Population study of the importance of rheumatoid factor isotypes in adults

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Abstract

Blood samples collected from 13 858 randomly selected subjects participating in a health survey in Iceland from 1974 to 1983 were tested for rheumatoid factor. Samples that were positive in a sensitive RF screening test were analysed further by the Rose-Waaler technique and an isotype specific enzyme linked immunosorbent assay (ELISA).

In 1987 the 173 available participants who were RF positive and 156 matched RF negative controls were evaluated clinically for rheumatoid diseases. RF levels and isotype patterns were more persistent in the patients with rheumatoid arthritis (RA) than in RF positive subjects who did not have overt RA. The prevalence of RA was only 19% in the participants who were RF positive in 1987. Forty per cent of the participants who had a persistent (four to 13 years) increase of IgA RF combined with either IgM or IgG RF were diagnosed as having RA. A positive correlation was found between RF levels and various manifestations of RA. This association was stronger for the IgA and IgG RF isotypes than for IgM RF. Excluding RF positivity as a diagnostic parameter, RA was diagnosed in 33 of the participants and 20 (61%) of these patients had increased levels of IgM and IgA RF. Patients with RA with bone erosions in their hands had higher levels of IgA RF than patients without erosions, but an association was not found between bone erosions and other RF isotypes.

None of the RF negative participants who were symptom free when the original blood sample was taken developed RA during the four to 13 year follow up period. In contrast, five symptom free RF positive participants developed RA during this period. These five patients had all had increased levels of at least two RF isotypes before the onset of their symptoms.

It is concluded that the IgA and IgG RF isotypes have a closer association with the clinical parameters of RA than IgM RF. Furthermore, increases in RF can precede clinical manifestations of RA and this applies in particular to the IgA and IgG RF isotypes.

(*Ann Rheum Dis* 1992; 51: 863–868)

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Accepted for publication 29 November 1991

The part played by RF in the pathogenesis of joint disease is still not clear, but measurements of rheumatoid factor are useful for the diagnosis of rheumatoid arthritis (RA), though RF can also be increased in some non-rheumatic diseases and in apparently healthy subjects.

Conventional agglutination tests for RF do not distinguish between different RF isotypes but favour the detection of polymeric RF, in particular IgM RF. Individual RF isotypes can now be determined by radioimmunoassay or enzyme linked immunosorbent assay (ELISA). A correlation has been reported between certain RF isotypes and disease manifestations and treatment responses in RA.[1–10] The findings have not been uniform, however, and further investigations are therefore required. It was first reported by Teitsson *et al* that increased levels of IgA RF early in RA might be a marker for the early development of bone erosions.[11] An association between IgA RF and erosions has now been confirmed in other studies,[2 12] though such a correlation has not always been found.[3 13]

Increases in RF may sometimes precede the development of clinical RA[14 15] and it has been reported that RF levels and patterns are similar in clinical RA and in the prerheumatoid state.[15] There are to our knowledge, however, no reports on the persistence of increases in RF isotype or RF patterns in population studies of patients with RA and subjects without rheumatic disease. Aho *et al* have estimated that approximately 5% of subjects with 'false positive' agglutination tests for RF later develop RA[14] but individual RF isotypes have not, as far as we know, been analysed in this context.

This paper reports the persistence of increases in RF isotype patterns during an observation period of four to 13 years and their relation with rheumatic manifestations in an Icelandic population. The point prevalence of RA and rheumatic manifestations was also analysed in relation to increases in RF isotypes and RF isotype patterns.

Patients and methods

GENERAL DESIGN

A long term health survey has been carried out in the Reykjavík area by The Icelandic Heart Association since November 1967. The original purpose was to study the incidence and prevalence of cardiovascular diseases and to assess the health and cost benefits of mass screening programmes. Collection of data relating to rheumatic diseases and RF started in 1968.[16]

Participants in the study were born between 1907 and 1935 and were selected randomly from all inhabitants of the Reykjavík area in Iceland. They answered, with the help of specially trained nurses, a questionnaire about past and present health status and were investigated for manifestations of cardiovascular diseases and

predisposing factors. Questions about musculoskeletal symptoms, such as joint pain and swelling, morning stiffness, and back pain were included. Between 1974 and 1983 a total of 16 299 blood samples were collected from 13 858 participants and these samples were all tested for increases in RF between 1984 and 1986 (fig 1).

MEASUREMENTS OF RF

RF agglutination tests

The 16 299 serum samples were initially screened for RF by a sheep red blood cell agglutination slide test (Rheumaton, Wampole Laboratories). Positive samples were further tested by the Rose-Waaler technique and a titre of 1/10 or greater was considered positive.

ELISA FOR DETERMINATION OF RF

All available Rose-Waaler positive samples were screened by an ELISA for increases of RF isotypes.[17] An additional 1086 Rose-Waaler negative samples were screened in this way for increases of RF isotype. All samples that were positive by this ELISA screening procedure were tested further by ELISA for increases of individual RF isotypes (IgM, IgG, and IgA).

Briefly, microtitre plates were coated with rabbit IgG and the remaining active binding sites blocked with bovine serum albumin. After incubation with serial dilutions of a standard and of test samples, alkaline phosphatase conjugated mouse monoclonal antihuman light chain antibodies were added. Absorbance was read at 405 nm after incubation with a *p*-nitrophenyl phosphate solution and the mean net absorbance was calculated for each test sample and serial dilutions of the standard. The standard was given a RF activity of 100 arbitrary units per ml (AU/ml) for each RF isotype. The unit value of each test sample was read against the dilution curve of the standard. The ELISA for individual RF isotypes was performed in the same manner, except that alkaline phosphatase conjugated mouse monoclonal antihuman IgM, IgG, or IgA antibodies were used for the detection of the solid phase bound RF. The intra-assay variability in this ELISA system is less than 6% and the interassay variability is approximately 20%.[17] The reproducibility of the ELISA was monitored by including in every test run two RF positive serum samples (high and intermediate) and one normal control serum sample.

The normal distribution of individual RF isotypes was determined by testing 200 randomly selected adults and the 5 and 2·5% cut off levels were 25 and 50 AU/ml respectively.

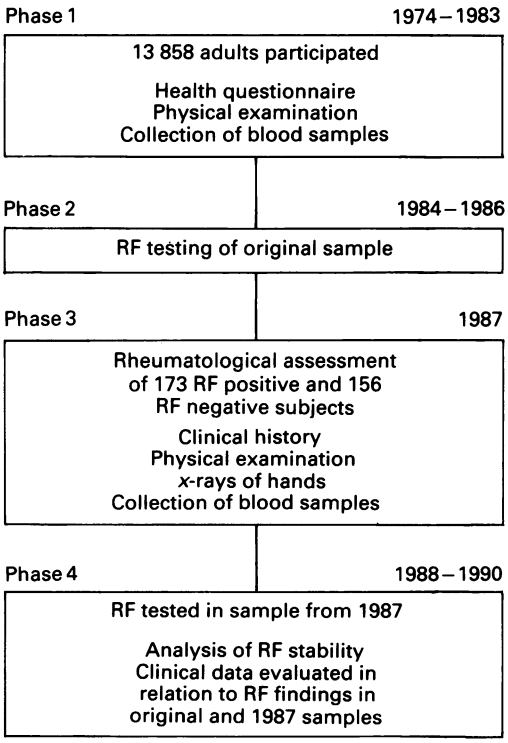

Figure 1 Design of study. RF=rheumatoid factor.

SELECTION OF PARTICIPANTS AND RHEUMATOLOGICAL ASSESSMENT IN 1987

From the original cohort of 13 858 participants all 270 available RF positive subjects and 223 age and sex matched RF negative control subjects were selected for a rheumatological evaluation in 1987 (fig 1). Table 1 gives the criteria for RF positivity.

An invitation was sent by post to all available participants. Non-responders were telephoned and those unable to attend the clinic were given the opportunity to be visited at home. Table 2 shows that the attendance rate was approximately 80% in the two groups. The participants were assisted by one of us (TJ) to answer a detailed structured questionnaire about past and present rheumatic symptoms (table 3). Several questions

Table 1 Criteria for RF positivity

1	Rose-Waaler titre ≥1/10
2	One RF isotype above the 97·5% cutoff level (50 AU/ml)*
3	Two or three RF isotypes above the 95% cutoff level (25 AU/ml)*

*AU=arbitrary units; see text.

Table 2 Attendance rate for clinical study in 1987

Subjects	*No RF positive subjects*	*No RF negative subjects*
Selected	270	223
Not alive in 1987	46	35
Moved away in 1987	8	3
Available for the study	216	185
Attending the study	173 (80%)	156 (84%)

Table 3 Clinical parameters assessed

Information obtained by questionnaire:
Pain in one or more joints
Pain in three or more joints simultaneously
Joint tenderness
Joint swelling
Morning stiffness
Back pain
Muscle pain
Infections and other disorders associated with increases in RF
Clinical procedures:
Examination of joints according to the ARA criteria
Radiographs of hands
New blood sample for RF testing

about infections and other RF related disorders were also included in the questionnaire. An examination of the joints was performed according to the American Rheumatism Association (ARA) criteria[18] and radiographs of the hands were evaluated for bone erosions by one of us (J Th). New blood samples were collected and tested for RF in 1988. Thus at least two blood samples taken at an interval of four to 13 years (mean 9·3 years) were available from each participant for the analysis of RF levels and patterns. Individuals with increases in RF that showed the same isotype pattern in the two (or all) samples were defined as having a persistent increase in RF. All clinical findings were recorded and assessed without knowledge of the RF results. The participants were classified as definite/classical RA, probable RA, or non-RA according to the ARA criteria,[18] but RF positivity did not count when the relation between rheumatoid morbidity and RF was analysed. Patients with definite/classical and probable RA were analysed together because of the low numbers in each group.

Mortality and incidence of cancer were also studied in relation to RF levels and the patterns and findings are reported elsewhere.[19]

STATISTICAL ANALYSIS

The χ^2 test (with Yates's correction for expected frequencies less than five) and the Mann-Whitney U test were used for the evaluation of statistical significance in relation to RF levels and patterns. Correlations were evaluated by calculating Spearman's rank correlation coefficient. The level of significance was $p<0·05$.

Results

PERSISTENCE OF INCREASES IN RF

Increases and patterns of RF isotypes were more persistent in the patients with RA than in subjects without RA (table 4). It is also clear that increases in IgM and IgA RF were more persistent than increases of IgG, both in the patients with RA and the subjects without rheumatic disease. Combined increases in IgM and IgA RF were significantly more persistent than other RF patterns. Of the subjects who were RF negative in the original sample 6% (10/156) had one or more RF isotypes increased in 1987, corresponding to an annual incidence of 690 in 10^5 subjects.

RHEUMATOID COMPLAINTS AND RF FINDINGS

Table 5 shows the cumulative prevalence of rheumatoid complaints in relation to RF findings in 1987. All symptoms and signs originating from peripheral joints were more common in the RF positive groups than in the RF negative group, and this difference was significant for joint swelling, tender joints, and pain in three or more joints simultaneously. Subjects with an increase in both IgM and IgA RF tended to have more symptoms than those with an increase of only one RF isotype. Interestingly, back pain was less common in participants with an increase in IgM or IgA RF than in the RF negative subjects.

PREVALENCE OF RA AMONG RF POSITIVE SUBJECTS

Excluding RF positivity as a diagnostic parameter, 33 of the 329 subjects who attended the clinical evaluation had probable or definite RA; table 6 shows the RF findings in these patients in 1987. Twenty (61%) of the patients with RA had increases of both IgM and IgA RF but seven (21%) had no increased RF isotype.

Of the 135 subjects with increased RF isotypes in 1987, only 26 (19%) had RA compared with seven (4%) of the 194 RF negative subjects. Fig. 2 shows, however, that the prevalence of RA was considerably higher in participants with persistent increases in RF and RF patterns and this applied in particular to the IgA and IgG RF

Table 4 Number (%) of participants with the same increase and pattern of rheumatoid factor (RF) in the original and 1987 samples

RF types	*Patients with RA**	*Participants without RA*
IgM RF	17/19† (89)	63/89 (71)
IgG RF	8/15 (53)	18/49 (37)
IgA RF	19/19 (100)	44/65 (68)
Rose-Waaler test	15/20 (75)	45/79 (57)
IgM+IgA RF	15/16 (94)	23/41 (56)
IgM+IgG RF	3/11 (27)	13/34 (38)
IgG+IgA RF	7/14 (50)	9/34 (26)

*RA=rheumatoid arthritis.
†Positive in 1987 and positive in original sample.

Table 6 Rheumatoid factor (RF) patterns in 33 subjects with rheumatoid arthritis

Increases in RF	*Number (%)*
IgM RF only	1 (3)
IgG RF only	2 (6)
IgA RF only	0 (0)
IgM+IgG RF	0 (0)
IgM+IgA RF	12 (36)
IgG+IgA RF	3 (9)
IgM+IgG+IgA RF	8 (24)
No RF isotype increased	7 (21)
Total	33

Table 5 Cumulative prevalence of manifestations of rheumatic disease in relation to rheumatoid factor (RF) findings in 1987. Results given as percentage of subjects

Manifestations of rheumatic disease	*RF negative (n=194)*	*Increases in RF*			
		IgM RF (n=103)	*IgG RF (n=37)*	*IgA RF (n=87)*	*IgM+IgA RF (n=62)*
Pain in one or more joints	58	68	59	67	66
Pain in three or more joints	12	21*	32**	26**	31***
Tender joints	29	47**	46*	46**	48**
Morning stiffness	34	41	46	45	47
Joint swelling	21	38**	38*	40***	48***
Back pain	47	32*	38	32*	31*
Muscle pain	37	34	38	30	29

Significance compared with the RF negative group: *$p<0·05$; **$p<0·01$; and ***$p<0·001$.

isotypes. Subjects with a persistent increase of IgA RF combined with either IgM or IgG RF showed the highest prevalence of approximately 40% (fig 2).

RA AND INCREASES IN RF ISOTYPES

Table 7 shows the prevalence of the individual ARA parameters in relation to the RF findings in the 1987 blood samples. All joint manifestations were more common in the IgG or IgA RF positive participants than in the IgM RF positive subjects. Moreover, levels of IgA or IgG RF correlated more strongly with the number of ARA parameters in the 144 participants who had swollen or tender joints than did the IgM RF levels (table 8).

Bone erosions in the hands were detected in nine of the patients with RA and these patients had higher levels of IgA RF than the 22 patients with RA who did not have detectable erosions (fig 3) (radiographs were not available for two of the patients with RA). This relation was not found for the other RF isotypes.

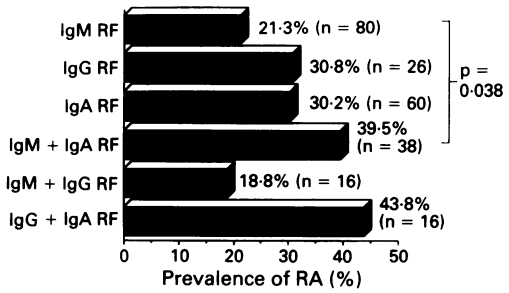

Figure 2 Prevalence of rheumatoid arthritis (RA) in participants with persistent increases in rheumatoid factor (RF) isotype in the original and 1987 blood samples.

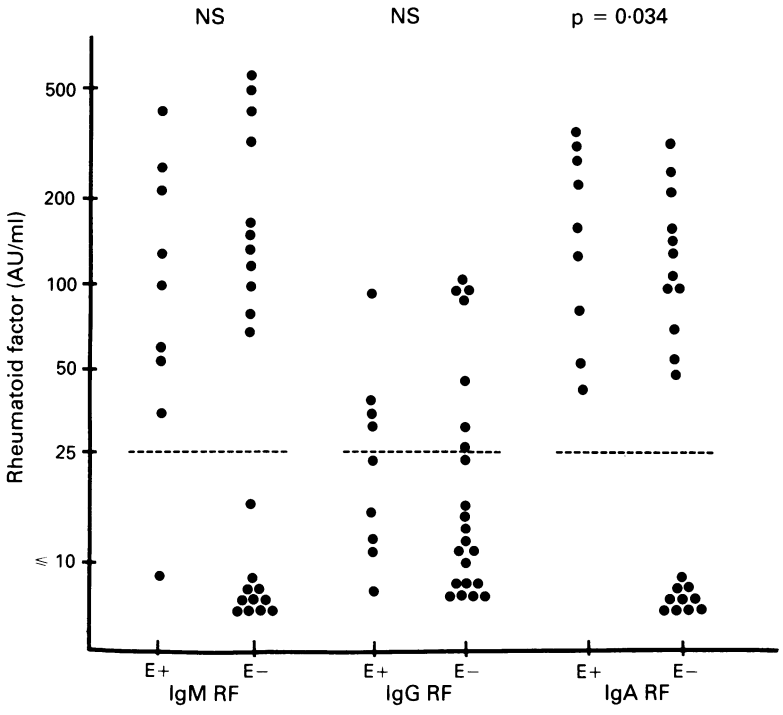

Figure 3 Rheumatoid factor (RF) levels in patients with rheumatoid arthritis with (E+) and without (E−) bone erosions in the hands. The horizontal dashed line indicates the 95% upper limit of normal values.

PROGNOSTIC VALUE OF INCREASES IN RF ISOTYPES

The prognostic value of increases in RF isotype in symptom free subjects was estimated by analysing all 197 subjects who did not have rheumatic symptoms when the original blood sample was collected between 1974 and 1983. Of these, 94 had been RF negative and 103 RF positive (table 9). The mean follow up time in 1987 was 9·3 years. None of the 94 RF negative subjects had developed RA during the follow up period but 5% of the IgM RF positive, 7% of IgG RF positive, 8% of IgA RF positive, and 8% of the Rose-Waaler positive subjects had developed RA. Thus symptom free subjects with increased IgA or IgG RF in the original blood sample had a higher risk of developing RA than the RF negative participants.

No difference could be found between RF levels or patterns in the original and 1987 blood samples in the five participants who developed RA during the follow up period.

Discussion

This paper reports a study of the association between rheumatoid manifestations and RF isotype patterns in a cohort of adults participating in a health survey in Iceland. Serum samples from 13 858 randomly selected subjects were first tested for RF by a sensitive screening procedure followed by the Rose-Waaler test, and Rose-Waaler positive samples were then

Table 8 Correlations between rheumatoid factor (RF) isotype levels and numbers of ARA parameters

RF isotype	*Spearman's rank correlation coefficient*	*Significance (p value)*
IgM RF positive	0·262	<0·002
IgG RF positive	0·485	<0·001
IgA RF positive	0·494	<0·001
Rose-Waaler positive	0·395	<0·001

Table 7 Prevalence of clinical manifestations in relation to rheumatoid factor (RF) findings in 1987. Results given as percentage of subjects

Clinical manifestation	*RF findings in 1987*			
	RF negative (n=194)	*IgM RF positive (n=103)*	*IgG RF positive (n=37)*	*IgA RF positive (n=87)*
Morning stiffness of one hour or more	6·3	14·6	21·6*	17·2*
Pain/tenderness in one or more joints	41·4	48·5	54·1	50·6
Joint swelling	7·3	24·3***	32·4***	34·5***
Swelling of second joint	2·6	16·5***	29·7***	21·8***
Symmetrical joint swelling	2·1	15·5***	29·7***	17·2***

Significance compared with the RF negative group: *p<0·05; **p<0·01; and ***p<0·001.

Table 9 Development of rheumatoid arthritis (RA) in relation to rheumatoid factor (RF) findings in the original blood sample

RF finding	*Development of RA during study period*			
	No with RA/total	*Percentage of subjects*	*Annual incidence (%)**	*Significance†*
RF negative	0/94	0	0	—
IgM RF positive	3/61	5	0·5	NS
IgG RF positive	3/43	7	0·8	$p<0·05$
IgA RF positive	4/53	8	0·8	$p<0·03$

*Epidemiological studies have shown the annual incidence for subjects over 40 years ranging from 0·074 to 0·157%.[23]
†Compared with the RF negative group.

tested for individual RF isotypes. The participants were considered to be RF positive if they had one RF isotype greater than the 97·5% or two or more RF isotypes above the 95% level of a distribution that was determined in 200 randomly selected adults. It seems logical to use the 95–97·5% diagnostic cut off limit for a disease such as RA with a prevalence of approximately 5% among subjects over 40 years of age.

The significance of RF isotypes in the general population has to our knowledge not been analysed before by studying a cohort derived from randomly selected subjects. In this study only a few subjects with persistent increases in RF had RA or developed RA. Participants with increased IgG or IgA RF, however, had a higher prevalence of RA than IgM RF positive subjects. Thus IgM RF was less specific for RA than the other RF isotypes and the highest prevalence was observed in subjects with an increase in both IgA and IgG RF. Furthermore, an increase in IgA RF showed a better correlation with the severity of joint manifestations and bone erosions than other RF isotypes.

In previous reports the prevalence of IgA RF in RA has ranged from 10 to almost 100%.[1–4 6 15 20 21] Most of our patients with RA had increases in IgM and IgA RF with or without an increase in IgG RF. These findings agree with those of Eberhardt *et al* who reported increases of both IgM and IgA RF in most patients with early RA.[13] Divergent findings may in part be due to methodological differences. Thus Tuomi *et al* [15] digested serum samples in pepsin before measuring IgA RF, a treatment that might destroy some of the IgA RF binding avidity. Similarly, Tarkowski and Nilsson used a DIG ELISA that may preferentially detect monomeric IgA RF.[2]

In agreement with other workers[22] we found that an increase in the IgM and IgA RF isotypes was more persistent than an increase in IgG RF, both in patients with RA and in subjects who did not fulfil the ARA criteria. The reason for the instability of increases in IgG RF compared with IgM and IgG RF is not known.

Increases in RF before the onset of clinical RA have been reported by other workers.[14 15] Aho *et al* estimated that only about 5% of RF positive subjects might develop RA.[14] Our findings agree with this estimate as 5–7·5% (depending on RF isotype) of the symptom free participants with increased RF developed RA during an observation time of four to 13 years. The incidence might, however, be much higher in subjects with a combined increase in IgA and IgM or IgG RF, but this could not be analysed in this study because only three subjects with this RF pattern were symptom free when the original blood sample was collected.

Conflicting findings have been reported on the association between RF isotypes and disease activity, extra-articular manifestations, and bone erosions in patients with RA. Thus a correlation has been reported between IgA RF and bone erosions in prospective and retrospective studies, though this association has not always been found.[2 3 9–13] These discrepancies may be due to differences in the selection of patients and the methods used for detection of the RF.

In summary, our findings indicate that RA can only be diagnosed in approximately 20% of subjects with an increase in one or more RF isotypes detected on a single occasion, though a persistent increase in RF, especially the IgA isotype, is associated with a much higher prevalence of RA. Furthermore, an increase in IgA or IgG RF may be more specific for RA and have a closer association with disease severity than the IgM RF isotype.

This study was supported by the Icelandic Science Foundation. We thank the staff at the Department of Immunology, Landspitalinn and the Heart Preventive Clinic, Reykjavík for their help during this study.

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