



## Left ventricular Diastolic dysfunction in Female Rheumatoid Arthritis Patients: Association to Insulin Resistance and Metabolic Syndrome

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### Abstract

**Background:** *Inflammation characteristic of active RA, likely plays a major role in cardiovascular disease. Cardiac involvement (pericardial, myocardial and endocardial) is known in patients of Rheumatoid arthritis.*

**Aim of this work:** *is to investigate left ventricular diastolic dysfunction (DD) in mildly active or remittent rheumatoid arthritis female patients and its association to insulin resistance and metabolic syndrome.*

**Patients and Methods:** *A total of forty eight middle aged female patients with rheumatoid arthritis compared to thirty age and sex matched apparently healthy participants as a control group were included. According to echocardiographic findings patients were classified into two subgroups: patients without diastolic dysfunction (without DD) and patients with diastolic dysfunction (DD).*

**Results:** *We found left diastolic dysfunction was less frequent in RA patients who are controlled or nearby (DAS28 score  $\leq 3.5$ ) than reported by other previous studies 7/48 (14.6%). Patients with diastolic dysfunction had statistically significant higher serum insulin level, fasting blood sugar, TNF $\alpha$ , insulin resistance and metabolic syndrome than RA patient without diastolic dysfunction.*

**Conclusion:** *We found left diastolic dysfunction was less frequent in patients how are controlled or nearby (DAS28 score  $\leq 3.5$ ), with a significant association between diastolic dysfunction and presence of insulin resistance with metabolic syndrome.*

**Keywords:** *Rheumatoid Arthritis, diastolic dysfunction, insulin resistance, metabolic syndrome.*

### Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects approximately 1% of the population, with a standardized mortality rate ranging from 1.28 % to 3.0 % <sup>(1)</sup>. Cardiovascular disease (CVD) is considered the leading cause of death in RA patients <sup>(2)</sup>. Large retrospective studies of RA patients have shown the risk of myocardial infarction (MI), adjusted for CV risk factors, to be increased by up to 2-

folds compared with control groups<sup>(3)</sup>. Two studies found that the increased risk of CVD in RA is comparable to that observed for patients with type 2 diabetes <sup>(4)</sup>. Moreover, in rheumatoid female patients, RA increases the risk of cardiovascular (CV) mortality by up to 50% compared with the general population <sup>(5)</sup>. Also, the pattern of CVD in RA patients appears to differ from that in the general population; RA patients are more likely not only to have silent ischemic

heart disease and experience sudden death but also to develop heart failure and die shortly thereafter<sup>(6)</sup>. Cardiovascular diseases (CVD) are more frequent and found prematurely in patients who suffer from a chronic inflammatory disease like RA. The inflammation found in RA was related to the accelerated atherosclerotic process. The synovitis in RA can lead to the release of a number of pro-inflammatory mediators<sup>(7)</sup> which can escape to the blood and can affect distant organs such as the liver, as well as adipose tissue or the endothelium<sup>(8)</sup>. This may lead to an unfavorable pro-atherogenic state. Insulin resistance can be considered as one of the consequences of inflammation<sup>(9)</sup>. We investigated left ventricular diastolic dysfunction (DD) as one of the cardiac complications in remittent or mildly active female rheumatoid arthritis patients assessed by DAS28 score and TNF- $\alpha$ .

## Patients and Methods

**A) Patients:** a cross-sectional case-control study done on a total of forty-eight in remittent or mildly active rheumatoid arthritis female patients compared to thirty matched sex and age apparently healthy participants as a control. The study was done from October 2013 to May 2015. Patients were selected and assessed from the outpatient clinics of rheumatology and rehabilitation, Internal Medicine departments. Patients were selected according to the American College of Rheumatology (ACR) criteria based diagnosis of RA and the European League Against Rheumatism (EULAR) Criteria, 2010<sup>(10)</sup>. Laboratory work was done in Clinical and Chemical Pathology department of Al-Azhar University Hospital in Assiut. While Cardiac assessment was done in Cardiology departments of Al-Azhar and Assiut Universities Hospitals. Inclusion criteria were female patients, less than 50 years old, in remission or mildly active disease state (disease activity score 28 (DAS 28)  $\leq$  3.5) and have disease duration more than one year. Excluded from this study male patients, female patients aged  $>$  50 years with DAS 28 score  $>$  3.5,

taking lipid-lowering drugs, diabetics, and smokers, any patient with congenital or ischemic heart disease all were excluded from our study. Informed consent was taken from each participant.

## B) Methods

**1-Full medical history:** including, duration of the disease history of disease-modifying antirheumatic drugs (DMARDs) (48 patients received Methotrexate in a dose of 10-12.5 mg/week and steroids in a dose  $\geq$  7.5 mg/day; NSAADS, and 5 patients received Hydroxychlor-oquine 250-500 mg/day in addition to previous drugs). Full medical examination was done for each patient including, general medical examination and joint examination, body weight, waist circumference<sup>(11)</sup> and BMI was calculated for each patient (kg/m<sup>2</sup>), blood pressure was measured in the sitting position. Disease activity was assessed by DAS 28 score. Metabolic syndrome (MS) was diagnosed in RA patients according to the International Diabetes Federation, 2006<sup>(12)</sup>.

**2-Laboratory work:** venous blood was withdrawn from all patients and control after an overnight fast and used for the following laboratory test; insulin, TNF- $\alpha$ , Rheumatoid factor and CRP. Rheumatoid factor and CRP were measured qualitatively by latex agglutination technique. Lipid profile, ALT, uric acid and fasting glucose were assayed by enzymatic colorimetric methods (Mindray BS380) chemistry auto analyzer. Risk ratio 1 was calculated by dividing total cholesterol/HDL-c (normal range:  $<$  4) and Risk ratio 2 was calculated by dividing LDL-c/HDL-c (normal range:  $<$  3). References ranges for Risk ratios 1 & 2 are based on **NCEP ATP III, 2001**<sup>(13)</sup>. Fasting insulin was measured by Quantitative Sandwich ELISA kit (DRG Insulin ELISA Kit, DRG Diagnostics, Germany)<sup>(14)</sup>. HOMA-IR was calculated online using HOMA2 model to evaluate insulin resistance, percentage B cell function and percentage insulin sensitivity<sup>(15)</sup>. **Quantitative determination of TNF- $\alpha$ :** was done by Sandwich ELISA kit

(AviBion Human TNF- $\alpha$  ELISA Kit, Orgenium Laboratories Business Unit, Vantaa Finland) <sup>(16,17)</sup>.

**3-Echocardiographic assessment:** was done to all participants.

Two-dimensional and real-time echocardiography was coupled with a continuous, pulsed-wave, color flow Doppler study. Echocardiography was done using a Hewlett-Packard Sonos4500: transthoracic 2.5 MHz transducer, equipped with Doppler and color flow capabilities (Hewlett Packard Medical Products Group, Andover, MA). Transthoracic echocardiography (TTE) was performed according to a standardized protocol and scan planes including the 4-chamber apical view, 2-chamber apical view, left parasternal long-axis view, and left parasternal short-axis view.

The following measures were recorded: end-diastolic diameter of the LV, end-systolic diameter of the LV, and fractional shortening. Also, the mitral valves were fully examined. Systolic pulmonary artery pressure was evaluated based on the degree of tricuspid regurgitation (TR).

Fractional shortening (FS) and ejection fraction (EF) according to **Simpson's formula** were calculated. To record transmitral flow the sample volume was carefully positioned at the tip of the leaflets of the mitral valve. The following variables were evaluated as parameters of left ventricular filling: peak of early diastolic (E), late diastolic (A) flow velocity, and E/A ratio. According to echocardiographic findings, patients were classified into two subgroups: patients without diastolic dysfunction (without DD) and patients with diastolic dysfunction (DD).

**4-Statistical analysis:** The collected data were revised, organized, tabulated and statistically analyzed using statistical package for social sciences (SPSS) version 23.0 for windows. Data are presented as the Mean  $\pm$  standard deviation (SD), frequency, and percentage. Categorical variables were compared using the chi-square ( $\chi^2$ ) and Fisher's exact tests. Continuous normally

distributed variables were compared using the Student t-test (two-tailed). Mann-Whitney U-test was used for comparison of nonparametric continuous variables. The level of significance was accepted if the P value < 0.05.

## Results

The waist circumference, systolic and diastolic blood pressure were significantly increased in patients with RA than in control group (P-value 0.005, 0.045 & 0.003 respectively) (table 1).

In the presented study, FBG, F. insulin, HOMA-IR, Serum uric acid, ESR and TNF were found to be significantly higher in RA patients (P-value: 0.004, 0.000, 0.000, 0.001, 0.000 and 0.000 respectively) (table 2). Lipid profile (total cholesterol, triglyceride, LDL, HDL) was significantly lower in RA patients than control group (P-value: 0.000 & 0.051, 0.000, 0.000 respectively) (table 2).

There were a significant increase in left ventricular dimensions in RA patients compared with control group including (LVSD, LVDD, IVS and LVPW; P value < 0.000, 0.003, 0.008, 0.012 and 0.040 respectively). In addition, there was a significant decrease in EF% in patients than control (P value 0.000) and a significant decrease in E/A ratio and prolonged E wave declaration time in RA patients compared with control (table 3).

Among RA patients, Seven (14.6%) out of 48 patients had DD. Patients with diastolic dysfunction (DD) were older and had longer disease duration with significant increase in waist circumference, BMI with p value: < (0.000, 0.000, 0.000 and 0.009 respectively). Also, significant increase in serum level of FBG, insulin and IR with P value (0.012, 0.000, and 0.005 respectively) with significant decrease in serum level of total cholesterol and LDL-c with P value: 0.023 & 0.026) in patients with DD than patients without. Although the level of TNF- $\alpha$  was within the normal range, we observed a significant difference between patients with DD than patient without (P value: 0.000) (table 2). Patients with

DD had higher systolic and diastolic blood pressure with lower value of E/A ratio and deceleration time than patients without. There is no significant difference as regard serum triglycerides, HDL-c, VLDL level , risk ratio 1, risk ratio 2, serum uric acid , ESR and DAS28

score with P value (0.137,0.143,0.135,0.204, 0.177, 0.980, 0.596 and 0.121 respectively) (table 4). We found a statistically significant increase in the incidence of metabolic syndrome in patients with DD than those without DD with p-value < 0.01 (table 5).

**Table (1):** Clinical and demographic data in RA Patients and Control Group.

Parameter	Control group (30) Mean ± SD	Patients group (48) Mean ± SD	Independent t-test	
			t	P-value
Age (yrs.)	39.23 ± 9.07	40.23 ± 6.65	0.561	0.577
BMI (kg/m <sup>2</sup> )	27.47 ± 3.20	26.91 ± 3.54	0.705	0.483
WC (cm)	85.10 ± 12.90	93.94 ± 13.15	2.909	0.005*
Syst. BP (mmHg)	118.33 ± 14.70	125.21 ± 14.36	2.040	0.045*
Diast. BP (mmHg)	73.50 ± 10.43	80.94 ± 10.30	3.089	0.003*

BMI: body mass index, WC: waist circumference, Syst. BP: systolic blood pressure, Diast. BP: diastolic blood pressure.

**Table (2):** Laboratory data in RA patients and normal control groups

Parameter	Control group (N=30) Mean ± SD	Patients group (N=48) Mean ± SD	Independent t-test	
			t	P-value
FBG (mg/dl)	82.00 ± 12.38	92.31 ± 16.12	2.992	0.004
TCh (mg/dl)	147.37± 31.15	86.13 ± 44.14	6.630	0.000
TG (mg/dl)	108.07 ± 21.08	83.60± 65.22	1.987	0.051
HDL-c (mg/dl)	38.23 ± 9.14	25.02 ± 15.03	4.333	0.000
LDL-c (mg/dl)	85.50 ± 36.68	44.23 ± 26.13	5.797	0.000
F. Insulin (IU/ml)	4.63 ± 2.27	11.76 ± 6.96	5.422	0.000
B (%)	85.65 ± 21.22	127.88 ± 45.17	4.792	0.000
S (%)	180.02 ± 62.95	91.99 ± 67.05	5.773	0.000
HOMA-IR	0.65 ± 0.30	1.68 ± 0.98	5.583	0.000
Uric acid (mg/dl)	3.35 ± 0.77	4.59 ± 1.93	3.350	0.001
ESR (mm/hr)	7.83 ± 2.39	72.08 ± 41.40	8.471	0.000
TNF-α (pg/ml)	34.17 ± 21.31	341.38±250.06	6.698	0.000

FBG: fasting blood glucose, TCh: total cholesterol, TG: triglycerides, HDL-c: high density lipoprotein, LDL-c: low density lipoprotein, ESR: erythrocyte sedimentation rate, B: beta cell function, S: insulin sensitivity, HOMA-IR: Homeostatic Model Assessment of Insulin Resistance, TNF- α: tumor necrosis factor- α.

**Table (3):** Echocardiographic finding in studied groups

	Control group (N=30) Mean ± SD	Patients group (N=48) Mean ± SD	Independent t-test	
			t	P-value
EF%	66.10 ± 5.09	60.83 ± 5.00	4.498	0.000
LVSD (cm)	2.46 ± 0.38	2.99 ± 0.88	3.116	0.003
LVDD(cm)	3.64 ± 0.18	3.86 ± 0.42	2.712	0.008
IVS (cm)	0.84 ± 0.12	0.98 ± 0.28	2.589	0.012
LVPW(cm)	0.81 ± 0.09	0.87 ± 0.14	2.090	0.040
E wave dec. time	116.50±13.3	126.11±22.83	2.091	0.040
E/A ratio	1.57 ± 0.11	1.40 ± 0.26	3.390	0.001

EF; Ejection Fraction, LVSD; left ventricular systolic dimension , LVDD; left ventricular diastolic dimension, Inter-Ventricular Sputum, LVPW; left ventricular posterior wall, E wave des. time ;E wave declarations time

**Table (4)** Demographic, clinical and laboratory data in RA patients with and without diastolic dysfunction

	Without DD No=41 (85.4%) Mean $\pm$ SD	DD No=7 (14.6%) Mean $\pm$ SD	Independent t-test	
			t	p-value
Age (years)	37.88 $\pm$ 6.28	47.71 $\pm$ 1.75	4.080	0.000
Duration(years)	4.31 $\pm$ 1.69	9.20 $\pm$ 2.61	6.512	0.000
WC(cm)	90.93 $\pm$ 10.76	111.57 $\pm$ 12.56	4.583	0.000
BMI(kg/m <sup>2</sup> )	26.37 $\pm$ 3.51	30.10 $\pm$ 1.50	2.749	0.009
E wave dec. time (ms)	118.50 $\pm$ 10.1	131.75 $\pm$ 31.19	2.207	0.032
E/A Ratio	1.46 $\pm$ 0.21	1.03 $\pm$ 0.21	5.007	0.000
Systolic(mmHg)	123.05 $\pm$ 13.60	137.86 $\pm$ 12.86	2.681	0.010
Diastolic(mmHg)	79.39 $\pm$ 9.89	90.00 $\pm$ 8.17	2.680	0.010
DAS28 score	2.82 $\pm$ 0.45	3.12 $\pm$ 0.55	1.580	0.121
Uric acid(mg/dl)	4.58 $\pm$ 2.02	4.60 $\pm$ 1.37	0.025	0.980
FBG(mg/dl)	89.95 $\pm$ 16.14	106.14 $\pm$ 6.09	2.603	0.012
TC(mg/dl)	92.05 $\pm$ 44.44	51.43 $\pm$ 21.30	2.357	0.023
TG(mg/dl)	89.41 $\pm$ 68.65	49.57 $\pm$ 17.96	1.514	0.137
HDL-c(mg/dl)	26.34 $\pm$ 15.82	17.29 $\pm$ 4.35	1.492	0.143
LDL-c(mg/dl)	47.66 $\pm$ 25.93	24.14 $\pm$ 17.80	2.299	0.026
VLDL(mg/dl)	18.00 $\pm$ 13.7	10.00 $\pm$ 3.74	1.523	0.135
Risk Ratio 1	3.73 $\pm$ 1.38	3.00 $\pm$ 1.41	1.290	0.204
Risk Ratio 2	1.89 $\pm$ 0.64	1.49 $\pm$ 1.08	1.372	0.177
Insulin(IU/ml)	10.02 $\pm$ 5.83	21.94 $\pm$ 3.35	5.233	0.000
ESR(mm/ml)	73.41 $\pm$ 44.39	64.29 $\pm$ 14.36	0.535	0.596
TNF- $\alpha$ (pg/ml)	297.92 $\pm$ 202.80	526.86 $\pm$ 465.38	2.213	0.032
HOMA-IR	1.52 $\pm$ 0.92	2.61 $\pm$ 0.76	2.959	0.005

**Table (5):** Frequency of Metabolic Syndrome in RA patients with and without diastolic dysfunction

	Without DD (41)		With DD(7)		Chi-square test	
	No.	%	No.	%	X <sup>2</sup>	P-value
Metabolic S.	10	24.39%	6	85.71%	7.547	0.006
Not Metabolic S.	31	75.61%	1	14.29%		

## Discussion

The term “metabolic syndrome” (MS) refers to a clustering of specific cardiovascular (CV) disease risk factors including central obesity, hypertension, high triglycerides, and low HDL levels whose underlying pathophysiology is thought to be related to insulin resistance <sup>(18)</sup>. High-calorie diet and physical inactivity which are traditional environmental risk factors are associated with obesity in RA patients. On the

other hand, persistent inflammatory activity, high-grade inflammation (associated with increased production of TNF- $\alpha$ ), muscle mass loss, decreased subcutaneous fat mass and decreased BMI, as well as low serum lipid levels and increased production of pro-inflammatory HDL and small dense LDL particles are associated with rheumatoid cachexia, which is associated with increased CVD mortality in RA <sup>(19)</sup>.



Our patients showed significantly increased insulin resistance (IR) and B cell function and decreased insulin sensitivity more than the healthy control group (table 2). Some studies<sup>(20,21)</sup> demonstrated the increased prevalence of IR in patients with RA compared with age, sex, and race matched control. However, *Garcia Diaz and coworkers*<sup>(22)</sup> showed no differences in HOMA and quantitative insulin sensitivity check index (QUICKI) values between RA patients and controls (74 cases and controls).

Insulin resistance in patients with active RA is associated with higher fasting plasma glucose, and systolic blood pressure levels and higher DAS28 values. Moreover, patients in the upper quartile of disease activity (DAS28 > 6.86) had more than six times increased risk (OR 6.4) for high insulin resistance<sup>(23)</sup>.

*Fontes-Carvalho and coworkers*<sup>(24)</sup> showed that metabolic syndrome (MS), or insulin resistance syndrome, is associated with changes in diastolic function which precede the onset of diabetes, being already present in pre-diabetic patients. In RA patients, diastolic dysfunction is one of the silent rheumatoid heart diseases<sup>(25)</sup>.

Many mechanisms involved in the association between insulin resistance and LVDD include: decreased myocardial energy supply due to changes in substrate utilization from glucose to free fatty acids<sup>(26)</sup>, increased myocardial interstitial fibrosis<sup>(27)</sup>, sympathetic nervous system activation<sup>(28)</sup>, increased afterload and impaired ventricular-vascular coupling as a result of arterial stiffness<sup>(29,30)</sup>, endothelial dysfunction<sup>(31)</sup> and increased myocardial oxidative stress<sup>(32)</sup>.

In women participating in the Nurses' Health Study (from 1976 to 1989 on 287 RA patients and 87019 normal control), the traditional CVD risk factors were found similar between those who had RA and those who did not. However, biomarkers of inflammation associated with CVD were generally elevated in women with RA<sup>(33)</sup>.

Six patients out of 7 (85.7%) with DD had MS while only 10 patients out of 41 (24.4%) without DD had metabolic syndrome (MS). Those patients

with metabolic syndrome were older in age and had longer disease duration. This was previously reported by others<sup>(34)</sup> who demonstrated that overweight and obesity in RA have biphasic role: it causes the relative risk of mortality (whether all-cause or cardiovascular) but irrespective of patient's age or duration of RA, and at the same time associated with considerably increased risks of comorbidities, total joint replacement, greater pain, medical costs, and decreased quality of life.

We categorized the RA patients into two subgroups according to presence or absence of diastolic dysfunction and we found seven patients out of 48 RA studied patients had diastolic dysfunction. The frequency of DD was 7/48 (14.58%). This finding is lower than that reported by others<sup>(35,36)</sup> which were 48.58 % and 42.2% respectively. The decrease in the incidence of DD in our patients may be attributed to: firstly, the fact that DD is increased with age and our patients are younger than 50 years in contrast to the other patients participating in the above studies whose age were above 50 years old. Secondly, the differences in disease activity as our patients were in remission or had mildly active disease. *Solomon and coworkers*<sup>(37)</sup> was stated that the absence of risk factors or markers of disease severity in RA patients does not lead to the development of any cardiovascular events in these patients while the presence of at least two traditional CVD risk factors and three or more markers of RA severity can lead to these CV events. A recent study<sup>(38)</sup> demonstrated that diastolic dysfunction in RA patients is closely associated with hypertension which is a traditional risk factor for CV events independent of disease inflammation and activity. Thirdly, our patients were ethnically different from other studied populations. *Juan and his colleagues*<sup>(39)</sup> investigated patients with RA in Latin America and found that 35.5% of them had CVD and attributed this to the different genetic burden of these patients that could be the cause of a higher prevalence of extra-articular manifestations (EAM).

In a metaanalysis done by *Fawad and his colleagues* <sup>(29)</sup> on 5,836 subjects, of whom 1,614 (27.7%) had RA. The mean duration of RA was 8.45 years. When given, the mean Disease Activity Score in 28 joints (DAS28) ranged from 3.8–5.9 for the RA patients. Six reported studies suggested that DD was not related to disease duration and/or disease activity, whereas 7 studies suggested such a link.

In our study, significantly elevated levels of TNF- $\alpha$  were found in RA patient's group compared to the normal control group. This relation between TNF- $\alpha$  and RA can be explained by the close link found between inflammation and IR. Inflammatory cytokines such as TNF- $\alpha$  may inhibit insulin signaling through inducing phosphorylation of IRS-1 at serine instead of tyrosine residues promoting insulin resistance <sup>(23)</sup>. This study found a significant increase in IR and TNF- $\alpha$  in RA patients with DD more than in those without. Many studies also found a link between IR and cardiac affection in RA including micro- and macro-vascular, valvular, myocardial, pericardial complications and atherosclerosis <sup>(41,42,43)</sup>. However, others like *Giles and coworkers* <sup>(44)</sup> did not find this link after 3 years follow-up of patients with RA.

Also, we found that total serum lipid profile in patients is less than the control group. Previous studies reported that female patients with RA were found to have significantly lower LDL-C levels than women in the general population <sup>(45,46)</sup>. We also found that patients with DD had lower total serum lipid profile levels than in those without, which could be due to receiving Hydroxychloroquine which has lipid lowering effect. The study done by *Liao and his colleagues* <sup>(47)</sup> found that the lipid profile levels and the risk of major cardiovascular events were non-linear in RA patients.

*Steiner and Urowitz* <sup>(48)</sup> stated that the analysis of lipid levels in the COBRA (Combination therapy in rheumatoid arthritis) study found that combination therapy with glucocorticoids, methotrexate, and sulfasalazine was associated

with a more rapid and favorable impact on the atherogenic index (total/HDL cholesterol ratio) in RA. *Dessein and Joffe* <sup>(43)</sup> found that corticosteroid use was not associated with dyslipidemia in RA patients but was associated with insulin resistance.

### Conclusion

We concluded that left diastolic dysfunction was less frequent in our patients who are controlled or nearby (DAS28 score  $\leq$  3.5) than reported by other previous studies, with a significant association between diastolic dysfunction and presence of metabolic syndrome with IR.

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