Original Article

Investigating the Association of Aortic Stiffness and Phase Angle with the Clinical Course of Rheumatoid Arthritis

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Abstract

Background: Aortic stiffness is an independent predictor of cardiovascular events which is increased in rheumatoid arthritis (RA). It can be measured by carotid-femoral pulse wave velocity (cfPWV). Phase angle (PhA) is lower in patients with cardiovascular disease and may be informative in assessing the clinical course of RA.

Materials and Methods: In this observational and cross-sectional study, all RA patients referred to the Imam Khomeini Hospital rheumatology clinic between September 2022 and March 2023 were included in the study. RA activity was assessed using the DAS28 criteria. In the patients, PhA and cfPWV were measured using Inbody-s10 and PulsePen tonometer instruments. The relationships between PhA, cfPWV, clinical course of RA, and CRP were evaluated using regression analysis.

Results: 53 patients were included in the study (83% female, mean age 46.5 years). Significant inverse relationships existed between PhA, CRP, and age (*P* value = 0.003, 0.0001, R: 0.69, respectively). People with aortic stiffness had a lower mean PhA (*P* value = 0.05). In patients with RA duration of less than 10 years, the cfPWV percentile and the prevalence of rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) positive cases were higher than in patients with RA duration >10 years (*P* values = 0.02, 0.01, respectively).

Conclusions: With increasing duration of RA, aortic stiffness and positive serology cases decreased. PhA and cfPWV may be useful in assessing the clinical course of RA to prevent cardiovascular events.

Keywords: Arthritis, carotid-femoral pulse wave velocity (cfPWV), C-reactive protein, rheumatoid**,** vascular stiffness

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Introduction

In the past two decades, chronic inflammation has emerged as a significant risk factor for cardiovascular diseases.[1] Aortic stiffness as early manifestations of atherosclerosis has been identified as an independent predictor of cardiovascular events and all-cause mortality in various populations.[2] Rheumatoid arthritis (RA) an autoimmune chronic inflammatory disease is associated with an increased risk of cardiovascular events.[3]

There is growing evidence suggesting a potential link between aortic stiffness and elevated cardiovascular risk.[4,5] While it is established that RA patient exhibit significantly higher levels of aortic stiffness, the relationship between aortic stiffness and disease progression remains unclear.[6,7]

One of the methods that can be used to evaluate the aortic stiffness in RA patients is the measurement of the wave

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transmission velocity by applanation tonometry, which is a measurement of the pulse wave velocity (PWV) between different areas of the arterial tree.[8] Another variable that can be assessed by applanation tonometry is the augmentation index (AIx). AIx is defined as the ratio of central augmentation pressure to central pulse pressure.[9,10] The loss of arterial elasticity and increased arterial stiffness result in faster pulse wave propagation. This accelerated reflection of the systolic wave from peripheral arteries back to the heart leads to an increase in AIx.

Bioelectrical impedance is the resistance of different tissues in the body to an electric current. The body offers two types of resistance (R) to an electric current: capacitive R (reactance or Xc) and resistive R (simply called resistance). Capacitive R comes from the cell membrane and resistive R comes from extracellular and intracellular fluid.[11] Capacitance causes a phase shift, or PhA. Lower values of the phase angle (PhA) indicate decrease in cell integrity or cell death, while higher values indicate healthy cell membrane, and PhA can be used as a prognostic factor for morbidity and mortality and is an alternative method for assessing mortality risk.[11,12]

Based on the previous studies, RA causes vascular stiffness, a meta-analysis conducted in 2019 showed that RA patients have significantly higher cfPWV than the control group,[13] and another study showed that every year of the patients' age RA is associated with a significant increase in vascular aging.[14] Given that RA patients are exposed to more cardiovascular events than the general population, early identification of RA patients at risk of cardiovascular events may lead to early initiation of cardiovascular disease prevention strategies, as well as reduced costs associated with complications caused by cardiovascular events. Identifying the relationship between the clinical course of RA and measures of aortic stiffness and PhA in RA patients using applanation tonometry and BIA may become a way to screen for cardiovascular disease in RA patients. As there is no study regarding the relationship between PhA with aortic percentile group. Also the association of aortic stiffness and PhA with the clinical course of RA has not been evaluated in Iranian RA patients; therefore, this study aimed to investigate the cfPWV, PhA; and their relationship with RA clinical course, and C-reactive protein (CRP).

Materials and Methods

All patients with RA aged above 18 years, who were referred to the rheumatology clinic of Imam Khomeini Hospital between September 2022 and March 2023, were included in the study. The diagnosis of RA was made by a rheumatologist based on the American College of Rheumatology/European League against Rheumatism 2010 (ACR/EULAR 2010) criteria.[15] Informed consent was obtained from each patient. Patients with a history of cardiovascular disease, including a history of acute coronary events, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), heart failure with reduced ejection fraction (HFrEF), chronic hypertension, as well as those with chronic kidney disease (GFR <60 ml/min), acute or chronic liver disease, diabetes mellitus, and patients using anti-hypertensive (ACE inhibitors, ARB, CCB, B blocker, a blocker, diuretics), anti-hyperlipidemia, or antidiabetic drugs were excluded from the study. Pregnancy or lactation was also another exclusion criterion.

1) Based on the previous studies, a minimum of five predictor variables and a squared multiple correlation coefficient of 0.28 ($R^2 = 0.28$) were considered. Using the sample size formula for the multiple linear regression model, considering $\alpha = 0.05$ and $\beta = 1\text{-}0.95$, and using G*Power 3.1.9.2 sample size calculation software, the minimum sample size was determined to be 50 people.

Initially, patients were seen by a faculty rheumatologist, and their demographic information (sex, age, height, weight, body mass index (BMI), smoking status, and duration of RA), clinical examination results, including number of tender joints and swollen joints was recorded. laboratory tests were also conducted, including erythrocyte sedimentation rate (ESR), CRP, rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP), and lipid profile (including high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride (TG), and total cholesterol). These data were recorded in a data-gathering form. For the patients, one-time blood sampling has been performed. However for those patients whose lipid profile, anti-CCP Ab and RF tests have been checked within the previous 6 months, and these tests have not been sent again. Patients were referred for bioelectrical impedance and applanation tonometry in private clinic, and then PhA and PWV variables were measured.

The scale was based on ACR/EULAR 2010 criteria which consist of four categories, each with a score: the number and type of joints involved; serology (RF and/or anti-CCP); acute phase reactants (CRP and/or ESR); and duration of symptoms (whether <6 weeks or ≥6 weeks). A score of 6 from ACR/EULAR 2010 means RA.[15] Varache *et al*. estimated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the ACR/EULAR 2010 to be 51, 90, 75.4, and 75.7 percent, respectively, in a 2-year cohort study.[16]

The DAS28 was used to assess RA activity based on tenderness and swelling in 28 joints of the body, blood ESR/CRP levels, and the patient's overall health. Based on the DAS28 criteria, patients can be classified into four groups (remission, low disease activity, moderate disease activity, and high disease activity).[17]

Two variables that were measured by applanation tonometry (PulsePen tonometer) were carotid-femoral pulse wave velocity (cfPWV) and augmentation index (AIx). cfPWV measures the velocity at which the pulse wave travels between the carotid and femoral arteries, while AIx was measured the increase in pressure after the first systolic shoulder of pulse

pressure to the peak aortic pressure. PhA which is quantified as the arc tangent (Xc/R) *180°/π was measured by Inbody S10 BIA device.

2) Descriptive statistics, including mean, standard deviation, median, interquartile range (IQR), and frequency indicators, were used to report the results. The normality of variable was tested using the Kolmogorov–Smirnov test. Multiple linear regression analysis was performed to determine the relationship between aortic stiffness and PhA values with other independent variables. Independent *t*-test and analysis of variance (ANOVA) (with the precondition of the equality of variances test) were used to compare group means for quantitative variables with normal distribution, and Mann–Whitney and Kruskal–Wallis for non-normal variables. Analyses were performed using SPSS 22 software (IBM Inc., Chicago, IL). A significance level of *P* values ≤ 0.05 was considered statistically significant.

Results

A total of 53 patients who met the eligibility criteria were included in the study at the Imam Khomeini Hospital clinic.

The mean age of the study participants was 46.5 (±12.04) years, with 44 (83%) female and 9 (17%) male. The average duration of RA was 109.42 months (±98.2). The mean duration of morning stiffness was 42.07 minutes (±83.86). 28.3 percent of the patients had morning stiffness (stiffness lasting more than 30 minutes). Each patient had an average of three joints affected (1.58 ± 3.10 tender and 1.41 ± 2.07 swollen joints). The knee joint (37.7%) and wrist joint (35.8%) were the most commonly affected joints. More data is available in Table 1 and Figure 1.

ESR, CRP, RF, anti-CCP, and lipid profiles were assessed (four patients had missing data for the last three variables). The results are presented in Table 2. Statistical analysis showed that the percentage of RF and anti-CCP positive cases was significantly higher in patients with RA duration ≤10 years than in patients with RA duration >10 years (*P* values = 0.02, 0.01, respectively).

The average cfPWV was 7.91 m/s (±1.72). 11.32 percent of the patients had aortic stiffness. The aortic stiffness was normal in 71.70%, and 16.98 of the patients had borderline aortic stiffness. Comparison of cfPWV and mean aortic stiffness percentile between men and women using Mann–Whitney and independent samples t-tests, respectively, did not yield any statistically significant difference (*P* values = 0.40, 0.52, respectively). The relationship between the cfPWV percentile and four groups of disease activity based on DAS28 was investigated using one-way ANOVA test, Despite the decrease in the cfPWV percentile with increasing disease activity, no statistically significant result was found (*P* value > 0.05) [Figure 2].

Multiple regression analysis showed that cfPWV increased only with age (*P* value = 0.001). The mean AIx was found to be 15.97% in women and 8.47% in men, with a statistically significant difference observed between genders using the Mann–Whitney test (*P* value = 0.007).

To evaluate the possible relationship between RA duration and aortic stiffness, we categorized the patients into two groups based on their RA duration: ≤10 years and >10 years.[14] The mean cfPWV was found to be 8.16 ± 1.92 m/s in patients with RA duration ≤10 years and 7.49 ± 1.26 m/s in patients with RA duration >10 years (*P* value = 0.17); however, the mean cfPWV percentile in patients with RA duration ≤10 years was significantly higher than that of patients with RA duration of >10 years (*P* value = 0.02). The mean AIx was 17.23 ± 11.15% in patients with an RA duration of less than 10 years and 15.4 ± 16.9 in patients with an RA duration of more than 10 years (*P* value = 0.22).

The possible association between cfPWV, PhA, and RF, anti-CCP was evaluated. The results showed no statistically

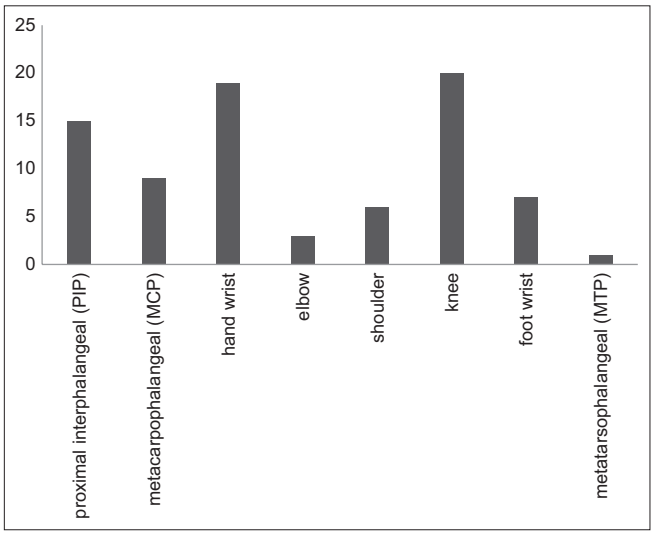

Figure 1: Number of patients with different joint involvement

Table 1: Clinical data of the patients

	Minimum	Maximum	Mean	Median	Standard deviation	Interquartile range
RA duration (month)	1.5	360	109.42	72	98.21	36-186
Morning stiffness (min)	0	360	42.07	10	83.86	10-30
Involved joints	0	26	3	2	4.69	0-2
Tender joints	0	17	1.58	0	3.109	0-4
Swollen joints	0	9	1.41	0	2.079	0-2

RA=Rheumatoid arthritis

significant association. Kruskal–Wallis test was used to compare AIx among different groups based on DAS28, and it was determined that there were no significant difference in terms of disease activity and AIx (*P* value = 0.34). Additionally, there were no significant difference in the relationship among AIx and DAS28ESR and DAS28CRP (*P* value = 0.77, 0.79, respectively).

The mean PhA measured was 5.0094 ± 0.81 degrees (the lowest 3.4 degrees and the highest 6.9 degrees). Among the 53 patients, 29 (54.7%) had a PhA <5.2 degrees, 18 (34%) had a PhA ≥5.2 and ≤6 degrees, and 6 (11.3%) had a PhA >6 degrees. The relationship between the PhA and RA activity based on the DAS28 criteria was investigated, and there was no significant statistical relationship (*P* value = 0.81 for ESR-based and *P* value = 0.65 for CRP-based DAS28).

Based on the DAS28 criteria, 18 patients were classified into different groups based on their disease activity: the remission group (18 patients), low disease activity group (nine patients), moderate disease activity group (21 patients), and high disease activity group (five patients). The relationship between PhA and RA activity based on this classification was investigated by one-way ANOVA test. Patients with high RA activity had lower PhA levels than other groups [Figure 3], but no statistically significant difference were observed (*P* value = 0.94).

The mean PhA was 0.93 ± 5.03 in men and 5.004 ± 0.78 in women, but there was no statistically significant difference between the PhA and gender, and RA duration (*P* value = 0.52, 0.27, respectively).

To evaluate the relationship between cfPWV and PhA, we categorized the patients into three groups based on their cfPWV percentile. A one-way ANOVA *t*-test and Tukey analysis showed that PhA was significantly lower in the aortic stiffness group (above the 95th percentile) (*P* value = 0.05). Regression analysis demonstrated a statistically significant inverse relationship between PhA and aortic percentile (*P* value: 0.05), CRP (*P* value: 0.008) and age (*P* value: 0.0001) and a direct relationship between PhA and waist circumference, and BMI (*P* value = 0.009, and *P* value = 0.004, respectively). In the above model, the multiple correlation coefficients and the coefficient of determination were 0.69 and 0.47, respectively. The regression coefficient for the three variables of BMI, CRP, and age was 0.44, 0.32, and 0.39, respectively. Other independent variables such as patients' lipid profile, ESR, RF, and anti-CCP levels did not exhibit any statistically significant association with PhA [Table 3].

Discussion

Our study aimed to assess the relationship between cfPWV, PhA, the clinical course of RA, and CRP. The results showed that PhA was lower in RA patients with aortic stiffness (above the 95th percentile) and higher CRP levels than in patients with stiffness below the 95th percentile and lower CRP levels.

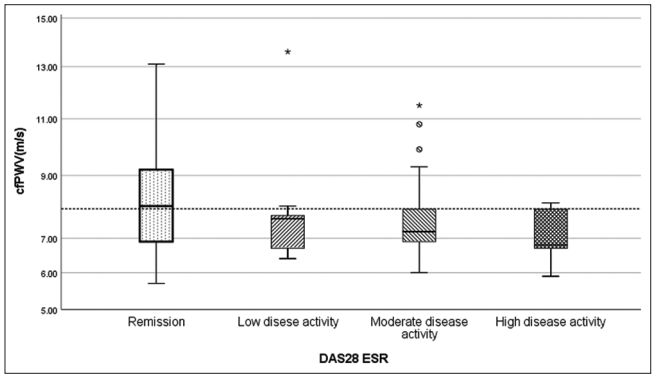

Figure 2: Pulse wave velocity means of four groups of RA activity based on DAS28ESR. The dotted line represents the average of all data

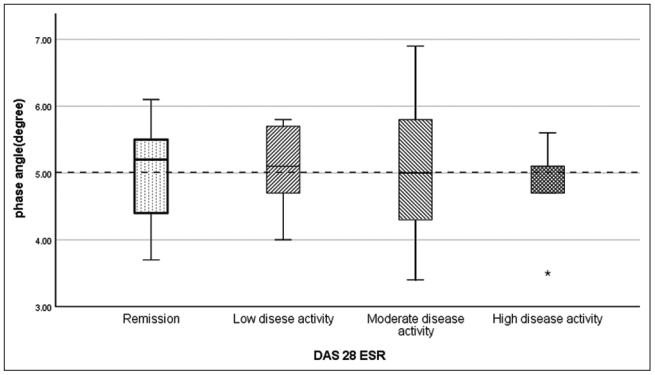

Figure 3: Phase angle in each group of disease activity in patients with RA based on DAS28ESR. The dotted line represents the average of all data

Table 2: Laboratory data of the patients

	Number	Minimum	Maximum	Mean	Median	Inter-quartile range	Standard deviation
ESR (mm/hour)	53	4.00	91.00	26.54	18	12-33	21.31
CRP (mg/dl)	53	0.18	70.00	12.54	4	2-20	17.29
Cholesterol (mg/dl)	49	107.00	225.00	174.06	169.5	150.25-195.75	35.84
TG (mg/dl)	49	45.00	328.00	123.89	102.5	102.5-158	58.88
HDL (mg/dl)	49	32.00	94.00	51.97	51.5	45-57.5	12.68
LDL (mg/dl)	49	58.00	171.00	96.95	91	76-110	27.035
RF (IU/ml)	49	2.50	512.00	71.13	18.5	6-95.75	112.02
anti-CCP Ab (IU/ml)	49	0.50	300.00	124.47	59.5	8.75-300	125.11

ESR=Erythrocyte sedimentation rate, CRP=C-reactive protein, TG=Triglyceride, HDL=High-density lipoprotein, LDL=Low-density lipoprotein, RF=Rheumatoid factor, anti-CCP=Anti-cyclic citrullinated peptide

Table 3: Regression coefficients related to the phase angle of rheumatoid arthritis patients with other variables

Variables	Correlation coefficient	*P*
BMI (kg/m²)	0.44	0.000
CRP (mg/dl)	-0.32	0.008
Age (year)	-0.39	0.000
ESR (mm/hour)	-0.15	0.27
RF (IU/ml)	0.04	0.97
Anti-CCP Ab (IU/ml)	0.22	0.13
TG (mg/dl)	0.3	0.06
Cholesterol (mg/dl)	0.14	0.31
HDL (mg/dl)	-0.06	0.66
LDL (mg/dl)	0.11	0.45
Aortic percentile class	-	0.05
Difference gender	-	0.52

BMI=Body mass index, ESR=Erythrocyte sedimentation rate, CRP=C-reactive protein, TG=Triglyceride, HDL=High-density lipoprotein, LDL=Low-density lipoprotein, RF=Rheumatoid factor, anti-CCP=Anti-cyclic citrullinated peptide. The $P \leq 0.05$ was considered as significance

Another important finding of our study was the relationship between RA duration with serology and aortic stiffness. The prevalence of positive RF and anti-CCP cases and cfPWV was higher in patients with an RA duration ≤10 years than in patients with an RA duration >10 years.

It is important to note that RA increases the risk of cardiovascular events[18] partially due to the inflammatory nature of the disease.[19,20] Although there have been reports of a reduction in cardiovascular events with the use of anti-inflammatory drugs, the risk of these events remains higher in RA compared to the general population.[21] Despite many recommendations to reduce cardiovascular risk factors, we still do not have specific biomarkers and therapeutic targets in this area for RA patients.[20]

Although not all studies agree on the effect of RA on arterial stiffness, most have found that the disease increases arterial stiffness and have attributed different factors to this increase.[6,13,22-26] To test whether there was a relationship between RA activity and cfPWV, we used the DAS28 criteria. Even though RA increases arterial stiffness according to most studies, in our study cfPWV was lower in patients with more disease activity (as measured by DAS28-ESR), the *P* value was 0.052 (based on multiple regression analysis), which is above the 0.05 cutoff. This non-significant *P* value may be partly due to the limited sample size of our study, which included only 53 patients. Another factor that may have influenced this result is the cross-sectional nature of our study. In a cross-sectional study by Ozisler, *et al*., no significant correlation was found between aortic stiffness (measured by transthoracic echocardiography) and CRP and ESR levels. As our study is a cross-sectional study, it is possible that patients who were in good condition according to the DAS28 criteria before the study had active disease at the time of the study and obtained higher scores, and vice versa; an explanation is also given by Ozisler in justifying the results of their study.[27] This discrepancy could potentially explain the inverse relationship observed between disease activity and cfPWV in our study. In a study by Crilly *et al.*, the relationship between the cumulative inflammatory burden in RA (as measured by one-year ESR values) and aortic stiffness was investigated. They found that one-year ESR values were significantly correlated with aortic stiffness as measured by pulse wave analysis.[28] Conducting longitudinal studies with larger sample sizes and measuring average RA activity over time (rather than measuring activity at a single point in time) may be effective in overcoming these limitations.

Our study also showed that the average cfPWV percentile in patients with RA lasting less than ten years was significantly higher than in patients with RA lasting ≤10 years. Many studies reported different results. Ozisler *et al*. found no correlation between aortic stiffness and RA duration.[27] In the case-control study performed by Slim *et al*., the duration of RA seemed to have a positive effect on aortic stiffness. They speculated that this positive reflection could be due to chronic cytokine release in RA patients with longer disease duration.[29] In a meta-analysis, Wang *et al*. found that groups with RA duration of less than 6 years had higher cfPWV levels.[13] Rodriguez-Carrio, *et al*. stated that a decrease in angiogenic T-cells (which are responsible for vascular repair) may be associated with vascular stiffness even in the early stages of RA.[30] The reason for the inverse relationship between RA duration and aortic stiffness in our study may be the longer use of anti-inflammatory drugs in patients with longer RA duration. Giollo, *et al*. found that TNF inhibitors were linked to reduced progression of aortic stiffness in RA patients.[31] What is clear, however, is that there are many unknowns in this area and more research is needed to uncover more facts.

In our study, the prevalence of positive serology (RF and anti-CCP) was higher in patients with an RA duration ≤10 years than in patients with an RA duration >10 years. We speculate that this observed association may be due to the longer use of anti-inflammatory medications in RA patients with disease duration of more than 10 years similar to the observed inverse relationship between RA duration and aortic stiffness.

The results showed that cfPWV increases with age, although this result is not far-fetched, as Qiu *et al*. have previously reported that blood vessels stiffen because of changes in the extracellular matrix and vascular smooth muscle cells.[32] Also, regarding the relationship between vascular stiffness and gender, our study showed that AIx is higher in women than in men, which means that vascular stiffness is higher in women. Yao Lu observed that vascular stiffness is higher in men from adolescence to 58 years of age and in women thereafter; although they used brachial-ankle pulse wave velocity (baPWV) to measure arterial stiffness.[33] Many factors have been proposed as the cause of the steeper increase in arterial stiffness after menopause, including hormonal changes and the accumulation of traditional risk factors.[33,34]

Our study has demonstrated that there is a significant inverse relationship between PhA and CRP, confirming the hypothesis that PhA decreases as CRP increases. This is in line with the results of Tomleri *et al.* and Stobäus *et al*. who found an inverse relationship between PhA and CRP.[35,36] Inflammation is a normal response of the immune system to maintain body homeostasis under challenging conditions such as injury and infection.[37] Since tissue resistance to electric current is a very important factor in determining PhA, this cell damage and loss of cell integrity may justify the decrease in PhA in cases of increased CRP. On the other hand, Mattiello *et al*. observed in a meta-analysis that the PhA decreases in old subjects and elderly people.[38] It has been shown that increasing age causes mild chronic inflammation,[39] which may justify the inverse relationship between PhA and age. Therefore, as Garlini *et al*. stated in their study, it can be said that the use of PhA can help assess the risk of mortality as well as in monitoring general health.[12]

Finally, there was a significant inverse relationship between PhA and aortic stiffness measured by cfPWV. In justifying this relationship, it can be stated that inflammation increases the vessels' stiffness and decreases the PhA.

Our study has some limitations:

1. The primary limitation of our study is the absence of a control group (normal population) with which to compare RA patients.
2. The calculation of the DAS28 criteria for RA does not take into account the involvement of the joints of the lower limbs, especially the ankles (in our study, eight patients had ankle involvement and one had first metatarsophalangeal joint involvement), which may make the relationship between actual RA activity and the DAS28 criteria weaker.
3. Even though severe dehydration and malnutrition can affect the PhA, it was not possible to investigate them in our study.
4. We could not perform quantitative analysis for anti-CCP levels. As it was not available in our hospital. In the Imam Khomeini Hospital Complex, anti-CCP levels above 300 are reported by the laboratory in one way, which makes quantitative analysis of this variable difficult.

Conclusions

Aortic stiffness and serological positivity decreased with increasing duration of RA, given the new treatment options and their reducing effect on vascular stiffness and serology. These findings suggest that PhA and cfPWV can be valuable in assessing the clinical course of RA and may help prevent cardiovascular events caused by RA by early identification of patients at risk. Longitudinal studies with a control group and a larger sample size may help to clarify the unknowns in this area, especially regarding the relationship between aortic stiffness and RA disease activity. Additionally, more detailed information on potential risk factors and age- and inflammation-related trajectories of vascular stiffness will contribute to future clinical use of PWV and BIA measurements as targets for preventive and therapeutic interventions.[33]

Ethics approval and consent to participate

The study received approval from the University Ethical Committee (Ethical code: IR.TUMS.IKHC.REC.1401.175). Patients and their caregivers were fully informed about the study and how it would be conducted, and they provided informed consent to participate. They had the right to withdraw from the study at any time without any impact on their treatment. Confidentiality of their information was assured, and all principles outlined in the Declaration of Helsinki were adhered to throughout the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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