The relationship between insulin resistance and left ventricular systolic and diastolic functions and functional capacity in patients with chronic heart failure and metabolic syndrome

Kronik kalp yetersizliği olan metabolik sendromlu hastalarda insülin direncinin sol ventrikül sistolik ve diyastolik fonksiyonu ve fonksiyonel kapasite ile ilişkisi

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Objectives: The relationship between chronic heart failure (CHF) and insulin resistance (IR) has long been recognized. We examined the relationship of IR with left ventricular (LV) systolic and diastolic functions and functional capacity of CHF patients with metabolic syndrome.

Study design: The study included 50 nondiabetic CHF patients with metabolic syndrome (NYHA class I-III; 40 men, 10 women; mean age 60±10 years). Metabolic syndrome was diagnosed according to the AHA/NHLBI (American Heart Association/National Heart, Lung, Blood Institute) criteria. Insulin resistance was determined by the homeostasis model assessment (HOMA). Pulse-wave Doppler echocardiography and tissue Doppler imaging were performed to assess LV structure and functions.

Results: Patients with LV ejection fraction ≤40% (n=25) had significantly higher NYHA functional class (p<0.001) compared to those with EF >40% (n=25). Fasting plasma insulin concentrations and HOMA-IR did not differ significantly in this respect. No significant differences were found in LV geometrical patterns, diastolic and systolic functions in patients with (HOMA ≥2.7; n=19) or without (HOMA <2.7; n=31) HOMA-IR. However, patients with HOMA-IR had a lower NYHA functional capacity (p<0.0001). HOMA-IR showed significant increases in parallel with NYHA functional class.

Conclusion: Our findings suggest that IR in CHF patients with metabolic syndrome is not associated with LV systolic and diastolic functions, but is strongly linked with worsening in NYHA functional capacity.

Key words: Echocardiography; heart failure; insulin resistance; metabolic syndrome X; natriuretic peptide, brain; ventricular dysfunction, left.

Amaç: Kronik kalp yetersizliği (KKY) ile insülin direnci (İD) arasındaki ilişki uzun zamandır bilinmektedir. Çalışmamızda KKY olan metabolik sendromlu olgularda İD'nin sol ventrikül sistolik ve diyastolik fonksiyonu ve fonksiyonel kapasite ile olan ilişkisi araştırıldı.

Çalışma planı: Metabolik sendromu olan 50 KKY hastası (NYHA sınıf I-III; 40 erkek, 10 kadın; ort. yaş 60±10) çalışmaya alındı. Diyabetin dışlandığı hasta grubunda metabolik sendrom tanısı AHA/NHLBI (American Heart Association/National Heart, Lung, Blood Institute) ölçütlerine göre kondu. İnsülin direnci için, homeostatik modelle değerlendirilen İD (HOMA-İD) hesaplandı. Sol ventrikül yapı ve fonksiyonu, nabızlı dalga Doppler ve doku Doppler görüntüleme yöntemleri kullanılarak ekokardiyografi ile değerlendirildi.

Bulgular: Hastalar sol ventrikül ejeksiyon fraksiyonunun (EF) ≤%40 (n=25) ve >%40 (n=25) olmasına göre değerlendirildiğinde, EF ≤%40 olan grupta NYHA fonksiyonel sınıfı daha ileri (p<0.001) bulunurken, açlık plazma insülini ve HOMA-İD değerleri açısından anlamlı fark yoktu. İnsülin direnci olan (HOMA ≥2.7; n=19) ve olmayan (HOMA <2.7; n=31) hastalarda sol ventrikül yapısı ve sistolik ve diyastolik fonksiyonları anlamlı farklılık göstermedi. İnsülin direnci olan grupta NYHA fonksiyonel kapasitesi daha düşük (p<0.0001) idi. HOMA-İD değerleri NYHA sınıfı arttıkça anlamlı yükselme sergiledi.

Sonuç: Metabolik sendromu olan KKY hastalarında İD, sol ventrikül sistolik ve diyastolik fonksiyon bozukluğu ile ilişkili bulunmadı, ancak NYHA fonksiyonel sınıfında bozulma ile ilişkili bulundu.

Anahtar sözcükler: Ekokardiyografi; kalp yetersizliği; insülin direnci; metabolik sendrom X; natriüretik peptit, beyin; ventrikül disfonksiyonu, sol.

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Chronic heart failure (CHF) is the ultimate end point of almost all cardiac diseases. Heart failure is currently considered to be one of the most important causes of mortality and morbidity worldwide. Apart from the classical risk factors of heart failure such as coronary artery disease, hypertension and diabetes mellitus,[1,2] insulin resistance (IR) has also recently been suggested to play a great role in its etiology.[3,4] This effect of insulin resistance which is independent of diabetes mellitus is mostly associated with increasing atherogenesis and to play a direct role in the pathophysiology of heart failure.[5-8] Similarly, metabolic syndrome considered as the clinical reflection of IR has been shown to increase the risk of developing of heart failure. Analysis of the National Health and Nutrition Examination Survey III (NHANES III) cohort demonstrated that patients with metabolic syndrome had a two-fold increased risk of developing heart failure.[9,10] Although the relationship of metabolic syndrome with heart failure has been greatly attributed to IR in the study, no cause-effect relationship has clearly been outlined taking into consideration the epidemiologic nature of the analysis. Research of cause-response relationship the literature has demonstrated that the question as to whether IR is the main cause of metabolic syndrome is unclear.

In this study, the effect of IR in CHF patients with nondiabetic metabolic acidosis on left ventricular (LV) systolic and diastolic functions, functional capacity of CHF patients and its relationship with brain natriuretic peptide (BNP), a prognostic factor of heart failure, were investigated.

PATIENTS AND METHODS

A total of 50 patients of more 20 years old (40 men, mean age 60±10; 10 women, mean age 63±8) who visited the cardiology outpatient clinic of our hospital between March and June 2007, with the diagnosis of CHF associated with coronary artery disease and who had nondiabetic metabolic syndrome were included in the study. CHF was defined as the presence of clinical heart failure symptoms (New York Heart Association – NYHA – class I-III) and signs, hospitalization due to diagnosis of heart failure at least once within the past 12 months and demonstration of objective evidence of structural or functional cardiac abnormalities at rest.[11] Patients were considered to have coronary artery disease in the presence of ≥50% narrowing of at least one coronary artery as observed on coronary angiography.

The following patients were excluded from the study: patients with left ventricular ejection fraction (EF) of >50%, NYHA functional class IV, hospitalization for decompensated heart failure within the last month, history of acute coronary syndrome coronary revascularization within the past 6 months, severe valve disease, atrial fibrillation, congenital heart disease or heart failure associated with non-ischemic cardiomyopathies, diabetes mellitus, chronic renal failure (serum creatinine level of >1.5 mg/dl in men and >1.3 mg/dl in women) or liver failure, chronic inflammatory and active infectious disease. Approval for the study was obtained from the Local Ethics Committee.

The diagnosis of metabolic syndrome was made according to the American Heart Association/National Heart, Lung, Blood Institute (AHA/NHLBI) criteria.[12] Metabolic syndrome was considered in the presence of three or more of the following: waist circumference (>102 cm in men and >88 cm in women), increased triglyceride level (≥150 mg/dL or drug treatment for increased level of triglycerides), decreased high density lipoprotein cholesterol (HDL-C) level (<40 mg/dL in men, <50 mg/dL in women or drug treatment for decreased level of HDL-C), high blood pressure (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or a history of hypertension and the use of antihypertensive drugs), increased fasting plasma glucose (FPG) level (≥100 mg/dL or the use of drugs for increased glucose level).

Waist circumference was measured parallel to the floor by a supported tape, from the narrowest section midway between the lower border of the costal margin and the iliac crest, while the trunk of the patient was naked and at the end of mild expiration. The weights and heights of the patients were obtained with the patients' clothing on. Body mass index was calculated using the weight(kg)/height(m)2 formula. Blood pressure was obtained from both arms with the patient in the sitting position using the Erka sphygmomanometer. A third measurement was performed in the arm with high blood pressure reading. A fourth measurement was performed and the average obtained when the difference was more than 20 mmHg. Medications used by the patients and any history of cigarette smoking were recorded. Functional capacities were evaluated according to the NYHA classification.

Total cholesterol, HDL-C, triglyceride, FPG, fasting plasma insulin (FPI), high sensitivity C-reactive protein (hs-CRP), and the N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were analyzed from blood samples obtained following a 12-hour fasting period. The plasma glucose level was measured by glucose oxidase enzyme using the colorimetric test method. On the other hand, triglyceride, total cholesterol, and HDL-C levels were measure using the Roche automated chemical analyzer. Low density lipoprotein cho-

Table 1. Demographic and clinical characteristics of the patients according to left ventricular ejection fraction (EF).

	EF ≤40% (n=25)			EF >40% (n=25)			
	Number	%	Mean±SD	Number	%	Mean±SD	*p**
Age			61.6±8.1			59.1±10.8	
Gender							
Male	21	84.0		19	76.0		
Female	4	16.0		6	24.0		
Cigarette smoking	8	32.0		5	20.0		
Hypertension	22	88.0		24	96.0		
Systolic blood pressure (mmHg)			133.2±17.3			139.6±20.5	
Diastolic blood pressure (mmHg)			82.8±10.6			85.0±10.0	
Waist circumference (cm)			105.1±6.5			103.4±11.0	
Body mass index (kg/m2)			29.2±3.9			28.7±4.7	
Total cholesterol (mg/dL)			188.3±45.9			177.0±37.0	
Triglyceride (mg/dL)			159.5±75.1			196.0±78.9	
LDL-cholesterol (mg/dL)			116.5±40.7			96.4±33.4	
HDL-cholesterol (mg/dL)			41.2±8.5			41.8±5.9	
Fasting plasma glucose (mmol/l)			5.9±0.6			5.6±0.6	
Fasting plasma insulin (ÌlU/ml)			10.1±6.1			7.7±4.7	
HOMA-IR (unit)			2.6±1.4			2.4±2.1	
Plasma NT-proBNP (pg/ml)			1556.9±2817.5			642.6±329.1	0.037
High sensitivity CRP (mgr/dL)			2.0±2.4			0.6±0.5	0.009
Medication							
ACEI/ARB	21	84.0		21	84.0		
Beta-blocker	21	84.0		21	84.0		
Loop diuretics	14	56.0		8	32.0		
Spironolactone	7	28.0		4	16.0		
Dioxin	6	24.0		3	12.0		
Statin	13	52.0		14	56.0		
Aspirin/clopidogrel	23	92.0		23	92.0		
NYHA functional capacity							<0.001
Class I	3	12.0		15	60.0		
Class II	13	52.0		7	28.0		
Class III	9	36.0		3	12.0		
Number of metabolic syndrome criteria							
3	13	52.0		14	56.0		
4	6	24.0		6	24.0		
5	6	24.0		5	20.0		

HOMA-IR: Homeostatic model assessment of insulin resistance; ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker. *Only significant values have been provided for comparison of both groups.

lesterol (LDL-C) levels were measured according to the Friedewald formula.[13] NT-proBNP and insulin levels were determined by the electroluminescence method using Roche kits, whereas the hs-CRP level was determined by the nephelometry using the Beckman-Coulter kits. The homeostatic model assessment of insulin resistance (HOMA-IR) was used to calculate insulin resistance [FPI (µU/ml) x FPG (mmol/l)/22.5].[14] Patients with a HOMA index unit of ≥2.7 were considered as having insulin resistance.[15] On the other hand, patients with FPG level of 100-126 mg/dL were subjected to an oral glucose tolerance test (OGTT). Those whose second-hour plasma glucose was ≥200 mg/dL were considered as diabetic.[16]

Echocardiographic evaluation was performed using the Vivid 7 Dimension echocardiographic device (Vingmed Ultrasound, GE, Horten, Norway), with the patient lying on the left lateral side. On the other hand, the parasternal long and short axis, apical two and four chamber views, as well as the left ventricular diameters, interventricular septum and posterior wall thickness as observed in the parasternal long axis view with the help of M-mode, were all assessed using two-dimension echocardiographic analysis.[17] Left ventricular EF was assessed using the modified Simpson's echocardiographic method. Pulsed-wave Doppler transmural flow measurements were performed from the apical four-chamber views. The E/A ratio, isovolumic relaxation time

Table 2. Demographic and clinical characteristics of the patients with (HOMA ≥2.7) and without insulin resistance

	EF ≤40% (n=25)			EF >40% (n=25)			
	Number	%	Mean±SD	Number	%	Mean±SD	*p**
Age			61.1±10.2			59.2±8.4	
Gender							
Male	27	87.1		13	68.4		
Female	4	12.9		6	31.6		
Cigarette smoking	3	9.7		10	52.6		0.002
Hypertension	27	87.1		19	100.0		
Systolic blood pressure (mmHg)			137.4±22.2			134.7±12.6	
Diastolic blood pressure (mmHg)			84.4±10.7			83.2±9.5	
Waist circumference (cm)			102.3±8.1			107.5±9.5	0.046
Body mass index (kg/m2)			27.6±3.7			31.1±4.4	0.004
Total cholesterol (mg/dL)			179.4±47.5			188.0±30.2	
Triglyceride (mg/dL)			156.2±70.4			213.0±79.9	0.011
LDL cholesterol (mg/dL)			106.5±42.4			106.3±31.4	
HDL cholesterol (mg/dL)			42.4±8.2			40.1±5.4	
Plasma NT-proBNP (pg/ml)			1058.9±2365.9			771.7±1539.3	
High sensitivity CRP (mg/dL)			1.5±2.3			1.0±0.8	
Echocardiographic findings							
Left ventricular ejection fraction (%)			40.0±8.5			41.2±6.8	
Left ventricular mass index (g/m2)			148.4±35.3			142.1±36.6	
Left ventricular diameter (cm)			5.6±0.8			5.4±0.5	
Mitral E/A ratio			1.0±0.5			1.0±0.5	
Deceleration time (msec)			206.0±61.6			205.2±43.6	
Isovolumic relaxation time (msec)			93.7±17.2			97.5±16.1	
Mitral annular lateral velocity (cm/sec)			8.1±3.0			8.6±2.9	
Mitral annular septal velocity (cm/sec)			6.4±1.7			7.6±1.6	0.02
Stages of diastolic dysfunction							
Grade 0	9	29.0		7	36.8		
Grade 1	14	45.2		9	47.4		
Grade 2	5	16.1		2	10.5		
Grade 3	3	9.7		1	5.3		
Medication							
ACEI/ARB	23	74.2		19	100.0		0.018
Beta blocker	25	80.7		17	89.5		
Loop diuretics	12	38.7		10	52.6		
Spironolactone	5	16.1		6	31.6		
Dioxin	4	12.9		5	26.3		
Statin	15	48.4		12	63.2		
Aspirin/clopidogrel	28	90.3		18	94.7		
NYHA functional capacity							<0.0001
Class I	17	54.8		1	5.3		
Class II	11	35.5		9	47.4		
Class III	3	9.7		9	47.4		
Number of metabolic syndrome criteria							<0.001
3	21	67.7		6	31.6		
4	9	29.0		3	15.8		
5	1	3.2		10	52.6		

HOMA-IR: Homeostatic model assessment of insulin resistance; ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker.
*Only significant values have been provided for comparison of both groups.

(IVRT) and the E-velocity deceleration time were calculated by measuring the E & A wave velocities with regards to the evaluation of left ventricular diastolic functions. After performing appropriate angular velocity and gain adjustments by activating the tissue Doppler function on the device, E-wave velocities of the interventricular septal and lateral segments were calculated from the mitral annular basal plane of the apical fo-

Table 3. Distribution of plasma NT-proBNP, high sensitivity CRP and HOMA-IR values and echocardiographic data of patents according to the NYHA functional classes

	NYHA class I (n=18)	NYHA class II (n=20)	NYHA class III (n=12)	p^*
Fasting plasma glucose (mmol/L)	5.5±0.6	5.9±0.5	6.0±0.7	0.037
Fasting plasma insulin (µlU/ml)	5.4±2.2	8.9±3.5	14.1±7.7	<0.001
Plasma NT-proBNP (pg/ml)	343.7±364.9	472.4±383.0	2654.5±3819.2	0.003
High sensitivity CRP (mg/dL)	0.5±0.3	1.0±0.8	2.9±3.1	0.001
HOMA-IR (unit)	1.3±0.6	2.8±1.9	3.7±1.9	<0.001
Echocardiographic findings				
Left ventricular ejection fraction (%)	45.3±4.6	39.8±7.3	34.5±8.4	0.001
Left ventricular mass index (g/m^2)	133.8±30.0	143.7±31.6	168.2±41.6	0.028
Mitral E/A ratio	0.9±0.4	0.9±0.4	1.4±0.6	0.012
Deceleration time (msec)	211.5±42.6	218.5±54.2	170.9±64.5	
Isovolumic relaxation time (msn)	94.1±12.1	99.7±15.9	87.6±22.7	
Mitral annular lateral velocity (cm/sec)	8.7±3.3	8.2±2.8	7.8±3.0	
Mitral annular septal velocity (cm/sec)	7.0±1.7	6.8±1.9	6.8±1.9	

NYHA: New York Heart Association; HOMA-IR: Homeostatic model assessment of insulin resistance. *Only significant values have been provided for comparison of both groups.

ur-chamber. Patients were classified according to these conventional echocardiographic findings, in terms of diastolic function.[18] The left ventricular mass index (LVMI) was calculated using the Devereux formula.[19]

Statistical analysis. The SPSS 12.0 for windows program was used for statistical evaluation. Continuous variable were expressed as mean±deviation, and categorical variables as frequency (%). The Student's t-test, Kruskal-Wallis and Mann-Whitney U tests were used for continuous variables during group comparisons, whereas the Chi-square test was used for categorical variables. A $p<0.05$ value was considered as statistically significant.

RESULTS

Patient demographic and clinical data in terms of the left ventricular EF (EF ≤40% and EF >40%) are shown in Table 1. No difference was found between the groups with regards to age, gender, blood pressure, waist circumference, body mass index, cigarette smoking and plasma lipid values. However, angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB), diuretics, beta blockers, spironolactone, digoxin, statin, and clopidogrel use was found to be similar in both groups. On the other hand, deterioration of functional capacity as assessed according to the NYHA was found to be more in patients with EF of ≤40% ($p<0.001$). There was no difference between the groups with regards to the number of metabolic syndrome criteria.

No significant difference was found between the groups with regards to FPG, FPI and HOMA-ID values. The plasma NT-proBNP and hs-CRP values were found to be significantly higher in patients with left ventricular EF of ≤40% (Table 1).

Comparison of the characteristics of CHF patients with and without IR according to HOMA values is shown in Table 2. Waist circumference, body mass index (BMI), triglyceride levels and frequency of cigarette smoking was found to be higher in CHF patients with IR. There was no significant difference with regards to age, gender, blood pressure, total cholesterol, LDL-C, HDL-C, plasma NT-proBNP and hs-CRP values ($p>0.05$). Patients with IR were found to more frequently use ACE-I/ARB ($p=0.018$), their NYHA functional capacity was lower ($p<0.0001$), and they had a higher number of metabolic syndrome criteria ($p<0.0001$).

Echocardiographic evaluation demonstrated no significant difference between patients with IR and those with IR, in terms of left ventricular EF, left ventricular diameter, left ventricular mass index (LVMI), mitral E/A ratio, deceleration time, IVRT and mitral annular lateral velocity (Table 2). On the other hand, the mitral annular septal velocity was found to be higher in patients with IR ($p=0.02$). No significant difference was found in the distribution of diastolic dysfunction stages between patients with IR and those without IR ($p>0.05$).

Classification of patients according to the NYHA functional class demonstrated that age, gender, cigarette smoking, waist circumference, BMI, lipid parameters, and the number of metabolic syndrome criteria were similar to the use of ACE-I/ARB, beta blockers, spironolactone, and statins. Prescription of the following drugs were found to be more in patients in the NYHA

functional class III, compared to those in the NYHA functional class I and II: digoxin (0%, 5%, 66.7% respectively, according to functional class; p<0.001) v and loop diuretics (27.8%, 40%, 75% respectively, according to functional class; p=0.032).

The FPG, FPI, HOMA-IR, plasma NT-proBNP and hs-CRP levels of the patients were found to increase with every increase in the NYHA functional class (Table 3).

Echocardiographic evaluation revealed that left ventricular EF decreased (p=0.001), whereas the mitral E/A ratio (p=0.012) and the LVMI (p=0.028) increased as the NYHA functional class increased in CHF patients with metabolic syndrome (Table 3). However, no significant difference was found in the deceleration time, IVRT, the mitral annular lateral and septal velocities in terms of the NYHA functional class (p>0.05).

DISCUSSION

Our study did not demonstrate any significant relationship of the left ventricular systolic and diastolic function with IR in CHF patients with metabolic syndrome. However, deterioration of functional capacity was found to be more in patients with IR. The HOMA-IR of the patients was observed to increase with every increase in the functional capacity.

Insulin resistance has been demonstrated to be a new risk factor for the development of heart failure. The role of IR in the pathophysiology of heart failure has been shown in experimental, small clinical and large population studies, particularly within the last decade. The most comprehensive data on this subject were obtained from two studies performed by the same study group in the same community.[3,20] Prospective, observational cohort studies conducted on approximately 3500 individuals demonstrated that IR was a strong predictor for the development of heart failure in middle-aged and elderly men.[3,20] The risk from IR was found to be independent of the other known risk factors including diabetes mellitus, by the end of the 20-year following period. The authors suggested that proinsulin and HOMA-IR levels could be a better risk predictor than the diagnosis of diabetes mellitus since the risk of heart failure starts increasing at the subclinical stage of impaired glucose metabolism. However, no generalization was made concerning these results on the study conducted only on males and involving only a certain age group, in respect of whether the results included females and the other age groups.

Atherosclerosis is thought to be the most important mechanism responsible for the relationship between IR and heart failure. IR increases the development of atherosclerosis through its role in endothelial dysfunction, fatty streaking, vascular cell and plaque formation.[21] It also has direct effects on the myocardium. IR causes hypertrophy and fibrosis of the myocardium by increasing the effects of accompanying factors such as hyperinsulinemia, angiotensin II-induced cellular hypertrophy and collagen formation.[22,23] These morphological and functional changes in the myocardium are suggested to lead to the development of heart failure by causing abnormality in left ventricular systolic and diastolic function.

Despite its role in the development of heart failure, no significant relationship has been demonstrated between IR and left ventricular systolic and diastolic functions. There are some studies in literature which have shown that abnormality in left ventricular systolic function turn to be more pronounced in patients with IR.[2,5] However, other studies have published results similar to those of our study suggesting that there was no significant relationship between IR and left ventricular systolic function.[4,15] On the other hand, diastolic functions have markedly been shown to be influenced by IR during the early stages.[24,25] Two possible reasons are suggested to be responsible for the varied results concerning the relationship of IR with left ventricular functions. The first of these involves the use of different patient groups. Previous studies have compared systolic and diastolic functions in patients with and without metabolic syndrome,[24,25] or where diabetic patients[15] were not excluded. On the other hand, all patents in our study had metabolic syndrome and CHF. As a result, the presence of IR in all of our patients at a particular rate is an expected finding. A similar number of metabolic syndrome criteria in patients with left ventricular EF of ≤40% and >40% supports our findings. The small number of our sample size may also have been responsible for the inability of the difference of HOMA-IR levels between the groups to attain statistical significance. Secondly, consideration of a HOMA index of ≥2.7 as IR in our study corresponds to the generally acknowledged definition of IR as the cut-off value of HOMA index. Many authors suggest different HOMA indexes in the definition of IR.[26,27] This suggests that differences may be observed depending on the source of the results of the values.

In our study, the mitral annular septal velocity was found to be higher in patients with a HOMA index of ≥2.7 compared to those with an index of <2.7. Despite the lack of difference between the patient groups in diastolic function criteria such as mitral valve IVRT, E/A ratio, deceleration time and the mitral annular la-

teral velocity, we could not clearly explain the high mitral annular septal velocity. We suggest that this finding, which does not support diastolic dysfunction, may be due to the coincidentally lesser effect of ischemia on the septal region of patients with a HOMA index of ≥2.7, leading to better function.

Observational and experimental studies have shown that inflammation plays an important role in the development of IR.[28,29] All components of metabolic syndrome have been show to have a relationship with moderate high levels of CRP, and their levels increase with every increase in CRP.[30] Despite results of our study which demonstrate a higher number of metabolic syndrome criteria in heart failure patients with HOMA index of ≥2.7, no significant difference was observed in the hs-CRP levels in patients with a HOMA index of <2.7. We could not compare these findings with results of any other study due to the absence of a similar study in literature. Our small sample size and the cut-off value allocated for HOMA-IR may have been instrumental in these findings.

Plasma BNP values are widely used in the diagnostic and prognostic evaluation of heart failure. There is an inverse relationship between BNP levels and left ventricular systolic function; BNP levels are known to increase as degree of left ventricular systolic function decreases.[31] As a result, the similar results of plasma NT-proBNP obtained in our study in patients with IR and those without IR may have been due to the similar left ventricular systolic functions. Many studies investigating the relationship of IR with plasma NT-proBNP have reported that different clinical conditions may lead to different interactions, and suggested that the patient's anthropometric and metabolic characteristics should be considered when evaluating this relationship.[32-34] There is an inadequate number of studies similar to our study which investigate the relationship between IR and plasma BNP in patients with heart failure. One study reported that functional capacity deteriorated with increases in IR, in patients with heart failure, however, plasma BNP were found to be decreased.[15] The authors could not clearly account for these interesting findings, and suggested that IR was a better predictor of functional capacity than BNP. Recently published results of another study demonstrated an inverse relationship between IR and plasma BNP in patients with heart failure.[35] Despite a large sample size of these study diabetic and nondiabetic patients with evaluated together,[15,35] and did not consider the presence of metabolic syndrome.[35] The absence of a significant relationship between IR and BNP is an expected outcome considering the close relationship of natriuretic peptide with lipid and glucose metabolism,[36] and the fact that all patients in our study had metabolic syndrome.

We demonstrated that left ventricular EF decreased, whereas the HOMA-IR, plasma NT-proBNP and hs-CRP increased as the NYHA functional class increased in chronic heart failure patients with metabolic syndrome. The HOMA index was found to remain the same in respect of left ventricular EF; however, it is interesting to observe that IR increased paralleled with deterioration in the functional capacity of the patients. Similar to results of our study, Suskin et al.[15] in their study published in 2000 could not demonstrate any relationship between IR and left ventricular systolic function in patients with CHF, and observed that deterioration of functional capacity was more pronounced in patients with IR. Unlike in the study mentioned, we demonstrated a significant relationship between IR and functional capacity, although we excluded diabetic patients. This result supports the hypothesis that IR contributed in deterioration of functional capacity in patients with heart failure.[15] The mechanism by which IR decreases functional capacity is not clearly understood. Although not investigated in our study, the possible reasons for the decrease in functional capacity under conditions of IR include abnormality in endothelial nitric oxide secretion, increased vascular resistance and the associated decrease in peripheral blood flow.[37,38] However, despite the similarity between the groups in factors which may affect insulin sensitivity such as age, arterial blood pressure, obesity and cigarette smoking, the increasing application of diuretic treatment (which may lead to IR)[39] as the NYHA class increased seems to have weakened this relationship.

Limitations of the study. The small sample size of our study and our inability to use the six-minutes walking test during evaluation of the functional capacity of the patients weakened the strength of our study. Another limitation was our use of clinically acceptable HOMA-IR for the determination of IR due to the ease of application, instead of applying standard tests (the clamp method or minimal model analysis).

In conclusion, IR can be said to cause deterioration in functional capacity although it did not affect systolic and diastolic functions in CHF patients with nondiabetic metabolic syndrome. This condition suggests that IR and metabolic syndrome which is its clinical reflection is a risk factor for CHF, as it is the case with other cardiovascular diseases. There is a need for prospective studies with a large patient group in order to confirm to this result.

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