Original Research Article

"STUDY OF QTc INTERVAL PROLONGATION IN DIAGNOSED CASES OF DIABETIC KETOACIDOSIS WITH REFERENCE TO ELECTROLYTE IMBALANCES"

Abstract

The present study investigate a QTc interval prolongation in diagnosed cases of Diabetic Ketoacidosis with reference to electrolyte imbalances. Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are dangerous manifestations of diabetes mellitus representing two extremes in the spectrum of uncontrolled diabetic state. DKA accounts for 14 percentages of all hospital admissions among diabetics and 16 percentages of all diabetes- related fatalities in India. The study was conducted in the ICU, general medicine ward and casualty under Department of Medicine at tertiary care hospital during August 2020 to July 2022. In present study QTc Maximum mean ±SD found in electrolytes abnormal group was 441.11 ± 16.49 and in electrolytes normal group was 424.41 ± 21.30, QTc Minimum mean ±SD found in electrolytes abnormal group was 393.69 ± 8.24 and in electrolytes normal group was 383.08 ± 15.99. QTc Dispersion mean ±SD found in electrolytes abnormal group was 48.75 ± 9.22 and in electrolytes normal group was 41.63 ± 9.88. QTc Mean mean ±SD found in electrolytes abnormal group was 417.41 ± 12.35 and in electrolytes normal group was 404.65 ± 15.81. It is suggested that QTc interval prolongation is an indicator of CAN (Cardiac Autonomic Neuropathy) and predictive tool for cardio-vascular mortality (worse outcomes) in patients with Diabetic Ketoacidosis.

Keywords: Diabetic Ketoacidosis, cardio-vascular mortality, hyperosmolar hyperglycemic state, Diabetes Mellitus

Introduction

Diabetes Mellitus is familiar to mankind from time immemorial. The term "Diabetes" was coined by Arateus Of Alexandria meaning "the melting down of the flesh and limbs into urine" in 1st Century A.D. In 1674, Thomas Willis coined "Mellitus" meaning "honey".[1]Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are dangerous manifestations of diabetes mellitus representing two extremes in the spectrum of uncontrolled diabetic state. DKA accounts for 14 percentages of all hospital admissions among diabetics and 16 percentages of all diabetes- related fatalities in India.[2] Diabetic Ketoacidosis as defined by Joslin is a triad of i) hyperglycemia[BSL>250], ii)ketosis and iii) acidosis[pH<7.3].[3] Various electrolytes are seen associated with diabetes. The most common electrolyte imbalance is hyponatremia, others are

hypokalemia, hypomagnesemia and hyperkalemia. During poorly controlled diabetes mellitus, glucose is an effective osmole and draws water from muscle cells resulting in hyponatremia.[2] Potassium is the principal intracellular cation and maintenance of the distribution of potassium between the intracellular and the extracellular compartments relies on several homeostatic mechanisms; when these mechanisms are perturbed, hypokalemia or hyperkalemia may occur.[4] Magnesium is the major intracellular divalent cation that forms a key complex with ATP and is an important cofactor for a wide range of enzymes, transporters, and nucleic acids required for normal cellular function, replication, and energy metabolism.[5,6] Diabetic patients with underlying conditions are predisposed to develop Hypophosphatemia. Cardiac autonomic nephropathy (CAN) is an impairment of autonomic control of cardiovascular system after ruling out other causes of dysautonomia[7]. However, symptomatic cases contribute to only 5 %. It is however associated with predisposition to ventricular arrhythmias. Hence, its early detection and prevention is essential. Currently, Cardiovascular autonomic reflex tests (CART) are the gold standard for diagnosing CAN in DM which includes heart rate variation to deep breathing, heart rate variation to Valsalva, heart rate response to standing and orthostatic hypotension[8,9,10].Some studies have shown a greater QT dispersion (QTd) in patients of diabetes mellitus suggesting it as a predicting tool for cardiovascular morbidity[11]. Arrhythmia, which forms part of CAN, can be detected as prolonged corrected QT (QTc) and dispersion QT (QTd) intervals. [12,13,14]

In diabetic ketoacidosis (DKA), ketosis or acidosis may directly affect cardiac repolarization with prolongation of QTc interval which may lead to arrhythmia[5]. Poor metabolic control and electrolyte imbalance in diabetic ketoacidosis (DKA) are known to cause prolonged QTc and QTd intervals[15,16,17]. Predictive value of QT interval parameters in diabetes mellitus has been greatly assessed before but their role in diabetic ketoacidosis (DKA) in reference to electrolyte disturbances are less evaluated.With this perspective in mind present study was conducted to find the possible role of QTc interval prolongation in patients of diabetic ketoacidosis with reference to electrolyte disturbance.

Aim

To study QTc interval prolongation in diagnosed cases of Diabetic Ketoacidosis with reference to electrolyte imbalances

Objectives

1. To study prolongation of QTc interval in diagnosed cases of Diabetic Ketoacidosis.
2. To study the relationship of QTc interval prolongation with electrolyte imbalances in diagnosed cases of Diabetic Ketoacidosis.

Study Design:

The present study is a Cross Sectional observation study.

Study Duration:

The study was conducted from August 2020 to July 2022.

Source of patient:

The study was conducted in the ICU, general medicine ward and casualty under Department of Medicine at tertiary care hospital.

Selection of participants:

Diabetic ketoacidosis (DKA) diagnosed by following criteria:

a. Blood glucose more than 250 mg/dl
b. Presence of ketonuria
c. Arterial pH of less than or equal to 7.30
d. Bicarbonate level of less than or equal to 18 mEq/l
e. An anion gap of more than 12(adjusted for albumin)
f. **Sample Size:** N=126

$\eta = Z^2 \times p\,(1\text{-}p)/\varepsilon^2$

Where p= population proportion 9%;

Z= z score 1.96 for 95% confidence interval

ε = margin of error 5% = 1.96 x 1.96 x 0.09 (1-0.09)

= 125.76 ≈ 126

Inclusion criteria:

Patients diagnosed with Diabetic ketoacidosis (DKA) of either sex, with age above 18 years old.

Diabetic Ketoacidosis diagnosed by all of the following criteria:

• blood glucose more than 250 mg/dl
• presence of ketonuria
• arterial pH of less than or equal to 7.30
• bicarbonate level of less than or equal to 18 mEq/l
• An anion gap of more than 12(adjusted for albumin)

Exclusion criteria:

1. Patients having any underlying condition that may predispose to the prolongation of the QTc interval as
   a. Structural heart disease (left ventricular hypertrophy, heart failure, myocardial ischemia)
   b. Endocrinopathies like Cushing's Syndrome, Hyperpituitarism, Hyperthyroidism
   c. Chronic Kidney Disease/Patients on Dialysis

d. Hypercholesterolemia

2. BMI more than 30 kg/m ^{2}
3. Patients who were taking medications known to affect QTc.
    a. Antibiotics fluoroquinolones, macrolides, trimethoprim, pentamidine, azole antifungals
    b. Antipsychotics- haloperidol, droperidol, thioridazine, pimozide
    c. Antiemetics- ondansetron, granisetron, metoclopramide
    d. Antiarrhythmics class-1a (quinidine, procainamide, disopyramide), class3 (amiodarone, sotalol, dofetilidev, ibutilide, dronedarone)

- **Study Procedure:**

Approval of institutional ethics committee was taken prior to commencement of present study. Present study was undertaken in the Department of General Medicine at tertiary care hospital. Total 126 patients fulfilling inclusion and exclusion criteria were enrolled. Details of the study was explained to all patients in their own language and written informed consent was obtained from all. Detailed history taking and clinical examination was performed. Details like age, sex and duration of diabetes was noted in each case.

A.ECG

ECG in the first 6 hours of admission and after the control of diabetic ketoacidosis episode was recorded. A 12 lead ECG is taken at 50 mm/second speed. RR interval, heart rate, QTc interval, QTc maximum, QTc minimum and QTc dispersion were calculated from the ECG.

Total 126 cases were grouped into 2 based on QTc interval prolongation as

a. **Group A (N=36):** Patients with prolonged QTc interval
b. **Group B (N=90):** Patients with normal QTc interval

B.Laboratory investigations

1. Random Blood Sugar (mg/dl)
2. HbA1c (mmol/l)
3. Serum Electrolytes
    1. Serum Na (mEq/l)
    2. Serum K (mEq/l)
    3. Serum Ca (mg/dl)
    4. Serum Mg (mg/dl)
    5. Serum Ph (mg/dl)

Autonomic Function Tests (AFT)

A battery of five autonomic function tests were done in all cases to assess CAN. A score of 0-2 is assigned to each test. The tests conducted were:

1. Postural fall in systolic blood pressure (BP)

2. Increase in diastolic pressure during hand grip
3. Deep breathing test
4. Heart rate response to standing

Total score ranged from 0–10. Based on the score obtained from the test, patients are divided in to three groups:

- Group 1 (Score >5): Severe autonomic neuropathy
- Group 2 (Score 2-4): Early autonomic neuropathy
- Group 3 (Score 0-1): No autonomic neuropathy

Operational Definitions

A.QT interval[31]

1.Normal QT interval

- Male: 0.397 seconds
- Female: 0.415 seconds

2.Normal corrected QT interval

- Male: 0.440 seconds
- Female: 0.460 seconds

B.Random Blood Sugar (mg/dl)

C.HbA1c (mmol/l)

D.Serum Electrolytes

1. Serum Na (mEq/l)-135-148mEq/l
2. Serum K (mEq/l)-3.5-5.5mEq/l
3. Serum Ca (mg/dl)-8.4-10.2mg/dl
4. Serum Mg (mg/dl)-1.6-2.3mg/dl
5. Serum Ph (mg/dl)-2.5-4.5mg/dl

E.Outcome

Outcome defined by recovery or mortality as Favourable or Unfavourable respectively.

Statistical Analysis:

Data collected compiled in MS EXCEL Sheet 2018. Analysis of Data is done by SPSS Software Version 2.0. Qualitative data tabulated in the frequency and percentage form. Quantitative data tabulated in the form of Mean and Standard deviation. Chi-square test has been used to test the proportions in association. Both Qualitative and Quantitative data represented in the form of visual impression like Bar Diagram, Pie Diagram. Microsoft word and Excel have been used to generate graphs, tables etc.

Observation and Results

Table 1: Distribution of Cases according to Age

Sr. No.	Age group (Years)	Group A N (%)	Group B N (%)	Total N (%)
1	**≤ 30**	0 (0 %)	1 (0.79 %)	**1(0.79%)**
2	**31 to 40**	1(0.79%)	10(7.9%)	**11(8.87%)**
3	**41 to 50**	27(21.42%)	62(49.2%)	**89(70.62%)**
4	**51 to 60**	6(4.76%)	13(10.31%)	**19(15.07%)**
5	**> 60**	2(1.58%)	4(3.17 %)	**6(4.75%)**
Total		**36 (29 %)**	**90 (71 %)**	**126 (100 %)**

Graph 1: Distribution of Cases according to Age

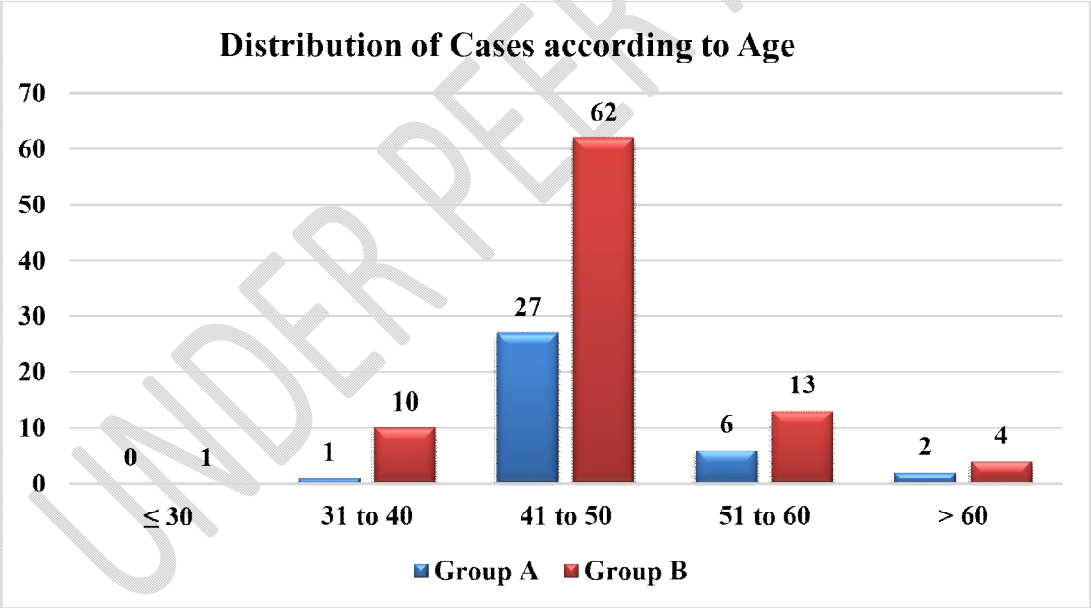


Table 2: Distribution of Cases according to gender

Sr. No.	Gender	Group A N (%)	Group B N (%)	Total N (%)

1	**Male**	29(23.01%)	52(41.26%)	**81(64.3%)**
2	**Female**	7(5.55%)	38(30.15%)	**45(35.7%)**
Total		**36 (28.56 %)**	**90 (71.41 %)**	**126 (100 %)**

Graph 2: Distribution of Cases according to gender

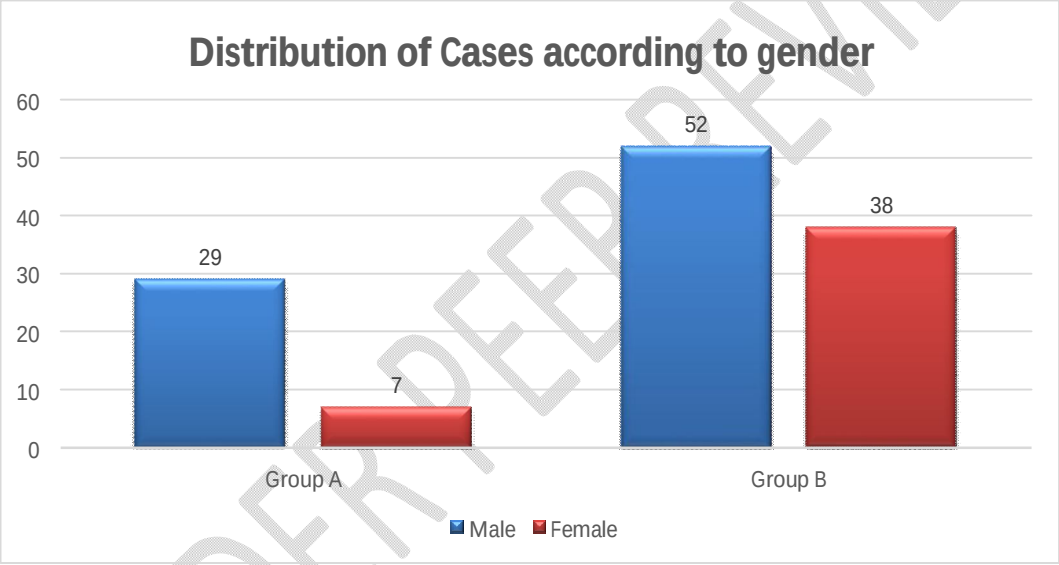


Table 3: Distribution of Cases according to duration of diabetes

Sr. No.	Duration of Diabetes (Years)	Group A N (%)	Group B N (%)	Total N (%)
1	**< 5**	0(0%)	2(1.6%)	**2(1.6%)**
2	**5 to 10**	27(21.42%)	71(56.23%)	**98(77.7%)**
3	**10 to 15**	7(5.55%)	13(10.31%)	**20(15.8%)**
4	**> 15**	2(1.6%)	4(3.17%)	**6(4.76%)**

Total	**36 (28.6 %)**	**90 (71.4 %)**	**126 (100 %)**

Graph 3: Distribution of Cases according to duration of diabetes

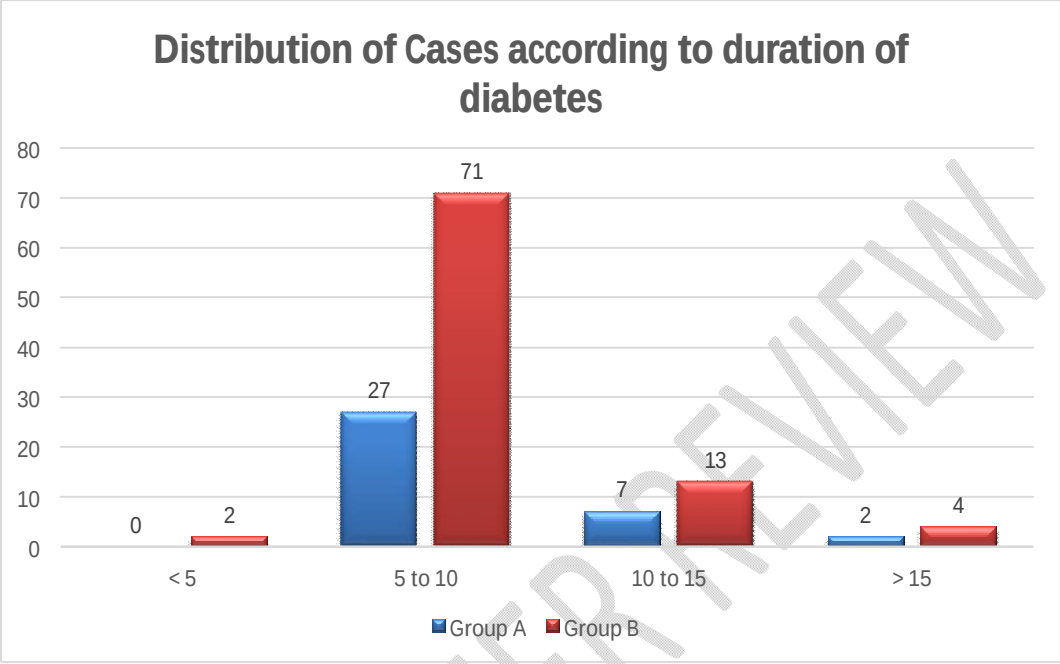


Table 4: Distribution of Cases according to HbA1c (mmol/l) levels

Sr. No.	HbA1c (mmol/l)	Group A 36 (29 %)	Group B 90 (71 %)	Total N (%)	P Value
1	**< 7**	**0 (0 %)**	**0 (0 %)**	**0 (0 %)**	
2	**7 to 10**	**34 (27 %)**	**63 (50 %)**	**97 (77 %)**	**0.003**
3	**> 10**	**2 (1.6 %)**	**27 (21.4 %)**	**29 (23 %)**	
4	**Mean ±SD**	9.2±0.41	9.6 ± 0.605		0.0004

Graph 4: Distribution of Cases according to HbA1c (mmol/l) levels

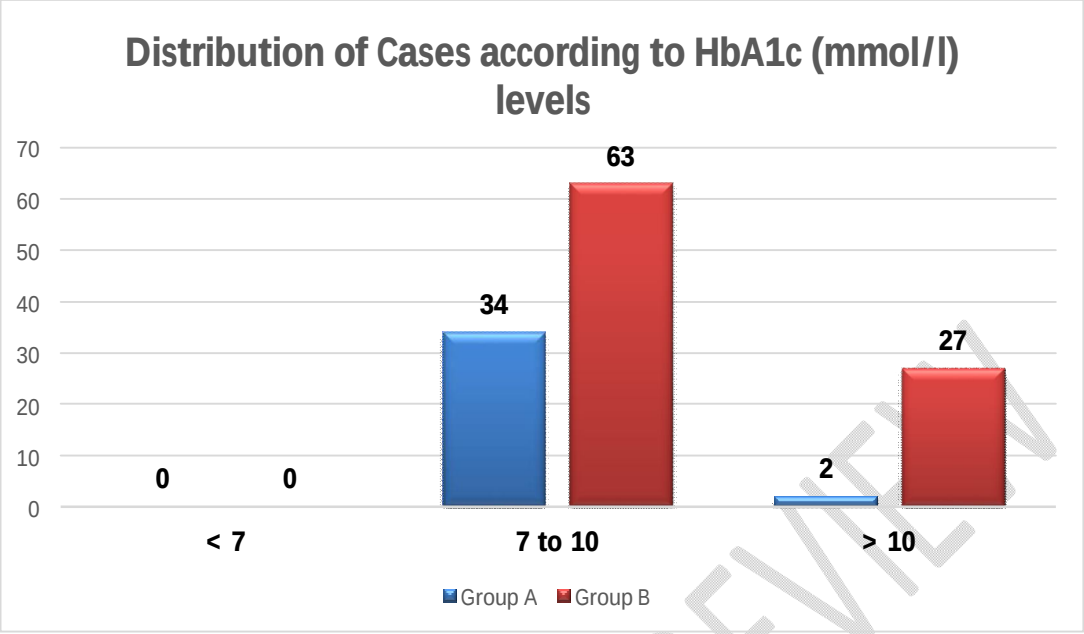


Table 5: Distribution of Cases according to QTc Profile

Sr. No.	QTc Profile	Electrolytes abnormal Mean ±SD	Electrolytes normal Mean ±SD	t Value	P Value
1	QTc Maximum	441.11 ± 16.49	424.41 ± 21.30	-4.222	< 0.0001
2	QTc Minimum	393.69 ± 8.24	383.08 ± 15.99	-3.779	0.0002
3	QTc Dispersion	48.75 ± 9.22	41.63 ± 9.88	-3.723	0.0003
4	QTc Mean	417.41 ± 12.35	404.65 ± 15.81	-4.338	<0.0001

Graph 5: Distribution of Cases according to QTc Profile

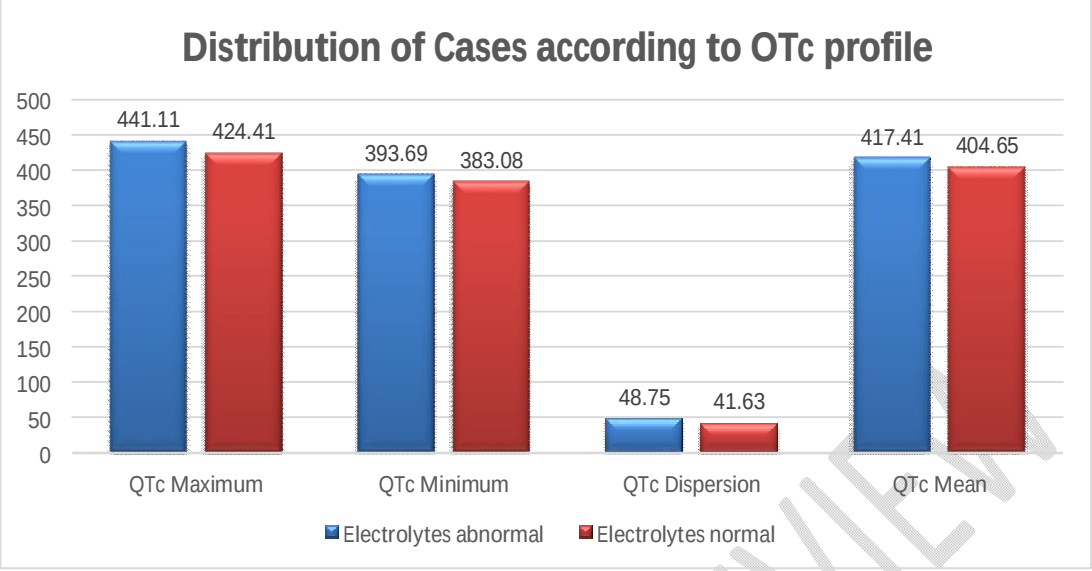


Table 6: Distribution of Cases according to serum electrolyte results

Sr. No.	Serum electrolyte results	Group A Mean ±SD	Group B Mean ±SD	t Value	P Value
1	**Serum Na (mEq/l)**	146.41 ± 6.78	143.92 ± 4.05	-2.53	0.01
2	**Serum K (mEq/l)**	4.2 ± 1.1	4.1 ± 0.54	-0.683	0.49
3	**Serum Ca (mg/dl)**	9.42 ± 1.35	9.4 ± 0.77	-0.105	0.91
4	**Serum Mg (mg/dl)**	1.96 ± 0.58	1.99 ± 0.44	0.31	0.75
5	**Serum Phosphorus (mg/dl)**	2.58 ± 0.72	3.03 ± 0.91	2.6	0.009

Graph 6: Distribution of Cases according to serum electrolyte results

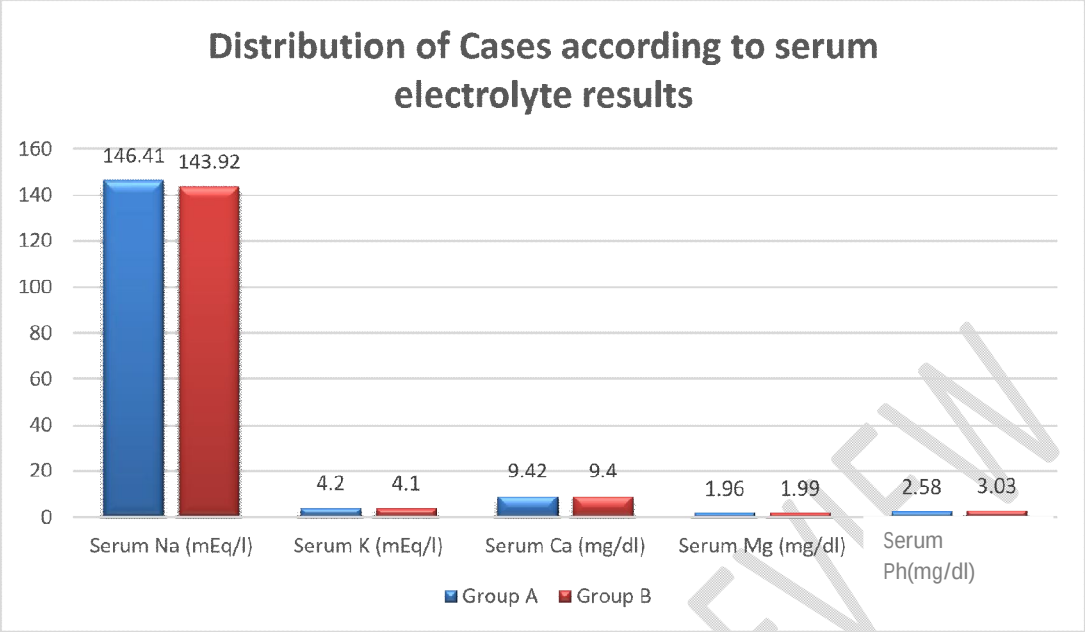


Table 7: Distribution of Cases according to electrolyte abnormality

Sr. No.	electrolyte abnormality	Group A	Group B	Total
1	Hyponatremia	5 (4 %)	3 (2 %)	8 (6 %)
2	Hypernatremia	23 (18 %)	16 (13 %)	39(30.95%)
3	Hypokalemia	20 (16 %)	15 (12 %)	35 (28 %)
4	Hyperkalemia	8 (6 %)	4 (3 %)	12(9.5%)
5	Hypocalcaemia	9 (7 %)	4 (3 %)	13 (10 %)
6	Hypercalcaemia	19 (15 %)	15 (12 %)	34(26.9%)
7	Hypomagnesemia	14 (11 %)	9 (7 %)	23 (18 %)
8	Hypermagnesemia	14 (11 %)	10 (8 %)	24(19.4%)
9	Hypophosphatemia	28 (22.5 %)	0 (0 %)	28 (22.5 %)
10	Hyperphosphatemia	0 (0 %)	19 (15 %)	19 (15 %)

Graph 7: Distribution of Cases according to electrolyte abnormality

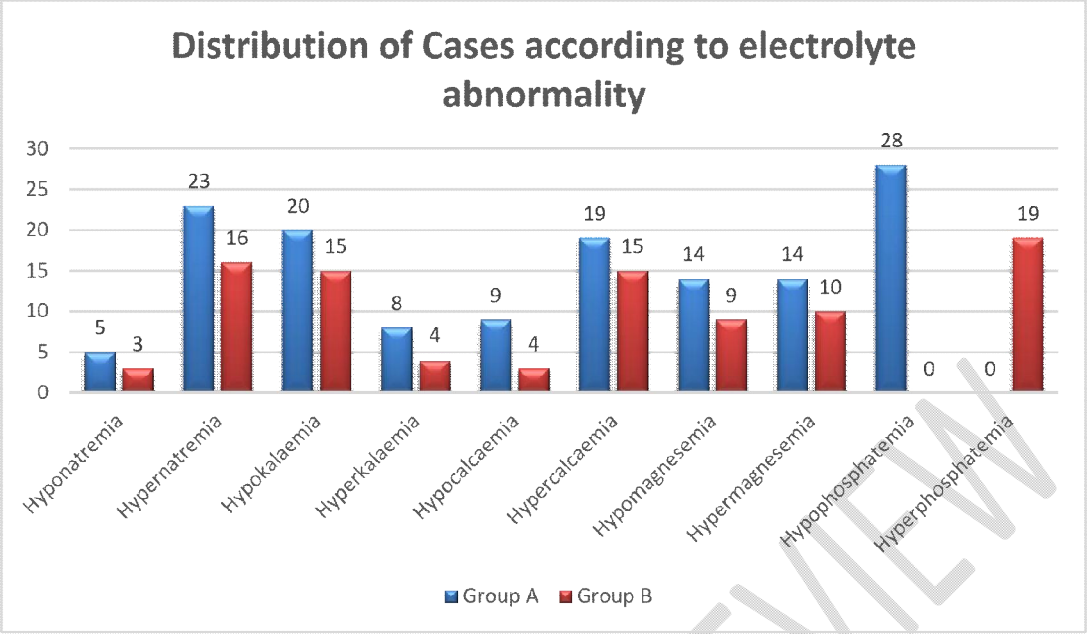


Table 8: Distribution of Cases according to correlation between serum electrolyte and QTc prolongation

Sr. No.	Serum electrolyte	Group A N (%)	Group B N (%)	Total N (%)	Chi square	P Value
1	**Abnormal**	28(22.5%)	19(15%)	**47(37.3%)**	**35.30**	**< 0.00001**
2	**Normal**	8(6.4%)	71(56%)	**79(62.6%)**		
Total		**36 (29 %)**	**90 (71 %)**	**126 (100 %)**		

Graph 8: Distribution of Cases according to correlation between serum electrolyte and QTc prolongation

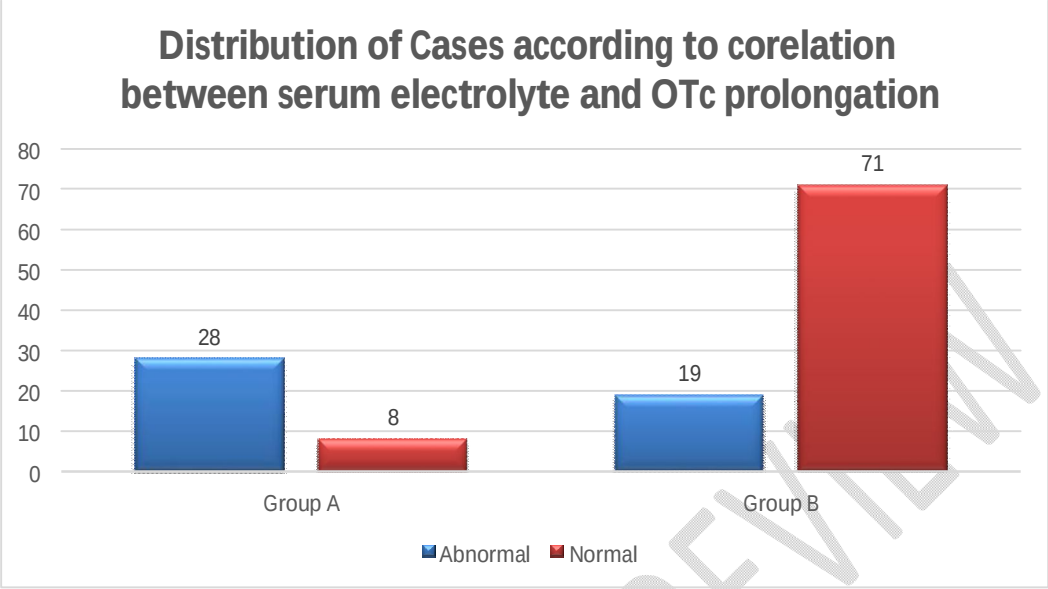


Table 9: Distribution of Cases according to Cardiac Autonomic Neuropathy Grade

Sr. No.	Cardiac Autonomic Neuropathy Grade	Group A N (%)	Group B N (%)	Total N (%)
1	**Grade 0**	2(1.6%)	45(35.7%)	**48(37.3%)**
2	**Grade 1**	10(8%)	13(10.3%)	**23(18.3%)**
3	**Grade 2**	24(19.04%)	31(24.6%)	**55(43.64%)**
Total		**36 (29 %)**	**90 (71 %)**	**126 (100 %)**

Graph 9: Distribution of Cases according to Cardiac Autonomic Neuropathy Grade

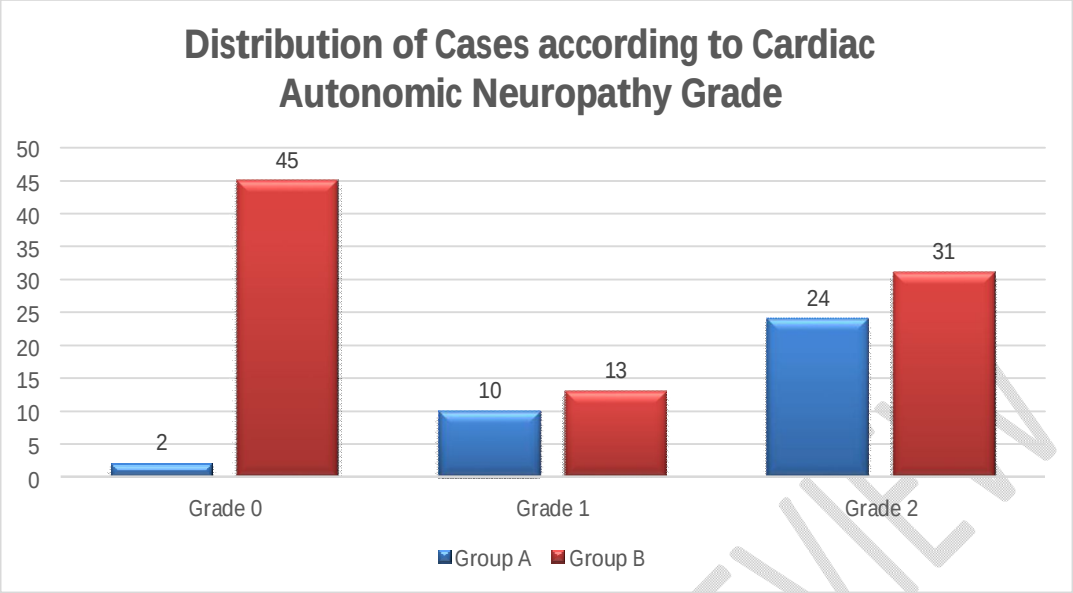
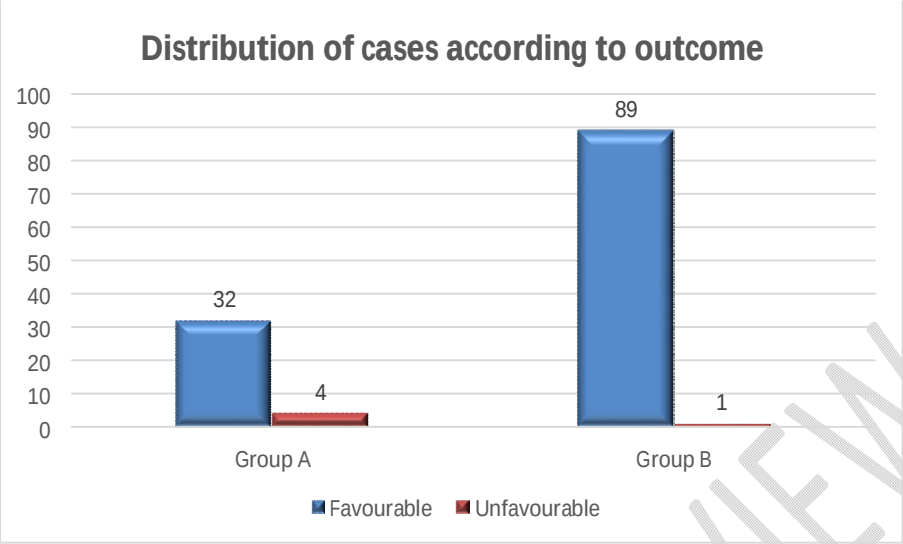


Table 10: Distribution of Cases according to outcome

Sr. No.	Outcome	Group A N (%)	Group B N (%)	Total N (%)
1	**Favourable**	32(25.4%)	89(70.6%)	**121(96.0%)**
2	**Unfavourable**	4 (3.2%)	1(0.8%)	**5(4.0%)**
Total		**36(28.6%)**	**90 (71.4%)**	**126(100 %)**

Graph 10: Distribution of Cases according to outcome



Discussion

Diabetic ketoacidosis (DKA) is the most common acute hyperglycemic complication associated with diabetes. According to a recent report diabetic ketoacidosis (DKA) affects approximately 8 per 1000 diabetics in a year which is associated with significant morbidity. Cardiac arrhythmia in diabetic ketoacidosis (DKA) is a well-known complication. Frequently missed cause of arrhythmia is QT interval prolongation, which could be associated with electrolyte disturbance. During diabetic ketoacidosis (DKA), ketosis or acidosis may directly affect cardiac re-polarization with prolongation of QTc interval, leading to arrhythmia and cardiac arrest. Keeping these scenarios in mind present study was conducted in 126 patients of diabetic ketoacidosis (DKA) fulfilling inclusion and exclusion criteria. Detailed history taking and clinical examination was performed in all cases and ECG in the first 6 hours of admission was recorded. A 12 lead ECG was taken at 50 mm/second speed. RR interval, heart rate, QTc interval, QTc maximum, QTc minimum and QTc dispersion were calculated from the ECG. Total 126 cases were grouped into 2 based on QTc interval prolongation as Group A (N=36) with prolonged QTc interval and Group B (N=90) with normal QTc interval. Laboratory investigations as random Blood Sugar, HbA1c (mmol/l) and Serum Electrolytes were performed in all and each patient is subjected to autonomic Function Tests. All results were compiled and analyzed.

Age & Gender

In present study maximum patients in Group A were between age group 41 to 50 years i.e. 27 (21.42 %). In group B also maximum patients i.e. 62 (49.2 %) were from age group 41 to 50 years. Male patients found in Group A were 29 (23.01 %) and Group B were 52 (41.26 %). Female patients found in Group A were 7(5.55%) and Group B were 38(30.15 %)

Duration of diabetes

In present study maximum patients i.e. 27 (21.42 %) in Group A were having diabetes for 5 to 10 years. In group B also maximum patients i.e. 71 (56.23 %) were having diabetes for 5 to 10 years.

HbA1c (mmol/l) level

In present study HbA1c (mmol/l) level was found between 7 to 10 in 97 (77 %) cases and >10 in 29 (23 %) cases. In Group A HbA1c (mmol/l) mean ±SD was 9.2 ± 0.41 and in Group B it was 9.6 ± 0.605

QTc Parameters

In present study QTc Maximum mean ±SD found in electrolytes abnormal group was 441.11 ± 16.49 and in electrolytes normal group was 424.41 ± 21.30, QTc Minimum mean ±SD found in electrolytes abnormal group was 393.69 ± 8.24 and in electrolytes normal group was 383.08 ± 15.99. QTc Dispersion mean ±SD found in electrolytes abnormal group was 48.75 ± 9.22 and in electrolytes normal group was 41.63 ± 9.88. QTc Mean mean ±SD found in electrolytes abnormal group was 417.41 ± 12.35 and in electrolytes normal group was 404.65 ± 15.81

Autonomic Neuropathy Grade

In present study in Group A Grade 0 CAN was found in 2 (1.6 %) and in Group B it was 45 (35.7 %). In Group A Grade 1 CAN was found in 10 (8 %) and in Group B it was 13 (10.3 %). In Group A Grade 2 CAN was found in 24 (19.04 %) and in Group B it was 31 (24.6 %)

Serum Electrolytes

In present study in Group A Serum Na (mEq/l) mean ±SD was 146.41 ± 6.78 and in Group B it was 143.92 ± 4.05. In Group A mean ±SD Serum K (mEq/l) was 4.2 ± 1.1 and in Group B it was 4.1 ± 0.54. In Group A Serum Ca (mg/dl) mean ±SD was 9.42 ± 1.35 and in Group B it was 9.4 ± 0.77. In Group A Serum Mg (mg/dl) mean ±SD was 1.96 ± 0.58 and in group (Group B) was 1.99 ± 0.44. In Group A Serum Phosphorus (mg/dl) mean ±SD was 2.58 ± 0.72 and in group (Group B) was 3.03 ± 0.91. In Group A Hyponatremia was 5 and in Group B it was 3. In Group A Hypokalemia was 20 and in Group B it was 15. In Group A Hypocalcemia was 9 and in Group B it was 4 and In Group A Hypomagnesemia was 14 and in Group B it was 9. In Group A Hypophosphatemia was in 36 and in Group B Hyperphosphatemia was in 19 cases. In Group A abnormal serum electrolyte was found in 28 (22.5 %) and in Group B in 19 (15 %). In Group A normal serum electrolyte was found in 8 (6.4 %) and in Group B in 71 (56 %). Result is statistically significant (P< 0.00001).

Outcome

In present study in Group A Favourable outcome was found in 32(25.4%) and in Group B it was 89(70.6 %). In Group A Unfavourable outcome was found in 4 (3.2%) and in Group B was 1(0.8%). Unfavourable outcome is defined by mortality and Favourable outcome is defined by recovery in our study.

Conclusion

The present study demonstrated that there is significant association between electrolyte abnormalities and QTc interval prolongation in patients with Diabetic Ketoacidosis. It also suggested that QTc interval prolongation is an indicator of CAN (Cardiac Autonomic Neuropathy) and predictive tool for cardio-vascular mortality (worse outcomes) in patients with Diabetic Ketoacidosis.

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