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Heart rate variability and increased risk for developing type 2 diabetes mellitus

Varijabilitet srčane frekvencije i povišen rizik od razvoja dijabetesa melitusa tipa 2

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Abstract

Background/Aim. To our knowledge there are no data about the relationship between elevated risk for developing type 2 diabetes mellitus (DM2) and altered cardiac autonomic function. The aim of this study was to evaluate the association between heart rate variability (HRV) and slightly increased risk for DM2. **Methods.** We evaluated 69 subjects (50.0 ± 14.4 years; 30 male) without DM2, coronary artery disease and arrhythmias. The subjects were divided into two groups according to the Finnish Diabetes Risk Score (FINDRISC): group I (n = 39) included subjects with 12 > FINDRISC ≥ 7; group II (n = 30) subjects with FINDRISC < 7. HRV was derived from 24-h electrocardiogram. We used time domain variables and frequency domain analysis performed over the entire 24-h period, during the day (06–22 h) and overnight (22–06 h). **Results.** Standard deviation of the average normal RR intervals was significantly lower in the group with increased risk for DM2 compared to the group II (127.1 ± 26.6 ms *vs* 149.6 ± 57.6 ms; $p = 0.035$). Other time domain measures were similar in both groups. The group I demonstrated significantly reduced frequency domain measures, total power – TP (7.2 ± 0.3 ln/ms² *vs* 7.3 ± 0.3 ln/ms²; $p = 0.029$), and low frequency – LF (5.9 ± 0.4 ln/ms² *vs* 6.3 ± 0.6 ln/ms²; $p = 0.006$), over entire 24 h, as well as TP (7.1 ± 0.3 ln/ms² *vs* 7.3 ± 0.3 ln/ms²; $p = 0.004$), very low frequency (6.2 ± 0.2 ln/ms² *vs* 6.3 ± 0.2 ln/ms²; $p = 0.030$), LF (5.9 ± 0.4 ln/ms² *vs* 6.2 ± 0.3 ln/ms²; $p = 0.000$) and high frequency (5.7 ± 0.4 ln/ms² *vs* 5.9 ± 0.4 ln/ms²; $p = 0.011$) during the daytime compared to the group II. Nocturnal frequency domain analysis was similar between the groups. The low diurnal frequency was independently related to elevated risk for diabetes mellitus (beta = -0,331; $p = 0.006$). **Conclusion.** The obtained results suggest that even slightly elevated risk for developing diabetes mellitus may be related to impaired HRV.

Key words:
heart rate; electrocardiography, ambulatory; diabetes mellitus, type 2; risk factors; predictive value of tests.

Apstrakt

Uvod/Cilj. U nama dostupnoj literaturi nismo našli podatke o povezanosti povišenog rizika od nastanka dijabetesa melitusa tipa 2 (DM2) i poremećaja srčane autonomne funkcije. Cilj rada bio je da se utvrdi povezanost između varijabiliteta srčane frekvencije i blago povišenog rizika od DM2. **Metode.** Ispitivano je 69 osoba (50,0 ± 14,4 god; 30 muškaraca) bez DM2 i koronarne bolesti, kao i bez poremećaja ritma. Ispitanici su bili podeljeni u dve grupe prema finskom skoru rizika od dijabetesa melitusa tipa 2 (*Finnish Diabetes Risk Score* – FINDRISC): grupu I (n = 39) činili su ispitanici sa 12 > FINDRISC ≥ 7 i grupu II (n = 30) sa FINDRISC < 7. Varijabilitet srčane frekvencije ustanovljen je na osnovu 24-h elektrokardiograma. Korišćene su vremenska i spektralna analiza za vreme od 24 h, u toku dana (06–22 h) i noći (22–06 h). **Rezultati.** Standardna devijacija prosečnih vrednosti normalnih RR intervala bila je značajno niža u grupi sa povišenim rizikom od DM2, nego u grupi II (127,1 ± 26,6 ms *vs* 149,6 ± 57,6 ms; $p = 0,035$). Tokom 24h u prvoj grupi primećena je značajno smanjena ukupna snaga – TP (7,2 ± 0,3 ln/ms² *vs* 7.3 ± 0.3 ln/ms²; $p = 0.029$) i niska frekvencija – LF (5,9 ± 0,4 ln/ms² *vs* 6,3 ± 0,6 ln/ms²; $p = 0,006$), a tokom dana značajno smanjenje TP (7,1 ± 0,3 ln/ms² *vs* 7,3 ± 0,3 ln/ms²; $p = 0,004$), vrlo niske frekvencije (6,2 ± 0,2 ln/ms² *vs* 6,3 ± 0,2 ln/ms²; $p = 0,030$), LF (5,9 ± 0,4 ln/ms² *vs* 6,2 ± 0,3 ln/ms²; $p = 0.000$) i visoke frekvencije (5,7 ± 0,4 ln/ms² *vs* 5,9 ± 0,4 ln/ms²; $p = 0,011$) u odnosu na grupu II. Nije bilo značajne razlike između grupa u spektralnoj analizi za noćni period. Niska frekvencija tokom dana bila je nezavisno povezana sa povećanim rizikom od DM2 (beta = -0,331; $p = 0,006$). **Zaključak.** Dobijeni rezultati ukazuju da čak i blago povišen rizik od razvoja DM2 može biti povezan sa izmenjenim varijabilitetom srčane frekvencije.

Ključne reči:
srce, frekvencija; elektrokardiografija, holter; dijabetes melitus, insulin-nezavisni; faktori rizika; testovi, prognostička vrednost.

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Introduction

Sympathetic and parasympathetic modulation of the autonomic nervous system is commonly assessed by heart rate variability (HRV) [1]. Impaired HRV reflecting autonomic dysfunction is related to many cardiovascular risk factors, especially glucometabolic abnormalities [2]. Many studies have previously revealed cardiac autonomic neuropathy in diabetic patients[1]. Parasympathetic dysfunction is associated with complex pathophysiological mechanisms in obesity, insulin resistance, as well as increased glucose production from the liver leading to atherosclerosis and cardiovascular morbidity [3].

The Finnish Diabetes Risk Score (FINDRISC) has been accepted for predicting 10-year risk of type 2 diabetes mellitus (DM2) in adults in the setting of known risk factors for cardiovascular diseases [4].

To our knowledge there are no data about the relationship between elevated risk for developing DM2 and altered cardiac autonomic function.

The aim of this study was to estimate the association between altered HRV and slightly elevated risk for DM2.

Methods

We evaluated 69 subjects (age 50.0 ± 14.4 years; 30 male) admitted to the Clinical Hospital Center in order to be evaluated for coronary artery disease. After excluding coronary disease (according to the medical history, 24-h electrocardiogram, echocardiography, exercise stress test), they entered the study. Other excluding criteria were: 30 > age > 70 years, pulmonary and renal diseases, arrhythmias, current medical treatment with beta blockers, calcium antagonists and antiarrhythmics.

All of the participants were asked to complete a form on age, medical history (antihypertensive drug treatment), history of high blood glucose level (discovered during medical examination, during an illness, or during pregnancy), health behavior (daily physical activity, daily intake of vegetables and fruits) and the family history of diabetes. Clinical examination included measurements of weight, height, body mass index (BMI) calculated by dividing the weight (kg) by the height squared (m^2), waist circumference (bellow the ribs, usually at the level of the navel). The total score for each subject was composed as the sum of the scores according to the questionnaire, BMI and waist circumference [4]. According to FINDRISC (Table 1), which considers several variables (age, BMI, waist circumference, physical activity, eating vegetables every day, using antihypertensive drugs, high blood glucose level and heredity for DM) we divided subjects into two groups [4].

Table 1

Type 2 diabetes mellitus risk assessment form

FINDRISC (p-points)	Questions (p-points)
Age	Using antihypertensive drugs regularly
0 p. Under 45 years	0 p. no
2 p. 45–54 years	2 p. yes
3 p. 55–64 years	High blood glucose level ever been found
4 p. Over 64 years	0 p. no
Body mass index	5 p. yes
0 p. < 25 kg/m^2 (%)	Heredity (diabetes type 1 or 2)
1 p. 25–30 kg/m^2 (%)	0 p. no
3 p. > 30 kg/m^2 (%)	3 p. yes – grandperent, aunt, uncle or first cousin
Waist circumference	5 p. yes – parents, brother, sister or own child
0 p. Men (women) < 94 (80) cm	Eating vegetables, fruit or berries every day
3 p. Men (women) < 94–102 (80–88) cm	0 p. every day
4 p. Men (women) < 102 (88) cm	2 p. not every day
Physical activity > 30 min	
0 p. yes	
2 p. no	

FINDRISC – Finnish Diabetes Risck Score:
Lower than 7 (low): estimated one in 100 will develop disease; 7–11 (slightly elevated): estimated one in 25 will develop disease; 12–14 (moderete): estimated one in 6 will devolop disease; 15–20 (high): estimated one in three will develop disease; Higher than 20 (very high): estimated one in two will develop disease.

The group I included subjects with slightly increased risk (12 > FINDRISC ≥ 7) predicting that one in 25 will develop DM2. The group II enrolled subjects with low risk (FINDRISC < 7), one in 100 might develop DM2 [4].

HRV was obtained from 24 h electrocardiogram Holter recordings (Argusys) using three channels (V1, V5, aVF). Electrocardiogram signals were digitalized, stored and analyzed using standard software program. According to the Task Force of the European Society of Cardiology we used time domain and frequency domain variables as markers of HRV [1].

Time domain measures included: standard deviation of all normal RR intervals (SDNN) that were considered as an estimate of overall HRV; standard deviation of the average normal RR intervals for all 5-minute segments (SDANN); average of the standard deviation of normal RR intervals for all 5-minute segments (ASDNN); percent of differences between adjacent normal RR intervals ≥ 50 ms (pNN50), root mean square of successive RR interval differences (RMSSD) [1].

Frequency domain analysis of RR intervals were carried out by Fast Fourier Transformation. The analysis of RR intervals were performed over the entire 24-h period, as well as

overnight (22–06 h) and during the day (06–22 h). The high frequency (HF) (0.15–0.40Hz) oscillation of HRV reflected mostly parasympathetic modulation of heart rate, the low frequency (LF) region of the power spectra (0.04–0.15 Hz) included the influence of both parasympathetic and sympathetic function. A very low frequency component (VLF) (0.015 - 0.04 Hz) was considered to reflect the mixture of neuroendocrine and parasympathetic modulation. The LF to HF ratio (LF/HF) was considered as an index of sympathicovagal balance. We used a logarithmic transformation of total power (TP) (ln/ms^2), VLF (ln/ms^2), LF (ln/ms^2) and HF (ln/ms^2) values [1].

Mean, minimal and maximal heart rates were also analyzed and compared among the groups.

The Ethics Committee approved the study protocol and consent procedures.

Statistical differences were considered significant when $p < 0.05$. Continuous variables were presented as mean ± standard deviation (SD) and were compared by using the Student's *t*-test for two independent samples since they showed the normal distribution. The differences in proportions were compared by using the χ^2-test. Pearson's correlation coefficient was used for determining the correlation between FINDRISC and HRV parameters. The variables which showed *p*-value < 0.050 were included into linear regression analyses, stepwise method. Regression analysis was used to determine independent predictors of elevated risk for DM2. The statistical method for evaluating the diagnostic accuracy of HRV parameters was receiving operating characteristics (ROC).

Results

There were 39 subjects in the group I (FINDRISC, mean 9.1 ± 1.3) and 30 individuals in the group II (FINDRISC, mean 4.1 ± 1.7). The individuals with elevated risk for DM2 were significantly older ($p = 0.000$). They had higher BMI ($p = 0.000$) and used antihypertensive drugs more frequently ($p = 0.000$). We observed more subjects in the group II with normal BMI ($p = 0.001$) and normal waist circumference ($p = 0.000$) compared to those in the group I. Both groups were similar in physical activities longer than 30 min daily, eating vegetables, heredity, and high blood glucose level (Table 2).

No significant differences were observed in the mean, maximal and minimal heart rate between the two groups (Table 3).

Time domain variables are presented in Table 4. SDNN was slightly shorter ($p = 0.057$) and SDANN ($p = 0.035$) was significantly shorter in subjects with increased risk for DM2.

Frequency domain measures over the entire 24 h differed significantly in TP ($p = 0.029$) and LF ($p = 0.006$), between the groups. Individuals in group I compared to the group II had significantly lower TP ($p = 0.004$), VLF

Table 2

Demographic characteristics of the studied subjects according to the FINDRISC

Parameters	Group I (n = 39)	Group II (n = 30)	*p*
Age (years), $\bar{x} \pm SD$	57.9 ± 9.6	39.4 ± 11.8	0.000
Male, n (%)	19 (48.7)	11 (36.7)	0.340
Body mass index (kg/m^2), $\bar{x} \pm SD$	26.2 ± 3.4	22.7 ± 3.7	0.000
< 25 kg/m^2, n (%)	10 (25.6)	20 (66.7)	0.001
25–30 kg/m^2, n (%)	26 (66.6)	10 (33.3)	0.008
> 30 kg/m^2, n (%)	3 (7.7)	0	0.252
Waist circumference (cm), (%)			
men (women) < 94 (80)	1 (2.6)	18 (60.0)	0.000
men (women)< 94–102 (80–88)	21 (53.8)	8 (26.7)	0.029
men (women) <> 102 (88)	17 (43.6)	4 (13.3)	0.008
Physical activity > 30 min, n (%)			
yes	7 (17.9)	9 (30.0)	0.264
Eating vegetables every day, n (%)			
yes	17 (44.1)	16 (53.3)	0.631
Using antihypertensive drugs, n (%)			
yes	19 (48.7)	2 (6.7)	0.000
High blood glucose level, n (%)			
yes	3 (7.7)	0	0.252
Heredity, n (%)			
yes (grandparent, aunt, uncle)	1 (2.6)	3 (10.0)	0.297
yes (parents, brother, sister)	3 (7.7)	0	0.252

FINDRISC – Finnish Diabetes Risck Score; Group I – subjects with 12 > FINDRISC ≥ 7; Group II – subjects with FINDRISC < 7.

Table 3

Mean, minimal and maximal heart rate in study groups

Heart rate (HR), bpm	Group I (n = 39) $\bar{x} \pm SD$	Group II (n = 30) $\bar{x} \pm SD$	*p*
HR	72.1 ± 11.5	77.2 ± 9.4	0.052
HR min	50.8 ± 14.2	53.9 ± 12.0	0.464
HR max	126.1 ± 30.3	138.7 ± 22.9	0.063

bpm – beats *per* minute; Group I – subjects with 12 > FINDRISC ≥ 7; Group II – subjects with FINDRISC < 7.

Table 4

Time domain and frequency domain variables in study groups

Variables	Group I (n = 39) $\bar{x} \pm SD$	Group II (n = 30) $\bar{x} \pm SD$	*p*
SDNN (ms)	141.6 ± 28.3	157.9 ± 41.4	0.057
SDANN (ms)	127.1 ± 26.6	149.6 ± 57.6	0.035
ASDNN (ms)	61.2 ± 21.9	65.7 ± 20.8	0.389
PNN50 (%)	10.9 ± 2.2	10.8 ± 8.4	0.942
RMSSD (ms)	46.3 ± 31.2	41.5 ± 22.9	0.484
24h-TP (ln/ms^2)	7.2 ± 0.3	7.3 ± 0.3	0.029
24h-VLF (ln/ms^2)	6.3 ± 0.2	6.4 ± 0.2	0.154
24h- LF (ln/ms^2)	5.9 ± 0.4	6.3 ± 0.6	0.006
24h- HF (ln/ms^2)	5.9 ± 0.5	6.0 ± 0.4	0.259
24h-LF/HF	1.1 ± 0.3	1.2 ± 0.3	0.128
Daytime TP (ln/ms^2)	7.1 ± 0.3	7.3 ± 0.3	0.004
Daytime VLF (ln/ms^2)	6.2 ± 0.2	6.3 ± 0.2	0,030
Daytime LF (ln/ms^2)	5.9 ± 0.4	6.2 ± 0.3	0.000
Daytime HF (ln/ms^2)	5.7 ± 0.4	5.9 ± 0.4	0.011
Daytime LF/HF	1.03 ± 0.0	1.04 ± 0.0	0.293
Night-time TP (ln/ms^2)	7.3 ± 0.4	7.4 ± 0.3	0.189
Night-time VLF (ln/ms^2)	6.4 ± 0.2	6.4 ± 0.2	0.580
Night-time LF (ln/ms^2)	6.0 ± 0.4	6.2 ± 0.4	0.122
Night-time HF (ln/ms^2)	5.9 ± 0.5	6.1 ± 0.4	0.167
Night-time LF/HF	1.0 ± 0.0	1.0 ± 0.0	0.979

SDNN – standard deviation of all normal RR intervals; SDANN – standard deviation of the average normal RR intervals for all 5-minute segments; ASDNN – average of the standard deviation of normal RR intervals for all 5-minute segments; pNN50 – percent of differences between adjacent normal RR intervals ≥ 50 ms; RMSSD – root mean square of successive RR interval differences; TP – total power; VLF – very low frequency; LF – low frequency; HF – high frequency; Group I – subjects with 12 > FINDRISC ≥ 7; Group II – subjects with FINDRISC < 7.

($p = 0.030$), LF ($p = 0.000$) and HF ($p = 0.011$) during the daytime. However, both groups were similar in all nocturnal frequency domain parameters (Table 4).

We found a significant negative correlation between the FINDRISC and TP (r = -0.263; $p = 0{,}029$); LF (r = -0.249; $p = 0.039$) over the entire 24 h hours. Diurnal variables such as: TP (r = -0.294; $p = 0{,}014$); LF (r = -0.331; $p = 0.006$); HF (r = -0.272; $p = 0{,}024$) and nocturnal HF (r = -0.279; $p = 0.020$) also inversely correlated with the FINDRISC (Table 5).

According to linear regression analysis, the stepwise method, which included independent HRV variables, that previously had expressed $p < 0.05$ and the FINDRISC as dependent variable, only daytime LF was independently related to elevated risk for DM2 (beta = -0.331, $p = 0.006$). A model summary is presented in Table 6 and the linearity of the association between the FINDRISC and daytime LF is presented in Figure 1. Other time domain and frequency domain variables did not reach a statistical significance as independent predictors.

Table 5

Correlation between the FINDRISC and measures of heart rate variability in the study subjects

Variables	r	*p*
SDNN (ms)	-0.210	0.084
SDANN (ms)	-0.270	0.065
ASDNN(ms)	-0.188	0.121
PNN50 (%)	-0.083	0.500
RMSSD(ms)	-0.045	0.715
24h- TP (ln/ms ^{2})	-0.263	0.029
24h-VLF (ln/ms ^{2})	-0.131	0.283
24h-LF (ln/ms ^{2})	-0.249	0.039
24h-HF (ln/ms ^{2})	-0.170	0.162
24h-LF/HF	-0.076	0.537
Daytime TP (ln/ms ^{2})	-0.294	0.014
Daytime VLF (ln/ms ^{2})	-0.204	0.093
Daytime LF (ln/ms ^{2})	-0.331	0.006
Daytime HF (ln/ms ^{2})	-0.272	0.024
Daytime LF/HF	-0.069	0.571
Night-time TP (ln/ms ^{2})	-0.198	0.103
Night-time VLF (ln/ms ^{2})	-0.038	0.758
Night-time LF (ln/ms ^{2})	-0.174	0.152
Night-time HF (ln/ms ^{2})	-0.279	0.020
Night-time LF/HF	0.189	0.121

SDNN – standard deviation of all normal RR intervals; SDANN – standard deviation of the average normal RR intervals for all 5-minute segments; FINDRISC – Finnish Diabetes Risk Score; ASDNN – average of the standard deviation of normal RR intervals for all 5-minute segments; pNN50 – percent of differences between adjacent normal RR intervals ≥ 50 ms; RMSSD – root mean square of successive RR interval differences; TP – total power; VLF – very low frequency; LF – low frequency; HF – high frequency; r – Spearman's correlation coefficients.

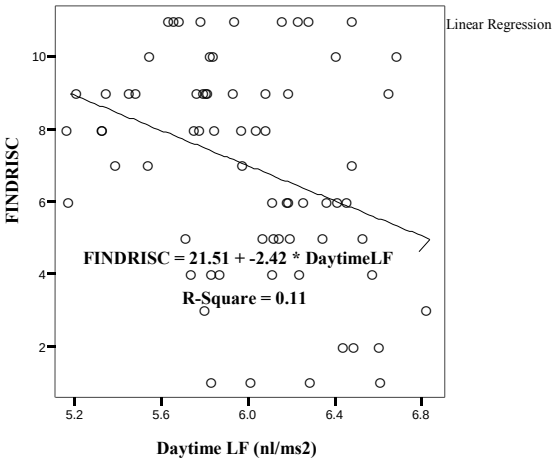

Fig. 1 – Linear regression model: Correlation between the FINDRISC and daytime low frequency (LF).
(FINDRISC – Finnish Diabetes Risk Score)

The area under the ROC curve show the significant average sensitivity of the daytime LF over the range of specificity in the group with FINDRISC < 7 (AUC = 0.72; $p = 0.002$) but not in the group with FINDRISC ≥ 7 (AUC = 0.251; $p = 0.000$) (Figure 2, Table 7).

Discussion

Previous investigations about HRV have reported autonomic failure caused by diabetes mellitus, arterial hypertension and/or metabolic syndrome [5]. Ten year risk of diabetes type 2 could easily be predicted by FINDRISC which is accepted as a noninvasive and reliable tool for screening for individuals who are at increased risk for DM2 [4].

To our knowledge this is the first study dealing with altered heart rate variability in subjects with elevated risk for DM2 assessed by the FINDRISC.

Our main findings were: shorter time domain measure (SDANN) and decreases in frequency domain parameters especially during the day (TP, VLF, HF, LF) in subjects with higher risk for DM2; negative correlation between the FINDRISC and frequency domain measures over entire 24 h (TP, LF); diurnal TP, HF, LF and nocturnal HF; the independent predictor for increased risk for DM2 was daytime LF.

Our study demonstrated a decrease in SDANN in subjects with elevated risk for DM2. Al-Hazimi et al. [6] also reported that all time domain parameters were lower in diabetic patients with and without diabetic neuropathy compared to normal controls [6]. A significant difference in

Table 6

Linear regression model: R Square Change statistics (model summary)

Model	R	R^2	Adjusted R^2		Std. error of the estimate	
1	0.331[a]	0.109	0.096		2.793	
	Change statistics					
	R^2 Change	F Change	df1	df2	Sig.	Durbin-Watson
	0.109		1	67	0.006	2.226

Predictor – Daytime low frequency (LF); b) Dependent variable – Finnish Diabetes Risk Score (FINDRISC).

Table 7

Area under the curve (AUC): test results for daytime low frequency (LF)

Area	Std. error [a]	Asymptotic Sig.b	Asymptotic 95% Confidence Interval	
			lower bound	upper bound
0.720	0.063	0.002	0.597	0.843

Predictor – daytime LF.

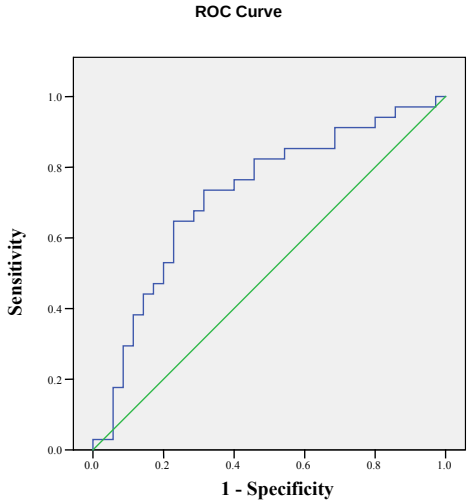

Fig. 2 – Sensitivity of daytime low frequency (LF) in the subjects with FINDRISC < 7.
FINDRISC – Finnish Diabetes Risk Score;

the time domain measures among diabetic patients and healthy volunteers were also found in the study by Seyd and al. [7].

We found a significantly reduced TP and LF during 24 h as well as a decrease in TP and LF during daytime in subjects with a higher FINDRISC. There were also strong inverse correlation between TP, LF over entire 24 h; daytime TP, LF and FINDRISC.

It was daytime LF that was found to be independently related to increased risk for diabetes mellitus type 2. Although we did not confirm a significant sensitivity of daytime LF for subject with FINDRISC ≥ 7, we obtained significant diagnostic accuracy for daytime LF in the group with lower risk for DM2 (FINDRISC < 7).

It has been accepted that the power in the low frequency band is commonly influenced by sympathetic oscillatory modulation, although a significant vagal component has been recognized, too [8].

In our study a significant decrease in daytime HF and negative correlation between daytime and nocturnal HF with the FINDRISC also suggested the impairment of the vagal component.

It seems that the decrease in HF and LF (both reflecting parasimpathetic oscillation) might present the beginning of impairment in the vagal fibre conduction in subjects with elevated risk for DM2. Although altered LF and HF were observed in our subjects with a higher FINDRISC, no change in sympathovagal balance was found. A reduced power in all spectral bands, as well as unchanged LF/HF ratio, are some of the most common manifestations related to diabetic autonomic neuropathy [1, 9].

The early complication of diabetes mellitus is autonomic neuropathy that is characterized by degeneration in small fibres. The pathophysiological mechanisms of altered HRV due to disturbances in small fiber conduction in patients with diabetes mellitus have already been reported [1].

A decrease in the power of LF and HF associated with diabetic patients even without evidence of autonomic neuropathy has been also reported [9].

Recent studies have suggested that even subjects with impaired glucose tolerance may show slower nerve conduction due to distal small fiber neuropathy [10]. According to Cardiovascular Health Study diminished HRV was also related with increased fasting glucose levels in non-diabetic subjects [11].

No previous research has investigated the relationship between HRV and higher risk for DM2. Our subjects with increased risk for DM2 according to the FINDRISC were older, had higher BMI, larger waist circumference and used antihypertensive drugs more frequently. It was reported that each of these risk factors is likely to alter HRV. A decrease in HRV could occur due to increasing age alone [12]. A significant increase in sympathovagal balance was revealed in obese subjects [13]. It was suggested that obesity especially abdominal visceral fat may significantly contribute to the sympathetic over-activity [14].

It has been also demonstrated that arterial hypertension is related to impaired HRV [15]. A decreased HRV associated with arterial hypertension was shown in the Framingham Heart Study [16]. It was also published that cardiac autonomic function was impaired even in white-coat hypertensive patients [17]. According to some investigators low HRV, demonstrating a relative sympathetic over-activity, may be associated with the development of metabolic syndrome and its components [18].

Therefore alteration in HRV in our subjects with the increased FINDRISC including higher mean age, BMI and the higher rate of arterial hypertension could be explained by the influence of age alone and other risk factors contributing to the pathogenesis of atherosclerosis that might also pay a role in the development of small nerve conduction disturbances. It has previously been demonstrated that lower heart rate variability is associated with the development of coronary artery disease in individuals with diabetes [19, 20]. There has been considerable discussion regarding the meaning and interpretation of LF/HF. Reduced LF/HF has also been recognized as a risk factor for cardiovascular disease [21, 22]. On the other hand a strong correlation was shown with each 1-point increase in the FINDRISC and 16–23% increase in the likelihood of cardiovascular disease and mortality [23–26].

Limitations of our study were the small study group, the fact that we excluded subjects with coronary artery disease, according to noninvasive diagnostic procedures, without performing selective coronary angiography. Also, self reported responses might not be absolutely exact. Hence, further studies on a larger sample are necessary to prove the relationship between the FINDRISC and impaired HRV.

Conclusion

Abnormal glucoregulation is associated with altered heart rate variability and cardiovascular autonomic diabetic neuropathy. The FINDRISC is an inexpensive, noninvasive and reliable tool to identify individuals at high risk for diabetes type 2. Our study is unique in that it deals with heart rate variability in subjects with slightly increased risk for diabetes type 2.

We found that subjects with higher risk for diabetes type 2 had also impaired heart rate variability, especially decreased standard deviation of the aberage normal RR intervals and reduced diurnal frequency domain measures, without significant changes in sympathicovagal balance.

It has long been known that impairment of heart rate variability is also closely related to cardiovascular mortality and morbidity.

Thus early detection of impaired heart rate variability may be the first sign of autonomic dysfunction suggesting further clinical evaluation of subjects with slightly increased risk for development of diabetes type 2. Evaluation of heart rate variability in subjects with increased risk for diabetes type 2 (FINDRISC $\geq$ 7) and *vice versa* might be useful for early detection of autonomic dysfunction related to altered glicoregulation.

Further larger studies would be also necessary to assess the risk for cardiovascular disease in subjects with higher risk for diabetes type 2.

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