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Evaluation of Cardiac Arrhythmias in Diabetic Patients Admitted to Intensive Care Unit with Acute Hyperglycemic Syndromes: Prospective One Year Study

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ABSTRACT

Background: The association among ketotic or hyperglycemic conditions and cardiac arrhythmias and sudden death increases possibility that ketosis or hyperglycemia may directly disrupt cardiac repolarization and hence be reason for arrhythmia and sudden cardiac death in these cases.

Objective: The goal of the research was to assess ECG variations among diabetic studied cases admitted in Intensive Care Unit (ICU) with acute hyperglycemic syndromes.

Patients and Methods: This study was prospective follow-up study and was conducted on patients admitted to medical critical care unit, Specialized Medical Hospital, Mansoura University during the period from January 2021 to January 2022.

Results: There was significant (P<0.001) decrease in average heart rate, p wave maximum, p wave dispersion, QT maximum, QT dispersion and QTc. The depressed ST segment decreased from 4.8% to 3.8% with no significant difference, while the percentages of all types of arrhythmias are decreased on recovery in comparison to their values on admission.

Conclusion: Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) could be associated with several types of cardiac arrhythmias, which attributed to hyperglycemia and ketoacidosis rather than electrolyte disturbances.

Keywords: Cardiac Arrhythmias, Diabetic, Hyperglycemic Syndromes.

INTRODUCTION

Diabetes mellitus (DM) is considered leading reason for disability worldwide and it is associated with more than twenty-five million deaths globally every year. The metabolic condition known as diabetes mellitus (DM) is characterised by hyperglycemia brought on by deficiencies in insulin production, insulin action, or both [1]. Its chronic hyperglycemia leads to end organ damage, dysfunction, and failure in organs and tissues containing retina, kidney, nerves, heart, and blood vessels[1].

According to International Diabetes Federation, if current trends continue, the global diabetes population will grow from 436 million in 2019 to 700 million by 2045. This population will expand by 96% in Middle East and North Africa area, from 55 to 108 million people [2].

Diabetic ketoacidosis and hyperglycemic hyperosmolar state are hyperglycemic crises that continue to be a major cause of hospitalizations. Historically, DKA and HHS were defined as a single entity before being recognized as distinct illnesses. Since the discovery of insulin, death rates for DKA and HHS have decreased, although hazard remains significant [3]. Diabetic ketoacidosis is a metabolic decompensation condition in which insulin insufficiency (relative or absolute) produces hyperglycemia as well as excess ketoacid generation, culminating in metabolic acidosis. Precipitating causes are usually infection or insulin omission. HHS is characterized by a significant hyperglycemia, hyperosmolality, and little or no ketosis. Infection, untreated diabetes, and drug misuse are all risk factors for HHS [4].

Atrial tachyarrhythmias may be initiated and maintained by prolonged atrial conduction and inhomogeneous sinus impulse propagation. Such a phenomenon might be represented in variations in inter-lead P-wave duration termed as P-wave dispersion (Pd) [5]. The association among ketotic or hyperglycemic conditions and cardiac arrhythmias and sudden death increases possibility that ketosis or hyperglycemia may directly disrupt cardiac repolarization and hence be a reason for arrhythmia and sudden cardiac death in these studied cases [6].

The goal of the research was to assess ECG variations among diabetic studied cases admitted in Intensive Care Unit (ICU) with acute hyperglycemic syndromes.

PATIENTS AND METHODS

This study was prospective follow-up study and was conducted on patients admitted to medical Intensive Care Unit, Specialized Medical Hospital, Mansoura University during the period from January 2021 to January 2022. This study was carried out on 189 patients presented by diabetic ketoacidosis and 19 patients with hyperosmolar hyperglycemic state. The sample size was designed to be convenient; all patients who met the inclusion criteria were enrolled in the research, unless they fulfilled any of the exclusion criteria or refused to cooperate. We included cases admitted to medical ICU for DKA or HHS and with age above 18 years old. But we excluded patients with

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cardiovascular diseases, patients known of having cardiac arrhythmias, patients with neurological damage, patients with severe renal insufficiency or liver damage, ventilated or sedated and acutely intoxicated patients, patients on medication that affects heart rhythm and patients having any electrolyte disturbance.

Methods

After appropriate emergency treatment, all patients were admitted directly to medical Intensive Care Unit and received continuous monitoring and treatment for DKA and HHS according to international guidelines.

All studied cases were subjected to the following:

- **Thorough medical history including:** Age, duration of diabetes mellitus, type of diabetes mellitus, type of antidiabetic medications, previous episode of DKA or HHS, symptom of the patients at presentation and possible precipitating factors for DKA or HHS.
- **Physical examination:** Vital signs: pulse, temperature, blood pressure, respiratory rate and oxygen saturation, signs of associated comorbidity as chronic liver disease, heart or renal disease and disturbed conscious level and its degree on Glasgow Coma Score.
- **Laboratory tests:** Plasma glucose level, HbA1c, serum sodium, potassium, chloride, calcium, magnesium levels, CBC, serum creatinine, BUN, pH, and sodium bicarbonate and anion gap in venous blood gas (VBG) sample and plasma osmolality were calculated through the formula: serum osmolality = 2(Na) + glucose/18 + BUN/1.
- **Electrocardiographic examination:** Pd, QTd were measured from at least nine leads. Measurements were made in 3 consecutive heartbeats and the average was calculated (Figs. 1 and 2).
- **2D echocardiography:** It was performed by an expert echocardiographer using LOGIQ F6 device, GE Healthcare, Waukesha, WI 53188, USA (Fig. 3). Patients were examined lying in left lateral position.
- General data were obtained included: Heart rate (HR; bpm), stroke volume (SV; ml) and cardiac output (COP; ml/min), ejection fraction (EF; %), fractional shortening (FS; %) and myocardial performance index (MPI).
- Right side function was assessed including: Right atrial diameter (RAD; cm), PD-TV-E/A ratio, pulmonary artery systolic pressure (PASP; mm/hg) and E/A ratio <0.8 was used as an index for RV diastolic dysfunction.
- Left ventricle size and function was assessed through: LV End diastolic volume (EDV; ml), LV end systolic volume (ESV; ml) and PD-MV-E/A ratio. LV systolic dysfunction was defined as EF ≤50%, while LV diastolic dysfunction was selected according to PD-MV-E/A ratio <0.8.

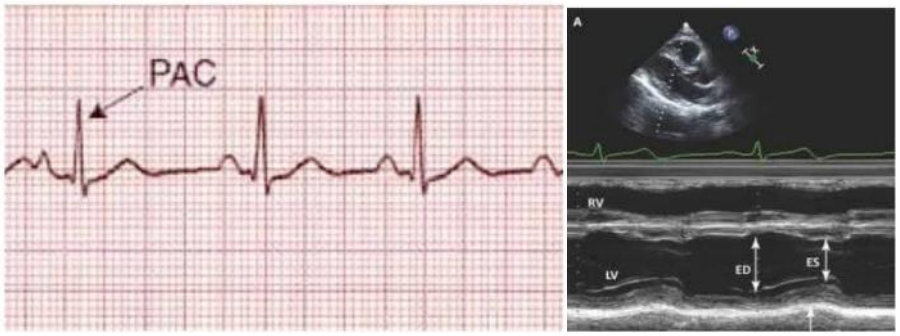

Figure (1): Example of ECG and ECHO of one of the studied patients presented with PACs on admission

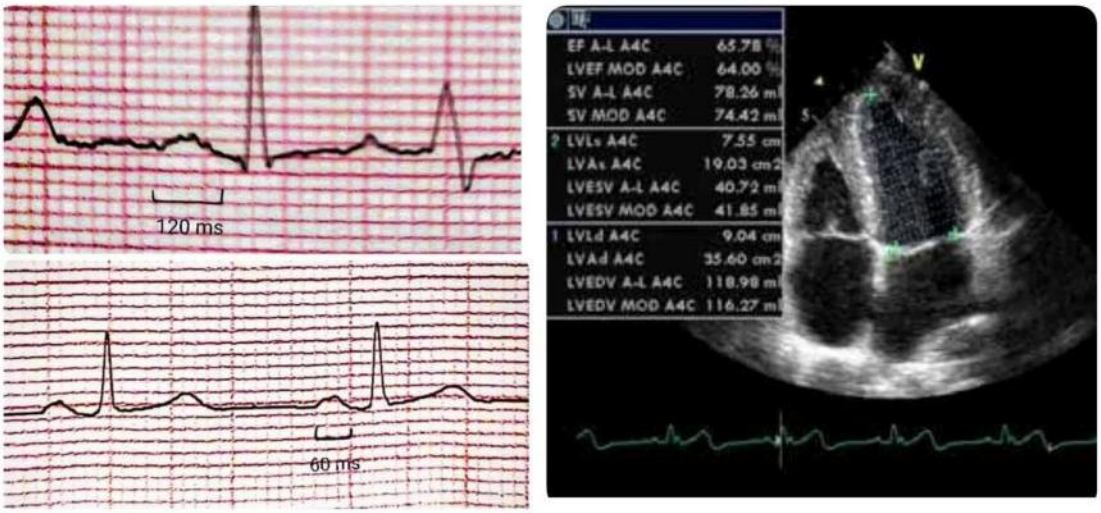

Figure (2): Example of ECG and ECHO of patient presented with P wave dispersion

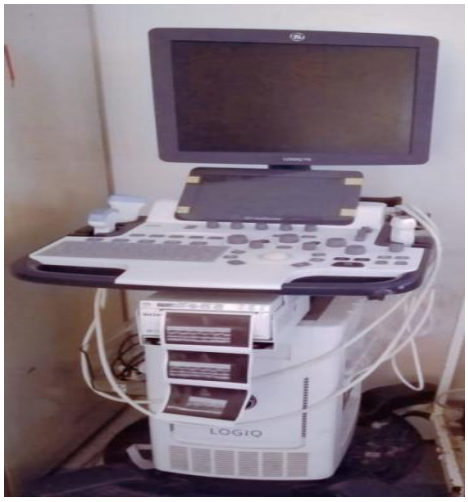

Figure (3): ECHO machine.

Ethical Considerations:

All cases under study gave their informed consent to take part in the study. After receiving clearance from the institutional review board and the Faculty of Medicine at Mansoura University, the Department of Internal Medicine approved conducting research. The entire process of conducting the study adhered to the Helsinki Declaration.

Statistical analysis: Using SPSS version 24, the collected data were coded, calculated, and statistically analysed. Qualitative data were shown as frequency and percentages and were compared by the chi square (X^2) test. Quantitative data were presented as mean, SD, and range and the paired t test was used to compare means of variables before and after treatment. P value < 0.05 was considered significant.

RESULTS

Table **(1)** and figure **(4)** show the characteristics of the studied patients. The age of the studied patients ranged from 18 – 87 years and 48.6% are below age of thirty. Nearly about two thirds were female and nearly three quarters were type I DM. As regard severity of the disease; 40.4% had moderate DKA and 9.1% had HSS. Most of the patients had GCS score of 15. Average duration of the disease was 8.07 years.

Table (1): Characteristics of the studied patients (n. 208)

Characteristics	Items	No	%
Age (years)	<30	101	48.6
	30-	48	23.1
	40-	16	7.7
	50-	17	8.2
	60-	16	7.7
	70-	7	3.4
	80-90	3	1.4
	Min – Max= 18 -87, Mean ± SD= 35.88 ± 16.87 years		
Gender	Males	76	36.5
	Females	132	63.5
Type	Type I	153	73.6
	Type II	55	26.4
Type of acute hyperglycemia	Mild DKA	63	30.3
	Moderate DKA	84	40.4
	Severe KA	42	20.2
	HHS	19	9.1
GCS	14	5	2.4
	15	203	97.6
Duration of DM (years)	0 (first time)	6	2.9
	1-	55	26.4
	5-	76	36.5
	10-	44	21.2
	15-	21	10.1
	20-25	6	2.9
	Min – Max= 0 -25, Mean ± SD= 8.07 ± 5.20 years		
Duration of recovery of hyperglycemic episode (hours)	8-	91	43.8
	24-	57	27.4
	48-72	60	28.8
	Min – Max= 8 -72, Mean ± SD= 31.61 ± 20.11 hours		
Duration of Stay in ICU (days)	1-2 days	84	40.4
	3-4 days	96	46.2
	5-6 days	28	13.5
	Min – Max= 1 -6, Mean ± SD= 2.94 ± 1.27 days		

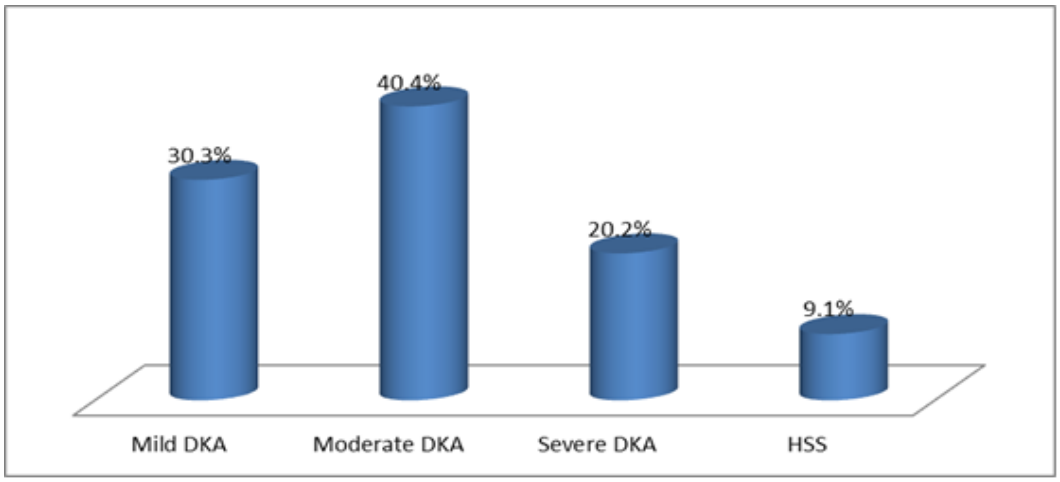

Figure (4): Severity of DM in the studied patients

Table (2): ECHO findings on admission among studied patients (n. 208)

ECHO findings	Minimum - Maximum	Mean ± SD
LVESD	22.0 – 39.0	32.08 ± 5.20
LVEDD	34.0 – 57.0	47.36 ± 6.71
EF	55.0 - 80	68.13 ± 7.30
FS	24.0 – 46.0	36.19 ± 6.41
Acceleration time	100.0 – 145.0	131.72 ± 11.37
AO	20.0 – 36.0	28.35 ± 5.01
LA	19.0 – 40.0	30.04 ± 6.27
IVS	7.0 – 11.0	8.97 ± 1.42
PWT	7.0 – 11.0	9.18 ± 1.39
E/A ratio	0.7 – 1.2	1.02 ± 0.16

Table **(3)** and figure **(5)** show that there was significant decrease in average heart rate, P wave maximum, P wave dispersion, QT maximum, QT dispersion and QTc. The depressed ST segment decreased from 4.8% to 3.8% with no significant difference, while the percentages of all types of arrhythmias were decreased on recovery in comparison to their values on admission. Figure **(6)** show a significant reduced percentage of patients having P wave dispersion, QT dispersion and QT corrected on recovery.

Table (3): ECG findings on admission and on recovery among studied patients (n. 208)

ECG findings	On admission		On recovery		Significance test
	Mean ± SD		Mean ± SD		
HR	86.96 ± 8.74		83.19 ± 9.10		t=4.255, P<0.001
P (min)	54.04 ± 18.63		54.13 ± 18.39		t=0.333, P 0.740
P (max)	103.17 ± 19.35		78.75 ± 19.86		t=16.937, P<0.001
Pd	48.37 ± 22.44		24.81 ± 12.18		t=15.963, P<0.001
PR interval	167.79 ± 27.08		166.83 ± 27.19		t=1.447, P 0.149
QRS duration	100.67 ± 16.02		100.38 ± 15.97		t=0.654, P 0.514
QT (min)	405.87 ± 25.06		405.67 ± 25.18		t=0.632, P 0.528
QT (max)	474.23 ± 48.85		441.35 ± 29.65		t=15.983, P<0.001
QTd	68.56 ± 33.27		35.67 ± 15.05		t=15.948, P<0.001
QTc	468.12 ± 49.34		404.46 ± 33.62		t=30.349, P<0.001
T wave	6.10 ± 1.38		6.15 ± 1.39		t=1.232, P 0.219
	No	%	No	%	Significance test
ST segment					
- **Isoelectric**	198	95.2	200	96.2	$\chi 2 = 0.231$,
- **Depressed**	10	4.8	8	3.8	P 0.630
Arrhythmias					
- **PVCs**	11	5.3	5	2.4	$\chi 2 = 2.341$, P 0.126
- **PACs**	13	6.2	4	1.9	$\chi 2 = 4.971$, P 0.026
- **Sinus tachycardia**	19	9.1	7	3.4	$\chi 2 = 5.911$, P 0.015

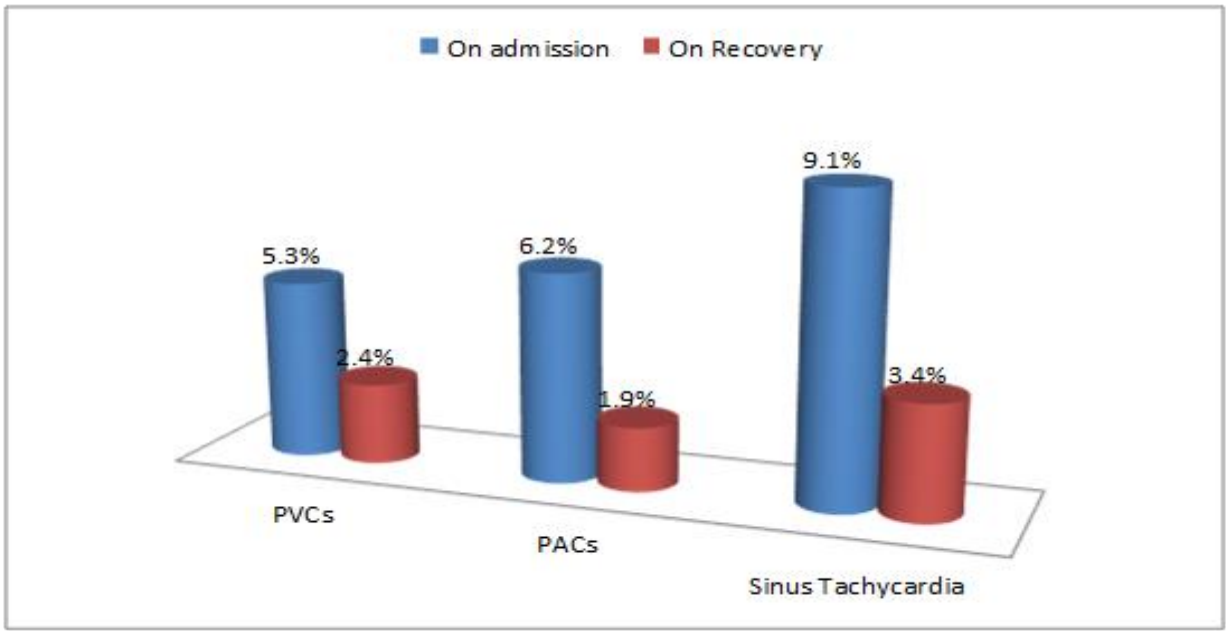

Figure (5): Percentage of arrhythmias on admission and on recovery

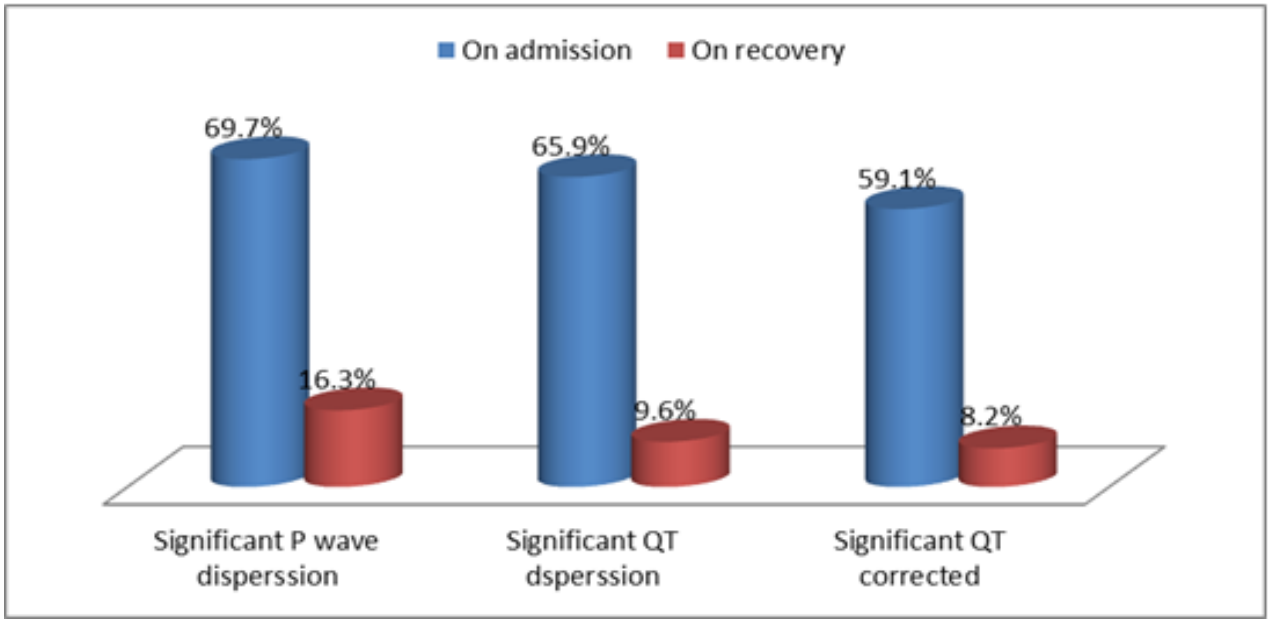

Figure (6): Percentage of P wave dispersion, QT depression and corrected QT on admission and on recovery

In table **(4),** by investigating the diagnostic value of RBG of presence or absence of arrhythmia, using ROC Curve, it was found that at RBG cut off point 436.5 mg/DL, the sensitivity of diagnosing arrhythmia was 100% and specificity was 60.9%. While table **(5)** shows that there was positive, moderate, significant correlation among heart rate and values of RBG. While, there were negative, mild, significant correlations among heart rate and pH and CHO_3 values. Also, there was positive, weak, significant correlation among heart rate and anion gap values.

Table (4): ROC curve for RBG in patients with arrhythmia

Case Processing Summary				
Arrhythmia	Valid N (listwise)			
Positive	39			
Negative	169			
Area Under the Curve				
Test Result Variable(s): Glucose Pre				
Area	Std. Error	Asymptotic Sig.b	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.968	0.018	0.000	0.932	1.004

Table (5): Correlation between heart rate and values of RBG, pH, HCO_3 and anion gap

Variables	**QT dispersion**	
	R	**P**
RBG	+ 0.581	<0.001
pH	- 0.204	0.003
CHO_3	- 0.185	0.008
Anion gap	+ 0.143	0.039
Severity	+ 0.121	0.081
Duration of the disease	- 0.030	0.665

DISCUSSION

Though coronary artery disease remains one of the most common diabetic cardiovascular side effects, arrhythmias are commonly documented in acute hyperglycemic states of DM. It is a significant and independent risk factor for DKA and HHS morbidity and mortality, which are usually, accompanied with rhythm disturbances for example atrial fibrillation and ventricular arrhythmia. In hyperglycemic crises, cardiac arrhythmia is frequently caused by electrolyte imbalance [7].

The current study was conducted on 208 patients admitted to medical Intensive Care Unit in Specialized Medical Hospital, Mansoura University. 189 patients presented by diabetic ketoacidosis and 19 patients with hyperosmolar hyperglycemic state. 33.3% of the patients with diabetic ketoacidosis were affected mildly, 44.4% were affected moderately, and 22.2% were severely affected. This result is in agreement with that of **Aygün *et al.*** [8] and **Mekonnen *et al.*** [9] in which there were a predominance of moderate DKA, 48.9% and 51.2% respectively, than other types. This difference could be attributed to selective inclusion criteria of the current study.

The included patients in the current study were younger (Mean±SD 35.88±16.8 years) than patients included in research conducted by **Nishikawa *et al.*** [10] (Mean±SD 46.4 ± 19.6 years). Meanwhile, in the study of **Mekonnen *et al.*** [9] the mean age of patients was much younger (33.30± 14.9 years).

In the present study, type 1 DM patients were more included than type 2 DM patients. Out of 208 patients, only 55 (26.4%) patients were type 2 and the others were T1DM. Similarly, the study conducted by **Nishikawa *et al.*** [10] demonstrated that the rate of type 2 diabetes was significantly lower, it was present in 39.1% of studied cases. **Mekonnen *et al.*** [9] and **Benoit *et al.*** [11] also revealed the same result of type I predominance. In contrast, type 2 diabetes was the most common type across patients hospitalized with acute hyperglycemic syndromes in nations with various genetic and socioeconomic backgrounds, according to research by **Seth *et al.*** [12] in India and **Shahid *et al.*** [13]**,** greater mean age in the latter two studies explained why type 2 diabetes was more prevalent in their trials, because type 2 diabetes is more common in older people. Patients aged 18 to 40 years old made up the majority of our sample, indicating that type 1 diabetes, rather than type 2 diabetes, is more likely to cause DKA development in our study.

In the current study, heart rate was shown to be considerably higher during DKA or HHS compared to heart rate following recovery. Sinus tachycardias were found in 9.1% of admitted patients and dropped to 3.4% after treatment. In support of the present result, another study by **Aygün *et al.*** [8] found increase in heart rate during acute hyperglycemic crisis more than heart rate after recovery. Additionally, the study of **Andersen *et al.*** [14] supported the same result of the faster heart rate at the time of acute hyperglycemic syndromes.

Concerning P-wave dispersion (Pd), which is a marker of atrial refractoriness heterogeneity, Pd prolongation suggests intra-atrial and inter-atrial non-uniform conduction. The research showed that Pd value was significantly higher during DKA or HHS (67.7%) than after treatment (16.3%) of all studied cases. Similar to the current research, another literature mentioned that Pd and Pmax during hyperglycemic attack was greater than 6 hours later from urinary ketone being negative [60 (40-100) ms; 40 (20-60) ms] [15]**.**

Moreover, **Eğil *et al.*** [16] described that the mean P wave dispersion before DKA treatment significantly increased compared to after treatment in pediatrics. Our results suggest rise of risk of atrial arrhythmia at the time of acute hyperglycemia in adult population.

Using the ROC curve to investigate the diagnostic value of RBG for the presence or absence of P wave dispersion during acute hyperglycemic crisis, it was discovered that at RBG cut off point 402.0 mg/DL, the

sensitivity of diagnosing P wave dispersion was 69.7 % and the specificity was 66.7 %.

A further ECG abnormality that occurs during acute hyperglycemic syndromes that is associated with a higher risk of ventricular arrhythmia, particularly Torsades de Pointes, is QTc interval prolongation [17].

In the present research, QTc prolongation was defined during DKA and HHS in 123 of 208 studied cases (59.1%). After treatment, QTc prolongation continued in 17 studied cases (2.1%). **Khalil *et al.*** [18] agreed with this result when found that the frequency of QTc prolongation without electrolyte imbalance was seen in 46 (63.9 percent) studied cases. In pediatric population **Kuppermann *et al.*** [19] support the result of prolonged QTc during hyperglycemic crisis.

It is worthwhile mentioning that there was no significant association between incidence of arrhythmias and duration of diabetes in the current study which exclude the role of autonomic neuropathy of diabetes. Also, in the present research cardiac arrhythmias could not be attributed to preexisting manifestations of diabetic neuropathy as most of them returned to normal after recovery from the hyperglycemic crisis.

CONCLUSION

In conclusion, DKA and HHs could be associated with several types of cardiac arrhythmias, this is attributed to hyperglycemia and ketoacidosis rather than electrolyte disturbances.

- **Competing interests:** None
- **Funding:** No fund
- **Conflicts of Interest:** The authors declare no conflicts of interest regarding the publication of this paper.

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