THE RELATIONSHIP BETWEEN SERUM LIPID FRACTIONS AND HEART RATE VARIABILITY IN DIABETIC PATIENTS WITH STATIN THERAPY

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Abstract

Background and aims. The aim of this study is to identify and highlight the relationship between serum lipid fractions and heart rate variability in diabetic patients receiving statin therapy.

Patients and methods. The study was performed in a group of 87 type 2 diabetic patients on statin associated therapy. All patients were on Holter ECG 24 hours monitored with three channel monitor (Labtech ECG Holter monitor), and data were analyzed on a commercially available software (Cardiospy PC SW/EV 5.02.06.02). Concentrations of biochemical parameters were determined using specific enzymatic assays on an autoanalyzer Olympus AU 680. In the studied patients, we analyzed Holter/24 hours monitoring reports with respect to heart rate variability indexes, arrhythmic events and myocardial ischemia.

Results. It was noticed that the mean values of serum TG were slightly elevated, TC levels were close to the limits specified by the guidelines for diabetic patients and for patients with cardiovascular diseases, with no significant differences between males and females. After analyzing the HRV in both time and frequency domains, we found no strong correlations between any of the HRV indexes and any of the lipid fractions.

Conclusions. The results suggest that statin therapy may reduce the autonomic impairment secondary to dyslipidemia.

Keywords: type 2 diabetes, statin therapy, heart rate variability, lipid fractions.

Introduction

It is well known that a decreased heart rate variability leads to increased cardiovascular risk, particularly to an increased arrhythmic risk both in patients with cardiovascular disease and healthy subjects. In the presence of cardiac autonomic neuropathy, diabetic patients with or without cardiovascular disease, have a decreased heart rate variability (HRV) related to increased mortality risk [1-3] HRV is a measure of the imbalance between sympathetic and parasympathetic autonomic activity, and its decrease is a sign of dominance of sympathetic activity.

Decreased HRV has been shown to be linked with the presence of cardiovascular disease, with the incidence and severity of ischemic heart disease, with the systolic heart failure and has been related with some cardiovascular risk factors [4]. Among them, several cross-sectional studies in non-diabetic adults evidenced that markers of autonomic function were negatively associated with fasting glucose, insulin resistance and all components of the metabolic syndrome [3,5]. Cardiovascular risk factors as high blood pressure can also alter heart rate variability. Among the studied risk factors are the different components of serum lipids, but the relationship between plasma lipid fractions and HRV have provided less consistent results. Some research has suggested that increased serum lipid fractions

as LDL cholesterol and total cholesterol were linked to a decreased HRV, although there are still some conflicting results [6-8]. So far no correlation has been definitively established between serum triglyceride values and HRV indexes. Correlations between serum lipid components and HRV were less studied in diabetic patients than in the general population with cardiovascular risk factors.

We raised the question whether these discordant results regarding the relationship between plasma lipid fractions and HRV could be in relation to lipid-lowering therapy applied to the diabetic and dyslipidemic patients. Thus, we aimed to investigate the relationship between lipid profile and HRV in diabetic patients with statin associated therapy. We aimed to find out if regardless of serum lipid fractions levels, statins may influence the relationship with HRV also through the direct effect of statin therapy on the atherosclerotic plaque and on ischemia in different vascular territories including coronary arteries.

Material and methods

From the original cohort (97 diabetic patients), we studied an extracted a group of 81 type 2 diabetic patients on statin associated therapy. All patients were admitted to the department of Cardiology, Rehabilitation Hospital Cluj-Napoca. The study protocol was reviewed and approved by the local institutional review board and the local Ethics Committee; an informed consent was obtained from every subject, according to the World Medical Association Declaration of Helsinki, revised in 2000, Edinburgh.

All patients were Holter ECG 24 hours monitored with three channel monitor (Labtech ECG Holter monitor), and data were analyzed on a commercially available software (Cardiospy PC SW/EV 5.02.06.02).

Patients were classified as diabetes patients on the basis of history regarding the duration of the disease or need for antidiabetic therapy. The diagnosis has been based on a previous diagnosis of diabetes based on: fasting glucose level >126 mg/dl on two measures or receiving diet therapy or taking oral antidiabetic therapy or receiving insulin therapy.

Criteria for inclusion in the study were type 2 diabetic patients with statin associated therapy (atorvastatin, simvastatin, pravastatin, rosuvastatin) but without considering the daily dose used at the time of admission in the study. The exclusion criteria were: presence of congestive heart failure, late stage of chronic kidney disease, acute ischemic coronary syndrome, associated antiarrhythmic therapy.

Venous blood samples were collected by venipuncture, after 12 hours fasting. Blood samples were collected in test tubes, preserved at 4°C and delivered to the laboratory department of the Rehabilitation Hospital Cluj-Napoca. The blood samples were centrifuged and the serum was collected. Concentrations of biochemical parameters were determined using specific enzymatic assays on an autoanalyzer Olympus AU 680. Fasting plasma glucose levels were measured by glucose-peroxidase colorimetric enzymatic method. Fasting plasma lipid profile assessed total cholesterol (TC), low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), and triglyceride (TG) levels. Serum TC levels were determined by the enzymatic method, HDL–C levels were determined by precipitation with $MgCl_2$ and phosphotungstate method. LDL-C levels were determined by precipitation followed by enzymatic method. Serum TG levels were measured by colorimetric enzymatic method. Serum creatinine concentrations were determined by the Jaffé method. Serum uric acid concentrations were measured by standard analytical method (uricase enzymatic test). In order to evaluate the renal function correctly, estimated glomerular filtration rate (eGFR) was calculated using the Modification Diet in Renal Disease (MDRD) equation, based on the concentration of serum creatinine: $175 \times$ serum creatinine$^{-1,154} \times$ Age$^{-0,203} \times 0.742$ (if female). The body mass index (BMI) was calculated as weight (kg)/height² (m²).

In the studied patients, we analyzed Holter/24 hours monitoring reports with respect to heart rate variability indexes, arrhythmic events and myocardial ischemia. Participants were instructed not to consume caffeinated food and beverages on the day of assessment and were also advised to maintain their usual daily activities. HRV was assessed in time and frequency domains. Time domain HRV indexes were calculated from 24 h ECG recordings: SDNN (standard deviation of all NN intervals), SDANN (standard deviation of the averages of NN intervals in 5-minute segments), 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). Frequency domain (spectral) indexes were then assessed: high frequency power HF (0.15-0.5 Hz), low frequency power LF (0.04-0.15 Hz), and the ratio of low frequency to high frequency (LF/HF ratio). The HF component reflects mostly parasympathetic activity and the LF component is mainly related to the sympathetic tone [9,10]. LF/HF ratio (during night and day periods) was calculated for each patient as a measure of sympathovagal balance [9]. The results of LF and HF are shown in normalized units.

Myocardial ischemia was diagnosed based on electrocardiographic ST changes, including ST depression (descendent or horizontal depression) more than 0.1mV and 1 min duration, at least two episodes/24 hours.

Arrhythmic events were quantified. Supraventricular ectopic complexes (PAC) were considered those with normal QRS morphology and were detected by their precocity in the cardiac cycle. Complexes considered to be ventricular ectopic complexes were visually analyzed and classified before validation monitoring reports. Recordings were analyzed for the occurrence and frequency of arrhythmic events. For the assessment of atrial ectopy

we used the following measures: average hourly isolated premature atrial beats (≥30 PAC/h), number of atrial tachycardia episodes/24h (AT/24 h) defined as three or more consecutive atrial ectopic complexes with mean RR length <600 ms/ per 24 h at a rate of ≥100 beats/minute. Assessment of ventricular ectopy was performed by measuring: hourly isolated ventricular ectopic beats (≥6 PVC), number of paired ventricular beats (CPL/24 h) defined as two consecutive ventricular extrasystoles, number of ventricular tachycardia episodes/24h (VT/24 h) defined as three or more consecutive ventricular ectopic beats, at a rate of ≥100 beats/minute, with mean RR length <600/ms.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 17 for Windows. Data normality was verified using the Kolmogorov–Smirnov criterion. Variables with a normal distribution are shown as means ± SD. Skewed data are presented as median [median (1st Quartile-3rd Quartile)]. A p value ≤0.05 for two sided comparisons was considered significant. Dichotomous variables are listed as percentages. Student's t-test was used for comparison of variables with normal distribution and Mann-Whitney U was used for comparison of variables with abnormal distribution. Univariate analysis was used to evaluate correlations between HRV indexes as dependent variables and HDL-C levels, LDL-C levels, TC, TG. Pearson's correlation was used for data with normal distribution, and Spearman's correlation was used for variables with abnormal distribution.

Results

The main clinical and demographic characteristics of the studied group are shown in table I.

Table II shows the mean values ± SD of serum lipids and fasting blood glucose in the studied group. It is noticed that the mean values of serum TG were slightly elevated, TC levels were close to the limits specified by guidelines

Table I. Main clinical and demographic characteristics of the studied group

Characteristics	Diabetic patients with statin therapy n (%)
Male	33 (40.71)
Hypertension	78 (96.29)
Coronary heart disease	58 (69.87)
Dyslipidemia	73 (87.95)
Heart failure	60 (72.28)
Diabetic retinopathy	1 (1.20)
Diabetic neuropathy	10 (12.04)
Myocardial infarction	5 (6.02)
Stroke	4 (4.81)
Insulin therapy	17 (20.98)
Diet/oral antidiabetic therapy	64 (79.01)
eGFR ≤ 60 (ml/min)	23 (27.71)
BMI ≥25 (kg/m²)	67 (80.72)

(eGFR – estimated glomerular filtration rate, BMI – body mass index)

for diabetic patients and for patients with cardiovascular diseases, with no significant differences between males and females.

Serum LDL-C mean values exceeded the levels recommended by American Diabetic association (ADA) [11] and American Heart Association (AHA) [12] guidelines (100mg/dl) and substantially exceeded 70 mg/dl recommended as the optimal value for diabetic and cardiovascular patients. Serum LDL-C levels were found to be higher than 70 mg/dl in 77 (93%) patients while in 51 (62%) patients LDL-C levels were found to be higher than 100 mg/dl. Mean values of HDL-C were decreased. HDL-C levels

Table II. Plasma lipid profile and fasting glucose in the studied group

Parameters	male	female	p value
TC (mg/dL)	179.63±50.52	183.91±39.02	0.37 NS
	[169 (139-207)]	[180 (154.5-216.5)]	
LDL-C (mg/dL)	113±42.54	117.65±33.18	0.38 NS
	[101.5 (82.5-129.5)]	[113.5 (92.5-140.5)]	
HDL-C (mg/dL)	35.36±7.70	37.22±10.75	<0.001
TG (mg/dL)	146.71±58.62	157.70±81.26	0.82 NS
	[138 (96-207.5)]	[143 (99-196)]	
Fasting glucose (mg/dL)	135.30±39.22	131.20±41.79	0.56 NS
	[124.5 (107-144)]	[124 (109-140.5)]	

(TC – total cholesterol, LDL-C low-density lipoprotein, HDL-C high-density lipoprotein, TG – triglyceride)

Table III. HRV indexes in time and frequency domains

HRV indexes	day	night	overall
SDNN (ms)	129.04±55.09	109.25±61.52	136.40±53.17
			[124 (94.5 - 172)]
SDANN (ms)	66.94±29.94	66.94±29.97	100.35±34.78
	[84 (65.5 - 105)]		
rMSSD (ms)	85.41±93.71	95.20±101.94	89.83±97.80
pNN50 (%)	23.06±29.10	31.95±52.06	23.61±28.44
LF (n.u)	44.63±9.88	45.98±10.20	45.73±9.82
HF day (n.u)	37.67±15.33	37.13±15.88	37.53±15.99
		[36.35 (21 - 49)]	
LF/HF ratio	1.49±0.95	1.49±0.90	1.49±0.91

(SDNN -standard deviation of all NN intervals
SDANN - standard deviation of the averages of NN intervals in 5-minute segments
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
HF - high frequency power HF
LF - low frequency power LF
LF/HF ratio - ratio of low frequency to high frequency)

Table IV. Correlation coefficients of HRV and serum lipid fractions

Parameters	HDL-C (mg/dl)	LDL-C (mg/dl)	TC (mg/dl)	TG (mg/dl)
SDNN overall (ms) ‡	-0.14 ρ	-0.1 ρ	-0.12 ρ	-0.12 ρ
rMSSD (ms) †	-0.14 r	-0.18* ρ	-0.19* ρ	-0.05 ρ
pNN50 (ms) †	-0.13 r	-0.12 ρ	-0.12 ρ	-0.04 ρ
SDNN day (ms) †	-0.06 ρ	-0.06 ρ	-0.09 ρ	-0.19* ρ
SDNN night (ms) †	-0.15 r	-0.08 ρ	-0.09 ρ	-0.02 ρ
rMSSD day (ms) †	-0.15 r	-0.19* ρ	-0.2* ρ	-0.08 ρ
rMSSD night (ms) †	-0.12 r	-0.1 ρ	-0.11 ρ	0.1 ρ
pNN50 night (ms) †	-0.09 r	-0.07 ρ	-0.07 ρ	-0.01 ρ
pNN50 night (ms) †	-0.11 r	-0.13 ρ	-0.15 ρ	-0.08 ρ
LH/HF night ratio †	0.01 r	0.08 ρ	0.08 ρ	0.05 ρ
LF/HF day ratio †	0.09 r	0.16* ρ	0.17* ρ	0.11 ρ
LF/HV overall ratio †	0.04 r	0.14 ρ	0.14 ρ	0.09 ρ
LFn night (n.u.) †	-0.04 r	0.03 ρ	0.02 ρ	0.1 ρ
LFn day (n.u.) †	0.08 r	0.18* ρ	0.17* ρ	0.07 ρ
HFn night (n.u.) ‡	0.1 ρ	-0.04 ρ	-0.03 ρ	0.1 ρ
HFn day (n.u) †	-0.11 r	-0.18* ρ	-0.18* ρ	-0.08 ρ
SDANN overall (ms) †	0.07 r	0.1 ρ	0.09 ρ	-0.18* ρ
SDANN night (ms) †	-0.05 r	0.03 ρ	0.07 ρ	0.15 ρ
SDANN day (ms) ‡	0.09 ρ	0.07 ρ	0.06 ρ	-0.22* ρ

(*p≤0.05, ρ Spearman correlation coefficient, r Pearson correlation coefficient, † data with normal distribution, ‡ skewed data
SDNN -standard deviation of all NN intervals
SDANN - standard deviation of the averages of NN intervals in 5-minute segments
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
HF n - high frequency power HF, normalized units
LF n - low frequency power LF, normalized units
LF/HF ratio - ratio of low frequency to high frequency)

were found to be higher in females (37.22 ± 10.75) compared with males (35.36 ± 7.70), with statistical significance (p=0.00081).

We analyzed HRV in both time and frequency domains. HRV indexes in time domain and frequency domain are presented in table III.

We found no strong correlations between any of the HRV indexes and any of the lipid fractions (table IV).

Overall rMSSD and day rMSSD showed a negative correlation with TC and LDL-C; day SDNN and overall SDANN showed a negative correlation with TG. HRV indexes analyzed in frequency domain (LF/HF day ratio, day LFn) showed a positive correlation with LDL-C and TC and day HFn showed a negative correlation with TC and LDL-C. We did not find correlations between HDL-C and HRV indexes.

The results of Holter monitoring concerning rhythm disorders are shown in table V.

Table V. Arrhythmic events in the studied group

Arrhytmic events	Patients n (%)	Average
≥30 PAC/h	8 (9.87)	275.25±145.52
AT/24h	6 (7.40)	1.16±0.37
≥6 PVC/h	33 (40.74)	1054.76±3425.60
CPL/24h	31 (38.27)	45.03±95.27
VT/24h	3 (3.70)	1.33±0.57

(PAC premature atrial complex, AT atrial tachycardia, PVC premature ventricular complexes, CPL ventricular couplets, VT ventricular tachycardia)

All patients presented atrial and/or ventricular arrhythmias on Holter ECG. Isolated ventricular extrasystoles ≥6 PVC per hour were detected in 33 (40.74%) patients, with an average of 1054.76±3425.60/24 hours, ranging from 160 to 25206. A number of 3 patients (3.70%) presented episodes of non-sustained ventricular tachycardia with 1 to 13 runs, ranging from 6 to 39 beats.

Discussion

As we have already shown, data regarding correlations between serum lipids and heart rate variability are controversial. In the general population, dyslipidemia may be an important factor for the development of autonomic dysfunction. Studies have shown that postmenopausal women with decreased values of HRV parameters also present a significant increase of TC, LDL-C and TG values, but insignificant decrease of HDL-C [7,13]. A previous study found a low HRV in both middle-aged women and men and also indicated that a decreased HRV might predict the incidence of coronary heart disease (CHD) [13]. On the other hand, a comparative study of plasma lipid profile in relation to HRV tests in healthy young population showed that TC and LDL-C levels were significantly increased in men. The same study showed that HDL-C levels were significantly decreased in men associated with decreased HRV compared with BMI and age matched women [8]. Most studies have revealed that decreased HRV, as a strong predictor for CHD, was associated with hypercholesterolemia [13-15]. It may be observed that all these studies emphasize that the pathological lipid levels are associated with decreased HRV.

Regarding diabetic patients, research on the relationship between serum lipids and HRV is scarce. It has been shown that in diabetic patients, an impaired function of autonomic nervous system, and a decreased HRV have been linked to an increased arrhythmic risk [1].

Decreased HRV and sympathovagal imbalance have been reported to be associated with cardiovascular excess mortality. The sympathovagal imbalance has been considered as the main pathophysiological basis of metabolic disorder in diabetes mellitus [16-19]. In the general population HRV shows negative correlations with all cardiovascular risk factors (overweight, hypertension, smoking, alcohol consumption, high non HDL-C levels). These associations are not identical for time and frequency HRV domains [15,20,21]. Age was inversely associated with frequency domain indexes but some studies found this association only in males [20].

HRV consistent values for standard measurements by age and gender in different populations are still not defined [18,19]. The Toronto International Consensus recommends the use of a set of HRV measurements (totaling seven tests) by adding to the CARTs another three tests of analysis in the frequency domain [22-25].

It is known that statins belong to drugs that increase HRV. Studies have investigated the effect of statin therapy on sympathovagal balance with controversial results. An improvement in the autonomic function has been reported in statin associated therapy in CHD and hyperlipidemia [26,27]. On multivariate analysis statin therapy was an independent predictor for an increased HRV [28-31]. Regarding the relationship between HRV and statin therapy, studies indicated that after atorvastatin therapy there were no correlations between HRV indexes and LDL-C levels [32]. A study of 37 subjects with combined hyperlipidemia, revealed that HRV indexes in time and frequency domains were improved by both atorvastatin and fenofibrate [33].

The present study aimed to evaluate HRV parameters and lipid profile in diabetic patients regarding the presence of the specific pattern of cardiac autonomic neuropathy in diabetic and dyslipidemic patients with statin-associated therapy and to assess whether there is an improvement in HRV parameters in relation to the reduction of lipid levels. Our data suggest that an increased level of TG was associated with a decreased SDNN, considered as a marker of overall HRV [34]. We found that increased levels of LDL-C and TC were associated

with decreased rMSSD and HFn day indexes, markers of parasympathetic function [10,35,36] suggesting that dyslipidemia contributes to an impaired parasympathetic function and these results are in accordance with previous studies regarding general population and type 1 diabetic patients [13,15,16,37]. We found that increased LDL-C and TC levels were associated with increased LFn, considered a marker of sympathetic overdrive [9,35]. An increased LF/HF day ratio, representing the sympathovagal imbalance [9,10] was associated with increased LDL-C and TC levels, and these results are in accordance with previous studies regarding the general population [19].

The study of arrhythmic events in relation to statin-associated therapy was not our goal. However, in the studied patients, the risk of arrhythmia is not high considering that malignant arrhythmias were present in a small percentage (three patients). Although decreased HRV has been associated with an increased arrhythmic risk and silent myocardial infarction [1], we could not directly quantify the reduction in overall HRV in our studied group. Considering that on Holter monitoring reports, we found a small incidence of malignant arrhythmias and we have not found ischemic episodes, we could appreciate that statin-associated therapy may improve HRV and reduce the clinical implications of the decreased HRV.

Based on the absence of strong correlations between lipid fractions and any of HRV indexes, we may consider that the effect of statins on HRV is more important than the effect derived from reducing the level of serum lipid fractions.

Our study has several potential limitations. Considering that it was performed in a single hospital it could be subjected to a bias inherent of this type of study. Also, it includes a small number of patients who have fulfilled the inclusion criteria. Regarding the assessment of HRV indexes, especially frequency domain indexes, the guidelines of the Task Force for Pacing and Electrophysiology [20] recommend optimal conditions as a temperature controlled and quiet room. In our study, these conditions could not be entirely fulfilled. On the other side in the group that we investigated, although serum lipid values exceeded normal values in a significant percentage of patients, the excess was modest and pathological mean values were not high.

Further research based on prospective studies, are needed to quantify the pleiotropic effects of statins related to HRV in diabetic patients.

Conclusions

The results suggest that statin therapy may reduce the autonomic impairment secondary to dyslipidemia. This can be an explanation for the small correlations between heart variability and lipid profile in diabetic patients treated with statins and represents another reason to recommend statin therapy in this category of patients.

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