ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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Relationship Between Cardiac Autonomic Function and Metabolic Syndrome in Patients with Cardiovascular Disease in Majmaah Region (Kingdom of Saudi Arabia): Case-Control Observational Study

Majmaah Bölgesi'nde (Suudi Arabistan Krallığı) Kardiyovasküler Hastalığı Olan Hastalarda Kardiyak Otonom Fonksiyon ile Metabolik Sendrom Arasındaki İlişki: Vaka Kontrol Gözlem Çalışması

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ABSTRACT Objective: Lacunae in literature persist regarding the mechanisms connected with the progression from metabolic syndrome (MetS) to Type 2 diabetes and cardiovascular disease (CVD). To validate heart rate variability (HRV), as a tool for progression of CVD in patients visiting cardiovascular outpatient clinic. **Material and Methods:** This cross-sectional study involved screening of 126 patients for the presence of one or more cardiometabolic risk factors and followed with HRV measurement after categorizing them as MetS+ or control MetS-. **Results:** Time domain analysis showed a significant reduction between male and female of MetS- and MetS+ While frequency domain analysis in MetS+ male showed no difference, MetS+ female showed significant difference in TP and HF indices. With increasing number of metabolic components, the MetS+ males exhibited significant decrease in the time domain and increase in frequency domain indices of HRV. Body mass index (BMI), waist circumference (WC), high-density lipoprotein (HDL), and triglyceride (TG) were associated with time and frequency domain of HRV among MetS+ and MetS- males and females. Low density lipoprotein (LDL) was a significant predictor of SDNN, RRSSD, and NN50 in patients with MetS+ while HDL was a significant predictor of Standard deviation of normal-to-normal intervals (SDNN) and pNN50. BMI was significant predictor of SDNN and pNN50 in MetS- patients and NN50 in MetS+ patients. In MetS+, the significant predictor of HF was WC, TG, HDL and LDL and that of LF were TG and LDL while in MetS-, WC was significant predictor of LF and HDL of LF/HF. **Conclusion:** MetS+ females showed lower vagal activity and decreased sympathetic predominance as compared to MetS males suggesting greater cardiovascular risk.

Keywords: Metabolic syndrome; heart rate variability; autonomic dysfunction; cardiovascular disease; insulin resistance; cardiometabolic risks

ÖZET Amaç: Metabolik sendromdan (MetS) Tip 2 diyabet ve kardiyovasküler hastalığa (KVH) progresyon mekanizmalarına dair literatürdeki eksiklik devam etmektedir. Bu çalışmada, kardiyovasküler poliklinik hastalarında, kalp hızı değişkenliğinin (KHD) kardiyovasküler hastalığın progresyonuna dair bir belirteç olduğunu doğrulamak amaçlanmıştır. **Gereç ve Yöntemler:** Bu kesitsel çalışmada, 126 hasta bir veya daha fazla kardiyometabolik risk faktörü varlığı açısından taranmış ve MetS+ veya kontrol MetS- olarak kategorize edildikten sonra KHD ölçümü ile takip edilmiştir. **Bulgular:** Zaman alanı analizi, MetS- ve MetS+ erkek ve kadınlarda TP ve HF indekslerinde önemli bir azalma olduğunu gösterdi. Frekans alanı analizinde, MetS+ erkekte TP ve HF indekslerinde fark izlenmezken, MetS+ kadında anlamlı farklılık görülmüştür. Artan metabolik bileşen sayısıyla birlikte MetS+ erkekler, KHD'nin zaman alanı indeksinde anlamlı bir azalma, frekans alanı indeksinde ise artış göstermiştir. Beden kitle indeksi (BKİ), bel çevresi (BÇ), yüksek dansiteli protein (HDL) ve trigliserid (TG), MetS+ ve MetS- erkek ve kadınlarda KHD'nin zaman ve frekans alanı ile ilişkilendirildi. MetS+ hastalarda düşük yoğunluklu protein (LDL), normal-normal aralıkların standard sapması (SDNN), RRSSD ve NN50 için HDL ise SDNN ve pNN50 için anlamlı bir prediktördü. BMI, MetS- hastalarda SDNN ve pNN50 için MetS+ hastalarda ise NN50 için anlamlı bir prediktördü. MetS+'de BÇ, TG, HDL ve LDL HF için TG ve LDL ise LF için anlamlı prediktörlerdi. MetS-'de BÇ LF için HDL ise LF/HF için anlamlı bir prediktördü. **Sonuç:** MetS+ kadınlar, MetS erkeklere kıyasla daha düşük vagal aktivite ve azalmış sempatik predominans göstermiştir, bu da kardiyovasküler riskin daha yüksek olduğunu düşündürmüştür.

Anahtar Kelimeler: Metabolik sendrom; kalp hızı değişkenliği; otonom disfonksiyon; kardiyovasküler hastalık; insülin direnci; kardiyometabolik riskler

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Over the years, heart rate variability (HRV) is used to enumerate the function of nervous system since it is simple and non-invasive.[1] Any reduction in the parameters of HRV envisages all-cause mortality concerning to cardiovascular complications, and accompanied with risk of developing metabolic syndrome (MetS).[2-8] Any compromise in autonomic function may be exclusively threatening to patients who are at higher risk of cardiovascular disease (CVD). The risk of mortality is two-fold in Type 2 diabetes patients with low HRV in comparison to those having normal HRV.[2] Although for short-term but studies having indicated that there may be positive autonomic effects, following changes in the pattern of lifestyle.[9-11]

As of date there is no definitive answer to establish specific limits of HRV for CVD risk as a result of congruency in literature that reports results on quartiles basis and such demands for having exhaustive research. Taking HRV parameters as an indication of important autonomic physiological responses, any alteration in the parameters of HRV raise an alarm of risk for particular disease process. Even though the knowledge of the physiological basis of HRV necessitates more exhaustive evidence-based research but prognostic value of HRV available in current literature signify it to be a useful global factor for developing cardiometabolic complications.

The present study aimed to find the possible association of HRV with CVD and MetS and also to investigate which cardiometabolic and cardiovascular risk factors is strongly associated with HRV parameters.

MATERIAL AND METHODS

PARTICIPANTS

A total of 126 patients having cardiovascular complications visiting cardiac outpatient clinic were screened for physical examination and biochemical analysis. Fifty-one [(n=51 (40.5%); male=30 (23.8%), female=21 (16.67%)] patients were grouped as MetS+ based on characteristics of MetS according to National Centers for Environmental Prediction (NCEP) adenosine triphosphate (ATP) III criteria.[7] Seventy-five (male=37 and female=38) patients who had only one cardiometabolic risk components were grouped as MetS-. Later 6 (2 males and 4 females) patients, of MetS+ and 25 (male=11, female 14) patients of MetS- were dropped from the study either upon their refusal or because of problems in saving or recording HRV or because of >3 ectopic beats. Finally, MetS+ group (n=45) had 28 males and 17 females whereas MetS- serving as control for MetS+ (n=50) had 26 males and 24 females (Figure 1).

This study was conducted in multicentre settings at Sudayr region, Majmaah, Kingdom of Saudi Arabia over a period of 1 year. The participants were recruited by both written and verbal information about the study. The participants were informed about their rights to leave the study at any time. This was a case-control observational study in which 2 groups (MetS+ and MetS-) differing in outcome. Participants aged between 18-70 years were enrolled in this study only if they had at least one MetS risk factor as per the NCEP-ATP III guidelines.[7] Also, individuals performing regular athletic activities or body-building exercises and yoga were excluded.[12,13]

METHODOLOGY

Participants reporting to the cardiac outpatient clinic, subsequent to fasting overnight were assessed for anthropometrics and cardiovascular complications. Waist circumference (WC) was taken from the center of iliac crest and final rib, and women having WC>88 cm or men having WC>102 cm were considered at risk for MetS.[7,14] Blood pressure (BP) were recorded 2-3 times in supine position during one-minute time intervals and reported as their average. A resting systolic blood pressure (SBP) of 135 mmHg and/or diastolic blood pressure (DBP) of 85 mmHg was used as index for the development of MetS risk factor.[7] Sample of blood was collected for fasting blood sugar, lipid profile [triglycerides (TG), high-density lipoprotein (HDL), low density lipoprotein (LDL)] and insulin. MetS risk was considered if fasting plasma glucose (FPG) was 6.1 mmol/L, TG 1.7 mmol/L and HDL 1.03 mmol/L (men) or 1.29 mmol/L (women).[7] Patients displaying 2 or more than 2 risk factors were considered of having MetS+, and those having only one risk factors were considered as control for MetS-.[7] Homeostatic model assessment of insulin resistance (HOMA-IR) was conducted using standard procedures.[15]

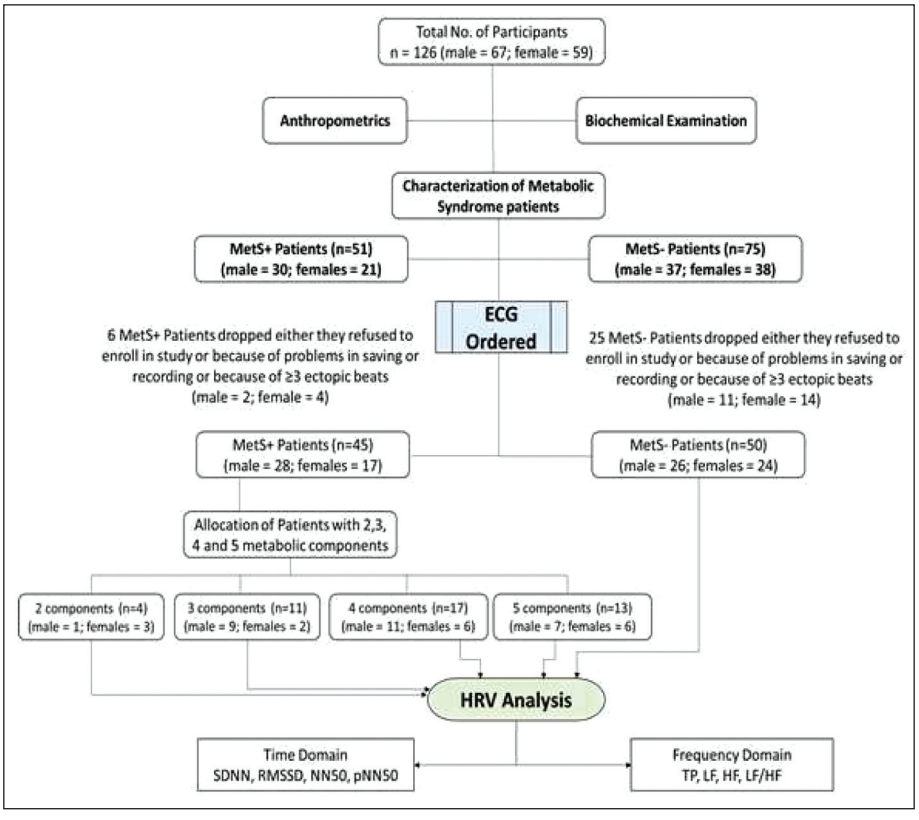

FIGURE 1: Participants and study design. MetS: Metabolic syndrome; ECG: Electrocardiogram; HRV: Heart rate variability; SDNN: Standard deviation of normal-to-normal intervals; RMSSD: Root mean square of successive differences; NN50: Normal-to-normal interval; pNN50: Percentage of normal-to-normal intervals greater than 50 ms; TP: Total power; LF: Low frequency; HF: High frequency.

Participants after having light snack were subjected to lead II electrocardiogram recording. Respiratory rate (RR) was measured by fastening a respiratory belt around the thorax. RR intervals (RRI) was taken for 10 minutes while maintaining the patient at supine position. In order to maintain the stability of all the signal recordings external factors like light intensity and noise levels were kept in check. Participants were directed to stay calm and awake. An electrocardiogram lead I was recorded at 1,000 Hz sampling rate and saved in a data acquisition system (PowerLab, ADInstruments, Australia) for analog-to-digital signal conversion using software-LabChart 7 Pro (ADInstruments).

An autoregression spectral analysis was used to quantify HRV power spectrum into conventional frequency-domain measures such very low frequency (VLF) (0.003-0.04 Hz), low frequency (LF) (0.04-0.15 Hz), high frequency (HF) (0.15-0.40 Hz), total power (TP), and the LF/HF ratio.[16] Standard deviation of all N-N intervals and root mean square of successive differences (RMSSD) (square root of the mean of the squares of differences over contiguous RRI).[17] The lab chart files were converted to text files for HRV analysis. The time series was carefully checked for ectopic or non-sinus beats. The inclusion was made only if 90% of the data were extracted. Time domain HRV analyses comprised of standard deviation of normal-to-normal intervals (SDNN) and RMSSD. The HRV spectrum was computed with the non-parametric fast Fourier transform method.

ETHICAL APPROVAL

The study protocol received institutional review board approval and all participants provided informed consent in the format required by the relevant authorities and/or boards. Ethical approval was obtained from the Institutional Ethical Committee, Majmaah University before the commencement of the study (No. MU1136) with reference No. MUREC-Jan.12/COM-2016 (12 January 2016). Necessary per-

mission was taken from the hospital authority. The data were kept confidential and is utilized only for this study.

STATISTICAL ANALYSIS

The data were edited, cleaned, and summarized using a excel master sheet and doubled entered into the SPSS (version-20) to analyze the data. The unpaired t-test was used to determine the normality of HRV characteristics in patients with MetS and those without MetS. For unequal variance in any variables, Welch's correction was used. Multiple linear regression was performed to determine the relationship between components of MetS and HRV parameters while controlling for other factors in the study. Two-sided $p \leq 0.05$ was considered as statistically significant for all statistical analysis.

RESULTS

SOCIODEMOGRAPHIC CHARACTERISTICS OF PARTICIPANTS

Baseline characteristics of selected subjects including the MetS patients are displayed in Table 1. The mean age did not differ significantly among the males and females of MetS- (control) and MetS+. The height of male and female between the 2 groups were not significantly different. The difference in the weight was significant between 2 groups among the females but not in the males. However, body mass index (BMI) was significantly more in both males and females of control and MetS group. There was significant difference in WC among the males between control and MetS but the difference was not significant among the females in the 2 group.

SBP was significantly higher in the MetS+ females as compared to MetS-, however the difference was not significant in males. DBP was significantly higher both in MetS+ males and in MetS+ females. Fasting blood sugar was significantly elevated in both MetS+ male and MetS+ females.

The lab analysis of lipid profile showed that TG was significantly greater in both MetS+ male and MetS+ females whereas HDL levels were significantly lower in MetS+ males and MetS+ females. There was no significant difference in the LDL levels

TABLE 1: Characteristics of participants.

	Control (MetS-)	Metabolic syndrome (MetS+)	p value
Sample (n)			
Male	26	28	
Female	24	17	
Age (years)			
Male	41.85±4.66	51.68±7.85	0.051
Female	43.58±7.07	48.82±8.93	0.053
Height (m)			
Male	1.73±0.06	1.59±0.09	0.081
Female	1.64±0.65	1.61±0.09	0.198
Weight (kg)			
Male	72.23±6.78	73.64±6.30	0.433
Female	59.42±8.21	74.71±6.85	<0.001
BMI			
Male	24.28±2.88	29.28±3.65	<0.001
Female	22.07±3.44	29.133.97	<0.001
WC (inches)			
Male	37.39±2.79	41.39±2.42	<0.001
Female	36.17±3.40	37.12±3.62*	0.401
SBP (mmHg))			
Male	128.27±8.94	136.25±9.39	0.002
Female	125.42±9.99	140.59±8.64	<0.001
DBP (mmHg)			
Male	83.85±5.35	94.61±9.50	<0.001
Female	79.58±7.21	94.18±7.18	<0.001
FBS (mg/dL)			
Male	98.61±18.43	128.39±19.81	<0.001
Female	90.77±7.69	126.88±18.14	<0.001
TG (mg/dL)			
Male	105.09±35.38	167.52±29.87	<0.001
Female	90.41±20.37	179.41±44.92	<0.001
HDL (mg/dL)			
Male	47.27±11.58	35.36±7.07	<0.001
Female	56.43±13.15	42.10±10.23*	<0.001
LDL (mg/dL)			
Male	132.56±11.79	127.84±8.22	0.097
Female	120.78±8.46	123.53±8.07	0.300
Insulin			
Male	7.44±1.70	10.68±4.10	<0.001
Female	6.10±1.19	9.97±3.49	<0.001
HOMA-IR			
Male	1.79±0.46	2.95±1.08	<0.001
Female	1.37±0.31	3.16±1.29	<0.001

MetS: Metabolic syndrome; BMI: Body mass index; WC: Waist circumference; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBS: Fasting blood sugar; TG: Triglycerides; HDH: High-density lipoprotein; LDL: Low density lipoprotein; HOMA-IR: Homeostatic model assessment of insulin resistance.
*P value of less than 0.05 is considered as statistically significant.

among males and females of 2 groups. Insulin levels were significantly higher in MetS+ males and MetS- females as compared to MetS-. The levels of HOMA-IR were significantly greater in MetS+ males and MetS- females as compared to MetS.

MEASURES OF HEART RATE VARIABILITY

The HRV analysis for time domain and frequency domain indices of HRV performed on MetS+ and MetS- patients is represented in Table 2. There was a significant difference in all the time domain indices [SDNN, RMSSD, NN50, percentage of NN50 (pNN50)] of HRV in MetS- (male and female) and MetS+ (male and female) groups. The TP was significantly lower in MetS+ females but there was no difference in MetS+ males. Similar results were seen with HF indices of frequency domain showing MetS+ females having significantly lower level and MetS+ males showing no difference. The in LF and LF/HF indices showed no significant difference among males or females of 2 groups.

The patients under the category of MetS+ (n=45) were counted for number of MetS components (NCEP) which is summarized in Table 3. MetS+ was present in 62.2% (n=28) of males and 37.8% (n=17) of females. Further, in males 3.6% (n=1) had 2 components, 32.1% (n=9) had 3 components, 39.3% (n=11) had 4 components and 25% (n=7) had 5 components of MetS. In females, 17.6% (n=3) had 2 components, 11.8% (n=2) had 3 components, 35.3% (n=6) had 3 component and 35.3% (n=6) had 5 components of MetS.

Figure 2 and Figure 3 compare means and standard deviations of time and frequency domains HRV indices of studied subjects in relation to the number of metabolic risk components. The associations between the number of MetS components (NCEP) and time and frequency domain of HRV are presented. There was no significant difference between MetS+ males and females having 2 metabolic components with any of the time domain indices of HRV. Associations between MetS component (NCEP) number and HRV frequency and time domain showed that there was no significance change in time domain between men and women with 2 metabolic components

TABLE 2: Characteristics of participants.

	Control (MetS-)	Metabolic syndrome (MetS+)	p value
Time domain indices of heart rate variability in MetS- (male and female) and MetS+ (male and female) groups			
SDNN			
Male	57.55±5.63	36.10±6.63	<0.001
Female	59.69±91.4	42.64±6.52	<0.001
RMSSD			
Male	65.94±15.74	35.46±13.70	<0.001
Female	71.83±20.26	42.07±13.63	<0.001
NN50			
Male	73.12±10.02	53.54±5.65	<0.001
Female	81.70±8.26	61.34±11.24	<0.001
pNN50			
Male	28.28±7.49	13.38±6.16	<0.001
Female	31.57±11.07	15.25±7.07	<0.001
Frequency domain indices of heart rate variability in MetS- (male and female) and MetS+ (male and female) groups			
ln TP (ms2)			
Male	8.75±1.60	8.18±1.96	0.244
Female	7.87±1.25	6.87±1.22	**0.014**
ln LF (ms2)			
Male	6.79±1.42	6.51±1.68	0.513
Female	6.40±1.95	5.79±1.46	0.261
ln HF (ms2)			
Male	6.42±1.88	6.82±1.73	0.419
Female	6.16±1.89	4.98±1.33	**0.024**
LF/HF			
Male	3.07±1.01	2.72±1.16	0.241
Female	2.67±1.13	2.51±0.94	0.623

The values are expressed as mean±standard deviation; statistical analysis was done by one-way ANOVA. The p<0.05 was statistically considered significant;
MetS: Metabolic syndrome; SDNN: Standard deviation of normal-to-normal intervals; RMSSD: Root mean square of successive differences;
pNN50: Percentage of normal-to-normal intervals greater than 50 ms;
TP: Total power; LF: Low frequency; HF: High frequency.

TABLE 3: Allocation of MetS+ patients based on the number of metabolic risk component.

Metabolic syndrome risk components	Males (n=28, 62.2%)	Females (n=17, 37.8%)
2	1 (3.6)	3 (17.6)
3	9 (32.1)	2 (11.8)
4	11 (39.3)	6 (35.3)
5	7 (25.0)	6 (35.3)

MetS: Metabolic syndrome.

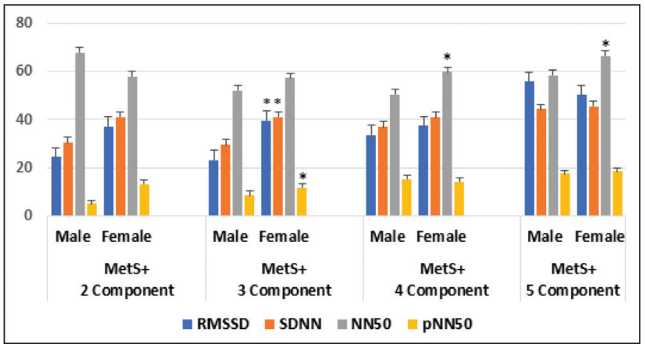

FIGURE 2: Time domain analysis of HRV in MetS+ based on number of metabolic risk components. *p value of less than 0.05 is considered as statistically significant. MetS: Metabolic syndrome; RMSSD: Root mean square of successive differences; SDNN: Standard deviation of normal-to-normal intervals; pNN50: Percentage of normal-to-normal intervals greater than 50 ms.

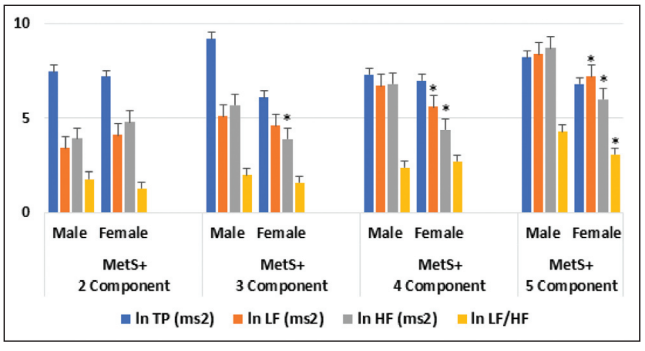

FIGURE 3: Frequency domain analysis of HRV in MetS+ based on number of metabolic risk components. *p value of less than 0.05 is considered as statistically significant. MetS: Metabolic syndrome; TP: Total power; LF: Low frequency; HF: High frequency.

of MetS+ having with any HRV time domain index. RMSDD (MetS+ male vs. female, 23.3 vs. 39.5; $p<0.05$), SDNN (MetS+ male vs. female, 29.4 vs. 41.1; $p<0.05$), and pNN50 (MetS+ male vs. female, 8.7 vs. 11.9; $p<0.05$) indices of HRV was significantly higher in MetS+ females as compared to MetS+ males having at least 3 metabolic components (Figure 2). NN50 was significantly raised (MetS+ male vs. female, 50.4 vs 59.6; $p<0.05$) in MetS+ females as compared to MetS+ males having at least 4 metabolic risk components and also significantly higher (MetS+ male vs. female, 58.5 vs. 66.3; $p<0.05$) in MetS+ females having 5 metabolic risk components (Figure 2).

In addition, there was no significant difference between the 2 metabolic components of MetS+ males and females with one of the HRV frequency domain indices (Figure 3). High frequency indices of HRV were found to be lower ($p<0.0001$) in MetS+ females having at least 3 metabolic risk components compared to MetS+ males. LF ($p<0.05$) and HF ($p<0.05$) indices of HRV were found to be lower in MetS+ females as compared to MetS+ males having at least 4 metabolic components. In addition, MetS+ females having at least 5 metabolic risk components showed a fall in LF ($p<0.05$), HF ($p<0.001$), and ratio of LF/HF ($p<0.05$) as compared to MetS+ males having 5 metabolic components (Figure 3).

RELATION BETWEEN TIME DOMAIN INDICES OF HEART RATE VARIABILITY IN METS- (MALE AND FEMALE) AND METS+ (MALE AND FEMALE) GROUPS

Correlation analysis was used to examine the relationship among time domain indices of HRV and anthropometric measurements, BP, lipid profile, insulin and HOMA-IR between MetS+ (male and female) and MetS- (male and female). There was no correlation between the age and any of the time domain indices of HRV among MetS- and MetS+ patients. There was a significant positive association between height and SDNN indices of MetS- males ($p<0.05$)

and inverse association between height and NN50 indices of MetS+ males (p=0.023). Weight of the participant was found to be inversely correlated with SDNN among MetS- males and MetS- females, NN50 among MetS- females (p<0.05) and positively correlated with RMSSD indices among MetS- (p=0.047). BMI was inversely associated with SDNN in both MetS- males (p<0.001) and females (p<0.001) and positively associated with pNN50 in both males (p=0.005) and females (p<0.05). There was no correlation between BMI and any of time domain indices of HRV and MetS- males, MetS- females and MetS+ males. WC was positively correlated with SDNN in MetS+ females (p<0.001), RMSSD of MetS+ females (p<0.001) and NN50 of MetS+ females (p<0.001). There was no correlation between the SBP, DBP & HOMA-IR and any of the time domain indices of HRV among MetS- and MetS+ patients. Fasting blood glucose was found to be inversely correlated with pNN50 indices of HRV among MetS- male (p<0.05) and positively correlated among MetS+ males (p<0.05). Insulin level was inversely correlated with SDNN indices of time domain of HRV in MetS- females (p<0.05).

RELATION BETWEEN FREQUENCY DOMAIN INDICES OF HEART RATE VARIABILITY IN METS- (MALE AND FEMALE) AND METS+ (MALE AND FEMALE) GROUPS

Correlation analysis was used to examine the relationship among frequency domain indices of HRV and anthropometric measurements, BP, lipid profile, insulin and HOMA-IR between MetS+ and MetS-. There was no correlation between the age and height and any of the frequency domain indices of HRV among MetS- and MetS+ patients. There was a significant positive association between weight and HF indices of MetS- female. BMI was not correlated with any of frequency indices of HRV neither MetS- and MetS+. WC was positively correlated with LF in MetS+ males, HF in MetS+ males (p<0.05) and the ratio of LF/HF in MetS+ males. There was no correlation between the SBP, fasting blood glucose, LDL and any of the frequency domain indices of HRV among MetS- and MetS+ patients. TG was found to be positively correlated with LF in MetS+ males, HF in MetS+ males and LF/HF in MetS+ males. HDL was inversely associated with HF indices of frequency domain of HRV in MetS+ females and LF/HF in MetS+ females. There was a positive association between HF indices of frequency domain of HRV and insulin levels in MetS+ females. Also, HOMA-IR was positively correlated with HF indices of frequency domain of HRV in MetS+ females.

LINEAR REGRESSION BETWEEN TIME DOMAIN INDICES OF HEART RATE VARIABILITY IN METS- AND METS+ GROUPS

Table 4 shows the relationship between frequency and time domain of HRV and different components of MetS (predictors). BMI was known to be a significant predictor of SDNN in MetS- patients while HDL and LDL were the significant predictors of SDNN in MetS+ patients. There was a negative relationship between SDNN and BMI in MetS- patients. In MetS+ patients, HDL had a positive relationship and LDL showed a negative relationship with SDNN.

None of the metabolic components predicted for RMSSD in MetS- patients. In MetS+ patients, LDL showed a negative relationship with RMSSD (Table 4). Further in MetS+ patients, there was a positive relationship between BMI and NN50 and negative relationship between LDL and NN50. BMI seems to be a significant predictor of pNN50 in MetS- patients and there was a positive relationship between DBP and pNN50. HDL being significant predictor of pNN50 had a positive relationship.

DBP was found to be a significant predictor of TP having a positive relationship in MetS- patients. WC was a significant predictor of LF in MetS- patients while TG and HDL were the significant predictors of LF in MetS+ patients. There was a positive relationship between WC and LF in MetS- patients. In MetS+ patients, TG showed a positive relationship while HDL showed a negative relationship with LF. In MetS+ patients, HF indices of HRV showed positive relationship between WC, TG and LDL while there was a negative relationship between HF and HDL. Further, HDL was found to have a negative relationship with ratio of LF/HF in MetS- patients while WC had a positive relationship with LF/HF in MetS+ patients (Table 4).

TABLE 4: Linear regression between time and frequency domain indices of HRV and different metabolic risk components in MetS+ patients.

HRV indices	Group	Metabolic risk factors	β	t	Sig.	95.0% confidence interval for β	
						Lower bound	Upper bound
Time domain analysis							
	MetS-						
		BMI	-0.957	-14.721	0.000	-5.933	-4.501
SDNN	MetS+						
		HDL (mg/dL)	0.358	2.475	0.018	0.052	0.531
		LDL (mg/dL)	-0.390	-2.828	0.008	-0.583	-0.096
RMSSD	MetS-						
		LDL (mg/dL)	-0.316	-2.182	0.036	-1.016	-0.037
	MetS+						
NN50	MetS-						
		BMI	0.265	1.866	**0.046**	0.096	1.370
	MetS+						
		LDL (mg/dL)	-0.322	-2.198	**0.035**	-0.665	-0.026
	MetS-						
pNN50		BMI	0.331	2.198	**0.043**	1.031	1.893
	MetS+						
		HDL	2.164	**0.037**	0.016	0.489	0.346
Frequency domain analysis							
	MetS-						
TP		DBP	0.395	2.514	**0.016**	0.017	0.161
	MetS+						
LF	MetS-						
		WC (inches)	0.295	1.925	**0.035**	0.017	0.936
	MetS+						
		TG (mg/dL)	0.300	2.090	**0.044**	0.000	0.027
		HDL (mg/dL)	-0.275	-1.356	**0.032**	-0.105	-0.071
HF	MetS-						
	MetS+						
		WC (inches)	0.544	4.678	**0.000**	0.156	0.396
		TG (mg/dL)	0.196	1.902	**0.040**	1.401	1.741
		HDL (mg/dL)	-0.244	-2.170	**0.037**	-0.096	-0.003
		LDL (mg/dL)	0.213	2.194	**0.041**	0.048	0.094
LF/HF	MetS-	HDL (mg/dL)	-0.308	-1.469	**0.039**	1.053	1.402
	MetS+	WC (inches)	0.338	2.080	**0.043**	0.002	0.201

HRV: Heart rate variability; MetS: Metabolic syndrome; SDNN: Standard deviation of normal-to-normal intervals; RMSSD: Root mean square of successive differences; pNN50: Percentage of normal-to-normal intervals greater than 50 ms; TP: Total power; LF: Low frequency; HF: High frequency; BMI: Body mass index; HDH: High-density lipoprotein; LDL: Low density lipoprotein; DBP: Diastolic blood pressure; WC: Waist circumference; TG: Triglycerides.

DISCUSSION

HRV is considered as an emerging, novel and non-invasive tool that measures autonomic function by quantifying the variation in time between consecutive heartbeats. Few cross-sectional studies have tested the associations of HRV with MetS to achieve the understanding of potential relationship between autonomic function and CVD progression. In the present study, we found a significant difference in most of the cardiometabolic risk factors between males and females of MetS- and MetS+. The inter-

pretation of results is challenging at times due to existence of various MetS definitions, heterogenous protocols for data collection and statistical analyses.[18,19]

Different studies analysing HRV have found that there is a decrease in both time and frequency domains in MetS+ suggesting of diminution in the autonomic cardiovascular control with different risk factors of MetS.[5,6,8,20] The present study showed a significant reduction in all indices of time domain HRV analysis between male and female of MetS- and MetS+.

Most investigations have found that standard frequency domain parameters of HRV represent distinct components of the autonomic nerve system. Many researches in this aspect mostly documented of reduced HF and LF, implying reduced vagal activity and increased LF/HF in women indicative of modified sympathovagal balance.[5,7,21-23] However, in the present study on comparing frequency domain HRV analysis between MetS- and MetS+ patients, it was found that male showed no significant difference in any of indices while MetS+ female showed a significant difference in TP and HF indices. Similar results have been documented in many studies suggesting reduced HRV in MetS females but not in males.[5,23] However, certain research have reported altered HRV in MetS males.[24]

Furthermore, according to one study, HF, LF, and TP are all indirectly and directly connected to the number of MetS components, whereas another study found that patients with two or more MetS components had lower SDNN, TP, and ultra low frequency (ULF) than those with 0 or 1 component.[8] In this study, MetS+ females having at least three components of MetS showed significantly higher values of RMSSD, SDNN, pNN50 indices of time domain HRV analysis and significantly lower HF indices of frequency domain HRV analysis as compared to MetS males with 3 metabolic risk factors. MetS+ male and female having four and 5 risk factors of MetS had significant differences only in NN50 indices of time domain HRV analysis. Frequency domain HRV analysis showed that there was a significant difference in HF and LF/HF between MetS+ male and female with 4 risk factors of MetS and in LF, HF, and LF/HF between MetS+ with 5 metabolic risk factors.

The sympathetic nervous system predominates in obesity and MetS in the baseline state, and the autonomic nervous system response to different sympathetic stimuli is decreased.[13,25] Weight loss aids in the restoration of autonomic nervous system function, as measured by HRV analysis.[26,27] In the present study, BMI showed a strong negative correlation with SDNN and a moderate positive correlation with pNN50 in MetS- male and females. BMI was a significant predictor of SDNN and pNN50 in MetS- patients and NN50 in MetS+ patients.

Studies have reported a negative association between WC and SDNN, VLF, LF, HF, LF/HF and LFnu though there were conflicting differences in results between the genders.[7,23] Contrary to this, another study investigated young adults and reported association of WC with reduced HF, LF and TP in males while women showed no associations.[5] In the present study, WC showed a strong positive correlation with SDNN, RMSSD, and NN50 indices of time domain HRV analysis in MetS+ female and a moderate correlation with LF, HF and a weak correlation with LF/HF indices of frequency domain HRV analysis.

One research found a link between HDL and night-time TP and VLF in the general population, as well as night-time VLF and LF in women, but no link between HDL and males.[10,23] In the present study, HDL had a significant positive correlation with SSDNN, RMSSD, NN50 in MetS males and a negative correlation with LF in MetS+ females and with LF/HF in MetS- females.

TG has been found to be associated with all HRV parameters in one study, whereas a different study displayed no associations in the entire population or more specifically in females.[23,28] TG, on the other hand, had a negative relationship with all HRV indices except LF/HF, or negatively associated with only ULF, VLF, LF and TP in men.[23,28,29] Conversely, we observed a positive correlation between TG and LF, HF, and LF/HF in MetS+ males.

Further, LDL was a significant predictor or SDNN, RRSSD, and NN50 in patients with MetS+

while HDL was a significant predictors of SDNN and pNN50. Both TG and HDL were significant predictor of LF and HF in MetS+ patients, WC and LDL were significant predictors of HF in MetS+ patient. In MetS- patients. WC was a significant predictor of LF and HDL was a significant predictor of LF/HF. This indicate that dyslipidemia has a significant contribution in the development of MetS and its management could be of great consequences in MetS treatment approach to stabilize the components of HRV that predicts mortality.

LIMITATIONS OF THE PRESENT STUDY

Our study has some limitations. First, the study included a relatively small number of subjects attending outpatient clinic at a single hospital unit, with only a small subset of this population being followed for a period of one year only. A larger sample size may have allowed for a higher statistical power. Secondly, this cross-sectional design does not allow conclusions about causal relationship. Thirdly, subjects using medications that are known to influence HRV were excluded, but it remains uncertain whether the medications that were used by some of the participants had an effect on the results. Lastly, we only measured short-term HRV at baseline and information of 24-h long-term HRV are lacking.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Moattar Raza Rizvi;* ***Design:*** *Moattar Raza Rizvi;* ***Control/Supervision:*** *Moattar Raza Rizvi, Abdulrahman Albougami;* ***Data Collection and/or Processing:*** *Moattar Raza Rizvi, Abdulrahman Albougami;* ***Analysis and/or Interpretation:*** *Moattar Raza Rizvi;* ***Literature Review:*** *Moattar Raza Rizvi, Abdulrahman Albougami;* ***Writing the Article:*** *Moattar Raza Rizvi, Abdulrahman Albougami;* ***Critical Review:*** *Moattar Raza Rizvi;* ***References and Fundings:*** *Moattar Raza Rizvi, Abdulrahman Albougami;* ***Materials:*** *Moattar Raza Rizvi, Abdulrahman Albougami.*

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