levels and the ease in calculating them when the serum albumin level is known, make obtaining the ACC concentration worthwhile, since it considerably increases diagnostic accuracy. When there was a TC concentration below 6.5 mg/dl, the patients had a 60% probability of presenting with severe AP. This predictive value is even superior to that of the APACHE-II score, and shows us the necessity of understanding TC properties as a prognostic factor of AP severity.¹⁸

CONCLUSION

We observed that corrected calcium and calcium is better and alternative marker for predicating the severity of disease because corrected calcium and calcium is having good PPV to indicate progression of damage and also a highly significant NPV to rule out severity of AP. We can use calcium and corrected calcium as valuable predictors for severity of AP as both these parameters are highly significant negative correlation with CTSI scoring. Beside this these parameters also have added advantage of evaluation on daily basis.

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