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Autoantibodies and Disability in Long-Standing Rheumatoid Arthritis

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Abstract
Objective: *This study analyzed RF and MCV relationship with HAQ score to predict disability in rheumatoid arthritis patient on DMARD therapy.*
Method: *This study was conducted among 92 female patients with rheumatoid arthritis selected from different rheumatology OPD clinic; RF, MCV, ESR, CBC, STDWL, SDAI, HAQ Di self-reports, VAS scale, deformity and disease comorbidity were recorded in this study.*
Results: *the results of this study showed, age 38.09±3.30 years, disease duration 6.45±1.17, rheumatoid factor 65.57±67.27, SDAI was 48.51± 25.02, STDL 26.15±13.30. HAQ-Di was 2.45±.1.17, anti-MCV 157.89±255.92, and VAS 5.92±2.65. There is a significant relation with MCV and positive correlation with extra-articular manifestation, Deformity and STDWLP<0.05. But, RF has a significant relation with STDWL, SDAI P<0.05. Otherwise, no significant relation was seen P>0.05. Functional disability HAQ, VAS, ACR CLASS) in the study group showed a significant relation with both RF and MCV; MCV more significantly than RF P<0.05 with a significant positive correlation between HAQ, VAS with MCV P<0.05 but, not with RF P>0.05.*
Conclusion: *HAQ score is the simplest possible tool used to assess RA disease activity and highest was recorded was after 5th years duration of the disease activity in this study, but it should be recorded regularly during follow-up of the patient with RA to predict early future disability.*
Keyword: *disability, RA, HAQ-di.*

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune joint disease that primarily targets the synovial membrane. With the progression of the disease and its perpetuation, the pathological process extends to involve mostly all articular components with a resultant joint failure and functional deterioration.[1] From the very beginning of RA discovery, many autoantibodies have been linked to its diagnosis, from the most famous rheumatoid factors (RF) to the most recent anti citrullinated cyclic protein antibodies (ACPA), as any criteria for diagnosis of RA always including at least one autoantibody. Autoantibodies mostly assessed for its validity in the RA diagnosis, sensitivity, and specificity, with differential results

between RF and ACPA that favors the ACPA over the RF as regards the specificity for RA but with low sensitivity.[1,2]

Among the ACPA family, the newest member is the anti-mutated citrullinated vimentin antibody (AntiMCV), which has a significant specificity for RA and found to be correlated with synovitis and radiographic progression in RA patients.[3]

Several in-depth studies investigate the role of autoantibodies in RA development, perpetuation, and progression.[1-4] The presence of high titer of autoantibodies at disease onset has been proved as a determinant of more aggressive disease with subsequent implications for the initial treatment strategy. The association between autoantibodies and RA severity at initial onset initiates in us a question about the effect of autoantibodies on functional ability in late RA patients.[1-4]

We designed the current study as a trial to evaluate the relation between RA autoantibodies in the form of RF and the newest member of ACPA family which is the AntiMCV; and the functional ability of long-standing RA patients.

Aim of the work

To investigate the relationship between rheumatoid factor, anti-mutated citrullinated vimentin and functional ability of long-standing rheumatoid arthritis patients.

Patients and Methods

Study design & setting: The current study was based on a cross-sectional hospital-based survey, conducted among female patients with rheumatoid arthritis presenting at outpatient rheumatology clinics of AL-AZHAR University Hospitals - Egypt through 2014 - 2016.

Inclusion Criteria

- Female patient's Rheumatoid arthritis diagnosed according to American College of Rheumatology Criteria 2010.
- On regular treatment by conventional DMARDs, low dose corticosteroids 5mg.
- Disease duration more than five years.

Exclusion Criteria

- Recent joint trauma or intra-articular procedures.
- Previous joint surgery.
- Patient's on biological therapy.

Data collection

- The data was collected through an interview questionnaire from all participants. A field survey was conducted after obtaining approval from hospital authority and Research Ethical Committee. The data was collected through Sept. 2014 -2016. The field work took 2 days/week in the rheumatology clinic and only 80 patients had met our research criteria.
- All patients were subjected to a full clinical history taking and examination.
- Functional classification according to The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis:
- Class I = able to perform usual activities of daily living (self-care, vocational, and avocational);
- Class II = able to perform usual self-care and vocational activities, but limited in avocational activities;
- Class III = able to perform usual self-care activities but limited in vocational and avocational activities.
- Class IV = limited in ability to perform usual self-care, vocational, and a vocational activities.
- Usual self-care activities include dressing, feeding, bathing, grooming, and toileting; vocational and avocational activities are both patient-desired and age-, and sex-specific, patients were questioned about their ability in the last month.[5]
- Health assessment questionnaire disability index :(HAQ-DI)
- The HAQ-DI is a validated generic measure of physical functioning

combining eight domains (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and other activities). Responses to each item ranged from 0 (no difficulty) to 3 (unable to do). The total score ranged from 0 to 3: 0–1 = mild difficulties to moderate disability; >1–2 = disability moderate to severe; and >2–3 = severe to very severe disability.[6]

- Intensity of pain (Pain VAS 0–10) was interpreted in three ranges: 0–3.5 = low level; 3.6–6.5 = average; and 6.6–10 =high level of pain sensation.[6]

Specimen Collection

7 mL of fresh venous blood were collected by venipuncture from all participants then delivered into the following tubes:

1- ESR tube (2 ml)

2- CBC tube (1ml)

3- Plain tube (4 mL) which was centrifuged after clotting then the separated serum was divided into 2 portions one used for the assay of liver functions, kidney functions, Random blood sugar and CRP while the other was kept frozen at – 20 c for assay of Anti-MCV and RF.

Another venous sample was collected after 12 hours fast for assay of lipid profile.

The following laboratory investigations were performed to all patients participating in this study:

1) Erythrocyte sedimentation rate
2) Semiquantitative measurement of C-Reactive protein by Latex agglutination methods using AVITEX Kit from Omega Diagnostics Group
3) Liver, kidney function tests, and Random blood sugar and lipid profile (all were done on autoanalyzer Modular P (Roche Diagnostics).
4) Complete Blood Count was done on automated haematology cell counter Sysmex Kx-21 N (Roche diagnostics).
5) Determination of Rheumatoid factor:

The RF was done using ACCUCARE RF-Turbilatex which is a turbidimetric test for the measurement of RF in human serum or plasma. Latex particles coated with human gammaglobulin are agglutinated when mixed with samples containing RF. The agglutination causes change, dependent upon The RF content of the sample that can be quantified by comparison from a calibrator of known RF concentration.

6) Assay of Anti-MCV antibody Was done by Anti-MCV ELISA Kit: Orgentec Diagnostika GmbH, Germany)

The microtiter plate provided in the Kit has been pre-coated with antigen, Standards or samples were added to the appropriate microtiter plate wells with a biotin-conjugated antigen next Avidin conjugated to horseradish peroxidase (HRP) was added to each microplate well and incubated then a TMP substrate solution was added to each well those wells that contain anti-MCV Ab, biotin-conjugated antigen and enzyme- conjugated Avidin will exhibit a change in colour. The enzyme –substrate reaction was terminated by the addition of sulphuric acid solution and the color change was measured spectrophotometrically at a wave length of 450 nm. The concentration of Anti MCV Ab in the samples was then determined by comparing the OD of the samples to the standard curve

Data Analysis: Data were entered, organized, tabulated and analyzed using the standard computer program SPSS version 21. Quantitative data were expressed as Mean ± SD, while qualitative data were expressed as frequency and percent. Student t-test was used to measure the difference between means of two quantitative groups, with the significant level set at 0.05, and highly significant at <0.01. The qualitative data X2 chi squared test the significant level set at <0.05

Results

Test of normalization of the study group variable showed a non-significant relation between HAQ and MCV, RF and SDAI. Kolmogorov Smirnov test was used to evaluate the normality of data. Values were expressed as mean ± SD for normally distributed variables and percentage of nonparametric data; baseline demographics and

clinical characteristics were compared between groups using X2-test (chi-square). Bivariate correlations were assessed using Pearson's and Spearman's correlation coefficients for normally and not-normally distributed data, respectively.

This study was conducted among female patients with rheumatoid arthritis selected from different rheumatology clinic in OPD; the following table showed descriptive analysis of the patients shows age 38.09±3.30 years, disease duration 6.45±1.17, rheumatoid factor 65.57±76.27, SDAI was 48.51± 25.02, STDL 26.15±13.30. HAQ-Di was 2.45±.0.58, anti-MCV 157.89±255.92, RF 65.57±76.27 and VAS 5.92±2.65. Blood sugar was 107±40.49 mg /dl with cholesterol was 213.68±31.96 Table (1).

Table 1: descriptive analysis of the patients

	Mean	SD	Range	Minimum	Maximum
AGE/years	38.09	3.30	13.00	32.00	45.00
DURATION/years	6.45	1.17	4.00	5.00	9.00
HAQ	2.45	.58	2.00	1.00	3.00
SDAI	48.51	25.02	109.00	8.00	117.00
STWDL	26.15	13.30	66.00	.00	66.00
RF Iu/mL	65.57	76.27	248.00	8.00	256.00
MCV mg/dl	157.89	255.92	1200.00	.00	1200.00
VAS= 10	5.92	2.65	10.00	.00	10.00
HB (gm/dL)	11.96	1.66	12	7.40	16.00
SUGAR (mg/dL)	107.14	40.49	209.00	74.00	283.00
Cholesterol (mg/dL)	213.68	31.96	161.00	135.00	296.00

(HAQ: health assessment questionnaire, SDAI: simplified disease activity index, STWDL: swelling, tenderness, warmth, deformity, limitation of motion; VAS: visual analogue scale)

Thirty-seven cases out of (92) 40.22% patients showed anemia of microcytic hypochromic anemia and normochromic normocytic anemia. two cases out of (92 cases) 2.17% of cases had a rheumatoid nodules, ten cases was recorded as a carpal tunnel syndrome in this study as 10.87% of cases had a bilateral CT syndrome, 4 out of (92 cases) has a dry eye 4.35% was associated in this study, 8 cases recorded in this study showed ischemic heart disease 8.70% of cases, and interstitial lung disease was presented in 2 cases (92) 2.17% of cases. 29 cases showed only arthritis 31.52%.

Follow-up of patients in this study showed increased comorbidity as follow:

DM (31.52%) was developed in 29 cases, 18 cases out of 92 cases showed HTN (19.56%); hypercholesterolemia in 31.61% of cases and 14.11% of them showed increasing Triglyceride level, and 12.69% of cases have increasing level of Cholesterol and TG level and rest of cases 41.32% were normal lipid profile.

Functional global assessment of the study group showed 51.10% of cases class I; 10.90% of cases have class II; 19.60% have class III and IV was 18.50% of cases.

The disease duration was the highest value around 6 years of 35.9% of cases, 22.80 of cases has five years durations, 21.70% of cases has 7 years duration. 13.0% at 8 years and 6.5% of cases have 9 years duration. The age was significantly correlated with duration r = 0.47 P<0.05, ACR Class r=0.4 P<0.05, with extra-articular manifestation r=0.046, P<0.05, cholesterol 0.57 P<0.05

This study showed 68.50% of patients with mild deformity as a fusiform swelling of PIP joint. The remaining 27.20% of patients have lower and upper limb deformity, and 4.3% of cases have a marked deformity.

This study was classified into two groups according to serum level of rheumatoid factor and MCV value (high-low) and showed that; there was a significant relation between serum level of MCV and normochromic anemia, microcytic hypochr-

omic anemia P<0.05 respectively; Also, there was a significant relation between high MCV level with subcutaneous nodule, IHD, Carpal tunnel syndrome P<0.05; while, low serum level of MCV was a non-significantly relation with dry eye P>0.05.

The RF showed, there was a significant relation to microcytic hypochromic anemia, carpal tunnel syndrome P<0.05 with high serum rheumatoid factor level while low serum RF is a significantly related to normochromic anemia P<0.05, otherwise no a significant relation between other factor P>0.05 table (2).

Also, in the study group; there was a significant relation between serum level of MCV and RF with VAS of patients, But HAQ-Di of the patient with high or moderate disease activity has a significant relation with MCV P<0.05; while the patient with low disease activity showed no significant relation with MCV P>0.05. This study showed no significant relation between disease duration, deformity, and serum level of low or high MCV vs RF P>0.05.figure (1).

Table (2): Relation between high vs low MCV and RF with Percentage of Extra-Articular Manifestation

Variable	MCV		P Value	RF		P Value
	High	Low		High	Low	
NNA	26.30	24.30	X^2 <0.05	18.40	32.50	X^2 >0.05
MCA	17.10	32.30		37.60	11.50	
Subcut. Nod.	8.8	2.90		6.10	7.00	
DRY EYE	1.8	14.30		4.10	9.30	
IHD	5.30	2.90		4.10	4.70	
CT SYND	28.10	11.40		18.00	16.30	
NORMAL	14.00	0		10.20	18.60	
DEFORMITY						
NO DEFORMITY	65.6	70.8	X^2 >0.05	72.1	65.3	X^2=1.1 >0.05
UL>LL	8.8	12.1		11.6	12.3	
UL=LL	25.6	17.1		16.3	22.4	

Figure (1): percentage of VAS – HAQ in relation to MCV and R.

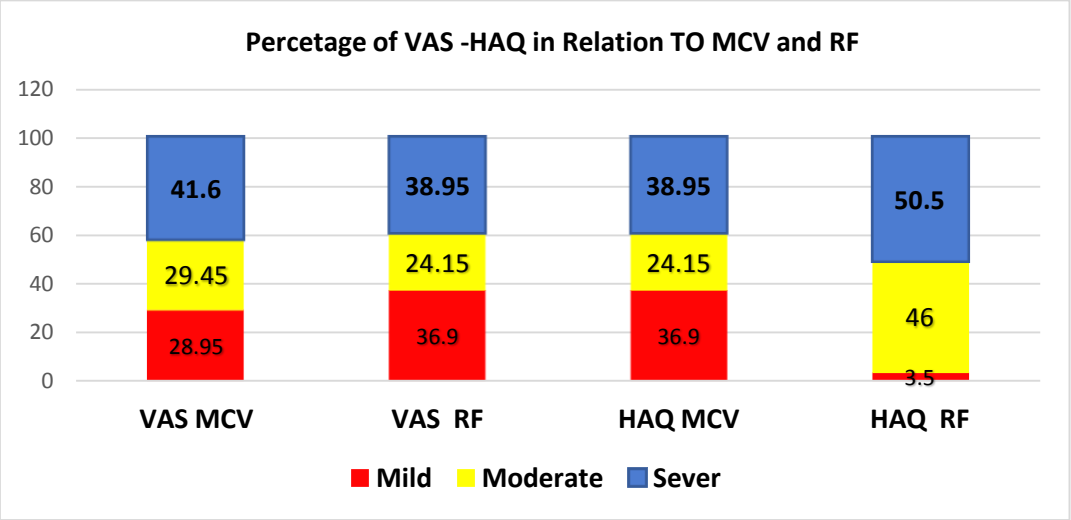

Table (3): relation of functional class to MCV and RF.

Disability	MCV	RF	P value
Functional classes 1	45.00	51.00	X^2=4.5 P<0.001 R=<0.01
Functional classes II	12.50	13.50	
Functional classes III	21.20	18.20	
Functional classes IV	21.30	17.30	
SJC	12±4	14±7	T =4.5 P<0.001
TJC	16±6	20±11	

Disability in rheumatoid arthritis can be explained as:

Pathological disability represented as (ESR, RF, MCV and disease duration, associated with DM, HTN, Hyperlipidemia); the impairment of function (SDWTL, Deformity, and nodules) and Functional and disability limitation (HAQ, VAS, ACR CLASS)

Pathological disability showed a significant relation between MCV P<0.05 and disease duration, but not with RF P>0.05 table (4); Also, ESR is showed a significant relation and correlation with RF and MCV P<0.05. Both RF and MCV showed a non-significant relation with DM or HTN or correlation with both group P>0.05. But, there was a significant relation with RF P<0.05 figure (2).

The impairment of function (SDWTL, Deformity, and nodules); there was a significant relation with MCV and positive correlation with extra-articular manifestation, Deformity and STDWLP<0.05. But, RF has a significant relation with STDWL, SDAI P<0.05. Otherwise, no significant relation was seen P>0.05.table (3).

Functional disability (HAQ, VAS, and ACR class) in the study group showed a significant relation with both RF and MCV P<0.05 with a significant positive correlation between HAQ, VAS with MCV P<0.05 but, not with RF P>0.05 table (4).

Figure (2): relation of disease duration to MCV and RF.

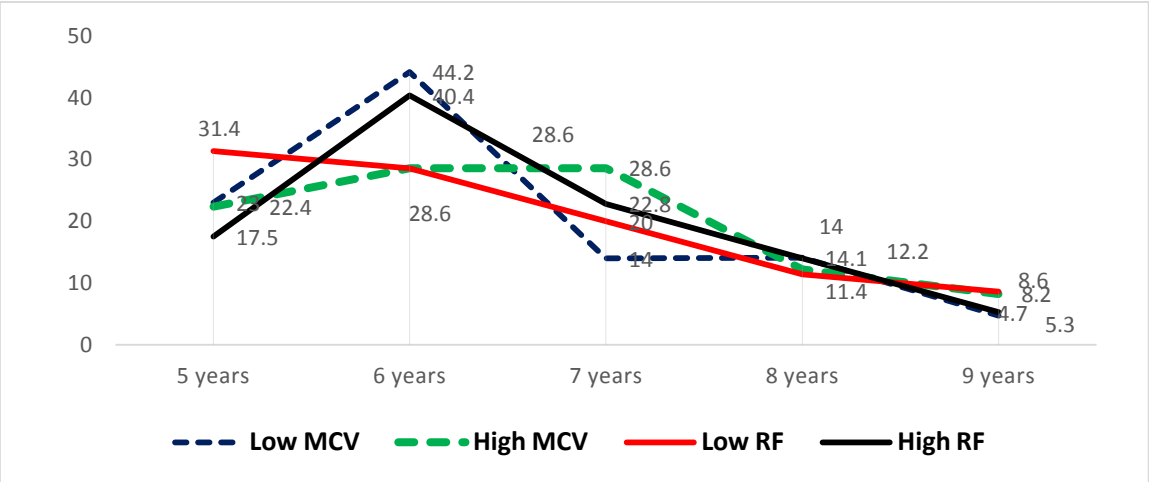

Table 4 Total MCV vs. RF Correlation

	RF	RF Correlation	MCV	MCV Correlation
DURATION	1.98 NS	r=0.56 **	5.67**	r=0.33 NS
ESR	4.78*	r=0.40 *	8.87**	r=0.5*
CRP	6.11**	r=0.54 *	5.77**	r=0.60**
DM	1.87 NS	r=0.12 NS	1.22 NS	r=0.15 NS
HTN	1.05 NS	r=0.02 NS	1.00 NS	r=0.05 NS
Hyperlipidemia	5.21**	r=0.14 NS	2.45 NS	r=0.24 NS
EXTRA	2.54 NS	r=0.04 NS	5.44**	r=0.44 *
DEFORMITY	2.23 NS	r=0.15 NS	4.23**	r=0.45**
STDWL	5.2 **	r=0.20 NS	5.67**	r=0.54 **
SDAI	6.91**	r=0.30 NS	7.87**	r=0.25 NS
VAS	6.86*	r=0.09 NS	7.17*	r=0.16 NS
ACR	2.12 NS	r=0.11 NS	4.23*	r=0.49 **
HAQ	4.38*	r=0.12 NS	4.78**	r=0.44 *

Limitation of this study

The assessment was done once in chronic RA > one-year duration, without a yearly assessment of the progression patients' disability (No follow-up). The study does not assess patients' adherence to his medication, and also, we don't include

radiographs of the feet or MSUS as a new tool for disease activity assessment. DAS score also was not calculated in this study.

Discussion

Rheumatoid arthritis is a chronic progressive course, observation of disease activity and ADL is necessary as an outcome measurement of the disease process, that might be reversible; VAS score, ESR, CRP, other comorbid condition has significant reduction of the capability of disease activity or ADL.

Rheumatoid arthritis is a chronic and progressive course; its seriousness may be necessary to observing that clinical course about disease; RA disease activity might be reversible. Those pain, (VAS) manifestation of inflammation, stiffness, joint swelling, (ESR Also CRP and Anemia) all of these factors are a significantly reduced capability to perform ADL activity of daily living (ADL) activity.[1]

Hazes et al., (2003), mentioned that, the managing of the patients with RA on DMARD therapy; disease disability measurement using HAQ score /ADL activity should put into consideration; family situation, social support services, present of other comorbid conditions (medically or physica-lly) has an impact on outcome measurement.[7]

Despite RA treatment, disease duration, remission or exacerbation, deformity, limitation of movement and decreased ADL activity, more common among the patients particularly over tolerant for the low socioeconomic standard of living, especially in the female who has a large family member, joint degeneration can be ended as a handicap patients.[1]

This study is done 92 female patients with rheumatoid arthritis and measurement of disease activity and functional disability in this female patient and impact on daily life of each patient, assay of RF, MCV, VAS, and HAQ assessment as a recognizable and reliable measure of RA health state.[7]

RF and anti-MCV serum level have clinical and prognostic valuable information for the clinician and patient; it can reflect disease severity/activity and disability and increased morbidity or mortality of RA patients.[7]

HAQ evaluation for the patient with chronic diseases, particularly RA is mandatory for all patients either patients' self-report HAQ or staff assistant in distinctive Rheumatology OPD with assessing those courses to evaluate the outcome of RA patients.[7]

Pease et al (1999), stated that, HAQ is the generally utilized as a functional outcome estimation for practical disability and most of the studies exploring the association between disease activity and pain, fatigue, organ damage (deformity), comorbid condition, also, it's associated with radiographic damage and/or clinical assessment of the patient.[8]

Chopra et al. (2002), demonstrated that most RA presented with high HAQ-scores. HAQ assessment can be used in the evaluation of pain and disability of RA patients, but, cannot detect differences in patients below HAQ score of 0.24; It was shown that the relationship between pain and disability varies in different rheumatic diseases. There was a loose relationship between pain and restricted activity.[9]

Taylor et al. (2008), mentioned that in his results have a positive correlation of the HAQ-DI and pain on work disability in RA patients with the poor functional ability.[6]

Similar finding observed in another study done by Susanet al, (1989), women have a more disability associated with the disease activity; as it has a larger impact on their work status than men do. 10

Our result showed a similarity with senra et al., results (2014) about the duration of disease 35.9% of cases around 6 years, 22.80% of cases around five years duration, and 7 years duration of 21.70% of patients. The age is correlated with duration r = 0.47 P<0.05, with extra-Articular manifestation r=0.04, P<0.05, cholesterol 0.57 P<0.05 and ACR class r=0.4 P<0.05.[11]

Also, this study indicated a noteworthy relation-ship between pain and joint destruction (deformity) with functional disability, increasing ESR is correlated with serum levels of RF and MCV as that predictor of poor functional status

and diminished their ability to adapt to commonly ADL activity.[11]

Also, in the study of Jansenet al., (2001), he has stated that the radiographic damage in seropositive RA reflect the outcome and functional state of RA patient with disease activity, and there is an association between radiographic damage and physical disability, it has an impact on individual and society in term of the costs of the disease outcome which agree with our results.[12]

Another study done by Ursum et al. (2010), showed no significant difference between seronegative or seropositive RA disease activity and PGA and had no effect on the outcome of RA disease activity which disagrees with the results of this study.[13]

Those with RA patients have a progressive span through those a considerable duration of their illness, which agree with our objective of the study, that may have been shed light on the parameter associated with disability in RA patients; there may be a huge correlation between (MCV, RF), Furthermore, duration, deformity, STDWL, SDAI and for HAQ score.[13]

Welsing et al (2001), who state that correlation between harm Also handicap need been damage and disability has been shown to be increased with increasing disease duration, also, no significant correlation between HAQ score and radiographic assessment.[14]

Disease activity and joint damage and extra-articular and or comorbidity in this study demonstrate the impact of functional global assessment measured by the HAQ could be explained largely by disease activity, additionally by joint destruction; in RA patient's disease activity HAQ is the most important determinant in the loss of function (ADL) and progressive joint damage. The deformity is an outcome parameter of long-term RA and, ultimately, functional disability, these findings have important implications.[14]

The result of this study agree with result of Senra et al., (2014) declares that the progressive nature of illness makes the ADL activity worse and difficult especially for patient who have a positive MCV more than positive RF.[11]

However, progressive physical disability and most of them need help from others, in performing basic tasks, HAQ-Di decreased with increased disease duration more than 5-6 years.[15-17]

The course and outcome of physical function in RA patients given the importance of maintaining effective functionality to ensure the continued performance of common daily activities. Through-out the course of the disease, the loss of physical function is mainly attributed to disease activity.[15-17]

In Conclusion: disability in RA patient, HAQ score self-report or physician reported should be assessed regularly in all rheumatology clinic; the study showed the significant differences between patient high vs. low serum RF /MCV; it correlated with disease activity, disease duration, measurement, and that may reflect on ADL and impact on patient outcome measures.

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