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Rheumatoid arthritis is associated with exacerbated body composition deterioration in Kazakh females

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ABSTRACT

Objective: The aim of this study was to assess the magnitude of changes in nutritional body composition components as a consequence of rheumatoid arthritis (RA) and the extent to which these components are associated with RA clinical characteristics, serologic markers, and osteoporosis-related phenotypes (OP-RPs). Early pathologic signs, if detected, could assist in future preventative techniques.
Methods: The study sample was comprised of 260 women with RA and 168 first-degree female relatives without RA who returned for body composition measurements using bioelectrical impedance analysis, from a previously established epidemiologic study conducted in Kazakhstan.
Results: In multivariate logistic regression, body composition components, the fat mass index (odds ratio [OR], 0.848; 95% confidence interval [CI], 0.786–0.913; $P < 0.001$) and the phase angle (PA; OR, 0.654; 95% CI, 0.467–0.826; $P = 0.001$), were independently and significantly negatively associated with RA after disease development. In multilinear regression analysis, PA was consistently associated with OP-RP, specifically concerning the spongial bone mineral density (BMDSPN) and cortical index, where ageing, reduced PA and increased disease duration explained 31.5% of BMDSPN and 37.3% of cortical index variation.
Conclusion: Data on RA in women in Kazakhstan consistently show that fat mass index and PA act as independent major covariates associated with RA affection status. These findings suggest exacerbated body composition deterioration when compared with healthy controls, potentially indicating the early appearance of sarcopenia and likely cachexic-like properties. The data also suggest that PA could serve as a potential predictor of RA prognosis, and the concomitant development of osteoporosis.

Introduction

Rheumatoid arthritis (RA) is a debilitating autoimmune disease that often leads to systemic-wide chronic inflammation and skeletal complications and is more often observed in women than in men [1]. Although RA itself is associated with joint inflammation and erosion, its comorbidities such as cardiovascular, musculoskeletal, respiratory, and gastrointestinal diseases and cancer, are mainly responsible for reduced life expectancy [1–4]. Moreover, patients with RA were observed to have a 54% higher mortality rate than the general population [4]. Cross-sectional and longitudinal studies reported that 20% to 30% of patients with RA become work disabled 2 to 3 y after the onset of the disease [5], demonstrating that early diagnosis and treatment of RA is essential.

Osteoporosis (OP), one of the most common comorbidities of RA, is twice as likely to occur in middle-aged women affected with RA [6]. A recent meta-analysis estimated that RA patients have 1.52 and 1.61 times the risk for developing overall fractures and fragility fractures, respectively [7]. In examining alterations in body composition, studies showed that loss of muscle mass and

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lean body mass are associated with the development of OP-like complications in patients with RA [8,9].

RA is also associated with cachexia, a metabolic irregularity related to rheumatoid cachexia, which is characterized by loss of body cell mass (BCM), resulting from chronic inflammation [10]. This loss is observed in the fat-free mass (FFM) component of skeletal and muscular structures, which, in turn, results in an increase in fat mass (FM) while body mass index is maintained [11], and was seen in two-thirds of patients suffering from RA [10].

BCM is considered responsible for regulating energy expenditure, protein requirements, and metabolic reactivity to physiologic stress [12]. Most cachexic patients are sarcopenic, which is defined as a decline in skeletal muscle mass and function [13]. Although sarcopenia is associated with old age, it is accelerated and typically severe in patients with RA [11,14]. One of the important characteristics of body composition changes, measured by bioelectrical impedance analysis (BIA), is the phase angle (PA). PA is derived from resistance (Rz) and capacitance reactance (Xc) of tissues, cell membranes, and non-ionic tissues [15]. Its measurement often is used as a prognostic marker of the severity of a variety of health conditions [16] and even as an indicator for mortality in many clinical situations [17].

It has been shown that RA comorbidities are associated with changes in body composition [18,19], which in turn contribute to the elevated morbidity and mortality rates in patients with RA, although the results are still sparse and contradictory. Thorough details of body alterations resulting from RA remain unclear, although these findings might be essential in detecting early pathologic signs that may occur, and further provide clinical implications in targeting and slowing the progression of RA and RA-associated OP. Aside from body composition variables, RA-associated serologic and clinical characteristics may elicit RA comorbidities. The constant state of inflammation with RA characterized by disease duration is a known risk factor for influencing RA comorbidities [20]. Disease activity, elevated rates of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and RF seropositivity are suggested as additional risk factors of altered body composition in patients with RA [21,22].

The main aim of this study was to determine whether the body composition phenotypes in patients with RA are associated with the established RA covariates by examining the relationship between body composition phenotypes and RA affection status, RA-associated serologic risk factors, and OP-related phenotypes (OP-RPs). The sample used in this study was from the native population of Kazakhstan.

Materials and methods

Participants

By design, this was a case–control, cross-sectional epidemiologic study, which was collected by our team in the Republic of Kazakhstan [23]. Because women are affected substantially more often than men, especially at a younger age [24], the present study was mostly focused on women. Of the 617 ethnic Kazakh women assessed in a previous study [23], 59.6% (368) were affected with RA, and 40.4% first-degree female relatives were unaffected with RA on the day of examination, whereas 428 women returned for a novel assessment of body composition variables, which are essentially nutritional indicators, during 2016 and 2017. Eligibility was defined in accordance with the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria [25], including a clinical assessment conducted by an expert rheumatologist, presence of at least one joint with definite swelling, which could not be explained by other illnesses and diagnosis verified by serologic tests. Individuals who returned were comprised of 60.7% (n = 260) women affected with RA and 39.3% (n = 168) unaffected first-degree female relatives. Using the preliminary data of spongial bone mineral density (BMDSPN), we estimated that the above sample sizes would be sufficient to confirm the sample specific means difference with 95% confidence interval (CI) and statistical power of at least 80%. The RA patients who participated in the body composition examination were similar in age (46.2 $\pm$ 0.7 versus 46.7 $\pm$ 1 y, $P = 0.723$), or in disease duration (65.7 $\pm$ 4.3 versus 58.8 $\pm$ 6.5 mo, $P = 0.378$) compared with those who did not return for the examination, respectively.

Anthropometric and body composition measurements

Anthropometric and body composition measurements were assessed by a trained physician through BIA, a widely accepted tool in assessing the nutritional composition of individuals, using the BIA101 device (Akern Bioresearch, Italy). BIA is a safe, reliable, simple, and inexpensive method to assess body composition including such basic parameters as body fat and body FFM [26]. Although the precision of assessing nutritional status between single- and multifrequency BIA devices has been debated, many studies report that despite the respective benefits and disadvantages of each device, single-frequency BIA (SF-BIA) is not inferior to multifrequency BIA [27–32]. In fact, its accuracy is comparable with the dual-energy x-ray absorptiometry (DXA) method, but does not expose individuals to any radiation [21,33]. The appropriate use of SF-BIA contains the intricate use of equations, which is explained in detail, and potentially overcomes the concern of SF-BIA in assessing intracellular water accurately [34].

In this study, BIA was used to measure the following parameters: resistance (Rz in Ω)—the effect of energy dissipation—and reactance (Xc in Ω)—the effect of energy storage. PA was calculated using Rz and Xc. FM, FFM, and muscle mass (MM) were all measured through the device and divided by height^2 to produce the corresponding indices: FMI, FFMI, and MMI, respectively. Additionally, total and extracellular body water (TBW and ECW) parameters, the sodium potassium pump (NAK), body cell mass (BCM in kg) and basal metabolic rate (BMR in kcal/d) were measured using BIA. Height (in cm) and weight (in kg) were additionally measured and used to derive BMI, as well as waist and hip circumferences (in mm) to derive waist-to-hip ratio index. In the present analyses, we focused on the BIA variables that significantly differed between the RA affected and unaffected individuals in the preliminary analyses, including BMI, FMI, MMI, PA, NAK, BMR, and BCM. Throughout the analyses, we noted that TBW is highly collinear with these variables and was therefore not considered in future analyses.

Osteoporosis-related phenotypes

Three OP-RPs were considered in this study. Cortical indices, which were derived from computed tomography (CT) scan measurements of cortical and medullar compartments of the ulna and radius bones. These measurements were used to calculate the ulna and radius cortical indices, respectively, and were further averaged to define the cortical index of ulna and radius bones (CIUR). Using CT methodology, the bone mineral density (mg/cm^2) of the medullar compartment of ulna (BMDSPN), another OP-RP, was measured. Sonographic ultrasound measurements of the distal forearm bone tissue were carried out to define ultrasound-based T scores. Further details on methods and descriptive statistics of these phenotypes were recently reported elsewhere [23].

Patient consent and ethics

All diagnostic measures were in compliance with the Helsinki Declaration. Written, informed consent was obtained following approval by the Kazakh National Medical University Ethics Committee.

Statistical analyses

Statistical analyses were conducted using standard statistical packages such as SPSS version 24 (IBM, Armonk, NY, USA) and Statistica 64 Version 13.3 (Dell Software, USA). The analyses were conducted in a pairwise manner, when applicable, and included two major stages. First, series of analysis of covariances were carried out to compare each of the body composition components between the RA affected and non-affected individuals, with age as a covariate; or linear regression analyses to test the associations with quantitative phenotypes (serologic tests and OP-RP). The latter analyses were carried out twice, in the entire sample of women, and in only RA-affected individuals. Once the major contributing body composition variables were established, a stepwise univariate multiple logistic regression analysis was performed to estimate between body composition variables and RA affection status. The purpose of conducting a stepwise univariate multiple logistic regression was to prevent collinearity and redundancy due to the intercorrelated nature of the BIA covariates.

The second stage of the analysis aimed to assess the association between body composition variables and RA characteristics, specifically serologic factors and OP-RP. Clinical characteristics (disease duration, morning stiffness, number of inflamed joints, number of painful joints, Disease Activity Score [DAS]28) and serologic factors (ESR, CRP, rheumatoid factor [RF], and anti-citrullinated protein antibodies [ACPAs]) significantly associated with RA were reported elsewhere [23]. These variables were first subjected to univariate analyses to test their associations with the body composition phenotypes. Once significant associations were found, multivariate linear regression analyses were performed in both the total sample and separately in the RA sample to detect significant and independent associations between serologic factors (or OP-RP) and each of the selected body composition variables.

Table 1
Comparative analysis of body composition in RA affected and unaffected women in study sample

Body composition variables	Affected women Mean (n = 260)	SE	Unaffected women Mean (n = 168)	SE	F-value
Age	51.29	0.66	39.05	0.89	87.36*,a
Rz	587.92	5.18	590.11	6.95	3.80†,b
Xc	48.39	0.56	51.14	0.64	0.74b
PA	4.76	0.05	5.05	0.06	12.55*,a
FMI	8.37	0.22	8.18	0.28	16.80*,b
FFMI	16.74	0.12	16.90	0.15	3.94†,b
MMI	9.79	0.1	10.23	0.13	9.85‡ b
TBW	33.1	0.28	33.36	0.35	6.47‡,b
ECW	17.36	0.15	16.92	0.17	0.27b
NAK	1.17	0.01	1.12	0.01	16.25*,b
BCM	20.53	0.27	21.90	0.34	10.05‡,a
BMR	1345.31	7.73	1384.82	9.89	10.02‡,a
BMI	25.00	0.26	25.10	0.31	15.10*,b
Weight	66.34	0.7	67.24	0.85	16.30*,b
Height	161.89	0.34	163.34	0.38	0.94b

ANCOVA, analysis of covariance; ANOVA, analysis of variance; BCM, body cell mass; BMI, body mass index; BMR, basal metabolic rate; ECW, extracellular water; FFMI, fat-free mass index; FMI, fat mass index; MMI, muscle mass index; NAK, sodium potassium pump; PA, phase angle; RA, rheumatoid arthritis; Rz, resistance; TBW, total body water; Xc, inductive reactance.
Summary of series of ANOVA (designated as a) and ANCOVA (designated as b) with age as a covariate, comparing RA-affected and unaffected women. For both ANOVA and ANCOVA *P*-values are presented.
*$P \leq 0.001$.
†$P \leq 0.05$.
‡$P \leq 0.01$.

Results

Body composition variables

Of the 428 assessed women, 60.7% (n = 260) had RA and 39.3% (n = 168) were healthy first-degree relatives. Table 1 shows the results of the comparison of body composition variables between the two groups. Because the women with RA were significantly older than the healthy controls (51.3 ± 0.7 versus 39.1 ± 0.9 y, $P <$ 0.0001) and age is a factor in the progression of body composition deterioration, age was controlled for when it was a significant factor. As seen, the majority of the body composition variables significantly differed between the women with RA and healthy controls. Judging by the *P*-values, the most significant differences were observed for PA, NAK, FMI, BMI, MMI, TBW, BCM, and BMR (Table 1).

Body composition changes as a result of RA

Series of logistic regression analyses were conducted to determine the association between body composition covariates and the diseased state of RA. FMI, NAK, BMI, PA, BCM, BMR, and MMI were tested in a stepwise manner. The analysis was initiated with FMI and additional covariates were subsequently incorporated, judging their association by likelihood ratio tests. If the covariate association was not significant, it was removed, and the next covariate was tested in conjunction with the first significant variable. If the odds ratio (OR) significantly increased, the covariate was considered for subsequent analyses until the final multivariate logistic regression analysis was achieved. The final logistic regression equation included three significant covariates: age, FMI, and PA (Table 2 and Fig. 1). As body composition variables were strongly correlated with each other, we were not surprised that only a few variables showed a significant and independent association with RA affection status. RA development was expectedly associated with an increased age; therefore a positive regression coefficient was observed. The apparent odds of RA disease diagnostics due to aging was 1088-fold higher (95% CI, 1.067–1.10; $P <$ 0.001) with every SD change. Conversely, body composition variables are a consequence of the diseased state. The two body composition variables that were retained in the final regression equation displayed decreased OR were FMI (OR, 0.848; 95% CI, 0.786–0.913; $P <$ 0.001) and PA (OR, 0.654; 95% CI, 0.467–0.826; P = 0.001), suggesting deterioration of FM and PA (Table 2).

Body composition and RA characteristics

To determine potential associations between body composition variables and RA disease characteristics (disease duration, morning stiffness, number of inflamed joints, number of painful joints and

Table 2
Main results of multiple logistic regression analysis of body composition components association with RA affection status (affected versus healthy controls)

RA-affected sample predictors							
						95% CI	
Variables	B	S.E.	Wald test	*P*-value (DF = 1)	OR	Lower	Upper
Age	0.084	0.010	71.16	<0.001	1.088	1.067	1.109
FMI	−0.165	0.038	18.82	<0.001	0.848	0.786	0.913
PA	−0.477	0.146	10.72	0.001	0.621	0.467	0.826
Constant	0.366	0.817	0.20	0.654			

ANCOVA, analysis of covariance; ANOVA, analysis of variance; BCM, body cell mass; BMI, body mass index; BMR, basal metabolic rate; FMI, fat mass index; MMI, muscle mass index; NAK, sodium potassium pump; PA, phase angle; RA, rheumatoid arthritis.
In addition to age, the following covariates were tested (shown in order of their significance of association to RA-affected patients compared with healthy controls as determined by ANOVA/ANCOVA): FMI, NAK, BMI, PA, BCM, BMR and MMI. Only statistically significant terms are shown in the table.

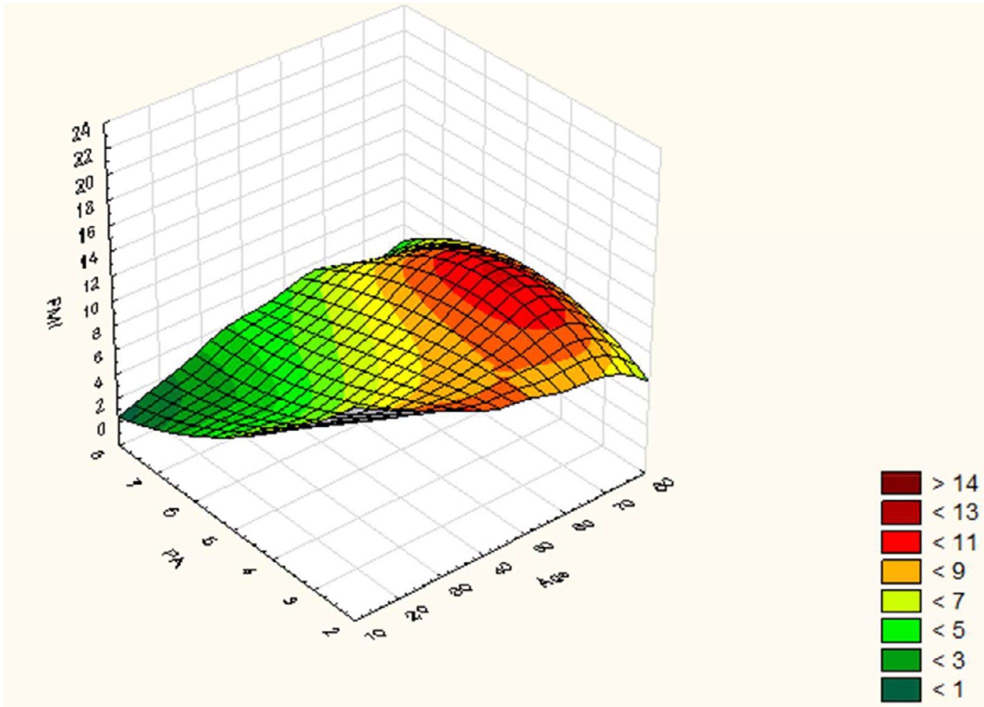

Fig. 1. Three-dimensional surface plot illustrating main body composition changes associated with RA affection status. The association of these variables shown in relation to age as one of the main predictors associated with RA affection. The presented data were adjusted and standardized in multiple regression analysis. The three-dimensional plot illustrates the major trends uncovered in the multiple logistic regression analysis, showing the significant, simultaneous association of FMI, PA, and age with RA affection. An increase in RA affection probability is shown by color change, from green (least likely affected with RA) to red (more likely affected with RA). Essentially, the graph shows that RA affection is most probably associated with increases in FMI and age, and a decrease in PA. FMI, fat mass index; PA, phase angle.

DAS28 scores) and relevant biochemical markers (ESR, CRP, RF, and ACPA), a correlation analysis was carried out (Tables 3 and 4). In the total sample, 10 of 28 correlations were nominally ($P < 0.05$) significant, which is substantially more than expected (1.4 by type 1 error). However, by the Bonferroni correction, only two correlations could be considered significant: between BMI and CRP and between NAK and RF. In the RA sample, only four correlations were nominally significant, which is just above the expected (3.15 by type 1 error), and no correlation survived the Bonferroni correction for multiple testing.

Table 3
Correlations between body composition variables and RA biochemical markers and disease characteristics in the total sample of women

	Total sample (N = 428)			
Variable	ESR	CRP	RF	ACPA
PA	−0.014	−0.108*	−0.109*	−0.083
NAK	0.093	0.023	0.148*	0.086
BCM	−0.014	−0.068	−0.099*	−0.107*
BMR	−0.012	−0.065	−0.097*	−0.106*
MMI	−0.016	−0.035	−0.074	−0.100*
FMI	−0.033	0.120*	−0.038	−0.038
BMI	−0.025	0.155*	0.002	−0.033

ACPA, anti-citrullinated protein antibody; BCM, body cell mass; BMI, body mass index; BMR, basal metabolic rate; CRP, C-reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; FMI, fat mass index; MMI, muscle mass index; NAK, sodium potassium pump; PA, phase angle; RA, rheumatoid arthritis; RF rheumatoid factor. Correlation matrices are presented by the total population and are used to assess body composition parameters (left column) and their associations with RA biochemical markers (ESR, CRP, RF, and ACPA).
*Correlation coefficient is significant at $P < 0.05$. Non-marked correlation coefficients were not statistically significant.

Body composition associations with OP-RP

Univariate linear regression analyses were conducted to determine significant body composition predictors of OP-RP. Additionally, several serologic factors and disease characteristics were included into analyses as covariates. The included covariates—age, affection status, and disease duration—were selected because they significantly correlated with OP-RP in a previous study [23], and in the univariate linear regression analyses (Supplementary Table 1). Subsequently, multilinear regression analyses were conducted for each of the OP-RPs, in the total sample and in the RA cohort only (Tables 5–8). In the total sample, for both variables CIUR and BMDSPN, the affection status was the most significant covariate, whereas in the RA sample this was the disease duration. Additionally, PA was significantly associated with CIUR in both analyses (Tables 5 and 6), and with BMDSPN in the RA sample, whereas NAK was a significant factor for BMDSPN in the total sample (Tables 7 and 8). When the ultrasound T-score phenotype was examined, we found that only affection status (in the total sample) or disease duration (in the RA cohort) and age were significant potential covariates. Body composition variables showed no significant correlation with the ultrasound T-score phenotype (Supplementary Table 2).

Discussion

The major aim of this study was driven by our intention to identify whether the alterations in BIA characteristics could be detectably associated with RA disease manifestation and progression. We aimed to evaluate the extent of body composition changes in relation to RA affection, while additionally considering the effect of RA concomitant

Table 4
Correlations between body composition variables and RA biochemical markers and disease characteristics in the sample of women affected with RA only

	RA-affected sample (n = 260)								
Variable	ESR	CRP	RF	ACPA	Disease duration	Morning stiffness	No. of painful joints	No. of inflamed joints	DAS28
PA	0.092	−0.100	−0.082	−0.056	0.026	0.016	0.057	0.018	−0.015
NAK	−0.001	0.027	0.150*	0.091	0.022	0.032	-0.034	0.010	−0.014
BCM	0.035	−0.073	−0.077	−0.097	−0.017	−0.019	−0.040	−0.053	−0.111
BMR	0.037	−0.068	−0.075	−0.094	−0.016	−0.020	−0.037	−0.054	−0.111
MMI	0.026	−0.050	−0.061	−0.094	−0.094	−0.095	−0.062	−0.057	−0.082
FMI	−0.061	0.094	−0.079	−0.079	−0.030	−0.129*	−0.099	−0.041	−0.010
BMI	−0.023	0.146*	−0.012	−0.039	−0.100	−0.146*	−0.133*	−0.063	−0.037

ACPA, anti-citrullinated protein antibody; BCM, body cell mass; BMI, body mass index; BMR, basal metabolic rate; CRP, C-reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; FMI, fat mass index; MMI, muscle mass index; NAK, sodium potassium pump; PA, phase angle; RA, rheumatoid arthritis; RF rheumatoid factor.
Correlation matrices are presented by the RA-affected population only and are used to assess body composition parameters (left column) and their associations with RA biochemical markers (ESR, CRP, RF, and ACPA) and RA disease characteristics (disease duration, morning stiffness, number of painful joints, number of inflamed joints, and DAS28; top row).
*Correlation coefficient is significant at $P < 0.05$. Non-marked correlation coefficients were not statistically significant.

characteristics, reflecting disease severity, and including serologic markers. We attempted to clarify whether and to what extent body composition features are associated with RA, and to subsequently identify a potential pathway-like linkage comprising RA disease characteristics, RA affection status, and changes in body composition.

Several body composition variables, specifically PA, NAK, BMR, BCM, MMI, FMI, and BMI were significantly associated with RA disease status. NAK and FMI were observed as significantly higher in women with RA than in healthy controls; whereas PA, BMR, BCM, MMI, and BMI were seen as significantly lower in those with RA compared with healthy controls. Many of these variables were not independent and significantly correlated with one another. Of them, however, NAK showed little correlation with other variables, but was in particular significantly higher in patients with RA than in healthy controls in the univariate analyses. Although NAK pump sites were lower in patients with RA [35], our findings are in agreement with the previous reports that suggested that corticosteroid use (consistent with our diseased cohort) likely causes an increased concentration gradient of NAK pump sites on human blood cells and skeletal muscle [36,37]. It also has been demonstrated that an increased concentration of NAK was associated with hypertrophy in cardiomyocytes, which may lead to dire pathologic consequences [38].

In the subsequent multivariate logistic regression analysis, the association between lower PA and higher FMI with RA suggests body composition deterioration following the disease state of RA. Due to the collinear nature of the body composition variables, we were not surprised that only these two variables showed an independent significant association with the RA disease status. Because PA was considered an indicator of malnutrition [16,39], the presence of PA and FMI are in accord with one another.

A lower PA is a phenomenon reoccurring in various diseases including RA [17], and is associated with increased oxidative stress and elevated inflammatory biochemical markers in older women [40] as well as mortality [17]. Studies have suggested that PA serves as a predictor for cellular and metabolic deterioration, BCM, and BMR [41–43]. BCM and BMR are both associated with adjustment of MM and FM after RA disease, whereas BCM previously has been suggested to serve as marker for rheumatoid cachexia [10,44,45]. The exacerbated changes observed in body composition in the present RA sample may predict the initial stages of rheumatoid cachexia. RA patients were seen to suffer from increased FM and reduced MM, which is potentially related to rheumatoid cachexic-like tendencies [11]. The interplay between these two body composition variables was suggested to result from higher inflammatory burden, potentially altering insulin function, which elicits a surplus of fat, which in turn impairs muscle function eventually leading to sarcopenia, cardiovascular disease, and other comorbidities [46].

Reports on BMI alterations in patients with RA are inconsistent. Although high BMI may predict the development of RA in women [47], low BMI in patients with RA is associated with low MM rather

Table 5
Main results of multiple regression analysis of CIUR in the total sample*

Dependent variable:	Total sample (N = 405) R = 0.312, R^2= 0.097, F(3,401) = 14.42, $P < .00001$, SE: 0.954			
CIUR- standardized before analysis†	B	SE	*t* (401)	*P*-value
Intercept	−0.3335	0.1575	−2.1175	0.0348
Z_Age	−0.2426	0.0522	−4.6480	<0.0001
Affection status	0.2379	0.1071	2.2205	0.0269
Z_PA	−0.1118	0.0482	−2.3185	0.0209

CIUR, Cortical indices of ulna and radius bones. PA, phase angle.
Results are presented by subsample and by phenotype. Only statistically significant terms are shown. The following covariates were included in the univariate regression analyses: disease duration, number of painful joints, number of inflamed joints, morning stiffness, DAS28, ESR, CRP, RF, ACPA, as was measured in a previous paper [23] age, menopause status age, affection status, PA, NAK, BCM, BMR, MMI, FMI, and BMI (Supplementary Table 1). Only significant terms assessed by univariate analysis were considered for multivariate regression analysis.
*All quantitative variables were standardized before statistical analysis (marked Z).
†During the initial stage of the analysis, the following variables were included: age, affection status, PA, BMR, and BCM. Only significant terms are shown in the Table.

Table 6
Main results of multiple regression analysis of CIUR in the RA-affected sample*

Dependent variable: CIUR- standardized before analysis*	RA-affected sample (n = 246) R = 0.373, R^2= 0.139, F(3,242) = 13.03, $P < 0.00001$, SE: 0.934			
	B	SE	*t*(242)	*P*-value
Intercept	−0.0004	0.0596	−0.0072	0.9943
Z_Age	−0.2788	0.0602	−4.6314	<0.0001
Z_Disease_Duration	−0.1693	0.0602	−2.8151	0.0053
Z_PA	−0.1541	0.0598	−2.5776	0.0105

CIUR, Cortical indices of ulna and radius bones; PA, phase angle; RA, rheumatoid arthritis.
Results are presented by subsample and by phenotype. Only statistically significant terms are shown. The following covariates were included in the univariate regression analyses: disease duration, number of painful joints, number of inflamed joints, morning stiffness, DAS28, ESR, CRP, RF, ACPA, as was measured in a previous paper [23] age, menopause status age, affection status, PA, NAK, BCM, BMR, MMI, FMI, and BMI (Supplementary Table 1). Only significant terms assessed by univariate analysis were considered for multivariate regression analysis.
*During the initial stage of the analysis, the following variables were included: age, disease duration, PA, BMR, and BCM. Only significant terms are shown in the Table.

than low FM, which was observed in the present study, and also consistent with another study [48]. Therefore, in comparing BMI and FMI, the latter is probably a more accurate indicator of body composition disturbances, which occurred as a consequence of the disease [49].

Although elevated FMI has been seen as a consistent consequential RA risk factor [22,50,51], PA has not yet been studied as extensively. To date, we are aware of only one study assessing PA alterations as a result of RA disease in a relatively small sample [39]. The observations in this study suggested that a lower PA may serve as an indicator of poor progression of RA, which seems to be apparent in the present study as well.

The second part of the present study considered the effect of RA clinical characteristics and biochemical markers on body composition components. Although RA status is closely correlated to potentially more severe body composition component changes [22,48,51], we were unable to find convincing evidence that would allow us to discern a causative link between RA clinical characteristics and/or biochemical markers and exacerbated body composition deterioration. The results were sporadic at best, suggesting that perhaps a different pathway exists in eliciting the development of body composition deterioration.

The present study also assessed the association between OP-RPs and body composition changes seen in RA. We previously showed that OP-RPs were significantly lower in patients with RA than in healthy controls [23]. In the RA sample, the decline of each OP-RP was clearly associated with disease duration. In the present study, low PA was consistently associated with CIUR and BMDSPN in patients with RA, regardless of other covariates. This observation is supported by a study conducted in the general Indian population proposing that bone mineral content (BMC) can be predicted using an equation derived from the parameter estimates obtained by BIA. The corresponding parameters included PA, suggesting that alteration in PA may be associated with alterations in BMC [52]. Recently, a study conducted in Japan recommended PA as a potential predictor of OP development [53]. These findings, taken together, suggest that PA may serve as a potentially powerful indicator in the prognosis of RA and OP development in patients with RA.

The present study included several limitations. Although we acknowledge that the mean ages between the affected and unaffected groups significantly differed, it is important to note that chronic diseases are prevalent in older age groups and therefore are more challenging to match, as is also asserted by the U.S. Department of Health and Human Services [54]. Considering this potential concern, age adjustment and use of age as a covariate was conducted statistically to limit these potential biases. Along with the use of these statistical techniques, the majority of analyses are devoted to the affected group only. Additionally, and most importantly, there is substantial overlap in the age ranges of the affected and unaffected groups in the present study, with an excess of older individuals in the RA sample. Menopausal status was not thoroughly assessed owing to the limited response of patients on this variable; however, age often was used as a covariate and thus the effects of menopausal status were essentially controlled for. Men were not assessed in this study, which restricts the conclusions to women. Yet, this also could be considered an advantage as there are very substantial sex-dependent differences in the age of

Table 7
Main results of multiple regression analysis of BMDSPN in the total sample*

Dependent variable: BMDSPN- standardized before analysis*	Total sample (N = 404) R = 0.606 R^2= 0.368, F(3,400) = 77.57, $P < 0.0001$, SE: 0.777			
	B	SE	I(400)	*P*-value
Intercept	−1.2393	0.1294	−9.5774	<0.0001
Z_Age	−0.2369	0.0421	−5.6307	<0.0001
Affection status	0.8909	0.0886	10.0565	<0.0001
Z_NAK	−0.0781	0.0395	−1.9787	0.0485

BMDSPN, spongial ulna bone mineral density. NAK, sodium potassium pump.
Results are presented by subsample and by phenotype. Only statistically significant terms are shown. The following covariates were included in the univariate regression analyses: disease duration, number of painful joints, number of inflamed joints, morning stiffness, DAS28, ESR, CRP, RF, ACPA, as was measured in a previous paper [23] age, menopause status age, affection status, PA, NAK, BCM, BMR, MMI, FMI, and BMI (Supplementary Table 1). Only significant terms assessed by univariate analysis were considered for multivariate regression analysis.
*During the initial stage of the analysis, the following variables were included: Age, affection status, PA, NAK, MMI, FMI, BMI, BMR, and BCM. Only significant terms are shown in the Table.

Table 8
Main results of multiple regression analysis of BMDSPN in the total sample and in the RA-affected sample*

Dependent variable: BMDSPN- standardized before analysis‡	RA-affected sample (n = 244) R = 0.315, R^2 = 0.099, F(3,240) = 8.82, $P < 0.00001$, SE: 0.956			
	B	SE	*t*(240)	*P*-value
Intercept	−0.0005	0.0612	−0.0079	0.9937
Z_Age	−0.1877	0.0618	−3.0367	0.0027
Z_Disease_Duration	−0.1917	0.0618	−3.1038	0.0021
Z_PA	0.1320	0.0614	2.1492	0.0326

BMDSPN, spongial ulna bone mineral density; PA, phase angle; RA, rheumatoid arthritis.
Results are presented by subsample and by phenotype. Only statistically significant terms are shown. The following covariates were included in the univariate regression analyses: disease duration, number of painful joints, number of inflamed joints, morning stiffness, DAS28, ESR, CRP, RF, ACPA, as was measured in a previous paper [23] age, menopause status age, affection status, PA, NAK, BCM, BMR, MMI, FMI, and BMI (Supplementary Table 1). Only significant terms assessed by univariate analysis were considered for multivariate regression analysis.
*During the initial stage of the analysis, the following variables were included: Age, disease duration, PA, NAK, MMI, FMI, BMI, BMR, and BCM. Only significant terms are shown in the Table.

onset, prevalence, and rate of progression of OP, which are well established and may complicate the results of analysis. BIA is different from other technologies such as DXA and quantitative ultrasound bone densitometry and may yield different results in the literature. Additionally, different BIA models exist, which may contribute to the difficulties of the direct comparison of the results from different studies. Yet, the extent and the direction of the present significant findings were consistent with other reports despite these differences.

Conclusion

We demonstrated that Kazakhstan women with RA demonstrated greater body composition deterioration than healthy controls, suggesting exacerbated development of sarcopenia and possibly cachexia in comparison with age-matched healthy women. The present study confirmed that RA eventually leads to an increase in FM and a loss of MM, which are most likely elicited by the inflammatory processes occurring in RA. Elevated FMI and reduced PA seem to be the most consistent and independent consequence of RA and serve as indicators for the initial stages of body composition deterioration. Additionally, PA, which is associated with the majority of the body composition parameters, appears to be the most indicative in predicting rheumatoid cachexic-like tendencies, among other comorbidities. Moreover, PA may serve as a useful indicator of RA prognosis, and predictor of RA-related OP progression.

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Supplementary materials

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