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# Relation of Parathyroid hormone to QT interval independent of serum calcium level in critically ill patients presenting with renal impairment.

**Osama Amin Abd Elhamid*, Remon Rafeek Michel*, Kamel Abd El Aziz Mohamed*, Ahmed Rostom Abd Elmonem*.**

** Critical Care Medicine, Faculty of Medicine Cairo University*

**Abstract:**

**Purpose:** To assess whether parathyroid hormone is associated with QT interval changes in critical ill patients presenting with renal impairment. **Methods:** This observational cohort study designed to examine ninety patients in the unit of intensive care who were admitted suffering from renal impairment whether as acute kidney injury or chronic kidney disease. Parathormone level, ECG and bedside echocardiography were done upon admission to the ICU. **Results:** Elevated PTH was associated with statistically significant longer corrected QT, (p-value = 0.002) with positive correlation (r = 0.326). The PTH level was statistically significant inversely correlated with EF (r = - 0.465), Na (r = - 0.226), ionized Ca2+ (r = - 0.222), and corrected Ca (r = - 0.222). The level of PTH was statistically significant positively correlated with creatinine (r = 0.216), K (r = 0.303), and PO4 (r = 0.214). The PTH level also showed a significant increase in patients with HTN compared to patients without HTN. There was an increased PTH level in patients with CKD when compared to non-CKD patients with a highly statistical significant difference. Moreover, a statistically significant increased PTH level was obtained in participants with ischemic heart disease as detected by the presence of RWMAs in echocardiography when compared to other non-ischemic participants without RWMAs. **Conclusion:** The abnormally high level of PTH is associated with more prolonged QTc intervals and is also associated with lower ejection fraction of the left ventricle.

**Key Words**: parathyroid hormone, cardiovascular risk, QTc, calcium, electrocardiogram.

## 1. Introduction:

The Parathyroid hormone (PTH) is the main regulator of bone and mineral metabolism, however abnormal cardiovascular (CV) events with elevated PTH levels are increasingly observed. Numerous publications indicate that primary hyperparathyroidism is associated with a risk of cardiac death [1-3] .

Also in secondary hyperparathyroidism (SHPT), it was evidenced that elevated PTH is independent risk factor of high CV mortality [4-5].

The Parathormone is responsible for serum calcium homeostasis that does not only affect cardiac physiology but also may exert an increased risk of CV events. Low serum calcium levels are could lead to QT interval prolongation which in turn is considered as a risk factor for sudden cardiac death, especially in cases with depressed left ventricular ejection fraction secondary to myocardial infarction (MI) [6].

There is insufficient data on the impact of elevated PTH on the QT interval in individuals without a diseased parathyroid gland. Moreover, previous available studies investigating PTH, QT interval and calcium are relatively little. So, more researches in this field can enhance stratification of cardiovascular risk or even conclude new personalized approaches to prevent and treat cardiac diseases.

This study aims to investigate the relationship between PTH levels and QTc independent of levels of serum calcium in cases admitted to the ICU with renal impairment as it postulates a probable link between high PTH and prolonged QTc and thus adverse cardiovascular events and sudden cardiac death.

## 2. Patients And Methods.

This observational cohort study was conducted on ninety admitted patients to the ICU of critical care medicine department at Kasr Alainy Hospital of Cairo University over a period from August 2023 to June 2024.

Inclusion criteria included: Admitted adult critically ill patients to ICU with serum creatinine level greater than 2 mg/dl whether as a case of acute renal insult or chronic renal disease, patients with normal sinus rhythm. Exclusion criteria included patients with history of parathyroid disease or surgical removal of parathyroid gland, patients with LBBB.

All patients underwent clinical assessment including full history taking and thorough physical examination. Full labs were requested upon entry to the ICU including complete blood picture, parathormone level, serum electrolytes e.g., sodium, potassium, magnesium, phosphorus, total calcium, and ionized Calcium, Urea,

creatinine, albumin, total bilirubin, and direct bilirubin and blood gases.

ECG and Cardiac measures: Twelve-lead ECGs have been done on early hospitalization adjusted at a paper speed 25 mm/s and voltage 10 mm/mV. ECG parameters included in the study were heart rate (HR) and QT interval. Bazett's correction: QTc = QT interval / √(60/HR) was used to calculate QTc interval depending on the raw ECG HR and QT interval. Echocardiography was done to assess ejection fraction of Left ventricle and the presence of SWMAs. APACHE II score was calculated based on data on admission.

**Ethical consideration**:

An ethical approval was obtained from Cairo University Human Research Ethical Committee with approval no MD-193-2022 and informed consent was taken from the patients or their first degree relatives.

**Statistical Analysis of Data**:

Statistical Program for Social Science (SPSS) version 24 was used for data analysis. Frequency and percentage were used to describe qualitative data. Normally distributed quantitative data were described as mean and standard deviation (SD) while non-normally distributed quantitative data were described as median (IQR). A discrete collection of numbers' mean, or average, is the central value, or more precisely, the sum of the values divided by the total number of values. A set of values' degree of dispersion is measured by the standard deviation (SD). Whereas a high SD suggests that the values are dispersed throughout a larger range, a low SD suggests that the values tend to be near the defined mean. By sorting all of the data points and selecting the one in the center, or by taking the mean of the two middle values if there are two, the median—the middle number—is discovered. Mann Whitney U test (MW) was done when comparing between two groups (for abnormally distributed data). Pearson's correlation coefficient (r) test was used to correlate between data. The confidence interval was set to 95% and the margin of error accepted was set to 5%. P-value was considered statistically non-significant (NS) if > 0.05, statistically significant (S) if < 0.05, statistically highly significant (HS) if < 0.01.

## 3. Results.

**Table 1: Description of demographic data in all studied patients:**

| | | Number of Studied patients (N = 90) | |
|---|---|---|---|
| **Age (years)** | **Mean ±SD** | 63.5 ± 13.6 | |
| | **Min - Max** | 18 – 92 | |
| **Gender** | **Male** | 46 | 51.1% |
| | **Female** | 44 | 48.9% |
| **Chronic diseases** | **HTN** | 43 | 47.8% |
| | **DM** | 46 | 51.1% |
| | **CKD** | 35 | 38.9% |
| | **ESKD** | 18 | 20% |

Table (1) shows that the mean age of all studied patients was 63.5 ± 13.6 years with minimum age of 18 years and maximum age of 92 years. There were 46 males (51.1%) and 44 females (48.9%) in our studied patients. There were 46 patients (47.8%) with HTN, 46 patients (51.1%) with DM, 35 patients (38.9%) with CKD in the studied patients and 18 patients (20%) with ESKD on regular dialysis.

**Table 2: Description of laboratory data in all studied patients:**

| N=90 | Minimum | Maximum | Mean | ±SD |
|---|---|---|---|---|
| **PTH (pg/mL)** | 32 | 342 | 139.4 | 77.9 |
| **Creatinine (mg/dL)** | 2.1 | 23.5 | 5.0 | 3.4 |

Table (2) shows that the mean PTH of all studied patients was 139.4 ± 77.9 with minimum PTH of 32 pg/ml and maximum PTH of 342 pg/ml. The mean Creatinine of all studied patients was 5.0 ± 3.4 mg/dl, respectively.

**Table 3: Description of ECG in all studied patients:**

| | | **Studied patients (N = 90)** |
|---|---|---|
| **HR (beat/min)** | **Mean ±SD** | 100.8 ± 20.6 |
| | **Min - Max** | 52 – 136 |
| **QTc (msec)** | **Mean ±SD** | 422.7 ± 42.2 |
| | **Min - Max** | 328 – 482 |

Table (3) shows that the mean HR and QTc of all studied patients were 100.8 ± 20.6 bpm and 422.7 ± 42.2 msec, respectively.

**Table 4: Description of ECHO data in all studied patients:**

| | | **Studied patients (N = 90)** |
|---|---|---|
| **EF (%)** | **Mean ±SD** | 48.4 ± 13.3 |
| | **Min - Max** | 20 – 70 |

Table (4) shows that the mean EF of all studied patients was 48.4 ± 13.3 with minimum EF of 20 and maximum EF of 70%.

**Table 5: Description of APACHE II score in studied patients**

| N=90 | Minimum | Maximum | Mean | ±SD |
|---|---|---|---|---|
| **APACHE II score** | 8 | 85 | 35.6 | 23.0 |

Table (5) shows that the mean SOFA, APACHE II score, and APACHE II (EMR%) of all studied patients were 5.4 ± 3.1, 19.9 ± 8.2, and 35.6 ± 23, respectively.

**Table 6: Correlation between PTH and QTc:**

| Variables | Pearson Correlation | |
|---|---|---|
| | **r** | **p-value** |
| **PTH vs QTc** | **0.326** | **0.002** [S] |

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant.
(r): Pearson correlation coefficient.

Table (6) shows a statistically significant (p-value = 0.002) positive correlation (r = 0.326) between PTH and QTc.

**Table 7: Correlation between PTH and Creatinine in all studied patients**

| Variables | Pearson Correlation | |
|---|---|---|
| | **R** | **p-value** |
| **PTH vs Creatinine** | **0.216** | **0.041** [S] |

Table (7) shows that there was a statistically significant positive correlation between PTH and Creatinine (r = 0.216).

**Table 8: Correlation between PTH and EF in all studied patients**

| Variables | Pearson Correlation | |
|---|---|---|
| | **R** | **p-value** |
| **PTH vs EF** | -0.465 | <0.05 |

Table (8) shows that there was a statistically significant negative correlations between PTH and EF (r = - 0.465).

**Table 9: Correlation between QTc and APACHE II in all studied patients**

| Variables | Pearson Correlation | |
|---|---|---|
| | r | p-value |
| QTc vs APACHE II score | 0.215 | 0.041[S] |

Table (9) shows that there was a statistically significant positive correlation between QTc and APACHE II (r = 0.041).

## 4. Discussion.

Our study enrolled 90 patients admitted to the ICU with impaired kidney function defined as serum creatinine > 2 mg/dL either as a case of acute renal injury or a case of chronic renal disease. Our results showed that in critically ill patients admitted to the ICU with renal impairment, elevated parathormone level is associated with prolonged QTc interval. It also showed elevated PTH is associated with both lower left ventricle ejection fraction and higher APACHE II score. In agreement, a study done by **Palmeri et al. 2018 [7]** demonstrated that elevated PTH levels were associated with prolonged QTc interval and concluded that high PTH could affect cardiac repolarization in patients with acute coronary syndrome.

Our results showed prolonged QTc interval is also associated with high mortality risk during ICU stay according to APACHE II score. Several researches suggested that the risk of cardiac death is higher in cases of primary hyperparathyroidism [3,8]. MoreoverRegardless of traditional CV risk factors, there is evidence that high PTH in secondary hyperparathyroidism is linked to increased CV mortality [5]. Also, abnormally high PTH was correlated to both hospital admission due to heart failure and increased risk of cardiac death [9]. Independent from serum calcium, PTH may directly affect the cardiomyocyte as evidenced that PTH receptor mRNA is found in human myocardium and its concentration increases after cardiac injury [10].

Moreover, vitamin D administration during treatment of secondary hyperparathyroidism have resulted in shortening the QTc independent of changes in serum calcium levels [11].

A little number of studies have investigated the relation between serum PTH level and both cardiac conduction and repolarization abnormalities. Two studies found that premature ventricular beats (PVC's) were more frequent in patients with primary hyperparathyroidism during exercise testing. **Pepe et al. (2013) [12]** found that

the average QTc values in primary hyperparathyroidism were within normal range, however their levels were significantly lower than the control group. Also It was demonstrated that primary hyperparathyroidism patients had a higher incidence of both supraventricular and ventricular premature beats in ECG monitoring for 24 hours.

Furthermore, it was found that both supraventricular and ventricular premature beats rates decreased significantly in primary hyperparathyroidism patients six months after parathyroidectomy, QTc values returned to normal levels. As a result, it was found that short QTc caused by hypercalcemia secondary to primary hyperparathyroidism increased the incidence of supraventricular and ventricular premature beats, and these arrhythmic events decreased significantly with parathyroidectomy. **Curione et al. (2010) [13]** also found that QTc was significantly lower in primary hyperparathyroidism patients, while QT dispersion was higher. Thus, it was found that the possibility of life-threatening arrhythmias in primary hyperparathyroidism patients increased. **Curione et al. (2010) [13]** showed that in primary hyperparathyroidism patients, both QT duration and QTc dispersion returned to their normal ranges after parathyroidectomy. It was concluded that the performed surgery in primary hyperparathyroidism reduced the myocardial electrical instability.

Conversely, a small study showed that the incidence of events on Holter monitoring in primary hyperparathyroidism was non-increased [14]. While another study showed persistent both supraventricular and ventricular premature beats even after surgical removal of parathyroid gland [15].

Our results showed that increased PTH is associated with reduced ejection fraction of left ventricle. In agreement with our results, numerous researches have found that in primary hyperparathyroidism, high PTH level is associated with increase in left ventricular mass (LVM), which is related to LVEF. Meanwhile other researches demonstrated the regression of this increase in LVM after parathyroidectomy [16-17]. In contrast with our results, some researches could not be able to detect this association [12,18-19].

Our results showed that high PTH level is associated with hypertensive patients. In agreement with our results, a prospective study by **Jorde et al. (2010) [20]** involving 1784 patients, showed that a change in systolic blood pressure during the seven-year study period was positively predicted by the baseline serum PTH levels (or the change in PTH levels during the study period).

In summary, there is a dearth of information on how increased PTH affects the QT interval in individuals who do not have parathyroid illness. Furthermore, there aren't many prior research looking at PTH, calcium, and the QT interval. Additional studies in this area may result in better cardiac risk assessment or perhaps new, individualized treatment and prevention strategies for heart disease.

## 5. Conclusions:

Elevated PTH level is associated with prolonged QTc interval and also associated with both low ejection fraction of the left ventricle and increased mortality evidenced by higher APACHE score.

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