ARRHYTMIC EVENTS IN TYPE 2 DIABETIC PATIENTS ON INSULIN THERAPY

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Abstract *Diabetes mellitus has been associated with increased cardiovascular disease mortality and sudden cardiac death. Present study aims to evaluate arrhytmic events in type 2 diabetic patients in relation to the type of medication used for the metabolic disease. We have studied by Holter ECG monitoring 71 diabetic patients, of whom 11 (15.49%) were following insulin therapy and 60 (84.51%) were receiving diet or oral medication. We found that diabetic patients with insulin therapy had a significantly decreased number of ventricular arrhythmic events, a significant decreased number of isolated ventricular ectopic beats, a significant decreased number of paired ventricular ectopic beats. The same trend was maintained regarding episodes of ventricular bigeminy and ventricular tachycardia episodes, but due to the low number of episodes of these malignant arrhytmias in the entire studied group, there were no statistically significant differences between the subgroup treated with insulin and the subgroup on diet/oral therapy.*

Key words: *ventricular arrhythmia, cardiovascular autonomic neuropathy, insulin therapy, diabetes type 2.*

1. Introduction

Cardiovascular disease remains the main cause of excess mortality in patients with type 1 and type 2 diabetes. Clinical studies have been reported among diabetic patients an increased incidence of fatal cardiac arrhythmias including ventricular fibrillation and sudden death [19].

Myocardial increased susceptibility to arrhythmias is an important feature of diabetic patients and is due to a number of structural and functional factors which are gathered under the generic term of metabolic cardiomyopathy [18]. It is well known that the autonomic nervous system has a major role in regulation of cardiovascular function. Cardiac autonomic neuropathy (CAN) is defined as the impairment of autonomic control of cardiovascular system in the presence of diabetes. CAN represents a damage to autonomic nerve fibers that innervate the both heart and blood vessels, causing an abnormal heart rate control and an abnormal vascular dynamics [22]. An

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increased sympathetic autonomic activity characterizes the clinical stage of CAN and leads to cardiomyocyte apoptosis and myocardial damage [1], [20]. Studies on animal model have been demonstrated that an increased susceptibility to ventricular arrhythmias is associated to an increased sensitivity to cathecolamines [2].

CAN is clinically manifested by orthostatic hypotension, by exercise intolerance, by persistent sinus tachycardia and by a decreased heart rate variability which is related to an excessive ectopic activity [17], [20]. In general population, including prediabetes patients, researches have proven that a decreased heart rate variability (HRV), marker of the autonomic dysfunction, has severe consequences related both to morbidity and mortality, independent of cardiovascular risk factors [7], [17], [22], [23].

The pathophysiological mechanisms related to an increased vulnerability to malignant arrhythmias are complex and still are not completely understood. In diabetes cardiomiopathy the risk factors for development of the arrhytmogenic substrate are considered the heterogeneity in atrial and ventricular repolarization, the extend of myocardial damage and the scar formation [19]. Prolonged QTc interval is often found in diabetic patients and it is considered a primary factor for the developement of malignant arrhytmias in this group of patients [18], [21]. One explanation of this phenomenon is that in diabetes there is a reduction in phosphoinositide 3 kinase (PI3K) signaling. PI3K regulates the action potential duration (APD) of cardiomyocytes, this signaling deficit is leading to APD prolongation reflected by prolonged QT interval [9]. Compared to general population who have impaired cardiac autonomic function secondary to other diseases, it has been shown that diabetic patients with cardiac autonomic neuropathy are at an increased risk of mortality and are more exposed to develop severe arrhythmias, cardiomyopathy, silent ischemia and sudden cardiac death rather than general population [1], [22].

2. Objectives

We aimed to study the incidence of arrhythmias in diabetes patients type 2 in relation to the type of medication followed for metabolic disease.

3. Material and methods

We studied a randomly extracted sample of 71 type 2 diabetic patients from the database of the department of Cardiology Rehabilitation Institute Cluj-Napoca. All patients were Holter ECG monitorized. Monitoring length was 24 hours. Data were analyzed with Cardiospy SW software. From medical records we extracted general statistics age, gender, associated pathologies and biochemical parameters (fasting glucose, HDL-C, TC LDL-C, triglyceride, creatinine. BMI was calculated (kg/m²). Patients were defined as diabetic patients based on fasting blood glucose ≥126 mg/dl, or those who were receiving diet, oral hypoglycemic therapy or insulin therapy.

Three channel (V1, V5, aVF) 24 hours monitoring reports were analyzed following:
  a. supraventricular and ventricular arrhythmic events
  b. average heart rate
  c. average QTc

- HRV indexes in time domain were: SDNN (standard deviation of all NN intervals), rMSSD (square root of the mean of the sum of the squares of differences between adjacent NN intervals), pNN50 (NN count divided by the total number of all NN intervals). The following HRV indexes in frequency domain were assessed: LF – power in low frequency domain (0.04-0.15 Hz), HF-power in high frequency domain (0.15-0.4Hz), LF/HF ratio (awake and asleep). HF and LF values were expressed in normalized units (n.u.)

All subjects were informed to abstain from caffeinated food, to maintain their usual activities and to continue their treatment regimens. The study was reviewed and approved by the local institutional review board and each subject signed an informed consent.

4. Statistical analysis

Statistical analyzes were performed using SPSSR version 15 for Windows. Continous variables were expressed as mean ± MDS. Dichotomous variables were listed as percentages. Data with normal distribution were compared using unpaired Student's t-test, p value <0.05 was considered statistically significant. Series of frequency were compared by Fisher contingency tables.

5. Results

The studied group had the following general and clinical characteristics: mean age 66.028 ± 8.638 years, gender distribution 31 (43.66%) males and 40 (56.33%) women, of whom a number of 11 (15 49%) patients were treated with insulin and 60 (84.51%) patients were following diet or/and oral hypoglycemic agents. Regarding the entire group, relevant associated pathologies to our study, were: hypertension (77.46%), ischemic heart disease (38.02%), heart failure (88.73%) and atrial fibrillation (21.12%). Analysis of the associated pathologies indicated no significant differences between diabetics treated with insulin versus diabetics without insulin therapy (Table 1). Mean values of the biochemical parameters and BMI are shown in Table 2.

Following the analysis of the 24 hours monitoring reports regarding average heart rate in the two groups of patients, we found a decreased average heart rate in the group treated with insulin (56.72±13.7) compared with the group on diet/oral therapy (69±11.9, p value 0.0015) and is of statistical significance (Table 3). Mean duration of QTc interval exceeded 440 ms in diabetic group withought insulin therapy (442.1 ±26.9), while mean duration of QTc interval in diabetic group with insulin therapy it was found to be 438±27.3 but we found no statistical diferences between the two groups regarding QTc interval. By analyzing Holter monitoring reports we found a significantly decreased total number of ventricular events in diabetic patients treated with insulin compared with the group on diet/oral therapy. In addition, in the group of patients with insulin therapy we found a decreased number of paired ventricular premature beats, ventricular bigeminy episodes and episodes of ventricular tachycardia (Table 4). Regarding HRV indexes we have not found significant differences between the two groups, although rMSSD index, marker of vagal modulation was found to

be higher in diabetes with insulin therpay and LF/HF ratio, marker of sympathovagal imbalance was found to be lower in group with insulin therapy (Table 3).

Associated pathologies   Table 1

Therapy	Hypertension n [%]	Ischemic heart diseasen [%]	Heart failure n [%]	Atrial fibrillation n [%]
Insulin therapy	8 [72.72]	5 [45.45]	8 [72.72]	3 [27.27]
Non insulin therapy	47 [78.33]	22 [36.66]	55 [91.66]	12 [20]
p value	0.5	0.22	0.08	0.25

Biochemical parameters, BMI   Table 2

Therapy	BMI kg/m²	Fasting glucose [mg/dl]	HDL C [mg/dl]	LDL C [mg/dl]	Triglyceride [mg/dl]	Creatinine [mg/dl]
Insulin therapy	32.07±9.23	134.09±37.13	35.63±9.66	114.63±25.7	128.09±55.9	1.76±1.49
Non insulin therapy	33.29±12.59	127.98±33.27	36.01±8.76	118.5±34.3	163.62±79.4	1.005 ±0.255
p value	0.35	0.35	0.45	0.33	0.08	0.063

Holter monitoring HRV indexes   Table 3

Therapy	HR average [bpm]	SDNN [ms]	rMSSD [ms]	pNN50 [%]	LF/HF ratio asleep	LF/HF ratio awake	mean QTc [ms]
Insulin therapy	56.72±13.7	134.27±54.9	88.36±81.5	21.69±21.7	1.29±1.2	1.31±0.99	438±27.3
Non insulin therapy	69±11.9	134.43±52.6	85.71±95.1	22.1±28.9	1.39±0.91	1.47±1.02	442.1±26.9
p value	0.0015	0.49	0.46	0.47	0.37	0.31	0.32

Holter monitoring -.Arrhytmic events   Table 4

	Insulin therapy	Non insulin therapy	p value
Total ventricular arrhythmic events	201.81±392.17	976.98±2358.09	0.01
Isolated ventricular premature beats	192.27±367.17	960.55±2339.95	0.0098
Paired ventricular premature beats	1.09±2.38	7.35±27.15	0.042
Ventricular bigeminy episodes	3.45±11.12	50.03±244.47	0.07
Ventricular tachycardia episodes	0.18±0.60	0.26±1.27	0.36
Total atrial arrhythmic events	544.09±1132.13	428.13±1132.21	0.37
Supraventricular premature beats	543±1130.89	424.53±1128.79	0.37
Paired supraventricular premature beats	0.272±0.64	0.916±0.66	0.026

6. Discussions

It has been shown that insulin is a pleiotropic hormone with multiple effects on glucose metabolism, on the immune system, on central nervous system and on cardiovascular system [8]. Studies have demonstrated that insulin increased cardiac contractility in isolated lung-heart preparations and increased arterial blood pressure in animals, but at present the underlying mechanisms of insulin positive inotropy are just partially known [13], [17]. Researches indicate that the essential cardioprotective action of insulin is exerted through upregulation of PI3K pathway and mitogen activated protein kinase pathway [8]. In present study we noticed a decreased heart rate average in the group of patients with insulin therapy compared to the group treated with oral antidiabetic medication and diet, a possible explanation for this result is that insulin may improve cardiac rhythm by optimizing cardiac function. Experimental studies involve several pathogenic pathways that impact autonomic function in diabetes including:

formation of advanced glycation end products, increased oxidative and nitrosative products, activation of the protein kinase C pathway, activation of polyADP ribosylation, activation of genes involved in neuronal damage [6], [10], [16]. Insulin has an antioxidant effect by restoring the activity of the primary antioxidant enzyme (glutathione peroxidase) and by reducing lipid peroxidation [3], [11], [24]. In addition, studies have demonstrated that insulin can prevent oxidative damage by reducing the formation of free radicals through the PI3K-Akt pathway and has an antiapoptotic effect [4], [15], [24]. It is well known the arrhythmogenic role of oxygen free radicals that compromise the activity of ion pumps and leads to electrophysiological damages that trigger malignant arrhythmias. In this context, normalization of blood glucose levels with insulin may diminish many of the damaging effects on the heart associated with hyperglycemia. It has been shown that insulin reduced coronary resistance and increased myocardial blood flow

[13], the vasodilatator effect of insulin has been also reported in human studies.

The relationship between control of hyperglycemia and cardiovascular risk is still controversial. Megatrials as ACCORD and ADVANCE have suggested that increased mortality with intensive glycemic therapy could be related to the negative effects of hypoglycemic events [25], [26]. In diabetic patients who have developed endothelial dysfunction, hypoglycemia leads to acute hemodynamic changes leading to an increased risk of major vascular events as myocardial infarction and stroke [5]. On the other hand, in diabetic patients hypoglycemia is associated with a significant prolongation of QTc interval leading to an increased risk of ventricular tachycardia and sudden death [12]. In addition, long term insulin trials have shown that insulin therapy is associated with weight gain and obesity which are independent risk factors for cardiovascular diseases [27].

7. Conclusions

Based on our findings we can assert that insulin therapy exerts cardioprotective effects.

In diabetic patients, cardiovascular risk reduction requires comprehensive assessment of all contributing risk factors. Therefore, individualized antidiabetic therapy becomes important in diabetic patients with concomitant cardiovascular diseases.

Acknowledgements

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