Original Paper

QRS and QT Interval Modifications in Patients with Type 2 Diabetes Mellitus

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ABSTRACT: Introduction: Diabetes Mellitus imbricates inflammatory processes on their pathophysiology, it could affect cardiac electrophysiology. Cardiac inflammatory process leads electrocardiogram changes. Nevertheless, there are discrepancies about whether it prolongs or decreases waves and intervals such as QRS and QT. Furthermore, QRS dispersion has not been studied. Objective: To identify QRS complex and QT interval modifications in type 2 diabetic patients. Methods: A descriptive cross-sectional study was carried out in 59 type 2 diabetic patients selected by non-probabilistic sampling. Electrocardiogram was performed, QRS and QT interval were measured manually by two observers. Dispersion of both variables was calculated to compare with normal values. Results: Two variables showed differences for sex, QRS dispersion was higher in females (45.84), p=0.0001 vs. reference value; QT dispersion (63.12) showed significance difference (p=0.0246) vs. reference value for males. Greater than five years of illness was related to higher QRS values (124.11 vs. 137.28), p=0.005 and corrected QT dispersion (61.81 vs. 78.79), p=0.022. Conclusions: The electrocardiographic differences between sexes may suggest a gender influence. The longer duration of diabetes diseases could increase cardiovascular risk of arrhythmias due to greater QRS duration and corrected QT interval prolongation.

KEYWORDS: *Diabetes Mellitus, electrocardiogram, QT dispersion, QRS dispersion.*

Introduction

Diabetes mellitus (DM) is a metabolic syndrome with great pathophysiological, biopsychosocial, and economic impact around the world and constitutes one of the greatest current public health problems [1,2].

Diabetic patients have two to four times the risk of ischemic heart disease (IHD) and cardiovascular (CV) mortality compared to non-diabetic patients who have suffered an acute myocardial infarction; therefore, diabetes mellitus is considered an "equivalent of cardiovascular disease (CVD)".

DM is an independent CVD factor and it is frequently associated with other cardioatherogenic risk factors [3,4].

Twelve-lead electrocardiogram (ECG)-derived prognostic markers have always been seductive in the study of any disease associated with increased cardiovascular risk [4].

Some electrocardiographic abnormalities have been repeatedly reported in patients with DM, such as: Increased P wave duration and its dispersion; decrease in R-wave voltage; changes in ventricular repolarization such as: ST-segment depression, increased QT interval and QT dispersion have been described, as well as nonspecific alterations of the T wave.

ECG changes have been implicated in the genesis of atrial and ventricular arrhythmias; also, they have been associated with a poor prognosis of the disease [5].

A recent study describes increased QRS duration and its dispersion (QRSd) in diabetic patients suffering from acute myocardial infarction [6].

However, the latter could be controversial, since other research has reported a decrease in QRS duration in both type 2 DM and gestational diabetes [7,8].

Intraventricular conduction disorders and axial QRS deviations have also been reported [9].

These alterations have been related to metabolic alterations of the diabetic patient (poor glycemic control), with other associated risks such as arterial hypertension and myocardial electrophysiological changes, related to the growth of cavities and/or myocardial fibrosis [3,10].

Although there are several published studies on this topic, including the work of Harms et al. [10].

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We consider there are still controversies about some electrocardiographic changes in type 2 diabetic patients (DM2).

There are discrepancies whether QRS duration is prolonged or decreased; in addition, we did not find nothing about QRSd related with DM".

That is why we intended to identify the existence of changes on QRS complex and QT interval in type 2 diabetic patients and describe the associated morbidities with another studied variables.

Methods

A descriptive cross-sectional study was conducted in patients with DM2, at the Diabetic Clinic, Villa Clara province, from July 2019 to December 2020.

The study population consisted 475 patients with DM2 treated at the Diabetic Clinic, and in the aforementioned period.

A non-probabilistic sampling method was performed and 59 patients were finally selected:

- Inclusion criteria
  Patients with a diagnosis of DM2 and who were older than 18 years.
- Exclusion criteria
  Those patients who are taking any type of QT interval prolonged drug [11].

For each patient, demographic variables (age and sex), risk factors (alcoholism, smoking, sedentary lifestyle) were studied; associated morbidities (hypertension, diabetic nephropathy, ischemic heart disease, diabetic polyneuropathy, hypothyroidism, hyperuricemia).

All patients underwent an electrocardiogram standardized to 25mm/s velocity and 10mm/mv, with Cardiocid BB electrocardiograph equipment (Central Institute of Digital Research ICID from Cuba) this electrocardiograph uses a bandpass filter between 0.05 and 150Hz, and a 60Hzhum filter.

Two observers measured the following variables on the electrocardiogram using a magnifying lens.

QT: It is the time in milliseconds from the beginning of the QRS to the end of the T wave when it reaches the isoelectric line or the end of the T wave can be marked at the nadir between the T and U wave if present). The QT interval is measured in all leads and averaged.

QTc: Corrected QT: Corrected according to Bazett's formula.

QTcd: QT was measured on 12 leads of the electrocardiogram and corrected according to Bazett's formula, the maximum and minimum were identified and the difference was calculated.

QRS duration:

The time in milliseconds from the beginning of the QRS to its end.

QRS dispersion: QRS was measured in the 12 leads of the electrocardiogram, the maximum and minimum were identified and the difference was calculated.

Mean normal values of electrocardiographic variables were reviewed in the literature, because of there are multiple references about it and values vary according to age, sex, body weight, ethnic groups studied, etc.

Therefore, it was necessary to authors to define specific ranges to use as reference normal values in this research [12-15].

- Mean value of QRS dispersion: 33.3 milliseconds (ms) for both sexes.
- Mean value to QRS complex duration:
  - Women mean value: 88ms
  - Men mean value: 94ms
  - Both sexes mean value: 91ms
- Mean value to QT interval duration:
  - Women mean value: 387ms
  - Men mean value: 380ms
  - Both sexes mean value: 384ms
- Mean value to corrected QT interval:
  - Women mean value: 414ms
  - Men mean value: 401ms
  - Both sexes mean value: 409ms
- Mean value to corrected QT interval dispersion:
  - Women mean value: 55ms
  - Men mean value: 45ms
  - Both sexes mean value: 47.8ms

Statistics

"Statistical Package for Social Sciences" (SPSS), version 20.0 for Windows was used for data management.

Frequencies and mean value with standard deviation (SD) were the summary of continuous data.

For categorical data, absolute numbers and percentages were used. variables with normal distribution were verified using the Kolmogorov Smirnov test with a significance threshold of p=0.05.

If continuous variables followed a normal distribution, Student's t-test was performed for one sample or for independent samples, and these results were compared with reference values from the literature.

Non-parametric Pearson Chi-Square test was used too.

Fisher's exact test was calculated when more than 20% of the expected frequencies presented values lower than five.

A 95% ($p<0.05$) was the level of significance adopted for statistical validation of the research results.

Ethics

All subjects studied signed the informed consent.

We respect the right to privacy of individuals in accordance with the World Health Organization (WHO) code of ethics (Helsinki Declaration) on human studies.

The study was approved by the Ethics Committee of the where the study was conducted.

Results

The female sex with 36 cases (61.02%) was mostly represented (Table 1).

Age from 50 to 59 years and 60 to 69 were the groups more predominance with 18 patients per each group (30.51%).

57.7 years was the mean age, being 55.7±13.1 and 59±11.8 years for males and females; respectively with no significant differences.

The results showed the frequency of patients under 59 years old is similar to the number of patients older than 59 years; for several years the incidence and prevalence of diabetes mellitus has been an epidemiological alarm.

Once the disease has been diagnosed, it is important to know the variables associated with a higher risk of complications

Table 1. Distribution of patients according to age and sex.

Age (years)	Sex				Total	
	Male		Female			
	N^O	%	N^O	%	N^O	%
<50	7	11,86	6	10,17	13	22,03
50 a 59	6	10,17	12	20,34	18	30,51
60 a 69	6	10,17	12	20,34	18	30,51
≥70	4	6,78	6	10,17	10	16,95
Total	23	38,98	36	61,02	59	100
Mean±SD	55,7±13,1		59,0±11,8		57,7±12,4	

(Mean Difference between sex) t=-1,002 p=0,302

Table 2. Distribution of patients according to risk factors and sex.

Risk factors	Sex				Total	
	Male		Female			
	N^O	%	N^O	%	N^O	%
Overweight and obesity	20	86.96	28	77.78	48	81.36
Hipertension	16	69.57	26	72.22	42	71.19
Family history of cardiovascular diseases	12	52.17	16	44.44	28	47.46
Diabetes mellitus of >5 years	12	52.17	14	38.89	26	44.07
Smoking	6	26.09	14	38.89	20	33.90
Sedentary lifestyle	4	17.39	12	33.33	16	27.12
Ischaemic heart disease	4	17.39	7	19.44	11	18.64
Coffee	4	17.39	6	16.67	10	16.95
Dyslipidemia	4	17.39	4	11.11	8	13.56
Hypothyroidism	1	4.35	4	11.11	5	8.47
Diabetic Polyneuropathy	1	4.35	1	2.78	2	3.39
Hyperuricemia	2	8.70	0	0.00	2	3.39
Diabetic Nephropathy	0	0.00	1	2.78	1	1.69
Alcohol intake	1	4.35	0	0.00	1	1.69

(Hypertension) X^2=0,048 p=0,826; Ischaemic heart disease X^2=0,039 p=0,843;
Overweight and obesity X^2=0,292 p=0,589; Diabetes mellitus of >5 years X^2=0,5382 p=0,4632;
Smoking X^2 0.5346 p=0.4647; Sedentary lifestyle X^2=1,0881 p=0,2969

According to risk factors and sex an analysis of patients was performed (Table 2).

There was a majority with overweight and obesity, 48 patients (81.36%), followed by hypertension (HBP) 42 patients (71.19%), without differences for sexes.

Overweight and obesity had a higher frequency in males (86.96%); while HBP and smoking were higher in women (72.22%) and (38.89%), respectively.

There were no significant differences between male and female.

Other variables that showed high percentages in the sample were family history of cardiovascular disease (47.46%) and suffering Diabetes mellitus more than 5 years (44.07%).

These two variables mentioned above show a higher frequency in the male sex (both with 52.17%) against 44.44% and 38.89%, respectively in women.

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Table 3. Distribution of mean of electrocardiographic values studied according to sex.

Dispersion and maximum duration	Sex				Sample values		t	**p**
	Male		Female					
	Mean	SD	Mean	SD	Mean	SD		
QRS maximum duration	126,93	15,15	131,82	19,84	129,92	18,18	-1,009	0,317
QRS Dispersion	38,80	12,60	45,84	15,57	43,10	14,78	-1,819	0,074
QT Interval	442,83	34,79	445,68	37,00	444,57	35,88	-,295	0,769
QT Dispersion	63,12	26,08	53,70	21,31	57,38	23,53	1,516	0,135
QTc Dispersion	76,16	32,38	64,90	25,49	69,29	28,64	1,489	0,142

SD: standard deviation

Table 3 shows the distribution of mean of electrocardiographic values studied according to sex.

Mean of the maximum duration of the parameters was greater in females (QRS maximum duration 131,82ms vs. 126,93ms in men), while the dispersion parameters were greater in males, except for QRS complex which was significantly exceeded by females, 45,84ms vs. 38,80ms in men.

In general, no significant differences were found.

It is noteworthy that the highest values of QRS dispersion was found in female sex.

QT interval dispersion (63,12ms vs. 53,70ms) and QTc (76,16ms vs. 64,90ms) were greater in male sex.

Differences were shown on sex although they did not become significant.

Table 4, when comparing mean values of the electrocardiographic variables from the sample studied with the mean values references of the literature, only QRS dispersion in men and QT interval in women did not show significant differences.

Table 4. Comparison between electrocardiographic parameters studied with the mean normal values of electrocardiographic parameters related to sex.

Comparison with NV	Male	Female
Maximum QRS duration	0,0000	0,0000
QRS Dispersion	0,0813	0,0001
Maximum QT Duration	0,0000	0,0000
QT Dispersion	0,0246	0,3047
QTc Dispersion	0,0008	0,0013

NV: mean normal values

A distribution of mean of electrocardiographic values studied according to the time of illness evolution is showed in Table 5.

Time of illness evolution was divided in less than five years or more than five years. Greater values were found in maximum QRS complex duration (137,28±18,87ms) and QT dispersion (64,39±25,47ms) and QTc intervals (78,79±32,06ms) when patients suffer DM greater than 5 years.

It was significant differences in the above variables related with time of illness evolution.

Table 5. Distribution of mean of electrocardiographic values studied according to the time of illness evolution.

Dispersion and maximum duration	Time of illness evolution				t	p
	<5 years		5 and more years			
	Mean	SD	Mean	SD		
maximum QRS duration	124,11	15,55	137,28	18,87	-2,939	0,005
QRS Dispersion	41,19	11,75	45,52	17,87	-1,121	0,267
maximum QT duration	447,36	31,47	441,03	41,17	0,670	0,505
QT dispersion	51,85	20,62	64,39	25,47	-2,090	0,041
QTc dispersion	61,81	23,51	78,79	32,06	-2,347	0,022

SD: standard deviation

When comparing electrocardiographic mean values variables of the studied sample with the reference values in the literature [12-15] (Table 6), all variables showed a significant difference regardless of whether the disease is less than or more than five years old.

It was excepted to QT dispersion, p=0,6098 in patients with less than five years suffering from the beginning of the disease.

Table 6. Comparison between electrocardiographic parameters studied with the mean normal values of electrocardiographic variables related to the time of illness evolution.

Electrocardiographic Variables	Time of illness evolution	
	<5 years	5 and more years
Maximum QRS duration	0,0000	0,0000
QRS Dispersion	0,0013	0,0030
Maximum QT duration	0,0000	0,0000
QT dispersion	0,6098	0,0080
Maximum QTc duration	0,0000	0,0000
QTc Dispersion	0,0069	0,0001

NV: electrocardiographic mean normal values.

Discussion

Although the study population consisted of 475 patients with DM2, only 59 were studied when we adjusted to the exclusion criteria, after verifying in each patient the prescription QT interval-prolonging drugs.

Finally, the sample was made up of a larger number of females, but without significant differences for age which in this demographic variable contributes to making the sample more homogeneous, at least about this aspect.

Related to risk factors studied, overweight and obesity, hypertension, family pathological history of cardiovascular disease and history of diabetes mellitus for more than 5 years, always exceeded the frequency of 50% in men and 40% in women.

Obesity, hypertension, and long-standing diabetes mellitus constitute systemic proinflammatory states with great cardiovascular repercussions and myocardial damage.

Ferrer-Orozco et al. [16], studied electrocardiographic changes in hypertensive patients vs. a control group and showed the QRS duration was higher in hypertensive patients than the normal population 116.07±16.41 vs. 101.43±5.35 (p=0.033); QRS dispersion was also greater in patients with hypertension vs. control group 44.64±19.72 vs. 30.71±6.16 (p=0.033).

Studies looking for electrocardiographic changes in DM without comorbidities have shown the presence of electrocardiographic modifications associated with the disease [17,18]; as well as the study by Ferrer-Orosco et al. [16] demonstrates it in hypertensive patients.

In both diseases (DM and hypertension), inflammatory and structural cardiac changes have been described that may be related to the electrocardiographic alterations described.

Therefore, it is really important to understand the association of DM with other comorbidities such as hypertension can constitute potential risks of adverse cardiovascular events, as it is widely reported.

Achieving the metabolic control of the DM and associated comorbidities is a primary recommendation.

It is common to find fibrosis and hypertrophy of cardiomyocytes, proteoglycan deposits in the postmortem heart of diabetic patients; adipose infiltration; microvasculature alterations in capillaries, arterioles and venules; all of the above generates changes in the basic electrophysiology of the myocardiocytes that causes changes to appear in the electrocardiogram [19].

The hyperglycemia observed in DM 2 only allows us to see the top of the dysmetabolic iceberg, it has been well described that obese patient with increased intra-abdominal (visceral) adipose tissue have increased insulin resistance.

The main factor contributing to insulin resistance is the alteration of the metabolism of non-esterified fatty acids.

In states of obesity, adipose tissue is also a paracrine organ that releases a number of cytokines.

Interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which can be produced in adipocytes, have been described as molecules involved in inflammation.

In patients with visceral obesity, macrophage infiltration of adipose tissue is described and this is related to the proinflammatory state described in these patients.

Adipose tissue can also synthesize anti-inflammatory substances, such as adiponectin, which is reduced in obese patients.

Adiponectin has insulin signaling-enhancing effects, which counteract atherosclerosis.

Reduced adiponectin is a factor responsible for the risk of atherosclerosis and increased incidence of diabetes. [3,20].

All these inflammatory changes lead to electrophysiological alterations of the myocardial muscle, altering the anisotropy and causing conduction and repolarization disorders translated into increased in QRS duration and its dispersion and QT interval as was demonstrated in this study.

However, the principal aim of this research is to clarify (in our sample) the controversies there is in literature still; some studies report prolongation of these intervals and others do not;

Likewise, they have reported the non-prolongation of these electrocardiographic variables respect to control groups in diabetics without cardiac autonomic neuropathy (ACN)

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and QRS and QT prolongation in DM2 with NCA [5,7-10].

Present study demonstrated an increased in ventricular depolarization and its dispersion (QRS) in women than in men; QRS dispersion value showed significance differences when compared to normal values, only in women.

However, QT interval dispersion showed higher and significant differences values in men.

The aforementioned may suggest that there is a gender influence.

A previous study [21], based on patients undergoing cardiac resynchronization, showed that women with left bundle branch block had greater QRS dispersion than men (48.0±24.0 vs. 37.14±13, 8ms; p=0.04). Chávez González et al. [22], demonstrated higher mortality due to infarction with increased QRS dispersion on first 48 hours and after 48 hours from the onset of the infarction mortality was more associated with increased QT interval dispersion; therefore, increased in QRS and QT dispersion may constitute cardiovascular risk variables associated with cardiovascular risk.

A study comparing women and men allows us to observe that in patients with DM2, women showed a higher percentage of hypertension 25 (44.6%) vs. 27 (36.5%) of men; women showed a higher proportion of body fat 44.7±5.4 vs. 31.3±5.2% men.

Hypertension and body fat are well-defined as cardiovascular risks associated with systemic proinflammatory states [23].

It is important to control the disease, as well as the risk factors and comorbidities associated with DM2, since inflammatory changes in the structure of the heart can modify the electrophysiology of these patients.

A study showed, in ST-segment elevation acute myocardial infarction: greater QRS duration and its dispersion were associated with appearance of ventricular arrhythmias and death, in this investigation 25 patients who presented malignant ventricular arrhythmias, 15 of them had personal history of diabetes mellitus.

Long-standing suffering diabetes mellitus increases the systemic proinflammatory risk with cardiac muscle involvement.

Thus, it may perhaps derive from the data obtained in this study group with more than five years of illness a wider QRS and also the greater QT dispersion and QTc.

Gupta S et al. 18 demonstrated greater electrocardiographic changes in asymptomatic patients with more than five years personal history of DM2.

Diabetes Mellitus constitutes a systemic proinflammatory state leads to anatomical and functional changes with described clinical and pathological evidence to lead increased cardiovascular risk, it could produce characteristic electrocardiographic changes related to the risk of sudden death.

Request to physicians about metabolic control and associated comorbidities is imminent.

DM2 constitutes a metabolic disease due to its autocrine, paracrine and endocrine alterations it leads to electrophysiological alterations of the heart these changes could be expressed with a longer QRS duration and its dispersion in women and the corrected QT interval and its dispersion in men.

As previously mentioned, it could have a gender implication.

The greatest expression, of electrocardiographic changes occurs with the long-standing diabetes mellitus is suffered.

Study limitations

The small sample studied was the main limitation of this study. Similar studies should be replicated and evaluated in a larger population.

Conclusions

QRS dispersion is a variable that has been studied for the first time in a diabetic population to evaluate its changes, since previous studies of acute ischemic heart disease have shown that the greater the QRS dispersion, the greater the risk of ventricular arrhythmias and death.

Electrocardiographic changes in diabetic patients may be a sign of target organ damage, considering that myocardial damage due to fibrosis has been demonstrated in long-term diabetics.

Long-term electrocardiographic changes in diabetic patients probably have a gender influence.

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Conflicts of interest

The authors have no conflict of interest to declare.

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