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ORIGINAL ARTICLE

Association of various risk factors with hypocalcemia in decompensated liver disease of viral origin.

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ABSTRACT… Objective: To determine the association of various factors with hypocalcaemia in individuals with decompensated cirrhosis with chronic viral hepatitis etiology. **Study Design:** Cross Sectional Observational Study. **Setting:** Department of Internal Medicine, Nishtar Medical University and Hospital Multan. **Period:** Six Months Extending from July, 2019 to December, 2019. **Material & Methods:** One hundred and seventy six patients were selected. **Results:** Among 176 study cases, 97 (55.1%) were male patients while 79 (44.9%) were females. Mean age of our study cases was noted to be 48.85 ± 8.13 years. Of these 176 study cases, 70 (39.7%) were from rural and 106 (60.3%) were urban background. Out of them, 124 (70.5%) were from poor families and remaining 52(29.5%) were middle class. Mean serum calcium level calculated was found to be 7.24 ± 0.87 mg/dl. Hypocalcemia was noted in 152 (86.4%) of our cases. It was seen that there was significant association among gender and hypocalcemia (p-value 0.000), poor socioeconomic status and hypocalcemia (p-value 0.014), obesity and hypocalcemia (p-value 0.009), duration of disease and hypocalcemia (p-value 0.001) treatment status and hypocalcemia (p-value 0.001), viral type with hypocalcemia (p-value 0.000). However no significant relation was discovered among hypocalcemia and age of patient and residential status of patients. **Conclusion:** We have noticed a very high distribution of hypocalcemia among decompensated cirrhotic having chronic viral hepatitis etiology. We also discovered that hypocalcemia had significant association with female sex, low socioeconomic fragment of society, longer duration of disease, untreated patients and hepatitis C related cirrhosis.

Key words: Decompensated Liver Disease, Hypocalcemia, Hepatic Osteodystrophy, Liver Cirrhosis.

INTRODUCTION

Hypocalcemia is a frequently observed biochemical defect in cirrhotics.[1] Normal serum calcium levels (8.5 to 10.5 mg/dl) are regulated by three major hormonal controls including parathormone (PTH), calcitriol i,e vitamin D, and calcitonin.[2,3] Serum calcium exists in two forms, nearly 50% of the total calcium is protein bound, and nearly other half exist as free ionized state and is active biochemically and physiologically.[4,5] That's why, its compulsory to correct serum calcium levels against serum albumin level before documenting hypercalcemia or hypocalcemia.[1] Hypocalcemia of cirrhosis is the result of multiple factors including poor nutrition, defective absorption of calcium, failure of vit. D activation and secondary deficiency of vitamin D, diuretics use for anasarca, parallel kidney disease, respiratory disease causing alkalosis.[6,7,8,9]

As the disease progresses from compensated cirrhosis to decompensated cirrhosis, there occurs functional impairment of liver, pressure in portal circulation increases and causes varices in esophagus and stomach, transudate ascites, spontaneous bacterial peritonitis and encephalopathy.[10] As the liver is the site for production of albumin which later binds with serum calcium in blood, a cirrhotic liver is not able to manufacture sufficient albumin to bind with calcium. As a result of fall in albumin, less calcium now binds with protein and hypocalcemia ensues.[11] Xing Z conducted a study in China and identified that low serum calcium levels

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were prevalent among 87.7 % of patients having decompensated cirrhosis.[12]

Data regarding low serum calcium levels (hypocalcemia) in cirrhosis is quite meager and yet none has studied the effect of various factors in predisposition of hypocalcemia of cirrhosis of viral origin. Although few studies have been done to see frequency of hypocalcemia and QT prolongation in our population yet none of them has studied the determinants of hypocalcemia among decompensated cirrhotic having viral etiology. Our study will lay down foundations and provide baseline data for frequency of hypocalcaemia among decompensated cirrhotic in our population. It will also identify determinants of hypocalcemia in patients with decompensated liver disease of viral origin. By utilizing the results of this study, future researchers will be able to chalk out plans regarding further studies. In long term it may guide clinicians to take steps to minimize disease morbidity and thus improve life quality of these patients by correcting their calcium levels. It may also guide about future treatment strategy regarding addition of calcium supplement in certain groups of cirrhotic patients.

To determine the association of various factors with hypocalcaemia in individuals with decompensated cirrhosis with chronic viral hepatitis etiology.

OPERATIONAL DEFINITIONS

Decompensated liver disease of viral origin

Any patient diagnosed with chronic viral hepatitis proved by HBV DNA or HCV RNA positivity having any two features of the followings; drowsiness/ coma, jaundice, edema feet, hematemesis and/or melena, ascites, low serum albumen, prolonged prothrombin time and sonographic features of shrunken liver, dilated portal vein and ascites.

Hypocalcaemia

Hypocalcaemia was established if corrected calcium level was less than 8.2 mg/dl.

MATERIAL & METHODS

This study was conducted in department of General medicine, Nishtar hospital Multan six months after approval from ethical review committee (No. 78/10/5/2019) from July, 1st 2019 to December, 31st 2019. After using appropriate formula sample size was calculated to be one hundred and sixty six (166) patients with decompensated liver disease of viral origin. A cross sectional study was planned. One hundred and sixty six patients with either sex and between 20 to 60 years age having decompensated liver disease of viral origin were included by non-probability consecutive sampling technique. Patients having history of alcohol intake, co-existing liver diseases like autoimmune and drug induced liver disease, known parathyroid hormone deficiency were excluded. After proper consent 10 ml of fasting blood sample was drawn and sent to laboratory for assessment of serum calcium and albumen. Data regarding serum calcium levels was entered in proforma. Data was analyzed by using SPSS version 24. Frequencies were calculated for categorical variables like gender, age groups, obesity and low calcium level. We calculated mean ±SD for quantitative variables including age, disease duration, therapy duration and body mass index. After applying chi square test association of hypocalcemia with various categorical variable was assessed. P-value ≤0.05 was taken significant statistically.

RESULTS

Among 176 study cases, 97 (55.1%) were male patients while 79 (44.9%) were females. Mean age of our study cases was noted to be 48.85 ± 8.13 years. We found that our study population had mean age 48.75 ± 8.43 years (with age range of 33 years to 60 years). Male patients population had mean age 51.17 ± 7.93 years while female patients had their mean age 48.90 ± 7.74 years. Mean serum calcium level calculated was found to be 7.24 ± 0.87 mg/dl. Hypocalcemia was noted in 152 (86.4%) of our cases (Table-I).

Hypocalcemia was more prevalent among female patients i,e 75(95%) out of 79 females had hypocalcemia while 78 (80%) males had hypocalcemia. Hypocalcemia had a strong statistical association with female gender. (Table-II) Of these 176 study cases, 70 (39.7%) were from

rural and 106 (60.3%) were urban background. Out of them, 124 (70.5%) were from poor families and remaining 52(29.5%) were middle class. We have noticed that mean body mass index (BMI) in our study cases was 23.89 ± 4.07 kg/m^2 and obesity was observed in 50 (28.4%) of our study cases. Mean for the duration of disease was found to be 27.11 ± 9.13 months and duration of disease was > 18 months in 96 patients (54.54%) of cases in remaining 80 (45.46%) patients had disease duration <18 months. Mean duration of disease therapy was 10.04 ± 2.58 months. Only 33 (18.7%) of the patient got curative treatment while 143(81.3%) were never treated by antiviral therapy. Among study sample, 33 (18.7%) of patients had hepatitis B while hepatitis C was etiological factor in 143 (81.3%) of our study cases.

It was seen that there was significant association among gender and hypocalcemia (p-value 0.000), poor socioeconomic status and hypocalcemia (p-value 0.014), obesity and hypocalcemia (p-value 0.009), duration of disease and hypocalcemia (p-value 0.001) treatment status and hypocalcemia (p-value 0.001), viral type with hypocalcemia (p-value 0.000). However no significant relation was discovered among hypocalcemia and age of patient and residential status of patients.

Low Serum Calcium	Patients Number (%)
Yes	152 (86.4%)
No	24 (13.6%)
Total	176 (100%)

Table-I. Hypocalcemia distribution in study cases.

Gender	Hypocalcemia		P-Value
	Yes	No	
Male (n = 92)	78	19	0.004
Female (n = 74)	75	04	
Total	176		

Table-II. Association of hypocalcemia with gender among decompensated cirrhotic with viral etiology.

Parameters	Groups	Hypocalcemia		P-Value
		Yes	No	
Age group	20-40 years (n=42)	34	08	0.103
	41-60 years (n=134)	121	13	
Residential status	Rural (n=70)	59	11	0.208
	Urban (n=106)	96	10	
Socioeconomic status	Poor (n=124)	114	10	0.014
	Middle (n=52)	41	11	
Obesity	Obese (n=51)	50	01	0.009
	Non-obese (n=125)	105	20	
Disease duration	< 18 month (n=80)	62	18	0.001
	>18months (n=96)	90	06	
Treatment status	Treated (n=33)	22	11	0.001
	Untreated (n=143)	131	12	
Viral etiology	Hepatitis B (n=33)	18	15	<0.001
	Hepatitis C (n=143)	136	07	

Table-III. Association of various risk factor with hypocalcemia in decompensated cirrhosis of viral

DISCUSSION

Cirrhosis is chronic inflammatory disease of liver parenchyma which finally leads to constellation of histological changes which comprise of regenerative nodules which are interspersed with fibrous septa. This histology is accompanied by portal hypertension and multiple complications of decompensated liver disease. As compensated cirrhosis progresses into decompensated phase, ascites, variceal bleeding, encephalopathy or spontaneous bacterial peritonitis ensues. Among these complications is hypocalcaemia which is not well studied so far. Data regarding various factors which can predispose to hypocalcaemia and hepatic dystrophy has not been extensively worked up yet.

We had a total of 176 study cases. Among 176 study cases, 97 (55.1%) were male patients while 79 (44.9%) were females. Nadeem et al[13] Farooqi et al[14] Alam et al[15] have also reported male gender predominance. We found that our study population had mean age 48.75 ± 8.43 years (with age range of 33 years to 60 years). Male patients population had mean age 51.17 ± 7.93 years while female patients had their mean age 48.90 ± 7.74 years. Nadeem et al[13] and Naheed et al[16] also reported similar age distribution. Among study sample, 33 (18.7%) of patients had hepatitis B while hepatitis C was etiological factor in 143 (81.3%) of our study cases. A study conducted by Nadeem et al[13] from Lahore has also reported hepatitis C being more predominant than hepatitis B i.e 77% vs 23 % in patients with liver cirrhosis.

In our study, hypocalcemia was stratified against gender, age, socioeconomic status, disease duration, residential status, duration on treatment, obesity and viral hepatitis. It was seen that there was significant association among gender and hypocalcemia ($p<0.001$), poor socioeconomic status and hypocalcemia ($p=0.019$), obesity and hypocalcemia ($p<0.001$), duration of disease and hypocalcemia ($p=0.009$) treatment status and hypocalcemia ($p=0.006$), viral type with hypocalcemia ($p<0.001$). However no significant relation was discovered among hypocalcemia and age of patient and residential status of patients.

Mean serum calcium level calculated was found to be 7.24 ± 0.87 mg/dl. Hypocalcemia was noted in 152 (86.4%) of our cases. In a Chinese study, Xing Z[12] found that hypocalcaemia was present in 87.7 % of patients with end stage liver disease. These findings of Xing et al[12] from China resemble to our study results. Kefalas CH et al.[17] has noted that calcium levels were in lower normal range rather than low (Mean 8.7mg/dl). Vitamin D deficiency also contributes to hupocalcemia of cirrhosis, and vitamin D insufficiency has been noticed very commonly ranging from 16% to 100% among patients having chronic viral hepatitis of viral origin.[18,19,20]

It is well reported in the literature that low serum albumin and critical illness result in low total calcemia. In patients with Cirrhosis, hypocalcemia may secondary to the multiple factors that includes imbalance of nutrients (malnutrition), abnormality in nutrient absorptions from GI, deficiency of vitamins that includes Vit-D, drugs may include loop diuretic, cinacalcet treatment, multiple infusions with citrated blood products. Electrolyte imbalances includes low level of magnesium, coexistence of renal diseases, respiratory alkalosis and paraneoplastic calcitonin are also considerable factors. The decrease in secretion of parathyroid hormone (PTH) may also lower the levels of calcium in blood and increases the levels of phosphorus in blood (hyperphosphatemia). In some literatures, blood transfusion is also considered as the factor which is due to the use of preservations.[21]

CONCLUSION

Hypocalcemia was seen to be very high in our settings. Significant association among gender and hypocalcemia, poor socioeconomic status and hypocalcemia, obesity and hypocalcemia, duration of disease and hypocalcemia, treatment status and hypocalcemia, viral type with hypocalcemia. However no significant relation was discovered among hypocalcemia and age of patient and residential status of patients. More studies are required to validate these findings and determine the role of any calcium supplementation in future treatment strategies.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Shahzad Alam Khan	Proposal of study, Data analysis.	
2	Nasir Jamal Khan	Joint proposal of study, Data analysis.	
3	Rizwan Hameed	Data collection, Analysis.	
4	Mehboob Qadir	Draft preparatin & Data collection.	
5	Muhammad Ilyas	Draft preparation & Proof reading.	
6	Muhammad Tahir	Contrubution to study design & Draft review.	