



# INCIDENCE OF ASYMPTOMATIC HYPOCALCAEMIA AND QT PROLONGATION IN PATIENTS WITH CHRONIC LIVER DISEASE

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## ABSTRACT

**BACKGROUND:** Chronic hypocalcaemia can occur in patients of chronic liver disease (CLD) due to Vitamin D dependent metabolism of calcium. Chronic asymptomatic hypocalcaemia usually goes unnoticed in such patients. However, it can cause significant QT prolongation, which is a significant marker for sudden cardiac death due to ventricular arrhythmias.

**OBJECTIVE:** To study patients with CLD and find out the incidence of asymptomatic but significant hypocalcaemia, causing QT prolongation on ECG and thus predisposing the patients at increased risk of sudden cardiac death.

**MATERIAL AND METHODS:** It was a descriptive, cross-sectional study of six months duration conducted in Jinnah Hospital, Lahore from September, 2014 to February, 2015. A total of 165 indoor and outdoor Chronic Liver Disease patients were evaluated. Data was recorded and analyzed by SPSS version 16.0

**RESULTS:** Out of 165 patients with End-stage CLD, hypocalcaemia causing QT prolongation was found in 62(37.5%) patients. While hypocalcaemia, without any significant QT prolongation, was seen in 78(47.2%) patients.

**CONCLUSION:** In this study we found that asymptomatic hypocalcaemia causing significant QT prolongation is a serious but often unnoticed adverse event in patients having CLD. It can lead to ventricular arrhythmias and can significantly contribute to mortality in such patients. Thus, an effort should be made to recognize significant hypocalcaemia and QT prolongation, even if asymptomatic, so that measures can be taken to correct the calcium levels and QT interval to avoid mortality due to these factors.

**KEYWORDS:** asymptomatic, hypocalcaemia, QT prolongation, Chronic Liver Disease.

## INTRODUCTION

**E**lectrolyte imbalance is a significant factor leading to increased morbidity and mortality in critically ill patients. Hypocalcaemia alone is present in 15-70% of ICU admissions. The underlying pathology can range from dietary insufficiency, metabolic disturbance and to drug interactions or adverse effects<sup>1</sup>.

Hypocalcaemia can present as an asymptomatic laboratory finding or as a severe, life-threatening condition. In presentation of acute hypocalcaemia, rapid correction is needed. However, chronic asymptomatic hypocalcaemia is generally well-tolerated, but treatment is needed to avoid long-term complications<sup>2</sup>.

The normal plasma calcium level is between 9-10.5 mg/dL<sup>3</sup>. The concentration of total calcium varies with the level of serum albumin, which is a

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calcium binding protein. In patients with chronic illness, malnutrition, cirrhosis, or volume over-expansion, serum albumin may fall with a reduction in its total level, but generally not the ionized fraction of serum calcium<sup>2</sup>. This is referred to as "factitious" hypocalcaemia. In hypoalbuminemia, one can calculate the corrected total serum calcium with the following formula<sup>2,3</sup>.

Corrected calcium (mg/dL) = measured total Ca (mg/dL) + 0.8 (4.0 - serum albumin [g/dL]), where 4.0 represents the average albumin level in g/dL.

The typical feature of acute hypocalcaemia is neuromuscular irritability. The patients may usually complain of tingling and numbness in their fingers, toes and around the mouth. This may be accompanied by lethargy and fatigue<sup>4</sup>. In severe cases, patient may have painful muscle spasms and even tetany. However, chronic hypocalcaemia may remain totally asymptomatic, being found out only after laboratory investigations<sup>5</sup>.

Another significant and rather grave manifestation of hypocalcaemia is prolongation of the QT interval on the ECG. This is of significance

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because QT prolongation is an important cause of sudden cardiac death (SCD)<sup>6</sup>. This is due to occurrence of acute ventricular arrhythmia following repolarization disturbances in the myocardium. QT interval is said to be prolonged if >440ms in men and >460ms in women. Common causes of QT prolongation are QT-prolonging drugs (e.g. macrolides, antihistamines, azole antifungals), hypocalcaemia, hypokalaemia and hypomagnesemia. Rare causes include congenital long QT syndrome<sup>7</sup>.

Metabolism of calcium in the body is, in turn dependent on Vitamin D metabolism. Inactive Vitamin D is metabolized to 25-hydroxyvitamin D3 in the hepatocytes and then to 1,25-dehydroxyvitamin D3 ( calcitriol) by the kidney. Calcitriol binds to receptors in the intestine which facilitate calcium transport there<sup>8</sup>. Also in conjunction with Parathyroid hormone, calcitriol stimulates calcium transport in the kidney and bone<sup>9</sup>.

Thus, hypocalcaemia is associated with inherited and acquired deficiency of Vitamin D. Common causes of Vitamin D deficiency include lack of exposure to sunlight, fat malabsorption syndromes, chronic liver disease and chronic kidney disease<sup>10</sup>. In our setup, chronic liver disease is very prevalent, usually secondary to chronic Hepatitis B and/ or C infection. Thus CLD is a very common cause of Vitamin D deficiency in our patients. Usually hypocalcaemia will not be evident even in presence of low levels of Vitamin D due to a compensatory rise in PTH. However once the calcium stores are completely depleted, hypocalcaemia will occur, which may go unnoticed<sup>11</sup>. However, even this unnoticed chronic hypocalcaemia can cause significant QT prolongation, which puts the patient at an increased risk of developing acute ventricular arrhythmias<sup>9</sup>.

However, there are very few studies correlating symptomatic hypocalcaemia causing QT prolongation to CLD in Pakistan. Our aim was to find out the incidence of such patients in our setup. Unlike acute hypocalcaemia, chronic hypocalcaemia is very easily corrected by oral vitamin D and calcium supplementation. Thus malignant arrhythmias can be prevented with just doing 12-lead ECG and getting serum calcium levels at regular intervals in indoor and outdoor patients having CLD.

#### MATERIAL AND METHODS:

The study was a cross-sectional survey, carried out in Jinnah Hospital, Lahore from September 2014 to February 2015. A total of 165 patients were selected by non-probability purposive sam-

pling. The patients included were diagnosed cases of post-infective chronic liver disease (hepatitis B and / or C), between 30-75 years of age of either sex, having no symptoms of hypocalcaemia.

The diagnosis of chronic liver disease was established on clinical and ultrasonographical criteria. Presence of Portal hypertension and ascites was also determined by ultrasonography.

Exclusion criteria included all patients of Ischemic heart disease, valvular heart disease, known cases of Long QT syndrome, chronic renal failure, patients taking anti-arrhythmics, digoxin, quinolones, macrolides, azole antifungals, antihistamines and patients having hypokalemia and hypomagnesemia.

Liver function tests, blood cell count and plasma electrolytes were obtained by standard laboratory procedure. Every patient was subjected to a 12-lead ECG and the heart rate adjusted QT interval (corrected QT interval, QTc) was calculated with Bazett's formula. A QTc of more than 460 ms was taken as prolonged. Data was interpreted using SPSS version 16.

#### RESULTS:

Out of 165 patients included, 74(44.9%) were female and 91(55.1%) were male. Mean age was calculated to be 48.33 (± 14.36) years.

The overall profile of the patients included in the study is shown in Table 1.

All patients included were having Post-infective chronic liver disease, with 64(38.8%) patients having Hepatitis B infection and 101(61.2%) patients having hepatitis C infection.

**Table 1: OVERALL PROFILE OF THE SUBJECTS**

<b>Total patients (n)</b>	165
<b>Female patients</b>	74(44.8%)
<b>Male patients</b>	91(55.1%)
<b>Mean Age ( yrs)</b>	48.33 (± 14.36)
<b>Mean Serum Calcium(mg/dl)</b>	7.9(±1.8)
<b>Mean QTc(ms)</b>	495(±13.55)

Hypocalcaemia was seen in 84.8%(140)patients and QT prolongation was found in 62(37.5%) patients. While hypocalcaemia without any significant QTc prolongation was seen in 78(47.2%) patients. Distribution of patients according to Child-Pugh Classification with relation to hypocalcemia and QT prolongation is shown in TABLE 2.

Out of the total 165 patients, 59 (35.8%) fell in Child-Pugh class A and out of those 18 (29%) patients were having significant hypocalcaemia



**Table 2: Distribution of patients according to Child-Pugh Classification**

CHILD-PUGH CLASS	TOTAL NO. OF PTS	NO. OF PTS WITH HYPOCALCEMIA & QT PROLONGATION
CHILD-PUGH A	59 (35.8%)	18 (29%)
CHILD-PUGH B	40 (24.2%)	24 (38.7%)
CHILD-PUGH C	66 (40%)	20 (32.3%)

with QT prolongation. 40 (24.2%) patients were in Child-Pugh class B, out of which 24 (38.7%) had hypocalcaemia with resulting QT prolongation. The remaining 66 (40%) patients were in Child-Pugh Class C and it was determined that 20 (32.3%) patients had significant hypocalcaemia with QT prolongation.

### DISCUSSION:

The QT interval is the time taken from the activation of the ventricular depolarization to the end of repolarization. A prolonged QT is a precursor for malignant ventricular arrhythmias and sudden cardiac death. Thus it contributes to increased morbidity and mortality<sup>5</sup>. It is usually seen with ischemia, cardiac dysfunction, QT prolonging drugs and rarely as congenital long QT syndrome. Hypocalcaemia is frequently seen and rapidly correctable cause of QT prolongation<sup>7</sup>. Most patients with end-stage liver disease have asymptomatic hypocalcaemia, contributing to QT prolongation. Thus this hypocalcaemia puts the patient at an increased risk of sudden cardiac death<sup>9</sup>. Bernardi et al. reported that QTc prolongation was correlated with the Child score and severity of the liver disease<sup>12</sup>. Studies show prevalence of QT prolongation in 23%-60% of CLD patients. QT prolongation was reported to be 60% in one study with the conclusion that QT prolongation was seen more in alcoholic cirrhosis, as compared to post-infective cirrhosis<sup>12</sup>. Another study by Sulehria et

al. showed the incidence of QT prolongation in 24% of cirrhotic patients. They determined that etiology and Child-Pugh class had no impact on the degree of Qt prolongation<sup>13</sup>. We reported QT prolongation in patients with chronic liver disease to be around 37%, similar to Sulehria et al.

Our aim was to find out the frequency of hypocalcaemia and prolonged QT interval in our tertiary care centre. We found that a significant number of patients have hypocalcaemia and associated QT prolongation. Chronic Liver disease is associated with electrolyte imbalance, but usually these are not treated unless patients are symptomatic. Our results show that hypocalcaemia and associated QTc interval prolongation should be ruled out in every cirrhotic patient presenting to the indoor and outdoor department. Also attempt should be made to correct the hypocalcaemia, as it can prevent the mortality associated with a prolonged Qtc.

We realize that this study has few limitations. Firstly, we studied only a limited number of patients and we feel that this study should be conducted on a larger sample population. Secondly, we did not assess QT interval variability or its effects on morbidity and mortality in chronic liver disease.

### CONCLUSION:

In this study we found that asymptomatic hypocalcaemia causing significant QT prolongation is a serious but often unnoticed adverse event in patients having CLD. It can lead to ventricular arrhythmias and can significantly contribute to mortality in such patients. Thus, an effort should be made to recognize significant hypocalcaemia and QT prolongation, even if asymptomatic, so that measures can be taken to correct the calcium levels and QT interval to avoid mortality due to these factors.



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