

# The Incidence of Peripheral Artery Disease in Patients with Rheumatoid Arthritis

MUBARAK ALI ANJUM<sup>1</sup>, MUHAMMAD JAVAID IQBAL<sup>2</sup>, IMRAN JOHER<sup>3</sup>, MUHAMMAD USMAN<sup>4</sup>, AAMIR HUSSAIN<sup>5</sup>, AFTAB RABBANI<sup>6</sup>

<sup>1</sup>Assistant Professor of Medicine, Aziz Fatima Medical and Dental College, Faisalabad

<sup>2</sup>Assistant Professor of Pathology, Aziz Fatima Medical and Dental college Faisalabad

<sup>3</sup>Assistant Professor, Department of Medicine, Sharif Medical College, Lahore

<sup>4</sup>Associate Professor of Pathology Aziz Fatima Medical and Dental College, Faisalabad

<sup>5</sup>Assistant Professor of Medicine, Fazaia Ruth PFAU Medical College, Karachi

<sup>6</sup>Associate Professor, Department of Medicine, Sharif Medical College, Lahore

Corresponding author: Dr Mubarak Ali Anjum, Email: [mubarak.ali12325@gmail.com](mailto:mubarak.ali12325@gmail.com) +92-345-7666825

## ABSTRACT

**Objectives:** The basic aim of this study was to find the expression of PAD in a group of Rheumatoid arthritis participants but with no record of any cardiovascular diseases.

**Methods:** On Ninety subjects with no record of considerable CVD but with RA a prospective observational non-experimental study was performed. Doppler spectral waveform analysis and Ankle Brachial Pressure Index for vascular judgment was performed.

**Place and Duration:** In the Medicine Department of Aziz Fatima Medical and Dental College Faisalabad for one-year duration from April 2020 to April 2021.

**Results:** In this study total 90 of participants were selected out of which 18 were males and 72 were females. The mean age for this study and time period of RA was  $62 \pm 9.01$  and  $11.8 \pm 11.2$  years respectively. It was noticed that seventy five percent of the subjects had triphasic waveforms in the Right foot while sixty percent had in the Left foot when examined the posterior tibial or PT artery. In sixty-eight percent of the total participants triphasic waveforms of the Dorsalis Pedis Arteries were found. Biphasic right was present in thirty percent subjects while biphasic left was present in thirty five percent subjects. Biphasic Dorsalis Pedis was found in forty percent participants of both feet. Only one subject was found with discontinuous monophasic PT of both feet.

**Conclusions:** Results show that ABPI index was discovered normal in majority of patients but waveform analysis was found suboptimal or biphasic in total of one-third of the participants. These results indicate that to find patients with early PAD the judgment of peripheral arterial perfusion should use both modes.

**Keywords:** Rheumatoid arthritis, ankle brachial pressure value, CVD risks hazards, screening.

## INTRODUCTION

Rheumatoid arthritis or RA primarily characterized by general inflammation, auto antibodies and continual synovitis<sup>1</sup>. It is multiplex inflammatory disease. RA is known as the intense across the area of inflammatory rheumatic conditions with cardiovascular disease (CVD) with high morbidity and mortality rate<sup>2-3</sup>. In Rheumatoid arthritis Atherosclerosis condition is common. It is linked with the chronic disease-related inflammation that involves the initiation of T- lymphocytes and phagocytosis<sup>4</sup>. Due to this reason, RA patients as compared to the general population show a higher chance of peripheral arterial disease. However, in the development of vascular disease, peripheral arterial disease has an important role but especially in the field of diabetes mellitus<sup>5</sup>. This entity seems to be under-diagnosed in RA. Although in the study of RA, testing for peripheral arterial disease is not normally performed. In diabetic and other high-risk populations, such abnormalities usually study by using diagnostic measures such as Doppler Spectral Waveform Analysis and ABPI<sup>6-7</sup>. It is very important to know that to anticipate cardiovascular disease and mortality ABPI has been notified as an excellent marker. In RA population advance characterization of subclinical PAD is of extreme importance, since atherosclerosis may stay clinically quiet for many years<sup>8-9</sup>. Therefore, the main objective of this research was to find the expressions of PAD in a selected group of RA patients but with no record of CVS diseases.

## METHODS

In the Medicine Department of Aziz Fatima Medical and Dental College Faisalabad for one-year duration from April 2020 to April 2021, this study was conducted. A total of ninety participants were enrolled first through the door basis. The Committee of Research Ethics passed out study procedure. All the participants also gave their permission for any type of data collection. According to the principles of the Declaration of Helsinki all the procedures were continued. The Participants who were selected for this study must be more than 18 years and also have a condition of Rheumatoid arthritis but with no history of any kind of cardiovascular disease. Those participants were rejected from our study who had any kind of record of diabetic issue, amputations, revascularization or ulcerations surgery also include those patients who were having treatment with anti-platelet and anticoagulant regimens.

A prospective non-experimental observational study was performed. During this whole research the clinical tools that were utilized were based on international guidelines and recommendations from literature. To keep track of all the information a database was constructed. After all the participants gave their permission their age, gender, Body Mass Index and duration of RA were noted down. To add on their medical history, blood assessments counting erythrocyte sedimentation rate, C-reactive protein, anti-cyclic citrullinated peptide antibodies, lipid profile and

rheumatoid factor were also noted. Additional information like smoking was also documented along hypertension and hypertensive therapy

Doppler spectral waveform analysis and ABPI for vascular judgment were performed. An experienced investigator continued both testing modes and examination methods that had the experience of more than 10 years. To avoid vasoconstriction or vasodilatation the room temperature of the place where this experiment was performed kept within twenty-one to twenty-three degree Celsius. Both testing modes were applied on all the subjects because when ABPI would not able to detect PAD then spectral waveform analysis may do so. To continue the experiment, it was asked from all subjects to lose all their tight clothes around their arm and wrist. Measurements were taken after a 5-minute break with the upper body in supine and as flat as possible. The Dopplex Assist vascular package that is consist of 8MHz probe with continuous wave Doppler wasutilized to calculate the remaining ABPI. This is also used to calculate the qualitative Spectral Waveforms of the dorsalis pedis and posterior tibial arteries. On the anatomical artery place the probe was kept steady by an angle between forty-five to sixty degrees till optimum Doppler signal was received.

Monophasic, biphasic, Triphasic, continuous and monophasic discontinuous are the classification of waveforms. The monophasic continuous, monophasic discontinuous andbiphasic waveforms were consideredanomalous and indicate the presence of PAD while triphasic waveforms were known as normal. ABPI value range within 0.9 to 1.9 was considered normal while value less than 0.9 indicate lower-extremity vascular disease in both feet. Calculation greater than 1.3 indicates the presence of extreme vascular calcification. To keep track of all the data it was noted down on spreadsheet in excel which was necessary for the interpretation of results. By utilizing SPSS 21.0all the analyses were performed in statistical manner. By Kolmogorov-Smirnov test the normal range for data was checked in statistical manner. However, to check the data one way analysis of variance was utilized.

### RESULTS

In this study total 90 of participants were selected out of which 18 were males and 72 were females. The mean age for this study and time period of RA was 62 ±9.01 and 11.8±11.2 years respectively.

The metabolic characteristics of the study population is given in Tabl-1

		Frequency (n=90)	Percent	Valid	Mean	SD
				Percent	Duration Years	
Gender	Male	18	20	20		
	Female	72	80	80		
BMI Category	Normal	28	31	28		
	Overweight	30	33	30		
	Obese	32	36	42		
Hypertension	No	52	58	57		
	Yes	38	42	43	8.01	6.780
Hypertension Controlled by medication	No	13	14	14		
	Yes	38	42	42		
	Non- Hypertensive	39	44			
Hypercholesterolemia	No	65	72	65		
	Yes	25	28	35	9.30	4.1358
Cholesterol Control	Diet	22	24	24		
	Diet & Medication	28	31	31		
	No Cholesterol	40	45			
Never smoked	No	42	47	47		
	Yes	48	53	53		
Family member with RA	No	69	77	77		
	Yes	21	23	23		
Family member with Hypertension	No	40	44	48		
	Yes	50	56	52		
Family member with Hypercholesterolemia	No	65a	72	70		
	Yes	25	28	30		
Family member with CVD	No	70	78	76		
	Yes	20	22	24		

It was noticed that seventy five percent of the subjects had triphasic waveforms in the Right foot whilesixtypercent had in the Left foot when examined the posterior tibial or PT artery. Insixty-eight percent of the total participants triphasic waveforms of the Dorsalis Pedis Arteries were found. Biphasic right was present in thirty percent subjects while biphasic left was present in thirty fivepercent subjects. Biphasic Dorsalis Pedis was found in forty percent participants of both feet. Only one subject was found with discontinuous monophasic PT of both feet.

The ABPI value was considered normal in ninety three percent participants within range of 0.9 to 1.29. In only

7% of the participants a little impediment was discovered within range of 0.81 to 0.89. The One-way Analysis of Variance was utilized to examine CVS against the ABPIs of the Left and right foot. These CDV risk hazards include examining of gender, hypertension, BMI, smoking, RA medications and hypercholesterolemia.

From all this only hypercholesterolemia was considered highly related to the ABPI with a value of 0.21. To examine any important difference differences between ABPI and the risk factors Analysis of Covariance or ANCOVA was performed. Hypercholesterolemia as an

important indicator was confirmed by last ANCOVA test.

ANCOVA test was highly unimportant for the right foot.

Examination of the surveyed co-variables associated with cardiovascular disease against the ABPIs of Left Foot given in Table-2

One-Way ANOVA of ABPI [L]					
Predictor	Categories	N	Mean	Std. Deviation	p-Value
Gender	Male	18	1.12	0.090	0.155
	Female	72	1.07	0.082	
	Total	100	1.05	0.085	
BMI	Normal	28	1.042	0.074	0.289
	Overweight	30	1.060	0.075	
	Obese	32	1.092	0.095	
	Total	90	1.079	0.085	
Hypertension	No	52	1.063	0.089	0.755
	Yes	38	1.071	0.069	
	Total	90	1.06	0.079	
Hypercholesterolemia	No	65	1.079	0.079	0.021
	Yes	25	1.031	0.070	
	Total	90	1.06	0.079	
Never smoked	No	42	1.082	0.090	0.12
	Yes	48	1.04	0.080	
	Total	90	1.05	0.081	
Analgesics	No	78	1.070	0.081	0.072
	Yes	12	0.10	0.039	
	Total	90	1.02	0.080	
NSAIDs	No	64	1.069	0.080	0.21
	Yes	26	1.033	0.075	
	Total	90	1.04	0.076	
DMARDs	No	15	1.060	0.075	0.420
	Yes	75	1.08	0.078	
	Total	90	1.06	0.075	
steroids	No	53	1.070	0.076	0.84
	Yes	37	1.068	0.079	
	Total	90	1.05	0.076	
Biologics	No	69	1.059	0.078	0.21
	Yes	21	1.090	0.087	
	Total	90	1.01	0.079	

Examination of the surveyed co-variables associated with cardiovascular disease against the ABPIs of Right Foot given in Table-3

One-Way ANOVA of ABPI [R]					
Predictor	Categories	N	Mean	Std. Deviation	p-Value
Gender	Male	18	1.12	0.090	0.17
	Female	72	1.07	0.082	
	Total	100	1.05	0.085	
BMI	Normal	28	1.042	0.074	0.43
	Overweight	30	1.060	0.075	
	Obese	32	1.092	0.095	
	Total	90	1.079	0.085	
Hypertension	No	52	1.063	0.089	0.81
	Yes	38	1.071	0.069	
	Total	90	1.06	0.079	
Hypercholesterolemia	No	65	1.079	0.079	0.13
	Yes	25	1.031	0.070	
	Total	90	1.06	0.079	
Cholesterol Control	Diet	42	1.082	0.090	0.87
	Diet & Medication	48	1.04	0.080	
	Total	90	1.04	0.080	
Never smoked	No	78	1.064	0.080	0.60
	Yes	12	0.09	0.040	
	Total	90	1.01	0.075	
Analgesics	No	64	1.068	0.075	0.15
	Yes	26	1.032	0.074	
	Total	90	1.03	0.074	
NSAIDs	No	15	1.059	0.074	0.16
	Yes	75	1.07	0.076	
	Total	90	1.05	0.074	
DMARDs	No	53	1.069	0.075	0.37
	Yes	37	1.067	0.078	
	Total	90	1.04	0.077	
Steroids	No	69	1.058	0.075	0.66
	Yes	21	1.089	0.084	
	Total	90	1.02	0.078	
Biologics	No	18	1.11	0.091	0.078
	Yes	72	1.06	0.081	
	Total	100	1.04	0.084	

ANCOVA test of Left ABPI against all variables given in Table-4

Source	Sum of Squares	df	Mean Square	F	P-value
Corrected Model	0.133	20	0.006	1.029	0.422
Intercept	1.20	2	1.20	169.42	0
Gender	0.009	2	0.009	1.250	0.270
BMI Scale	0.012	1	0.007	0.91	0.423
Hypertension	0.004	2	0.004	0.81	0.368
Cholesterol	0.048	2	0.048	7.12	0.02
NSAIDs	0.002	2	0.003	0.21	0.645
Analgesics	0.013	2	0.011	1.76	0.20
DMARDs	0.006	2	0.006	0.985	0.331
Steroids	0.001	2	0	0.062	0.812
Biologics	0.008	2	0.007	1.210	0.265
Never smoked	0.008	2	0.008	1.34	0.249
Age	0.002	1	0.002	0.096	0.761
RA Duration	0.006	2	0.006	0.97	0.319
Total Blood cholesterol	0.002	1	0.002	0.093	0.78
HDL	0	1	0	0.002	0.981
LDL	0	1	0	0.045	0.831
RA Factor	0.005	1	0.005	0.95	0.340
CRP	0.008	1	0.008	1.30	0.260
ESR	0.003	1	0.003	0.64	0.430
Error	0.55	95	0.006		
Total	109.10	100			
Corrected Total	0.512	97			

## DISCUSSION

This study explains us the importance of utilizing ankle-brachial value and arterial spectral waveforms in patients with record of RA for PAD testing<sup>10</sup>. This study shows the important restriction of using ABPI test in indication of PAD in patients with record of RA. The outcomes of the study clearly show in-combabilities in both ABPI and Doppler waveform analysis because it differs from the ABPI results in most of the chosen participants<sup>11-12</sup>. In spite of a 'normal ABPI' result most of the patients, waveform analysis demonstrates distorted vascular function as one third of subjects showed biphasic waveforms in one or both feet. Outcomes of recent study showed that only one percent of the participants had extreme PAD, which may be symptomatic<sup>13</sup>. While on the other side only twenty nine percent of patients showed biphasic waveforms showing initial stages of subclinical PAD. These observations present that almost one third of RA patients may suffer from early PAD and the silent clinical presentation may result in underdiagnosis in subjects<sup>14</sup>. The major feature of selected subjects, is the absence of major co-morbidities, which is critical for the analysis of the results of the study<sup>15</sup>. We chose to exclude other factors such as people with diabetes, as well as those with ulcer or cardiovascular disease that had such conditions and treatments, from our analysis because our aim was to create an important, rather than exacerbated CVD risk factor in our study. In the literature, both type 1 diabetes and rheumatoid arthritis have been shown to have identified CVD risk factors that are linked to each other<sup>16-17</sup>. Raynaud hancy, a distinct type of Raynaud than syndrome, is said to put people at a higher risk of developing PAD than the general population. Angiogenesis (the sprouting of pre-existing vessels from their existing networks of old vessels, Ang) or the recruitment of EPCs (peripheral production) are two common ways for new blood vessels to form (vasculogenesis). Providing space and restoring blood flow to tissues are critical for wellbeing, as are compensatory procedures for collateral circulation in ischemic areas<sup>17-18</sup>. According to study, EPC concentrations in the peripheral blood have a clear inverse association with the risk of

cardiovascular disease. While the number of circulating endothelial progenitor cells in RA decreases, the disease's susceptibility to vascular dysfunction improves. This is believed to be due to the discovery of fewer endothelial progenitor cells, which may result in decreased vessel development and a higher risk of cardiovascular disease<sup>19</sup>. Wolfe and Mich have shown in studies that functional and quantitative tumor necrosis factor alpha, as well as other inflammatory mediators of expression reported to be problematic in RA, are related to increased mortality in RA patients. It's also complicated by a heightened systemic inflammatory response, which contributes to the inflammatory arterial dysfunction seen in our RA patients<sup>20</sup>. This is attributed to the improvement in cardiovascular disease and the normalization of systemic inflammatory burden seen in patients treated with targeted therapies. Latest research on biologic therapies for CVD and CVD risk factors has demonstrated their beneficial results on others, such as lowering systemic inflammation numbers and their functional importance on cholesterol parameters, over the last 25 years<sup>21</sup>. According to this study, 96 percent of co-no similarity patients (those who had all of the same common complications) had normal ABPI (or albumin-bolus) test results when they had no other systemic conditions. However, qualitative Spectral Waveform analysis revealed that one-third of the sample had suboptimal/mildly adequate arterial perfusion, indicating a reduced level of arterial blood supply<sup>22</sup>. They discovered a significant link between the study's findings and Chuang et al findings, which show that RA patients with other health conditions, especially those involving multiple risk factors, are more likely to develop PAD. In comparison to results from a case-control study, which showed an increased risk of developing arachnid in patients with RA relative to healthy people, this conclusion was drawn<sup>23</sup>. Our study began with the aim of determining whether there is a correlation between rheumatoid arthritis and arterial disease in the first place, as previous results were contradictory. PADS, which was previously thought to be different from the other risk factors listed in this study, now appears to be linked to RA on its own. Doppler-method [audio and transducers for

calculating the shift in the volume of a blood flow of the vessels in blood flow] has an advantage over ABPI because it [is claimed to be capable of measuring the flow in calcified arteries. They are able to detect shifts in ABP earlier than with traditional ABP readings by using the Doppler waveform. This study also shows us that additional functional screenings such as toe brachial and toe pressure indices must be completed to find whether PAD is really existing in case those discrepancies happen between two screening modes for PAD namely Doppler and ABPI analysis<sup>24-25</sup>. Identification of PAD in early stage of RA patients helps in the control of cardiovascular diseases and CVD risk stratification which better prolong results in patients. It is noticed that the time period of RA does not have any effect on arterial perfusion but the time period of the condition among out subjects was ranged from two to twenty-four years<sup>26</sup>. In our study between RA time period and ABPI and Waveform analysis no important differences were discovered. An important link between increase serum cholesterol levels and ABPI value is noticed according to cardiovascular diseases. The only restriction that is noticed in this study is the restriction of noticing down the participants that was taking anti-depressants. Due to this reason author was not aware about the effects of this kind of medication that can also relate with and thus the judgement of vascular supply. It is necessary to do more experiments in this area in command to know about the relation between and individual comorbidities thus to recognize which aspects are taking part to PAD in these people

## CONCLUSION

All the results pointed that ABPI value was found normal in the bulk of participants but almost in one-third of the study participants waveform analysis was abnormal. This all gives us the information that participants with normal ABPI value but abnormal waveforms some subjects could consider normal by mistake. This study explains us that for assess peripheral arterial perfusion, judgment should use both modes and if they do not relate with each other than those patients should be monitored according to the conditions. If we diagnose PAD at early stage then we can identify cardiovascular risk hazards that can hold long-term complications, better results and decrease the financial problems on both patients and health care center. In RA patients, testing for peripheral perfusions must use spectral waveforms as a part of assessment.

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