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ORIGINAL ARTICLE

The clinical value of anti-cyclic citrullinated peptide (anti-ccp) antibodies and insulin resistance (IR) in detection of early and subclinical atherosclerosis in rheumatoid arthritis (RA)

Mohamed abdel kader abdel wahab [a,*], **Abdo El Laban** [b], **Aml Aly Hasan** [b], **Ayman Farouk Darweesh** [b,1]

[a] *Cardiology Department, El Minya university, Egypt*
[b] *Rheumatology Department, El Minya university, Egypt*

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KEYWORDS

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Abstract *Background:* Patients with rheumatoid arthritis (RA) have increased coronary atherosclerosis possibly related to several factors including insulin resistance. Anti-CCP antibodies are highly specific for RA but their association with cardiovascular morbidity has not been examined by enough studies.

Aim: The aim of this study was to evaluate the role of anti ccp antibodies and IR for detection of early and sub-clinical atherosclerosis in RA patients.

Subjects and methods: 56 RA patients and 19 age and sex matched healthy subjects were included in the present study. All patients and controls were subjected to full history, clinical examination, and laboratory investigations (including CBC, ESR, high sensitive CRP, rheumatoid factor and lipid profile). All patients were also subjected to measurement of intima-media thickness (IMT) of both carotid arteries as well as the flow mediated dilatation (FMD) of brachial artery. Also, measurements of IR (by HOMA 2) and anti-CCP were done for all subjects.

Results: IMT was significantly increased ($P = 0.01$) and FMD significantly decreased ($P = 0.001$) in RA patients than controls in spite of the absence of significant differences in traditional atherosclerotic risk factors. Both IR and anti-CCP (which are significantly increased in RA compared to controls, $P = 0.02$ and 0.001 *respectively*) were significantly positively correlated to IMT ($P = 0.009$ and 0.001 *respectively*) and negatively correlated to FMD ($P = 0.0005$ and 0.005 *respectively*).

* Corresponding author. Tel.: +20 01005616107.
E-mail address: makader1999@yahoo.com (M.a.k.a. wahab).
[1] Tel.: +20 01006861136.

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Conclusion: IR and anti-CCP may be helpful in the early detection of subclinical atherosclerosis in RA patients.

1. Introduction

Patients with rheumatoid arthritis (RA) have increased coronary atherosclerosis possibly related to increased prevalence of visceral adiposity, insulin resistance, and metabolic syndrome.[1] Insulin resistance (IR) is the condition in which normal amounts of insulin are inadequate to produce a normal response from fat, muscle and liver cells. Roughly half of IR is genetically determined and half is acquired (one quarter from obesity and one quarter from physical inactivity).[2,3]

IR is associated with atherosclerotic risk factors which included in the metabolic syndrome such as hypertension, hyperlipidemia, and obesity that subsequently accelerate the development and progression of atherosclerosis; it was reported that there was peripheral IR associated with carotid as well as coronary artery atherosclerosis in RA patients and related to disease activity in absence of metabolic syndrome features; so impaired insulin sensitivity further predicts cardiovascular disease independent of other metabolic syndrome features.[4,5]

Some immunological markers, such as rheumatoid factor and anti-CCP are more encountered in RA with extra-articular manifestations, and anti-CCP antibodies have been shown to be highly specific for RA and are more predictors, (even stronger) of disease severity and activity than rheumatoid factor. But until now, their association with cardiovascular morbidity has not been examined by enough studies.[6]

2. Patients and methods

Fifty-six (56) RA patients were included in the present study: forty (40) women and sixteen (16) men, and their age ranged from twenty (21) to forty-nine (49) years and disease duration ranged from six months to fifteen years. Patients were diagnosed according to the American College of Rheumatology (ACR) 1987 revised criteria for the classification of rheumatoid arthritis (Appendix A). Nineteen (19) age and sex matched healthy subjects were recruited as controls.

Exclusion criteria: Known atherosclerotic complications such as stroke and myocardial infarction: those undergoing hemodialysis, peripheral vascular disease, malignancy, or infections, and hypertensive and diabetic patients were excluded.

All patients and controls were subjected to full history taking, clinical examination, and laboratory investigations (including CBC, ESR, high sensitive CRP, rheumatoid factor and lipid profile). All patients were also subjected to measurement of intima-media thickness of both carotid arteries as well as the flow mediated dilatation of brachial artery.

Calculation of insulin resistance by HOMA2-IR method: UBI MAGIWEL insulin quantitative kit is a solid phase enzyme linked immunosorbent assay (ELISA) and this test is designed for in vitro quantitative measurement of insulin in human serum and plasma.

IR was calculated according to the HOMA homeostasis model as [serum insulin (μU/ml) × plasma glucose (mmol/L)/22.5].[7] The output of the HOMA2 model was calibrated to give a beta-cell function of 100% and an IR of 1 as normal. Therefore, values were considered abnormal when HOMA2-IR was > 1.[8]

Anti-CCP: CCP IgG ELISA is a semi-quantitative enzyme linked immunosorbent assay for the detection of IgG anti-CCP in patient sera. The newer version of anti-CCP (anti-CCP2) was used because it is more sensitive.[9] Less than or equal to 5 u/ml = Negative and more than 5 u/ml = Positive.[9]

3. Carotid ultrasound measurements

Carotid ultrasound evaluation was done for all subjects in this study to determine the intima media thickness (IMT) and to detect carotid plaques with the high-resolution B-mode ultrasound equipment Medison 9900 multibeam 30 UL (Korea) equipped with liner probe (7.5 MHz) with the use of a standardized protocol.[10]

Individuals were investigated in the supine position and IMT of the far wall was evaluated as the distance between the luminal–intimal interface and the medial-adventitial interface about 1.5 cm proximal to the carotid bifurcation. IMT measurements were obtained from 4 contiguous sites at 2 mm intervals, and calculation of the average was done. The mean IMT (the mean of both right and left side) was assessed. At the same time the maximum IMT (the highest value either right or left) was also assessed. IMT is consider abnormal if >.072 cm.[11]

Plaques: These were defined as focal widening relative to adjacent segments, with protrusion into the lumen of calcified or noncalcified material.[12] All ultrasound measurements were performed by the same examiner who was unaware of subject characteristics.

Endothelial function: To assess endothelial function non-invasively with B-mode ultrasound, conduit vessel endothelium-dependent vasodilatation was induced by reactive hyperemia, while endothelium-independent vasodilatation was induced by administration of sublingual nitroglycerine (glyceryl trinitrate (GTN)).[13]

Measurements were made of changes in the diameter of the brachial artery using color duplex Doppler ultrasound. The ultrasound examination was performed in quiet room at temperature between 21 C and 32 C. Subjects rested in a supine position for 15 min before examination. A B-mode scan was obtained of the right brachial artery in longitudinal section. A resting measurement was taken and called pre-flow mediated dilatation (pre FMD), and a pneumatic cuff was then inflated to a pressure of 200 mmHg for 5 min, then the diameter of the artery was recorded again 45–60 s after deflation (post FMD). A period of 15 min was allowed for recovery before testing for endothelium-independent relaxation. A repeat baseline measurement of the diameter was before a 400 μg dose of

sublingual GTN spray was administrated (pre GTN). The brachial artery diameter was again measured 3–4 min after the GTN was given (post GTN).[14]

A single investigator performed all imaging and analysis, blinded to the subject's disease.

FMD, GTN, and dilatation ratio were calculated as follows:

FMD = (Post FMD – Pre FMD)/Pre FMD × 100.

GTN = (Post GTN – Pre GTN)/Pre GTN × 100.

Dilatation ratio = FMD/GTN × 100.

3.1. Statistical analysis

Data were coded, entered and analyzed by the statistical Package for the Social Sciences (SPSS for windows version 11.0). Parametric data were reported as mean ± SD, while non-parametric data were expressed as number and percentage. A Student *t* test and the chi-squared (χ^2) test were used to compare variables for testing statistical significant difference between two groups and the differences were considered significant at a two-tailed $p \leqslant 0.05$ and Mann–Whitney Test was used to study the correlations of the nonparametric variables.

4. Results

There is no significant difference in age and sex between both groups (Table 1).

Table 1 Demographic data of patients and control group.

		Patients (N = 56)	Control (N = 19)	P-value
Age	Range	21–49	22–49	0.350
	Mean ± S.D.	36.50 ± 7.22	34.6 ± 8.22	
Sex	Male	9 (16.07%)	3 (15.8%)	0.977
	Female	47 (83.92%)	16(84.2%)	

Carotid IMT was significantly increased in RA patients compared to controls while there is significant decrease in FMD and dilatation ratio in RA patients compared to controls (Tables 2 and 3, Fig. 1).

The prevalence of insulin resistance is significantly increased in patients than in controls. Furthermore, there is significant increase in insulin resistance level as well as anti-CCP in rheumatoid arthritis compared to controls (Tables 4 and 5, Fig. 2).

Table 5 and Fig. 2 showed that there is significant increase in ESR and CRP (acute phase reactant) in rheumatoid patients compared to controls

Results of this study revealed that there is no significant difference in traditional atherosclerotic risk factors between patients and controls (Table 6).

Results of the current study revealed significant correlation between insulin resistance and carotid IMT (Table 7).

Also, there is significant negative correlation between insulin resistance and flow mediated dilatation and dilatation ratio in rheumatoid patients (Table 8).

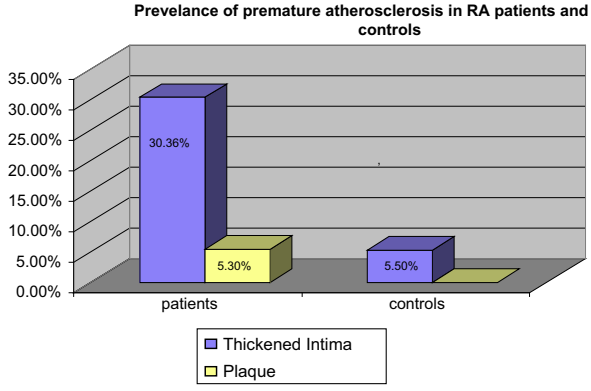

Figure 1 Prevalence of premature atherosclerosis in RA patients and controls.

Table 2 Comparison of endothelial function in RA patients and controls.

		RA patients (n = 56)	Controls (n = 19)	P
Pre.fmd (average)	Mean ± SD	3.69 ± 0.51	3.9 ± 0.49	0.121
Post.fmd (average)	Mean ± SD	4.32 ± 0.60	5.11 ± 0.52	0.0001
Fmd %	Mean ± SD	17.30 ± 7.72	28.52 ± 10.11	0.001
Pre.GTN (average)	Mean ± SD	3.71 ± 0.54	3.91 ± 0.49	0.150
Post.GTN (average)	Mean ± SD	4.63 ± 0.72	4.89 ± 0.62	0.131
GTN.dilatation %	Mean ± SD	24.87 ± 9.02	25.72 ± 9.67	0.727
Dilatation ratio	Mean ± SD	0.71 ± 0.261	1.078 ± 0.189	0.0001

FMD = flow mediated dilatation, GTN = glyceryl trinitrate.

Table 3 Comparison of ultrasonographic duplex findings in RA patients and controls.

		RA patients (n = 56)	Controls (n = 19)	P
Mean IMT	Mean ± SD	0.057 ± 0.016	0.050 ± 0.007	0.01
Lt. IMT	Mean ± SD	0.057 ± 0.016	0.049 ± 0.008	0.01
Rt. IMT	Mean ± SD	0.068 ± 0.087	0.0495 ± 0.0869	0.11
Maximum	Mean ± SD	0.0597 ± 0.017	0.0526 ± 0.008	0.02

IMT = intima media thickness.

Table 4 Prevalence of insulin resistance in rheumatoid arthritis patients and controls.

	Patients (N = 56)	Controls (n = 19)	P
Presence of insulin resistance	51 (91.1%)	7 (36.8%)	0.005

HOMA2-IR = homeostasis model assessment, IR = insulin resistance.

Table 5 Laboratory features of RA patients and controls.

	RA patient (n = 56) Mean ± SD	Controls (n = 19) Mean ± SD	P
ESR (mm/h)	40.82 ± 42.27	16.26 ± 8,74	0.0001
US-CRP	70.4 ± 61.71	0.54 ± 0.64	0.0001
Anti ccp	85.11 ± 81.98	0.86 ± 0.46	0.0001
HOMA2-IR	87.96 ± 270	5.34 ± 8.4	0.02

ESR = erythrocyte sedimentation rate, HOMA2-IR = homeostasis model assessment, IR = insulin resistance.

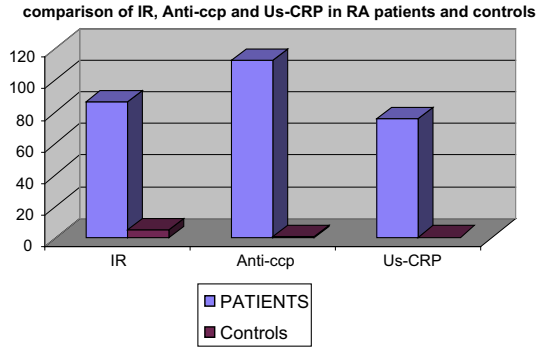

Figure 2 Comparison between IR, Anti-ccp and Us-CRP in RA patients and controls.

Table 6 Atherosclerotic risk factors in rheumatoid patients and controls.

	RA patient (n = 56) Mean ± SD	Controls (n = 19) Mean ± SD	P
FBS (mg%)	90.7 ± 17.43	88.42 ± 10.27	0.5
Total cholesterol (mg/dl)	166.25 ± 30.76	170.42 ± 36.65	0.63
Triglycerides (mg/dl)	90.70 ± 30.72	81.42 ± 26.8	0.22
HDL (mg/dl)	42.8 ± 3.4	42.37 ± 4.4	0.63
LDL (mg/dl)	114.45 ± 33.4 8	122.26 ± 35.41	0.406

There is significant positive correlation between anti-CCP and carotid IMT (Table 9) while anti-CCP is significantly negatively correlated with FMD as well as dilatation ratio (Table 10).

5. Discussion

In the past 20 years, the life expectancy of patients with rheumatoid arthritis (RA) has been shown to be reduced by three to ten years as compared to that of the general population. Currently, cardiovascular disease (CVD) is the major cause of death in patients with RA, and acute myocardial infarction can be up to four times more frequent in these patients. The autoimmune systemic inflammatory response, along with the presence of metabolic syndrome (MetS),

Table 7 Correlation between insulin resistance and Ultrasonographic duplex findings in RA patients.

Duplex findings	IR	
	(r)	P
Rt IMT	0.051	0.71
Lt. IMT	0.266	0.005
Mean IMT	0.344	0.009
Maximum IMT	0.344	0.009

IMT = intima media thickness, (r) = correlation coefficient.

Table 8 Correlation between insulin resistance and endothelial function in RA patients.

Endothelial function	IR	
	(r)	P
Pre.fmd (average)	0.139	0.308
Post.fmd (average)	−0.091	0.04
Fmd %	−0.403	0.005
Pre.GTN (average)	0.141	0.23
Post.GTN (average)	0.039	0.715
GTN dilatation %	0.123	0.301
Dilatation ratio	−0.112	0.012

(r) = correlation coefficient, FMD = flow mediated dilatation, GTN = glyceryl trinitrate.

Table 9 Correlation between anti-CCP and Ultrasonographic duplex findings in RA patients.

Duplex findings	Anti-CCP	
	(r)	P
Rt IMT	0.24	0.06
Lt. IMT	0.47	0.0001
Mean IMT	0.45	0.001
Maximum IMT	0.46	0.0001

Table 10 Correlation between anti-CCP and endothelial function in RA patients.

Endothelial function	Anti-CCP	
	(r)	P
Pre.fmd (average)	0.27	0.23
Post.fmd (average)	−0.22	0.02
Fmd %	−0.09	0.005
Pre.GTN (average)	0.26	0.39
Post.GTN (average)	0.17	0.72
GTN dilatation %	0.29	0.31
Dilatation ratio	−0.43	0.001

doubles the risk for fatal or non-fatal CVD and coronary atherosclerosis, regardless of age and sex.[15]

Endothelial dysfunction and atherosclerosis may be subclinical at early stages, and thus the ability to detect them with non-invasive techniques is crucially important, particularly in populations at increased risk for cardiovascular disease, such as those with rheumatoid arthritis. This may allow the identification of interventions that may reverse these processes early on. One of the best non-pharmacological interventions that may achieve this is physical activity.[16]

Among imaging techniques, the early determination of common carotid intima-media thickness (ccIMT), flow-mediated dilation (FMD), and nitroglycerine-mediated dilation (NMD) may be useful to determine atherosclerosis and endothelial dysfunction.[17]

Results of this study showed the comparison between 56 RA patients and 19 controls with respect to ultrasonographic duplex findings of carotid arteries and the endothelial function; as two markers of subclinical atherosclerosis, there were overall higher prevalence of premature atherosclerosis in RA patients than controls. In the first, seventeen (17) patients have thickened IMT (30.36%) and only three (3) patients (5.4%) had atherosclerotic plaque while, one (1) of controls had thickened IMT (5.3%) with no detected plaque formation.

In addition, the mean IMT was significantly higher in RA patients than our healthy controls (0.57 ± 0.051 versus 0.49 ± 0.072 mm respectively with $P = 0.01$). Also, FMD ($P = 0.043$) and dilatation ratio ($P = 0.00$ l) were significantly lower in patient than controls.

In accordance with our result, a study by La Montagna et al. [8] showed that 50% of patients with RA have atherosclerosis; mean IMT was 0.75 ± 0.11 mm. The 45 RA patients were, ranging from 0.56 to 0.99 mm. In the 48 control subjects, mean IMT was 0.65 ± 0.09 mm ranging from 0.48 to 0.88 mm ($P < 0.001$). In addition, other studies, using a control group, also confirm that the prevalence of the disease is higher in RA patients than in the controls.[18,19]

These findings indicated that accelerated atherosclerosis is a well defined feature of rheumatoid arthritis in agreement with many other studies.[20–23]

Epidemiological studies have used different cut off values for IMT in the general population. Differences in the site and method of carotid measurement may account for different results. In Doria et al. study normal IMT was defined when complex intima-media is >0.09 mm; therefore, IMT values 0.09 mm were considered indicative of thickened intima [10] while in another study, the subclinical atherosclerosis IMT cut-off value detected was >0.07 mm.[11] In our study as well as in previous studies[24,25,8] intima-media thickness was considered abnormal if >0.072 mm.

In our study in spite of the presence of accelerated atherosclerosis in rheumatoid patients, the prevalence of traditional cardiovascular risk factors in rheumatoid arthritis patients and controls was of no significant difference. On the other hand, increased prevalence of insulin resistance in RA compared to controls ($p < 0.001$) was found, which may be the factor promoting atherosclerosis.

Furthermore, results of this study revealed that insulin resistance is significantly correlated with IMT and significantly negatively correlated with flow mediated dilatation and dilatation ratio.

These results are supported by previous study[18] which found no differences in atherosclerotic risk factors between patients with RA and controls. However, In the RA group, the median carotid IMT was significantly greater than in controls. They concluded IR in the setting of active rheumatoid disease may contribute to mechanisms of accelerated atherogenesis observed in patients with RA.

This is in accordance with Dhawan and Quyyumi[26] who concluded that the increased cardiovascular disease risk in RA patients seems to be independent of traditional cardiovascular risk factors.[26] Several other pathogenic mechanisms include insulin resistance that subsequently leads to endothelial dysfunction, a decrease in endothelial progenitor cells, and arterial stiffness, which are the congeners of accelerated atherosclerosis observed in RA patients.

This is similar to previous study found that increased prevalence of insulin resistance has been observed in patients with rheumatoid arthritis.[27] Also, other authors concluded that insulin resistance has been shown to be an independent risk factor for ischemic heart disease and had long been known to occur in RA.[28]

The same result obtained with other authors who showed a significantly higher prevalence of IR in RA patients and pointed out a significant association between IR and subclinical atherosclerosis.[8]

In agreement with our results, Chung et al.[29] concluded that patients with RA have a higher prevalence of the metabolic syndrome including insulin resistance than control subjects.[29] Inflammation-associated metabolic syndrome is a mechanism that may contribute to increased coronary-artery atherosclerosis in RA.

Beyond the traditional cardiovascular risk factors, chronic systemic inflammation has been shown to be a crucial factor in atherosclerosis development and progression from endothelial dysfunction to plaque rupture and thrombosis.[30] Inflammation disturbs biochemical pathways involved in homeostasis of the endothelium. Research has established clear links between inflammatory mediators, particularly C-reactive protein and tumor necrosis factor alpha, with endothelial dysfunction, and atherosclerosis.[16]

Inflammation is considered to be an important risk factor for premature atherosclerosis in RA. This was a very consistent finding in the present study as measured by acute phase reactants including highly sensitive CRP and erythrocyte sedimentation rate.

Higher levels of ESR ($P < 0.001$) and CRP ($P < 0.001$) were detected in RA compared to healthy controls in agreement with previous study in which higher levels of ESR ($P < 0.001$) and CRP ($P < 0.001$) also were detected.[19] These data definitely support systemic inflammation as a factor of importance for premature atherosclerosis in RA patients.

The inflammation may be the underling mechanism linking the insulin resistance with atherosclerosis in rheumatoid arthritis. This explanation is supported by Goshayeshi et al.[31] which concluded that the impact of chronic inflammation on atherosclerosis and insulin resistance has been observed in several autoimmune diseases especially in Rheumatoid arthritis (RA), which is the most common autoimmune arthritis.[31] Also, High-grade systemic inflammation is implicated in the development of insulin resistance in these patients.[27]

Among immunological and metabolic laboratory markers, anticyclic citrullinated peptide (anti-CCP) antibodies may be

involved in the development of vascular disease in RA.[32] Also in our study anti-CCP antibodies were positive in forty-seven (47) patients (83.9%) and ranged from 1 to 312 ng/ml with mean of 85.11 ± 81.98. While in Pereira et al. [19] study anti-CCP antibodies were positively detected in fifty-six (56) RA patients (78.9%), in Gerli et al.[8] study, fifty-two (52) of the eighty-one (81) patients (64.2%) analyzed tested positive for anti-CCP antibodies.

Anti-CCP positively correlated with ultrasonographic duplex findings of IMT of carotid arteries left IMT, mean IMT, and maximum IMT ($P = 0.0001$, 0.001 and 0.0001 respectively) but negative correlation was found with parameters which assess the endothelial function of RA patients: post FMD, FMD percent and dilatation ratio ($P = 0.02$, 0.005 and 0.001 respectively).

This in agreement with Gerli et al.[8], who to our knowledge, first showed an association between anti-CCP and subclinical atherosclerosis in patients with RA.

In contrast, Pereira et al.[19] study showed that although anti-CCP antibodies have been shown to be significantly associated with RA patients group their association with IMT as subclinical atherosclerosis parameter; was not of significant results.

Since previous study has confirmed that anti-TNF-α therapy improves insulin resistance, beta-cell function, and reverted defects in the insulin signaling cascade in active RA patients with high insulin resistance,[32] we can recommend other study to verify the effect of this therapy in regression of subclinical atherosclerosis.

6. Limitations

This study has several limitations. First, the cross-sectional nature may fail to estimate the true magnitude of the contribution of variables, a prospective study might demonstrate a greater effect over time and the sample size did not allow evaluation of other potential predictors of increased IMT in our RA patients.

Another important factor is that although we viewed carotid atherosclerosis as a marker for overall atherosclerotic burden, this disease may progress in other vascular territories including the coronary circulation, at different rates, and the results of this study may not be generalizable to atherosclerosis in other major vascular beds.

7. Conclusion

IR and anti-CCP may be helpful in the early detection of subclinical atherosclerosis in RA patients.

Conflict of Interest

The authors declare that there are no conflicts of interest.

Appendix A

A.1. The 1987 revised American rheumatism association criteria for rheumatoid arthritis

THE 1958 revision of the American Rheumatism Association's (ARA) 1956 criteria for rheumatoid arthritis has now been in use for some 30 years. This classification system has been accepted and used by the current generation of rheumatologists and few studies on RA do not include in their methods section the statement '... patients with classical or definite RA (ARA criteria) were studied'.

A.1.1. The 1958 criteria, though, have their drawbacks

First, the distinction between classical, definite and probable RA is unhelpful. Few distinguish between classical and definite and, as has been pointed out, 'probable RA' is probably not RA.

Second, since 1958, our understanding of other disease entities presenting as polyarthritis has changed. Thus the HLA-B27 related spondarthropathies are not now considered as seronegative RA and any classification system for the latter would need to make that discrimination.

Third, some of the 1958 criteria, for example mucin clot and biopsy of subcutaneous nodule, do not reflect actual clinical practice and in reality are not used.

Finally, the individual criteria themselves are fairly loosely defined, in terms of both nature and duration, and thus there is anxiety about their low specificity (the number of false positives).

With these issues in mind the ARA commissioned a sub-committee in 1983 to produce a revised criteria set for RA. The results of their deliberations were published in March this year.

In brief, in the new version there is only one degree of diagnostic certainty of RA, requiring four of the seven listed criteria. There is a greater emphasis on involvement of the wrist and hands (MCP and PIP joints) and the older redundant features (mucin clots, synovial and nodule biopsy) have been dropped. In addition the definition of some of the features has been hardened, for example morning stiffness has to be presented for at least 1 h.

The patient database used to generate these criteria was also analyzed using the method of classification trees, a method previously used in rheumatology in developing criteria for osteoarthritis.

The results of this analysis are to generate a number of subsets containing combinations of individual criteria.

Two subsets emerged (arthritis, i.e. soft tissue joint swelling, in at least 3/14 candidate joint groups, plus either radiograph changes or rheumatoid factor) which in combination were almost as sensitive (86%) in identifying RA as the value of 91% for the rule requiring 4^7 criteria. *The addition of a further three subsets:*

1. Arthritis in three joint groups including MCP and wrist.
2. Arthritis in one joint group bilaterally plus rheumatoid factor.
3. Arthritis of MCP or wrist plus rheumatoid factor, increased the sensitivity of the classification tree derived criteria to 93.5%.

The specificity was 89% for both classification methods (conventional and subset) against 'consecutive' attenders with diseases other than RA.

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Osteoarthrosis (or SLE). Further, no patient from 137 normal individuals was positive for RA by either of the classification methods.

Table A.1 Comparison of 1987 with 1958 criteria.

1987	1958
1. Morning stiffness in and around joints at least 1 h	1. Morning stiffness
2. Soft tissue joint swelling observed by physician at least 3/14 joint groups (R or L: MCP, PIP, wrist, elbow, knee, ankle, MTP)	2. Swelling of a joint
3. Soft tissue joint swelling in a hand joint (MCP, PIP or wrist)	3. Swelling of another joint
4. Symmetrical swelling of one joint area in (2) above	4. Pain on movement or tenderness in a joint
5. Rheumatoid nodule	5. Symmetrical swelling
6. Rheumatoid factor by method positive in $<5\%$ normal population	6. Rheumatoid nodule
7. Radiograph changes on wrist/hands: erosions or juxta-articular osteoporosis	7. Rheumatoid factor
	8. Radiograph changes
	9. Mucin clot
	10. Synovial biopsy
	11. Nodule biopsy
RA = 4/7 criteria	Classical RA = 7/11 criteria
	Definite RA = 5/11 criteria
	Probable RA = 3/11 criteria

A.2.1. Are there any drawbacks to the new criteria?

First, the development of alternative formulations may be a source of confusion. Most clinicians will presumably prefer the conventional ATI form. As the criteria stand an investigator could accept RA as either positive for 4/7 criteria or conforming to one of the five subsets. It might be useful for the first few years to specify in any publication which method was chosen as it could conceivably explain differences in results between studies.

Second, the patients studied to formulate these criteria were current attenders with established disease (mean duration 7.7 years), whereas diagnostic criteria are of greatest utility in early disease. Thus the sensitivity of these criteria at diagnosis remains unknown.

Third, there are no exclusions, as with the original criteria, and it appears likely that patients with other inflammatory poly-arthropathies, particularly SLE, psoriatic arthritis and reactive arthritis, would satisfy the new rules.

In use, therefore, readers would wish to know that these diseases had been excluded. Further, in populations where the occurrence of rheumatoid arthritis is reduced relative to that of other peripheral joint inflammatory arthropathies, the predictive value (proportion of all those satisfying criteria who have RA) of the criteria in both the clinic and the community will be lower than in the US population studied.

Fourth, the exclusion of the shoulder from the list of involved joints might be a surprise to many, as shoulder involvement is not a rare event in RA. Despite these drawbacks the new criteria are a step forward in removing the problems listed above in the 1958 version. It is accepted that European investigators will probably have to fall into line and begin to use these criteria but both indicate which formulation they are using and be aware of the problems of not excluding other diseases.

Finally, diagnostic criteria have many uses. The clinical trialist will want very specific criteria whereas the epidemiologist will also (see Table A.1).

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