HSJ Health Sciences Journal
HCI HOSPITAL DE CLÍNICAS DE ITAJUBÁ-MG ENSINO E PESQUISA

ORIGINAL ARTICLE

Quality of life and strength, but not cytokines, are associated with DAS-28 in active and inactive rheumatoid arthritis

Qualidade de vida e força, porém não as citocinas, estão associadas ao DAS-28 em pacientes com artrite reumatoide na fase ativa e inativa

Marina Silva Travizan[1], Cristiane Vitaliano Graminha[1], Cristhiane Molinero Andrade Ratkevicius[2], Thaís Soares Farnesi Assunção[2], Reginaldo Botelho Teodoro[3], Gabriella Stefenoni Krüger[3], Erik Augusto Jerônimo[1], Rodolfo Pessato Timóteo[4*]

[1]Departamento de Fisioterapia Aplicada, Universidade Federal do Triângulo Mineiro, Uberaba, MG, Brasil.
[2]Departamento de Microbiologia, Imunologia e Parasitologia, Universidade Federal do Triângulo Mineiro, Uberaba, MG, Brasil.
[3]Disciplina de Reumatologia, Universidade Federal do Triângulo Mineiro, Uberaba, MG, Brasil.
[4]Disciplina de Patologia, Universidade Federal do Triângulo Mineiro, Uberaba, MG, Brasil.

KEYWORDS
Rheumatoid Arthritis
Quality of Life
Pain
DAS-28
SF-36
Hand Strength

ABSTRACT

Objective: Evaluate and correlate data between relevant cytokines, disease progression, and handgrip and quality of life among RA patients at different stages of disease progression. **Method:** Thirty-three RA patients were recruited for analysis, using comparisons and correlations, between levels of circulating cytokines (IFN-γ, TNF-α, IL-4, IL-6, IL-10, IL-17, IL-1β, and TNF receptors I and II), activity of the disease (evaluated using the DAS-28), handgrip (Hydraulic dynamometer), and quality of life (SF-36). **Result:** RA patients in different disease stages showed increases of IL-6 and IL-10 compared control group. Positive correlation between IL-6 with TNF-α, and IL-4 with IL-10 was found. Handgrip strength and quality of life were not related to cytokine levels. However, remission patients had better strength and quality of life indices compared to the active patients. In addition, handgrip of the non-dominant side, physical functions, role limitations physical health, pain, energy/fatigue and social functions have a negative correlation with the DAS28-PCR. **Conclusion:** High levels of IL-6 and IL-10 were observed in the chronic RA patients, but the values did not show correlation with disease activity, handgrip strength and quality of life. Disease activity show correlation with handgrip strength and quality of life. Furthermore, remission patients had better strength and quality of life indices compared to the active patients.

PALAVRAS-CHAVE
Artrite Reumatóide
Qualidade de Vida
Dor
DAS-28
SF-36
Força da Mão

RESUMO

Objetivo: Avaliar e correlacionar dados entre citocinas relevantes, progressão da doença, preensão manual e qualidade de vida entre pacientes com AR em diferentes estágios de progressão da doença. **Método:** Trinta e três pacientes com AR foram recrutados para análise, por meio de comparações e correlações, entre níveis de citocinas circulantes (IFN-γ, TNF-α, IL-4, IL-6, IL-10, IL-17, IL-1β e receptores de TNF-I e -II), atividade da doença (avaliada pelo DAS-28), preensão manual (dinamômetro hidráulico) e qualidade de vida (SF-36). **Resultado:** Pacientes com doença ativa e inativa apresentaram aumento de IL-6 e IL-10 comparados ao grupo controle. Foi encontrada correlação positiva entre IL-6 com TNF-α e IL-4 com IL-10. A força de

*Corresponding author:
Universidade Federal do Triângulo Mineiro
Addr.: Av. Getúlio Guaritá, s/n, Bairro Abadia, Uberaba, MG, Brasil. CEP: 38015-050.
Phone: +55 (34) 3318-5203
E-mail: rodolfo_pessa@hotmail.com

This study was conducted at the Universidade Federal do Triângulo Mineiro.
Conflicts of interest: No conflicts of interest declared concerning the publication of this article.
Funding information: This study was funded by the Fundação de Amparo à Pesquisa de Minas Gerais (FAPEMIG).
Submitted 31 Oct 2023, revised 21 Mar 2024, accepted 31 Mar 2024, published 16 May 2024

How to cite this article: Travizan MS et al. Quality of life and strength, but not cytokines, are associated with DAS-28 in active and inactive rheumatoid arthritis. HSJ. 2024;14(1):e1493. https://doi.org/10.21876/hsjhci.v14.2024.e1493

ISSN 2966-0408/© 2024 HSJ. This is an open-access article distributed under a CC BY license. (https://creativecommons.org/licenses/by/4.0/)

preensão e a qualidade de vida não relacionaram aos níveis de citocinas. Entretanto, pacientes em remissão apresentaram melhores índices de força e qualidade de vida comparados aos pacientes com doença ativa. Além disso, preensão manual do lado não dominante, e quesitos dos SF-36, apresentam correlação negativa com o DAS28-PCR. **Conclusão:** Foram observados níveis elevados de IL-6 e IL-10 nos pacientes com AR crônica, mas os valores não mostraram correlação com DAS-28, força de preensão manual e SF-36. A atividade da doença apresenta correlação com força de preensão manual e qualidade de vida. Além disso, os pacientes em remissão apresentaram melhores índices de força e qualidade de vida em comparação aos pacientes ativos.

BACKGROUND

Protein levels have shown association with disease progression in Rheumatoid arthritis (RA), including autoantibodies, rheumatoid factor, immunoglobulin M, and cytokines[1]. Predetermined sets of these biomarkers are called multi-biomarkers disease activity test (MBDA) related to disease evolution and seem to offer a promising way to obtain early diagnosis, predict the prognosis in RA, and evaluate the effectiveness of drug treatments[2-4]. In patients with early and late RA, IL-6 and TNF are evident in the pathogenesis of RA. The inhibition of then through monoclonal antibodies can control the disease in most cases[5].

Regardless of the promising effects of new drugs, the entire perspective of insertion of IL-6, TNF alone in clinical practice failed precisely because of the lack of correlation between disease activity and circulating levels of these cytokines[6]. This lack of correlation with disease activity is associated with multisystem factors such as: age, circadian rhythm, diet, exercise and stress. Given the complexity of RA, it is unlikely that a single cytokine may provide sufficient discrimination. Biomarker signatures may represent more realistic approach for the future of personalised medicine in RA[7].

On the other hand, IL- 6 and TNF-α blood levels are associated with lower skeletal muscle mass index. Gradual loss of skeletal muscle mass and chronic inflammation, are linked to altered body composition and impaired physical functionality, which are important contributing factors to the disabling process in AR[8]. Furthermore, levels of these same cytokines in AR patients were inversely proportional to the handgrip[9] and these cytokines were strongly associated with the presence and duration of the AR inflammatory state[10].

Therefore, muscle strength (handgrip) would be an evaluative item that can associate cytokines and disease activity? And, what would be the importance of measuring to handgrip in the disease progression of RA? Try to heal these questions, we evaluate and correlate data between cytokines, disease progression, and physical and psychological factors (handgrip and quality of life) among RA patients at different stages of disease progression.

METHODS

The study recruited thirty-three patients with diagnosis of RA as described by the American College of Rheumatology (ACR). This patient group (PG) was under treatment and follow-up at the Rheumatic and Collagen Diseases Outpatient Clinic, in the Maria da Glória Outpatient Center at UFTM (Minas Gerais State, Brazil). The inclusion criteria were: age over 18 years; RA with a duration of disease/symptoms of ≥ 6 months; Rheumatoid factor (RF) positive; Following up in the clinic with combined DMARDs including Methotrexate and/or glucocorticoids at stable doses for > 4 weeks. Exclusion criteria for this cohort included: The presence of a clinically significant comorbid condition, others diseases and acute or chronic infection that can interfere with cytokine expressions. Were considered RA patients in disease remission DAS 28 < 2.6.

According to DAS-28 data PG were divided into two groups: with disease in remission (RP) and active disease (AP).

The control group (CG) was composed of healthy individuals age over 18 years who were previously questioned about the existence of disease and drug use. For inclusion in the control group, the participant should not have had any disease with inflammatory, infectious, and/or neoplastic characteristics, and should not have used any anti-inflammatory medication in the last 30 days.

This study was approved by the Research Ethics Committee of the Federal University of Triângulo Mineiro (UFTM, protocol n° 056661/2019).

Clinical information

The RA patients provided personal data (age and gender) and information concerning the drugs used and the duration of treatment. Collection of venous blood from the controls for determination of cytokine levels was performed on the same day as assessments using the DAS-28.

Measurements of cytokines and receptors

The levels of TNF-α, IL-4, IL-6, IL-10 and soluble TNF receptors (sTNF-RI and sTNF-RII) were determined with specific kits (R & D Systems®, San Diego, CA, USA), based on "sandwich" type immunoenzymatic ELISA assays, according to the instructions of the manufacturer.

Analysis of disease progression using the DAS-28

Disease activity index values were determined using the Disease Activity Score 28 (DAS-28). The calculations of the values for these questionnaires were previously performed by the physician responsible for and follow-up. The DAS-28 counts the number of painful and swollen joints in 28 joints (shoulders, elbows, wrists, metacarpophalanges, proximal interphalanges, knees), global health assessment (scale 0-100) by the patient, assessment of the activity of disease by the patient and physician (0-10) and markers of inflammatory activity made within a period of up to two weeks before the consultation (ESR - erythrocyte

sedimentation rate and CRP - C-reactive protein). If the patient's clinical condition had changed after taking the inflammatory markers, these were not taken into account and a new assessment was scheduled. Patients with categorical CRP results (reactive or non-reactive; < or >) were not considered for the calculation of indices that take CRP into account. Laboratory tests were performed at the Central Laboratory of the HUWC and the methods used were: VHS (Automated Sedi-System) and PCR (Roche-Cobas immunoturbidimetry). DAS28 was calculated using a computer program for specific DAS calculation, using both ESR and CRP (mg/dL), the patient's global health assessment, and the number of painful and swollen joints (28 joints)[11].

Hand grip strength assessment

According to guidelines of the American Society of Hand Therapists- (SATM)[12], the subject was seated, positioned with the shoulder adducted, the elbow flexed at 90º, the forearm in a neutral position, allowing the wrist position to vary from 0 to 30º of extension. When the subject was ready, he was encouraged by a standard verbal command (recorded in audio) to press the dynamometer with maximum isometric effort, which was maintained for about 5 seconds. No other body movement was allowed. The test was carried out by alternating hands with no need to rest, this procedure was done three times, and the average of the three measurements was used as the final result.

The hydraulic dynamometer used will be the Saehan®, which structurally and functionally resembles the Jamar Analogue Hand® hydraulic dynamometer[13]. According to Reis and Arantes[7], the Saehan® hydraulic dynamometer is valid, reliable, and comparable with the Jamar Analogue Hand® hydraulic dynamometer.

Quality of life assessment

Was used the Item short-form health survey SF-36, translated, and validated for Portuguese[14] for quality of live assessment.

After weighing the data, the Raw Scale calculations was performed the transformation of the values obtained in the questions into grades ranging from 0 (zero) to 100 (one hundred), where 0 was equivalent to the worst result and 100 the best for each domain, equivalent to 8 domains. For transformation, these notes was entered into a standard calculation.

The domains evaluated were: functional capacity, limitation due to physical aspects, pain, general health status, vitality, social aspects, emotional aspects and mental health.

Statistical analysis

All the measurement data were analyzed considering their distribution and variance. *Kolmogorov-Smirnov* test was used for normality. F test was used variance analysis. For comparing three groups, the non-parametric *Kruskal-Wallis* test was applied when the data distribution was non-Gaussian, while the parametric ordinary one-way ANOVA was applied when the data followed a Gaussian distribution.

Correlation analyses were performed using the *Pearson* test in cases of Gaussian distribution, while the Spearman test was used for non-Gaussian distributions. The differences were considered significant when $p<0.05$ (5%).

The statistical analyses and construction of graphs were performed using Graphpad Prism® v. 9.0 software (GraphPad, La Jolla, CA, USA).

RESULTS

The control group (CG) consisted of 10 men and 13 women, while the patient group (PG) consisted of 8 men and 25 women. CG and PG presented similar ages (Mann Whitney test, p=0.968). The treatment time of the PG varied between 9 months and over 20 years. According to DAS28-CRP data it was found that 45.45% of the patients (N=15) were in remission phase, 12.2% low activity (N=4), 30.3% moderate (N=10) and 12.12% high activity (N=4). At the time of research 14 patients (42,42%) used prednisone, 18 (54,54%) used methotrexate and 4 patients (12,12%) used any biologic (2 patients used certolizumab, 1 patient used infliximab, and 1 patient used etanercept). In turn, the PG divided into patients with active disease (AP) and in remission (RP). These clinical data are shown in Table 1.

AP (N=18) and RP (N=15) showed no differences between them in terms of cytokine levels. Although, showed increases of IL-6 and IL-10 compared CG (*Kruskal-Wallis* test, $p<0.0001$). IL-4, TNF-α and soluble receptors did not present significant differences between patients and CG

Table 1 – Clinical data of the AR patients (AP and RP) and control group (CG).

	N	Mean	SD
Age (years)			
CG	23	47.94	6.73
AP	18	49.00	9.37
RP	15	48.13	12.28
Gender M/F		---	---
CG	M=10; W=13		
AP	M=6; W=12		
RP	M=1; W=13		
Disease activity (DAS28-PCR)			
Hight	4		
Moderate	10		
Low	4		
Remission	15		
Treatment time (years)	33	10.15	7.44
Prednisone	14 (42.42%)		
Metrotrexate	18 (54.54%)		
Any biologic	4 (12.12%)		

N=number of the patients; M=Mans; W=Women; SD= Standart derivation; AP= activity patients; RP= Remission patients; CG= Control group; M= male ; F = female.

(*Kruskal-Wallis* test, p>0.05) (Figure 1). Due to the different actions of IL-6 and IL-10, it was of interest to investigate possible correlations between their levels. Application of the *Spearman* test revealed no correlation between blood levels of the two cytokines in the patients (r = 0.244, p = 0.192). But there was a positive correlation between IL-6 with TNF-α (r=0.4046; p=0.0195) and IL-4 with IL-10 (r=0.479; p=0.0048) (Figure 2).

Handgrip strength and quality of life domains evaluated by the SF-36 were not related to cytokine levels in this study. However, the RP group had better strength and quality of life indices compared to the AP. The handgrip strength of the RP group was greater when compared to the AP group on the dominant and non-dominant sides (p=0.0458 and p=0.0228 respectively, Figure 3A and 3B). Median values average on the dominant side between RP and AP were 8.95 Kgf and 3.5 Kgf respectively, resulting in a difference of 39.1% between groups in the dynamometry test. Non domiant side presented 9.6 Kgf and 3.0 Kgf respectively between grous RP and AP, resulting in a difference of 31.25% in the dynamometry test (Figure 3).

Furthermore, it was verified that the strength of the non-dominant side had a negative correlation with the DAS28-PCR for both groups (r=-0.525; p=0.004, Spearman test, Figure 3C). Although only the non-dominant side correlated with DAS28, there was a correlation of handgrip strength between the dominant and non-dominant sides in the group of patients evaluated (r=0.685; p<0.0001, Spearman test, Figure 3D).

Among the domains evaluate by the SF-36, physical capacity, pain, vitality and social aspects showed significant differences when compared between RP and AP (Figure 4). Most patients in the RP group (85%) had values above 50 in the physical functions and pain items. 64% of the AP had values below 50 for physical functions and pain (Figure 4). Negative correlations were also verified between DAS28 and the items SF-36 physical functions, role limitations physical health, pain, energy/fatigue and social functions. Among these, physical functions and pain were the ones that most correlated with DAS28-PCR values. Correlation values (r values) are expressed in (Figure 5) (Spearman test, p<0.05).

DISCUSSION

For a better monitorization of the disease activity has proposed a test that includes several biomarkers under the name "multi-biomarkers disease activity test (MBDA)". Of these, IL-6, TNF and TNFR-I relationships of the patient global assessment of disease activity (DAS28, CDAI,

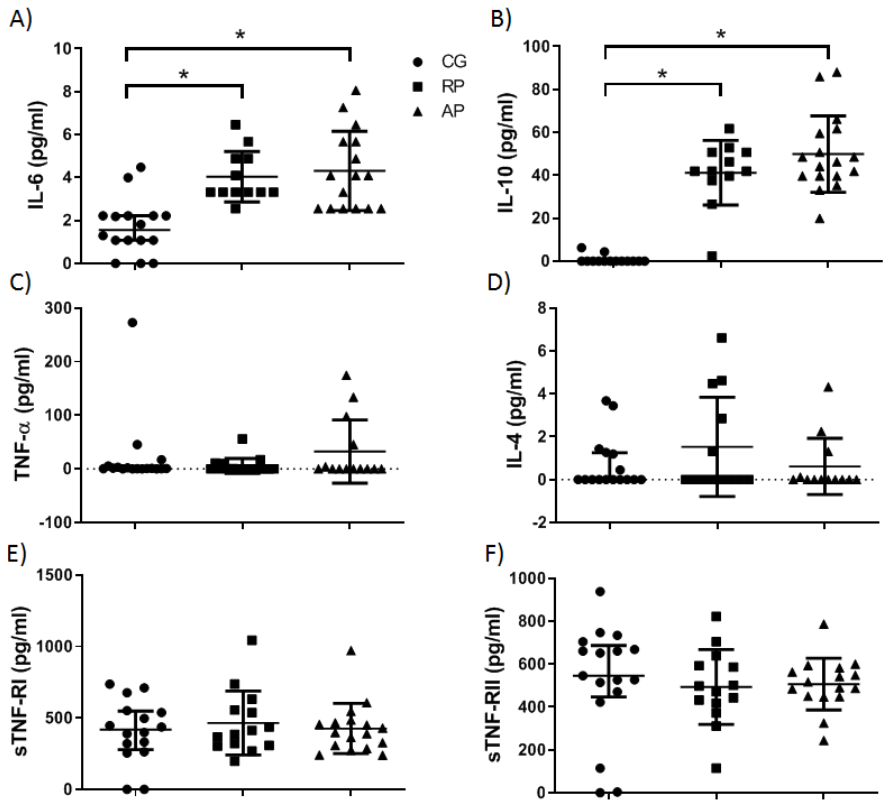

Figure 1 – Comparative graphs of circulating cytokineand receptors levels between control group (CG). remission patients (RP) and active patients (AP) with rheumatoid arthritis (AR). A-D graphs representes pictograms values per milliliter (pg/ml) of circulating cytokines. E and F graphs represent TNF receptors values in pictograms per milliliter (pg/ml). * Values considered statistically significant p<0.05. *Kruskal-Wallis* test with *Dunn's* post-test.

HSJ. 2024;14(1):e1493 | https://doi.org/10.21876/hsjhci.v14.2024.e1493

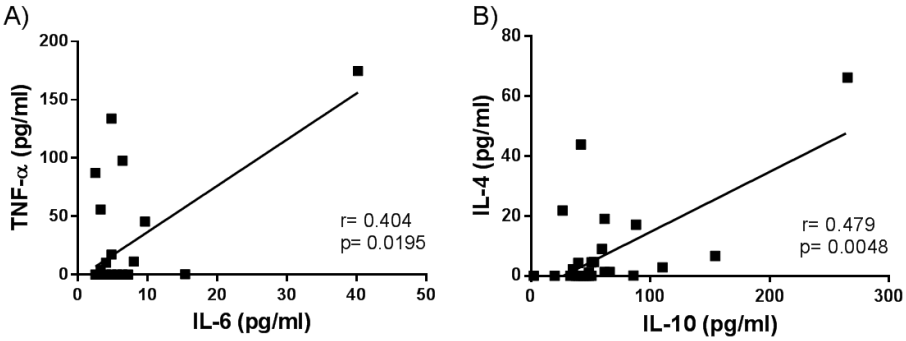

Figure 2 – Cytokines correlations. A) TNF-a and IL-6 correlations. B) IL-4 and IL-10 correlations. Values of the levels in picograms for mililiters (pg/ml). Spearman test. linear regression 95% confidence intervals. significative values p<0.05.

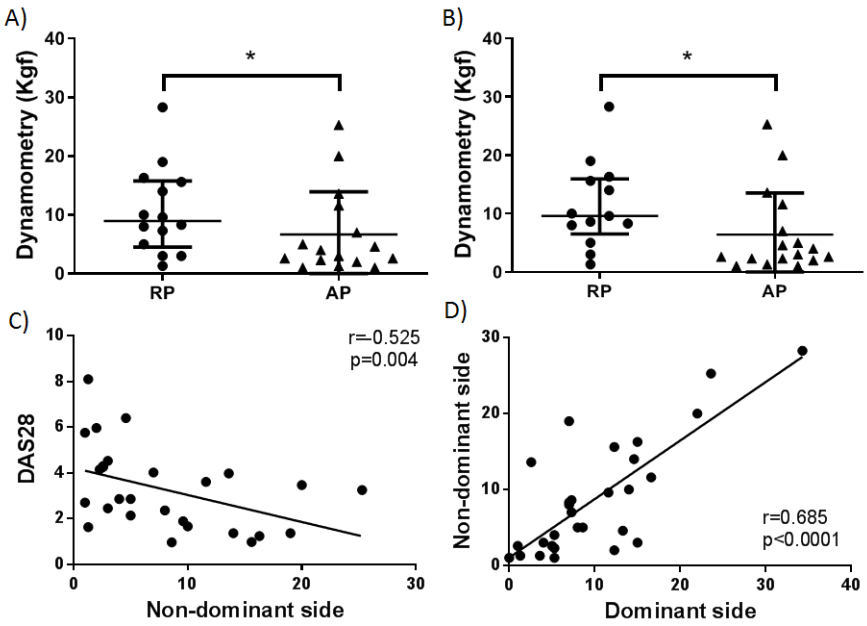

Figure 3 – Comparison of handgrip strength between groups of active (AP) and remission (RP) patients with rheumatoid arthritis. (A) Dominant site values. (B) Non dominant site values. * Values considered statistically significant p<0.05. Mann-Whitney test. Graphs C and D: DAS28 and non-dominant site. D) Dominant and non-dominant site correlations. Values of the levels in picograms for mililiters (pg/ml). Spearman test. linear regression 95% confidence intervals. significative values p<0.05.

SDAI).[6] The use antibodies monoclonal to block cytokines or receptors reinforces the central theory of the IL-6 and TNF importance in RA pathophysiology[15].

The levels of IL-10 and IL-4 increase during the treatment of the disease, being cytokines predominant in patients in the chronic phase[16]. This effect occurs probably due to the action of the main drugs used to control the disease, such as methotrexate and glucocorticoids. This has been known for over two decades[17]. Eighteen patients in our study were using methotrexate and/or prednisone for at least three months. This may explain the predominance and equivalence of IL-6 and IL-10 levels in both RP and AP groups.

In pathophysiological context, IL-6 and TNF levels are associated with disease progression and its destructive effects. IL-10 and IL-4 levels are associated with joint protective effects[18]. These protective effects have been confirmed in in vitro experiments which IL-4, IL-10, and IL-13 were all able to significantly inhibit the production of IL-1beta, TNF-alpha, IL-6, and IL-8 by freshly isolated RA synovial tissue cells[19]. High IL-6 production and low IL-10 production support a role dysregulated cytokine production in disease severity predicting disease severity in autoantibody-positive and autoantibody-negative patients, respectively[20]. Our study showed that patients considered to be in the chronic phase of the disease under different drug treatments had increased levels of circulating IL-6 and IL-10. This data demonstrates that regardless of the evolution of RA, assessed by DAS-28, IL-6 and IL-10 remain at increased levels in patients when compared to people without the disease.

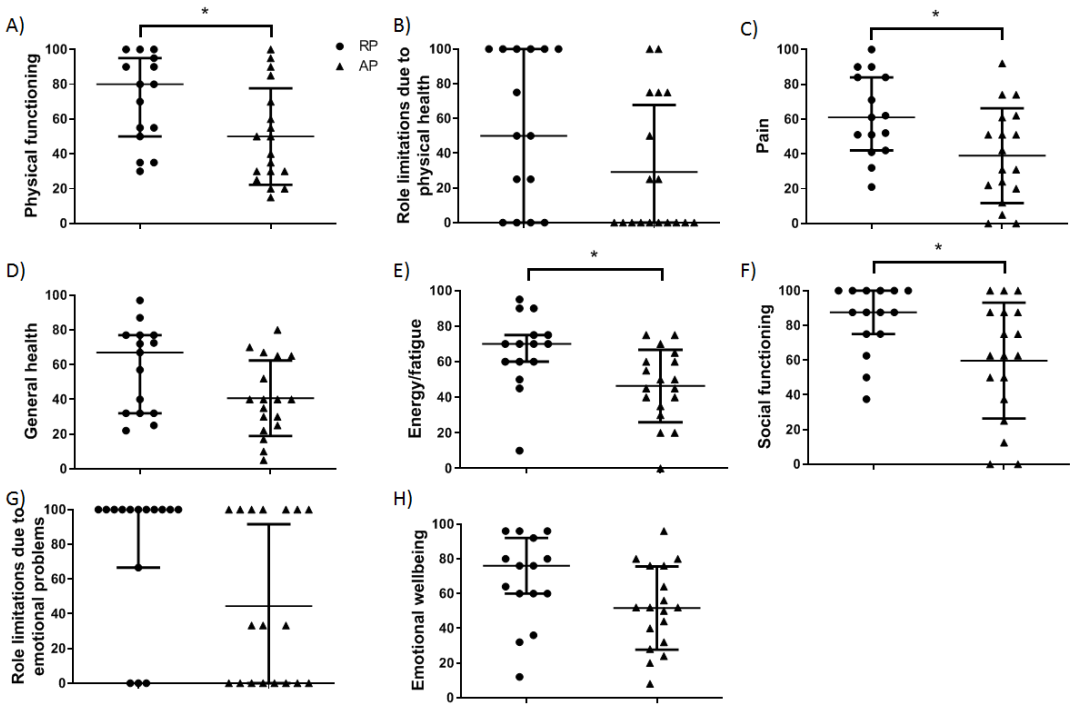

Figure 4 – Comparative graphs of SF-36 dominions between remission patients (RP) and active patients (AP) with rheumatoid arthritis (AR). A-H graphs represent respective dominions values SF-36. * Values considered statistically significant p<0.05. Mann-Whitney test.

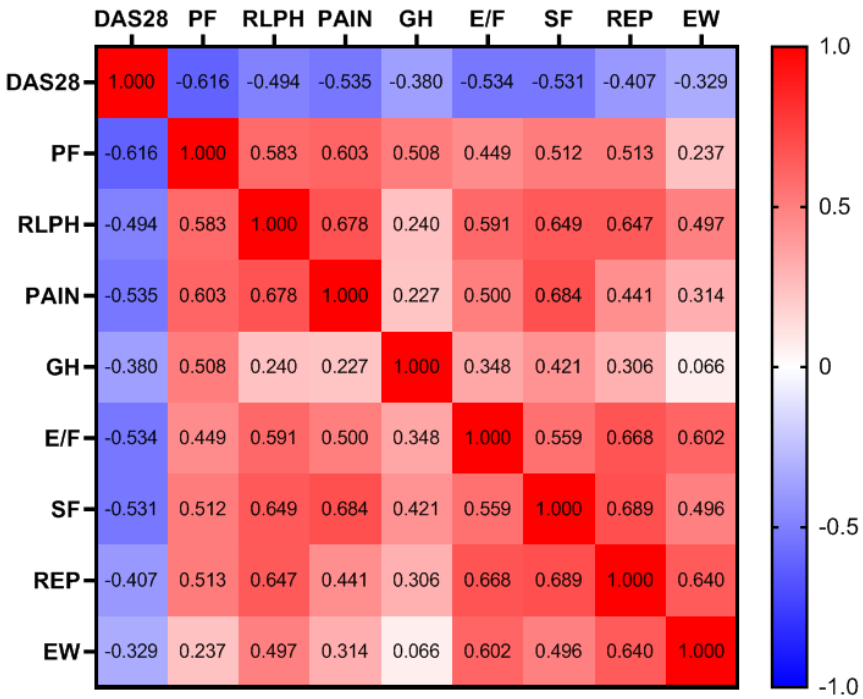

Figure 5 – Correlation matrix between DAS28 and SF-36 dominions. The color gradient indicates the strength of correlation (the blue gradient indicates positive correlation and the red gradient indicates negative correlation). The "r" values into the gaps. Values considered statistically significant p<0.05. Spearman test. Physical functions (PF). role limitations physical health (RLPH). pain (PAIN). general health (GH). energy/fatigue (E/F). social functions (SF). role limitations due to emotional problems (REP). emotional well-being (EW).

HSJ. 2024;14(1):e1493 | https://doi.org/10.21876/hsjhci.v14.2024.e1493

Lower skeletal muscle mass index had associations with IL-6 and TNF-α blood levels[8,21]. Furthermore, the levels of these same cytokines were inversely proportional to the handgrip[9]. These same relationships were also observed in patients with RA. Handgrip strength is strongly associated with the presence and duration of an inflammatory state as rheumatoid arthritis.[10] These facts corroborate the protective effect against the loss of muscle mass associated with the use of anti-rheumatic drugs that modify biological diseases (DMARDs)[22]. The levels of cytokines evaluated in this study did not correlate with handgrip strength or with SF-36 domains. However, we show that grip strength and some SF-36 domains differ between of active and inactive RA patients groups. Hand grip strength was greater in the RP group on the dominant and non-dominant sides. This fact was confirmed by the analysis of the correlation of handgrip values, which was inversely proportional to disease activity (DAS-28). This result corroborates other studies[23]. In addition, was possible to verify that the mean handgrip of the patients evaluated in our study showed a reduction between 64% and 80% when compared to the means of people without the disease. The strength of the patients who participated in our study was approximately 10 kgf less compared with no disease persons. This data was possible through the analysis of means of the normal population[24-27].

Handgrip strength can collaborate in the assessment of disease activity in an outpatient setting[23]. However, this relationship is part of a complex issue, taking into account inflammatory mechanisms currently being studied. In AR patients, a decreased ability to produce handgrip strength may be directly linked to pain and edema. This inability triggers impacts on quality of life[28,29]. Therefore, we used the SF-36 as a complement in the assessment of physical and psychological aspects in this study. Whereas joint damage and joint pain are evaluated by Disease Activity Score 28 (DAS-28)[11], it was not the aim of this study to re-evaluate the joints. As recommended in the handgrip strength test, we only take into account the patient's ability to perform or not perform the test. All patients in this study were able to perform the test without pain reports. Therefore, we consider that the value of the handgrip test performed indicates the consequences caused by momentary pain, deformities and loss of strength caused by the disease over time. Concerning this theme we conclude that the value of handgrip strength complements the assessment of RA, while the values of the quality of life items are indicative of loss of physical and psychological function.

Some studies have identified differences in quality of life between patients with RA and the general population[30]. And although all SF-36 domains have less in individuals with rheumatic diseases, RA patients present scores in the 'physical performance' domain[31]. Our study also looked at this characteristic, and in turn we found statistical differences in physical function, pain, and energy/fatigue. Another observation was that most RP (85%) had values above 50 in the physical functions and pain items. 64% of the AP had values below 50 for physical functions and pain. Despite this observation, we were unable to find SF-36 values that could categorize the state of disease progression or even distinguish patients in active or inactive disease. But given our data, the difference in physical capacity issues between patients with the disease considered active or inactive is evident. The fact is that despite the role limitations physical health item not having presented statistical difference (p=0.07) between AP and RP, it can be observed a frequency of values equal to zero (worst result) higher in the AP group. As can be seen in Figure 4B, 10 patients of the AP group presented value equal to zero. The RP group had 4 patients with a value equal to zero.

CONCLUSION

Based on the pointed questions, the lack of correlation between handgrip strength and circulating cytokine levels indicates that measuring the strength of patients with chronic RA cannot contribute as an association factor between IL- 6, IL-10, and disease progression. However, patients with inactive disease had greater strength and better quality of life scores compared to patients with active disease in chronic phase. This handgrip and SF-36 showed to be good complementary indices for monitoring the evolution of the disease, given the disease activity show correlation with handgrip strength and quality of life.

REFERENCES

1. Derksen VFAM, Ajeganova S, Trouw LA, van der Helm-van Mil AHM, Hafström I, Huizinga TWJ, et al. Rheumatoid arthritis phenotype at presentation differs depending on the number of autoantibodies present. Ann Rheum Dis 2017;76(4):716-20. http://doi.org/10.1136/annrheumdis-2016-209794. PMid:28283528.
2. Gavrilă BI, Ciofu C, Stoica V. Biomarkers in rheumatoid arthritis, what is new? J Med Life 2016;9(2):144-8.
3. Ma MHY, Defranoux N, Li W, Sasso EH, Ibrahim F, Scott DL, et al. A multi- biomarker disease activity score can predict sustained remission in rheumatoid arthritis. Arthritis Res Ther 2020;22(1):158. http://doi.org/10.1186/s13075-020-02240-w. PMid:32580789.
4. Hambardzumyan K, Saevarsdottir S, Forslind K, Petersson IF, Wallman JK, Ernestam S, et al. A multi-biomarker disease activity score and the choice of second-line therapy in early rheumatoid arthritis after methotrexate failure. Arthritis Rheumatol 2017;69(5):953-63. http://doi.org/10.1002/art.40019. PMid:27992691.
5. Noack M, Miossec P. Selected cytokine pathways in rheumatoid arthritis. Semin Immunopathol 2017;39(4):365-83. http://doi.org/10.1007/s00281-017-0619-z. PMid:28213794.
6. Milman N, Karsh J, Booth RA. Correlation of a multi-cytokine panel with clinical disease activity in patients with rheumatoid arthritis. Clin Biochem 2010;43(16-17):1309-14. http://doi.org/10.1016/j.clinbiochem.2010.07.012. PMid:20655893.
7. Reis MM, Paula MMA. Medida da força de preensão manual-validade e confiabilidade do dinamômetro saehan. Fisioter Pesqui. 2011;18(2):176-81. http://doi.org/10.1590/S1809-29502011000200013.
8. Ramírez-Vélez R, Sáez De Asteasu ML, Martínez-Velilla N, Zambom-Ferraresi F, García-Hermoso A, Recarey AE, et al. Circulating cytokines and lower body muscle performance in older adults at hospital admission. J Nutr Health Aging 2020;24(10):1131-9. http://doi.org/10.1007/s12603-020-1480-7. PMid:33244573.

9. Yen DH-T. Handgrip strength, tumor necrosis factor-α, interlukin-6, and visfatin levels in oldest elderly patients with cognitive impairment. Exp Gerontol 2020;142:111138. http://doi.org/10.1016/j.exger.2020.111138. PMid:33122129.
10. Beenakker KGM, Ling CH, Meskers CGM, de Craen AJM, Stijnen T, Westendorp RGJ, et al. Patterns of muscle strength loss with age in the general population and patients with a chronic inflammatory state. Ageing Res Rev 2010;9(4):431-6. http://doi.org/10.1016/j.arr.2010.05.005. PMid:20553969.
11. Medeiros MMC, Oliveira BMGB, Cerqueira JVM, Quixadá RTS, Oliveira ÍMAX. Correlação dos índices de atividade da artrite reumatoide (Disease Activity Score 28 medidos com VHS, PCR, Simplified Disease Activity Index e Clinical Disease Activity Index) e concordância dos estados de atividade da doença com vários pontos de corte numa população do nordeste brasileiro. Rev Bras Reumatol 2015;55(6):477-84. http://doi.org/10.1016/j.rbr.2014.12.005.
12. American Society Hand Therapy. The hand: examination and diagnosis. 3rd ed. New York: Churchill Livingstone; 1983.
13. Reis MM, Arantes PMM. Medida da força de preensão manual-validade e confiabilidade do dinamômetro saehan. Fisioter Pesqui 2011;18(2):176-81. http://doi.org/10.1590/S1809-29502011000200013.
14. Cicconeli RM, Ferraz MB, Santos W, Meinão I, Quaresma MR. Brazilian-Portuguese version of the SF-36. A reliable and valid quality of life outcome measure. Rev Bras Reumatol 1999;39:143-50.
15. Senolt L. Emerging therapies in rheumatoid arthritis: focus on monoclonal antibodies. F1000Res 2019;8:F1000 Faculty Rev-1549. http://doi.org/10.12688/f1000research.18688.1. PMid:31508202.
16. Gerli R, Bistoni IO, Russano A, Fiorucci IS, Borgato L, Cesarott MEF, et al. In vivo activated T cells in rheumatoid synovitis. Analysis of Th1- and Th2-type cytokine production at clonal level in different stages of disease. Clin Exp Immunol 2002;129(3):549-55. http://doi.org/10.1046/j.1365-2249.2002.01913.x. PMid:12197898.
17. Barnes PJ. Anti-inflammatory actions of glucocorticoids: molecular mechanisms. Clin Sci (Lond) 1998;94(6):557-72. http://doi.org/10.1042/cs0940557. PMid:9854452.
18. Relić B, Guicheux J, Mezin F, Lubberts E, Togninalli D, Garcia I, et al. IL-4 and IL-13, But Not IL-10, protect human synoviocytes from apoptosis. J Immunol 2001;166(4):2775-82. http://doi.org/10.4049/jimmunol.166.4.2775. PMid:11160344.
19. Morita Y, Yamamura M, Kawashima M, Aita T, Harada S, Okamoto H, et al. Differential in vitro effects of IL-4, IL-10, and IL-13 on proinflammatory cytokine production and fibroblast proliferation in rheumatoid synovium. Rheumatol Int 2001;20(2):49-54. http://doi.org/10.1007/s002960000074. PMid:11269532.
20. Marinou I, Healy J, Mewar D, Moore DJ, Dickson MC, Binks MH, et al. Association of interleukin-6 and interleukin-10 genotypes with radiographic damage in rheumatoid arthritis is dependent on autoantibody status. Arthritis Rheum 2007;56(8):2549-56. http://doi.org/10.1002/art.22814.
21. Byun MK, Cho EN, Chang J, Ahn CM, Kim HJ. Sarcopenia correlates with systemic inflammation in COPD. Int J Chron Obstruct Pulmon Dis 2017;12:669-75. http://doi.org/10.2147/COPD.S130790. PMid:28255238.
22. Torii M, Hashimoto M, Hanai A, Fujii T, Furu M, Ito H, et al. Prevalence and factors associated with sarcopenia in patients with rheumatoid arthritis. Mod Rheumatol 2019;29(4):589-95. http://doi.org/10.1080/14397595.2018.1510565.
23. Espinoza F, Le Blay P, Coulon D, Lieu S, Munro J, Jorgensen C, et al. Handgrip strength measured by a dynamometer connected to a smartphone: a new applied health technology solution for the self-assessment of rheumatoid arthritis disease activity. Rheumatology (Oxford) 2016;55(5):897-901. http://doi.org/10.1093/rheumatology/kew006. PMid:26867731.
24. Caporrino FA, Faloppa F, Santos JBG, Réssio C, Soares FHC, Nakachima LR, et al. Estudo populacional da força de preensão palmar com dinamômetro Jamar. Rev Bras Ortop 1998;33(2):150-4.
25. Mitsionis G, Pakos EE, Stafilas KS, Paschos N, Papakostas T, Beris AE. Normative data on hand grip strength in a Greek adult population. Int Orthop 2009;33(3):713-7. http://doi.org/10.1007/s00264-008-0551-x. PMid:18414855.
26. Adedoyin RA, Ogundapo FA, Mbada CE, Adekanla BA, Johnson OE, Onigbinde TA, et al. Reference values for handgrip strength among healthy adults in Nigeria. Hong Kong Physiother J 2009;27(1):21-9. http://doi.org/10.1016/S1013-7025(10)70005-1.
27. Wang Y-C, Bohannon RW, Li X, Sindhu B, Kapellusch J. Hand-grip strength: normative reference values and equations for individuals 18 to 85 years of age residing in the United States. J Orthop Sports Phys Ther 2018;48(9):685-93. http://doi.org/10.2519/jospt.2018.7851. PMid:29792107.
28. Azevedo AFB, de Petribú KCL, Lima MN, Silva AS, Rocha JA Fo, Mariano MHQA, et al. Quality of life of patients with rheumatoid arthritis under biological therapy. Rev Assoc Med Bras 2015;61(2):126-31. http://doi.org/10.1590/1806-9282.61.02.126. PMid:26107361.
29. Azevedo LF, Costa-Pereira A, Mendonça L, Dias CC, Castro-Lopes JM. Epidemiology of chronic pain: a population-based nationwide study on its prevalence, characteristics and associated disability in Portugal. J Pain 2012;13(8):773-83. http://doi.org/10.1016/j.jpain.2012.05.012. PMid:22858343.
30. Campos APR, Silva CM, de Castro SS, Graminha CV. Depressão e qualidade de vida em indivíduos com artrite reumatoide e indivíduos com saúde estável: um estudo comparativo. Fisioter Pesqui 2013;20(4):401-7. http://doi.org/10.1590/S1809-29502013000400016.
31. Salaffi F, Carotti M, Gasparini S, Intorcia M, Grassi W. The health-related quality of life in rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis: a comparison with a selected sample of healthy people. Health Qual Life Outcomes 2009;7(1):25. http://doi.org/10.1186/1477-7525-7-25. PMid:19296831.

Individual contribution of the authors:
Study conception and design: RBT, MST
Data collection: RPT, MST, EAJ, GSK
Data analysis and interpretation: Not applicable.
Manuscript writing: RBT, MST
Critical review of the text: RBT, MST
Final approval of the manuscript*: RPT, MST, EAJ, GSK, RBT, CVG, CMAR, TSFA
Statistical analysis: RBT
Overall responsibility for the study: RBT, MST
*All authors read and approved the final version of the manuscript submitted for publication by HSJ.