Anti-Mutated Citrullinated Vimentin Antibodies in Rheumatoid Arthritis compared with anti-cyclic citrullinated peptides

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Abstract: Background: Rheumatoid arthritis (RA) is characterized by synovial joint inflammation, which often leads to progressive joint destruction and disability. Several other auto-antibodies specific to RA have been found. Among them, antibodies against cyclic citrullinated peptides (CCP) are useful for diagnosing RA. Antibodies to mutated citrullinated vimentin (MCV) were described recently in RA. The aims of this study were to evaluate the usefulness of anti-MCV for diagnosing and assessing severity of RA compared to anti-CCP. **Patients and methods:** We studied 50 RA patients (aged 18 - 60 years with 80% females) and 25 healthy controls, matched age and sex. Functional disability was evaluated using Health Assessment Questionnaire (HAQ). CBC and ESR for all subjects were done. Anti-CCP and anti-MCV levels were assayed using ElISA technique. IgM rheumatoid factor was determined by turbidimetry. Postero-anterior radiographs of hands, wrists, and forefeet were taken. **Results:** RA group was significantly higher than control group as regard ESR, CRP, RF, Anti-CCP, and Anti- MCV. Also, Anti-MCV had higher parameters than each of RF or anti-CCP as regard sensitivity, specificity, positive predictive value, negative predictive value and odd ratio in diagnosing RA and prognostic assessment. A significant correlations of RF with Anti-CCP and Larsen score, Anti-MCV with disease duration, VAS, HAQ, DAS 28, ESR, Anti-CCP and Larsen score, and there were significant correlations of Anti-CCP with VAS, DAS 28, RF, Anti-MCV and Larsen score. **Conclusion:** Anti-MCV antibody is very useful in RA since higher sensitivity and specificities are obtained compared with the anti-CCP assay and RF.

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1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disease characterized by chronic joint inflammation that often leads to destruction of bone and cartilage, as well as the presence of autoantibodies including rheumatoid factor (RF) and highly RA-specific anti-cyclic citrullinated peptide (anti-CCP) antibodies (**Avouac et al., 2006**). Rheumatoid factors (RFs) were the first biological markers discovered for RA and remain the only laboratory criterion included in the American College of Rheumatology criteria for RA classification (**Arnett et al., 1988**). Citrullination as well as anti-citrullinated protein/peptide antibodies (ACPA) have been implicated in the pathogenesis of RA (**Bodnár et al., 2012**). ACPAs have a high specificity for RA. Since the first description of RA-specific antibodies to citrullinated peptides, several citrullinated proteins have been proposed as physiological targets for ACPA specificity, such as fibrin (**Masson-Bessiere et al., 2001**), Epstein-Bar virus nuclear antigen (**Pratesi et al., 2006**), α-enolase (**Kinloch et al., 2005**) and vimentin (**Vossenaar et al., 2004**). In later years, the appearance of anti-citrullinated protein antibodies (ACPAs) has become a hallmark for the diagnosis and prognosis of RA (**Ruyssen-Witrand et al., 2012**). Vimentin is an intermediate filament that is widely expressed by mesenchymal cells and macrophages and easy to detect in the synovium. Modification of the protein occurs in macrophages undergoing apoptosis, and antibodies to citrullinated vimentin may emerge if the apoptotic material is inadequately cleared (**Vossenaar et al., 2004**). Recently, citrullinated vimentin, a protein highly released in synovial microenvironment, has been identified as potential autoantigen in the pathophysiology of RA and an enzyme-linked immunosorbent assay (ELISA) for the detection of Antibodies directed against a mutated citrullinated vimentin (anti-MCV) was developed (**Bartoloni et al., 2012**). Several studies demonstrated that anti-MCV antibodies have the same specificity as anti-CCP antibodies, but with better sensitivity (**Sghiri et al., 2008**). Early treatment improves the outcome and therefore early diagnosis is crucial (**Roland et al., 2008**). Antibodies to other citrullinated peptides or proteins have been suggested as good candidates for diagnosing RA

(**Aletaha et al., 2010**). In recent years, many studies have evaluated the presence of anti-MCV, anti-CCP antibodies, and RF in RA patients (**Al-Shukaili *et al.*, 2012**). The aims of this study were to evaluate the usefulness of anti-MCV for diagnosing RA including correlation with disease activity, compared with anti-cyclic citrullinated peptides (anti-CCP).

2. Patients and methods:

A total of 75 individuals consisted of 50 patients with the diagnosis of RA and 25 healthy subjects as a control are collected for this study. The study population was selected consecutively among patients who presented to the outpatient of Rheumatology clinics of Al-Hussein and Sayed Galal hospitals. At enrollment caretakers provided informed consents and the following data were collected: age, gender, duration of RA, treatment and hospital admission. The RA group Comprised 50 patients of age ranged from 18-60 years. They were 40 females and 10 males. Their disease duration ranged from 6 months to 22 years. Diagnosis of RA was based and confirmed according to (ACR)/ (EULAR) 2010 criteria **(Aletaha et al., 2010).**

The control group comprised 25 healthy subjects with matched age and sex.

All patients with RA received prior medications. The drugs taken at the sampling time included 5 -10 mg of prednisolone, methotrexate varying from 10 -15 mg/week, 200 mg hydoxychloroquine and NSAIDs.

All patients were subjected to complete history taking and full clinical examination with special attention to musculoskeletal system and functional disability was evaluated using the Health Assessment Questionnaire (HAQ) to calculate the disability index (DI) (**Bruce & Fries 2005**). The eight categories assessed by the DI are 1) dressing and grooming, 2) arising, 3) eating, 4) walking, 5) hygiene, 6) reach, 7) grip, and 8) common daily activities. The difficulty during each of these acts was assessed as follows: zero= without any difficulty, one=with some difficulty, two=with much difficulty and three=unable to do, then the sum of the categories scores is calculated and divided by the number of categories. This gives a score in the 0-3 range. Laboratory investigations through collection of Five ml of blood were withdrawn from each patient into two tubes: 2ml of blood were immediately citrated for complete blood count (CBC) by Coulter device and erythrocyte sedimentation rate determination (ESR) by westergren method. 3ml of blood were allowed to be clotted, 1 hour later centrifuged for fifteen minutes and collected serum was stored at -30ºC for determination of the following: Serum CRP: by turbidimetry quantitative determination (**Otsuji et al., 1982**), Serum RF: by turbidimetry for quantitative determination (**Winkles et al., 1989**), Anti-CCP IgG by ELISA method by using Orgentec and Dia Sorin Kits **(Ronnelid et al., 2005)** and an enzyme-linked immunosorbent assay (ELISA) (Orgentec Diagnostika, Mainz, Germany) for the detection of Antibodies directed against a mutated citrullinated vimentin (anti-MCV) with the recommended cut-off value of 20 U/ml (**Bang et al., 2007**). Postero-anterior radiographs of hands, wrists, and forefeet were taken at inclusion in the study and on the day of sample collection. Joint destruction was classified by comparison with standard reference films according to the Larsen-Dale index (**Larsen et al., 1977**). The joints assessed for this index are the wrists, all metacarpo-phalangeal joints (=10), all proximal interphalangeal joints (=8), both first interphalangeal joints in the hands (=2), metatarso-phalangeal joints II-V (=8), and both first interphalangeal joints in the feet (=2). Thus, 32 joints are scored in all. The degree of erosive damage is the most decisive criterion in grading and the finding of at least one definite erosion in the radiographs was sufficient to consider the patient as having erosive disease. The Larsen score is the total sum of the grading in all 32 joints, with a range of 0-200. The x rays were read by two independent readers.

Statistical Methods:

Data analysis was performed using SPSS version 20 software (SPSS Inc., Chicago, IL, US). The association between the categorical variables was tested using Chi-square test. Because the data was not normally distributed, a nonparametric test was used and the medians with interquartile range are presented. To test whether the medians of two unpaired sets of measurement are different from each other, we used the Mann-Whitney test. The level of significance at was taken at 95% confidence interval (CI), r value was considered weak if < 0.25, mild if > 0.25-< 0.5, moderate if > 0.5 -< 0.75 and strong if > 0.75. P-value is considered significant if < 0.05.

3.Results:

Of 50 patients with RA, 46 patients were positive for anti-MCV antibodies (92%), 36 patients were positive for anti-CCP antibodies (72 %), 26 patients were positive for RF (52%), any of them were positive in 47 patients (94%) and all of them positive in 21 patients (42%). By contrast, of 25 healthy controls, 1 person was positive for anti-MCV antibodies (4%), 2 persons were positive for anti-CCP antibodies (8%), 4 persons were positive for RF (16 %) any of them were positive in 9 subjects (36%) and all of them positive in no subjects (0%).

Table (1) showed the descriptive statistics of RA patients included in the study.

Variables	Minimum	Maximum	Mean ± SD
Age (years)	18	64	44 ± 12
Duration of disease (years)	1	23	7.4 ± 5.7
Tender joint count	7	28	20. ± 7.4
Swollen joint count	5	23	12 ± 4.9
VAS	6	9	7.4 ± 1.3
HAQ	0.25	2.9	1.5 ± 0.7
DAS28	4.9	8.6	6.9 ± 0.97
ESR (mm/hr)	10	95	41.0 ± 24
CRP (mg/L)	0.4	132	17 ± 24
RF (IU/ml)	0.5	231	77 ± 90
Anti – CCP (U/ml)	0.9	3955	651 ± 955
anti MCV (U/ml)	6.0	340	87 ± 84
Larsen score	25	100	51 ± 19

Table (2) showed the difference between RA and control group regarding; ESR, CRP, RF, Anti -CCP, anti-MCV and Larsen score. RA group was significantly higher than control group as regard ESR, CRP, RF, Anti-CCP, and Anti- MCV.

Variables	RA	Control	P- value
ESR (mm/hr)	41 ± 24 (N=50)	14 ± 6.8 (N=25)	< 0.0001
CRP (mg/L)	17 ± 24 (N=50)	1.8 ± 1.5 (N=25)	0.0021
RF (IU/ml)	77 ± 90 (N=50)	3.8 ± 7.8 (N=25)	0.0001
Anti-CCP (U/ml)	651 ± 955 (N=50)	14 ± 9.4 (N=25)	0.0014
Anti-MCV (U/ml)	87 ± 84 (N=50)	10 ± 5.0 (N=25)	< 0.0001

Table (3) showed the sensitivity, specificity, positive predictive value, negative predictive value and odd ratio of RF, anti-CCP, anti-MCV, each of them and sum of them in diagnosing RA. Anti-MCV had higher parameters than each of RF or anti-CCP.

	Sensitivity	Specificity	+ve Predictive Value	-ve Predictive Value	Odds ratio
RF≥25 U/ml	52 %	84 %	87 %	47 %	5.7
Anti-CCP≥25 U/ml	72 %	92.00 %	94.74 %	62.16 %	29.57
Anti-MCV≥20 U/ml	92 %	96.00%	97.87 %	85.71 %	276
Anti-CCP or RF or Anti-MCV	94 %	72 %	83.93 %	84.21 %	27.85
Anti-CCP , RF and Anti-MCV	42 %	100%	100.00 %	46.3 %	37.17

Table 4 showed the correlation of RF, Anti-MCV and Anti-CCP with other parameters in RA group, there were significant correlations of RF with Anti-CCP and Larsen score, Anti-MCV with disease duration, VAS, HAQ, DAS 28, ESR, Anti-CCP and Larsen score, and there were significant correlations of Anti-CCP with VAS, DAS 28, RF, Anti-MCV and Larsen score.

Correlation	RF		anti - MCV		anti - CCP	
	r	p	r	p	r	p
with Age	0.152	0.32	-0.08	0.585	0.102	0.5
with disease-duration	0.18	0.23	0.3	0.046*	0.277	0.06
with VAS	0.22	0.15	0.44	0.002*	0.452	0.002*
with HAQ	-0.055	0.72	0.15	0.31	0.159	0.29
with DAS28	0.25	0.096	0.33	0.026*	0.314	0.036*
with ESR	-0.0179	0.91	0.20	0.178	0.169	0.26
with CRP	-0.058	0.7	0.04	0.81	-0.043	0.78
with RF			0.29	0.053	0.3	0.046*
with Anti CCP	0.3	0.046*	0.87	<0.0001*		
with Anti MCV	0.29	0.053			0.87	< 0.0001*
with Larsen score	0.33	0.027*	0.32	0.03*	0.448	0.002*

*= significant

4. Discussion:

RF and anti-CCP antibodies have been shown to be present prior to the appearance of clinical symptoms of arthritis suggesting that the initial immune dysregulation in RA occurs years before symptomatic disease (**Van Venrooij et al., 2011**). The development of a sensitive and specific biomarker for the diagnosis of RA, which could be detected in early disease and offer a prognostic indication for disease course, would enable RA patients to be identified, monitored, and treated appropriately to curtail disease morbidity and establish remission. The presence of citrullinated vimentin in the joint, its intracellular localization and the necessity of citrullination of vimentin to bind HLA-DR clearly show the importance of citrullinated vimentin in the pathogenesis of inflammation in RA (**Van Steendam et al., 2011**).

The main focus of our study was to investigate the usefulness of anti-MCV for diagnosing and assessing severity of RA in comparison to anti-CCP. In recent years, many studies have evaluated the presence of anti-MCV, anti-CCP antibodies, and RF in RA patients. In our study, at the cutoff values recommended by the manufacturer, the sensitivity and specificity of RF, anti-CCP, and anti-MCV in diagnosing RA were that, Anti-MCV had higher sensitivity and specificity than each of RF or anti-CCP.

Our result is supported by **Yang et al., 2005** who stated that, CCP is not expressed in the synovium, and citrullinated proteins expressed in the rheumatoid joint would probably be more relevant as targets of auto-antibodies used to diagnose RA. Citrullinated vimentin is present in synovial membranes and is released in increased amounts in response to growth factors and proinflammatory cytokines, suggesting involvement in the pathophysiology of RA (**Yang et al., 2005**). Our results as regard to the sensitivity were in agreement with several reports; **Liu et al., 2009** and **Al-Shukaili et al.,2012** showed that the sensitivities of anti-MCV antibodies was the highest in comparison to anti-CCP antibodies and RF were (78.2% and 72%), (61.8% and 52%), and 72.4% and 57%), respectively. While a contradictory to **Maraina et al., 2010**, who stated that the sensitivity of RF was higher than the sensitivity of anti-CCP or anti-MCV antibodies. Also, contradictory to **Bartoloni et al., 2012**, who stated that, anti-MCV demonstrated lower sensitivity than anti-CCP.

As regard to the specificity our findings were parallel to **Roland et al., 2008**, and **Damjanovska et al 2009,** showed that, the specificity of anti-MCV antibodies was the highest in comparison to anti-CCP antibodies and suggested that anti-MCV antibodies may be valuable for diagnosing RA in anti-CCP-negative patients without replacing them as an equivalent number of anti-CCP-positive RA patients test negative for anti-MCV. While a contradictory to, **Soos et al., 2007, Sghiri et al., 2008 and Al-Shukaili et al., 2012,** who stated that; the specificity of anti-CCP antibodies was higher than that of anti-MCV antibodies or RF. These results may be changed to be parallel to our results and obtain the same specificity as that of anti-CCP, if the manufacturer cutoff point is changed as the claim of **Roland et al., 2008** as, 11.8% of anti-CCP-negative RA patients were positive for anti-MCV, furthermore, in 7.9% of patients meeting ACR criteria for RA but having negative tests for anti-CCP, anti-MCV antibodies were positive although RF was negative. Also, the higher specificity of both anti-CCP, and anti-MCV antibodies may be due to what is documented by **Engelmann et al., 2009**; the Cross-reactivity experiments between anti-MCV and anti-CCP revealed that only a part of the anti-MCV antibodies react with CCP and vice versa, indicating that anti-MCV and anti-CCP antibodies target different epitopes this may explain the highly +ve correlation between both antibodies (table 4).

When comparing patients with established RA versus control patients, reported sensitivities and specificities of anti-MCV ranged from 54%% to 74.5% versus 79% to 93.1%, respectively **(Dejaco et al., 2006, Bizzaro et al., 2007, Coenen et al., 2007, , Sghiri et al., 2008, Ursum et al., 2008, and Raza et al., 2010)**. Also, in comparing patients with established RA versus control patients, reported sensitivities and specificities of anti-CCP ranged from 41% % to 70.1% versus 91% to 98.7%, respectively **(Goldbach-Mansky et al., 2000, Dejaco et al., 2006, Khalifa and Abdelfattah, 2008 and Ursum et al., 2008).**

Our study also showed anti-MCV antibodies have a higher positive predictive value and odd ratio for the prediction of developing RA, compared to anti-CCP antibodies or RF, indicating that anti-MCV antibodies may be a better prognostic indicator. This finding was in agreement with **Soos et al., 2007 and Al-Shukaili et al., 2012**, as the summation of the positivity in our study for anti-MCV anti-CCP and RF provided 100% specificity and positive predictive value in RA that is not too much different than that of anti-MCV antibodies alone 96% and 97.62% in their study, respectively.

Our study showed that, the diagnostic and prognostic performances of the anti-MCV test met that were reviewed by **Luime et al., 2010** as a higher significant correlation with DAS28 than anti-CCP (table 4). They stated that anti-MCV can be used as an alternative for anti-CCP as a diagnostic marker

Luime et al., 2010. **Qin et al., 2011,** conclude from a meta-analysis on anti-MCV ELISA results that serum MCV may have significant value in the diagnosis of RA. Information on the prognostic performances is limited and contradictory to **Luime et al., 2010**.

In our study, the correlation between anti-MCV levels and CRP, DAS28, or its separate components tender joint count, ESR and CRP was rather low, and was absent between anti-MCV levels and swollen joint count. Also, we stated a mild positive correlation between anti- MCV levels and the radiographic changes but lower than anti-CCP and RF. This may describe the negative correlation of anti- MCV with HAQ (table 4). Some studies showed a stronger correlation of levels of anti-MCV with clinical parameters (ESR, swollen joint count, physician's assessment of disease activity and DAS-28) compared with anti-CCP levels, making anti-MCV a better prognostic marker for future radiographic changes **(Innala et al., 2008, Mathsson et al., 2008 and Wagner et al., 2009)**. Others found no correlation between anti-MCV and DAS-28 or additional clinical utility of the anti-MCV test **(Bang et al., 2007, Ursum et al., 2008 and Raza et al., 2010)**. Also, in cohort study of 76 anti-MCV-positive patients with early arthritis the median anti-MCV level and DAS28 score both decreased over time, GEE (general estimation equation) analysis revealed a rather small association between anti-MCV levels and DAS28 score over 2 years of follow up. This implies that a large decline in anti-MCV level is needed to yield a substantial decrease in DAS28. A minimal reduction of 0.6 points in DAS28 is necessary for a moderate response, according to the European League Against Rheumatism response criteria (**Van Gestel et al., 1996**).

At the study of 14 eligible studies by **Luime et al., 2010**; 11 included diagnostic data and 3 included prognostic data; the evidence from the diagnostic case-control studies suggests that anti-MCV may be used as an alternative for anti-CCP. While, the prognostic evaluation of anti-MCV was limited by differences in study methodology, outcome and statistical modelling. Individual studies showed moderate associations for anti-MCV and radiological progression with the strength of the association comparable to that of anti-CCP as what is shown by our study.

We also, found that, positive significant correlation between Anti-MCV and disease duration, with agreement of **Damjanovska et al., 2009**, who studied patients with early RA but these patients had a broader window of disease duration compared with the studies of **Mathsson et al., 2008** and **Liu et al., 2009** (2 years vs 12 months).

In our study we observed that, Also, because of the mild positive correlation between anti-MCV levels and parameters of disease activity and weak correlation with HAQ, it is not useful to monitor disease activity with anti-MCV levels.

Also, in our study, we observed that, in spite of low correlation for anti-MCV, anti-CCP antibodies, and RF in RA patients, it was the lowest for anti-MCV that, might means that it is couldn't be affected by age like RF (Table 4).

Conclusion: we can conclude that anti-MCV antibody is very useful in early RA since higher sensitivity and specificities are obtained compared with the anti-CCP assay and RF. Also, because of the mild positive correlation between anti-MCV levels and parameters of disease activity and Larsen score while, a weak correlation with HAQ, it is not useful to monitor disease activity with anti-MCV levels.

Competing interests: The authors declare that they have no competing interests.

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