Low Mannose Binding Lectin Predicts Poor Prognosis in Patients with Early Rheumatoid Arthritis. A Prospective Study

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ABSTRACT. ***Objective.*** To determine whether low mannose binding lectin (MBL) is associated with poor prognosis in rheumatoid arthritis (RA) and whether patients with RA have increased frequency of MBL deficiency.

Methods. Patients with recent onset symmetric polyarthritis (< 1 year, median 3 mo) were recruited if they had not been treated longer than 2 weeks with disease modifying drugs. They were reevaluated after 6 months and their disease activity and progression were correlated with their MBL concentration, rheumatoid factor (RF) isotypes, and C-reactive protein (CRP). Sixty-three female patients with advanced RA were also analyzed.

Results. Sixty-five patients with early arthritis fulfilled American College of Rheumatology criteria for RA and 52 were followed for 6 months or longer. Low MBL was associated with raised RF, IgA RF in particular ($p = 0.02$), and also with a combined elevation of IgM and IgA RF ($p = 0.035$). Patients with low MBL (lowest 25th percentile) showed less improvement after 6 months of treatment than patients in the highest MBL quartile. This applied to the Thompson joint score ($p = 0.03$) and grip strength ($p = 0.004$). Low MBL was also significantly associated with radiological joint erosions at recruitment and at 6 month followup ($p = 0.039$); and the group with advanced RA also showed a significant association between low MBL concentration and radiological damage ($p = 0.036$). However, neither patient group had increased frequency of MBL deficiency compared to healthy controls.

Conclusion. Low MBL predicts poor prognosis in patients with early RA. (J Rheumatol 2001; 28:728–34)

Key Indexing Terms:
MANNOSE BINDING LECTIN RHEUMATOID ARTHRITIS RHEUMATOID FACTOR
JOINT EROSIONS PROGNOSIS

Mannose binding lectin (MBL) is a sugar binding collectin that has a role in innate immune defences. It binds to terminal sugar residues present on the surface of many microorganisms, resulting in activation of the complement components C4 and C2, thereby promoting phagocytosis and complement mediated killing of microorganisms[1,2]. The concentration of MBL in serum varies widely (0–10,000 ng/ml), and low MBL is mainly associated with 3 structural mutations in the MBL gene (in codons 54, 57, and 52) or with polymorphism in the promoter region[1-3]. Further, MBL may show up to 2-fold increase during acute phase responses[4]. Between 2 and 7% of Caucasians have been reported to be homozygous for the mutation in codon 54[5-7], and the mutation in codon 57 is even more common in black Africans[6,8,9]. MBL deficiency has been associated with increased susceptibility to infections[7,10-12], most strikingly in patients treated for hematologic malignancies (J.C. Jensenius, personal communication). Recent reports also suggest that MBL deficiency may also be associated with increased frequency of systemic lupus erythematosus[12-15] and rheumatoid arthritis (RA)[16,17], whereas other studies have not confirmed this[18-20]. It has also been suggested that RA patients with low MBL levels develop the disease at a younger age[16,21] and have more severe disease course than patients with higher MBL levels[16-18]. In view of the important role that MBL is thought to play in innate immunity[1] and the postulated involvement of infectious agents in the pathogenesis of RA[22] we studied the association of this protein with RA. Although various prognostic markers for severe RA are known, they do not accurately predict the prognosis of early RA.

We describe the first results of a prospective study on the correlation of MBL concentration with disease progression

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and RF isotypes in early RA. Patients with advanced RA were also assessed for comparison.

MATERIALS AND METHODS

The study was carried out in accordance with the Helsinki Declaration, and it was approved by the Ethics Committee of the University Hospital in Iceland and the Icelandic Computer Database Committee.

Participants with early RA. Patients with symmetric polyarthritis of recent onset (< one year) were recruited from outpatient clinics, irrespective of RF as measured by agglutination and ELISA, if they had not been treated longer than 2 weeks with disease modifying drugs. Table 1 shows their age and sex distribution, duration of joint pain or swelling when they entered the study, and their drug therapy at 6 month followup. Sex distribution of this group was even. There was no clinically significant association between MBL levels and drug therapy at 6 months. The patients were all assessed by rheumatologists (AV and AJG) and by a specially trained physician. The evaluation included a standardized questionnaire, examination, and routine laboratory tests including C-reactive protein (CRP). Disease activity and progression were assessed by the Thompson 38 joint score[23] and grip strength[24]. Radiographs were taken of hands and feet at entry and after 6 months. When the data were analyzed 65 patients who fulfilled at least 4 of 7 criteria of the American College of Rheumatology (ACR) for RA had been recruited, and 52 had been evaluated at 6 month followup. Clinical and radiologic assessments and laboratory tests were carried out and analyzed independently in a blinded manner, and after the initial evaluation the patients received therapy according to the standard practice in Iceland.

Participants with longstanding RA. To study the relationship between MBL concentrations and longterm outcome in RA, 63 female patients with advanced RA were also evaluated by a standardized questionnaire and examination. Their age at disease onset and disease duration and drug therapy at the time of the study are shown in Table 1. In addition to the clinical assessment, radiographs of their hands were examined by Sharp criteria[25] as modified by Kaye, *et al*[26]. Score > 100 indicates severe joint damage.

Controls for distribution of MBL concentrations. MBL was measured in 330 adult Icelanders, including 130 who were selected at random and 200 blood donors. No significant difference was observed in MBL levels of these 2 control groups.

Measurement of MBL. We used a sandwich ELISA system, adopted from Claus Koch at the Statens Serum Institut (SSI), Copenhagen, Denmark[27]. Briefly, microtiter wells (Maxisorb, Nunc) were coated by overnight incubation at 4°C with monoclonal mouse anti-human MBL antibody (clone 131-1; SSI) in phosphate buffered saline (PBS) without azide. Two dilutions of the test sera (1/25 and 1/200) were then incubated 1 h at room temperature together with a serial dilution of a standard calibrated with highly purified MBL obtained from SSI. Sera that were low in MBL were retested at 1/3 and 1/9 dilutions. Biotinylated Mab 131-1 diluted 1:6000 was then added for 1 h at room temperature followed by horseradish peroxidase labeled streptavidin (S-5512; Sigma, St. Louis, MO, USA) at 1:8000 for a further 1 h at room temperature. After 5 min incubation with tetramethyl benzidine (507605; Kirkegaard & Perry Laboratories, Maryland, MD, USA) the reaction was stopped with 0.18 M H_2SO_4 and the absorbance read at 450 nm. The microtiter wells were washed 3 times with PBS/0.5 M NaCl/0.5% Triton X-100 (Sigma) after each step. Three control sera with low, medium, and high MBL concentration were included in each test run to monitor assay variability. The lower detection limit of the assay was 20 ng/ml. No evidence was found for interference by RF in this system. Thus, wells coated with 1/25 dilution RF positive MBL deficient sera did not bind the biotinylated mouse anti-MBL antibodies, nor did MBL coated wells bind IgG from IgG-RF positive human sera. The intra and interassay variabilities were 10% and 12%, respectively. MBL concentrations were measured in every patient at entry and at 6 month followup. Clinical data were analyzed in relation to the initial MBL concentration.

Measurement of RF. RF was measured by agglutination using the RAPA kit (Fujirebio Inc., Tokyo, Japan) according to the manufacturer's instructions, and also by an isotype-specific ELISA[28]. Briefly, heat inactivated sera (56˚C for 30 min) were tested at a dilution of 1/40 against a serial dilution of a local standard that had been calibrated against an International Reference Preparation (SSI, Copenhagen). The local standard was given an arbitrary value of 100 units for each RF isotype (AU). Alkaline phosphatase conjugated mouse monoclonal anti-human light chain IgG, IgM (Sigma), and IgA (Pharmingen) antibodies were used for detection of the respective RF isotypes. Three RF positive and one RF negative control sera were included in each test batch to monitor assay variability. RF values above the upper 95% cutoff level (≥ 25 AU/ml) for 200 healthy subjects were considered elevated for each RF isotype.

Statistical analysis. Student's t test was used to compare continuous variables between 2 groups and the Mann-Whitney rank-sum test when the distribution of values did not fulfill the distribution criteria for the t test. Pearson's correlation was used to investigate correlation between 2 continuous variables. Fisher's exact test was used for comparison of 2 independent proportions. All tests were 2 sided and the level of significance was set at $p < 0.05$.

RESULTS

Distribution of MBL concentrations. The distribution of MBL concentrations in controls was not significantly

Table 1. Patients' characteristics and treatment.

	Prospective Group with Early RA (n = 65)	Transectional Group with Advanced RA (n = 63)
M/F	31/34	0/63
Age at onset, yrs (range)	53 (17–80)	58 (24–78)
RF positive, %	53	56
Disease duration, median (range)	3 mo (1–12)*	14 yrs *(1–48)
Drug therapy**, %		
Methotrexate	76	65
Steroids	38	24
Plaquenil	16	27
Salazopyrin	14	8
NSAID	33	59

*Duration from onset of joint pain or swelling. **The prospective group at 6 month followup and the transectional group at the time of study.

different from that observed in patients with RA (Figure 1). Relatively few individuals had MBL levels around 50, 150, and 400 ng/ml, possibly reflecting different populations with respect to MBL mutations and promoter polymorphisms (R. Steffensen, personal communication). As MBL induced deposition of complement onto appropriate microorganisms usually cannot be detected *in vitro* at MBL concentrations below 400 ng/ml[29], it was decided to classify individuals with MBL levels at study entry of 400 ng/ml or less as low in MBL. This concentration corresponded closely to the cutoff level for the lowest 25th percentile in the prospective group. The MBL concentrations were practically the same in each of the patients at entry and after 6 months' followup ($r = 0.9$, $p = 1 \times 10^{-19}$). No patients who were under the lowest 25th percentile at entry had MBL concentrations above this level after 6 months and vice versa.

The incidence of low MBL (< 400 ng/ml) was not increased among the patients compared to the controls, and this also applied to MBL levels below previously reported cutoff values of 150, 50, or 20 ng/ml. Further, the patients with early or advanced RA were not significantly different

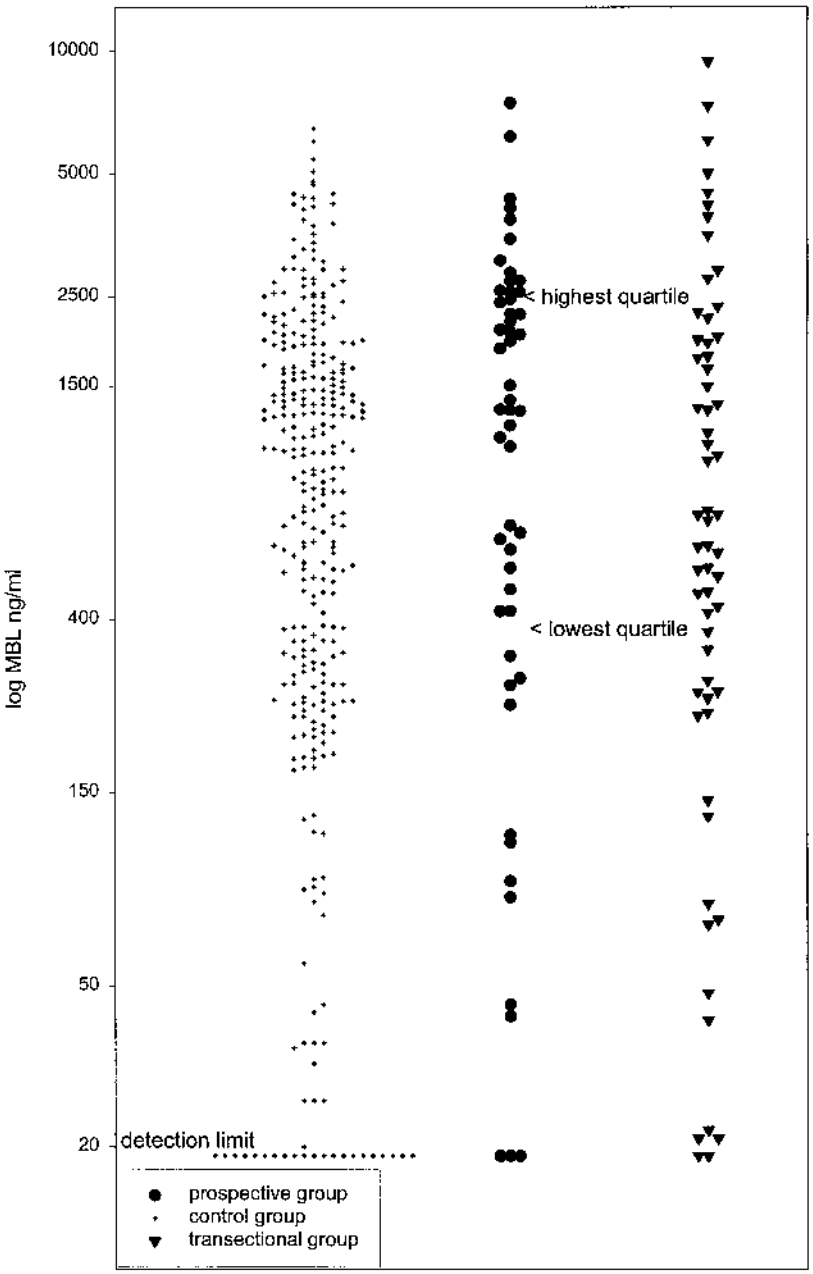

Figure 1. MBL concentrations in RA patients and controls. The distribution was not significantly different between controls and patients. The cutoff for the lowest 25th percentile was about 400 ng/ml.

Table 2. Numbers of patients with early RA having radiographic joint erosions at 6 month followup*.

	MBL Concentration, ng/ml			
	< 150	> 150	Lowest 25th Percentile	Highest 25th Percentile
Erosion	4**	4	4**	0
No erosion	5	37	8	13
p†	**0.026**		**0.039**	
RR	4.2		∞	
95% CI	1.4–12.3		∞	

*Radiographs were not available from 2 patients at 6 month followup. **All 4 had erosions when they were recruited to the study and their disease duration did not differ from the study group as a whole. † p values are significant.

with respect to the distribution of MBL levels or the frequency of MBL deficiency (Figure 1).

MBL concentrations and joint erosions in the early RA group. Although only 8 of the 52 patients with early RA had developed radiological joint erosions at 6 months, there was a significant association between low MBL and radiological joint erosions at the 6 month followup (Table 2). Thus, no patient with MBL concentration in the highest 25th percentile had joint erosions, compared to 4 in the lowest 25th percentile, and those 4 all had MBL concentration lower than 150 ng/ml. Further, these 4 patients had all developed erosions when they entered the study, and the median duration of their disease was 3 months, the same as for the study group as a whole.

Changes in disease activity after 6 months of treatment. At 6 month followup the great majority of the patients had been treated with disease modifying drugs or steroids (Table 1) and many had shown a marked clinical improvement. However, patients with relatively low MBL showed significantly less improvement than those with high concentration of MBL (Figures 2 and 3). This applied both to the Thompson joint score (p = 0.03) and grip strength (p = 0.004). It should be noted that patients with low MBL did not show a significant improvement in Thompson joint score, but those with high MBL had a highly significant improvement (p = 0.0003) (Figure 2). The MBL levels at study entry were also analyzed for those patients who showed the least and the most marked improvement (lowest and highest quartiles) for each of the disease activity variables after 6 months, including CRP. The patients who

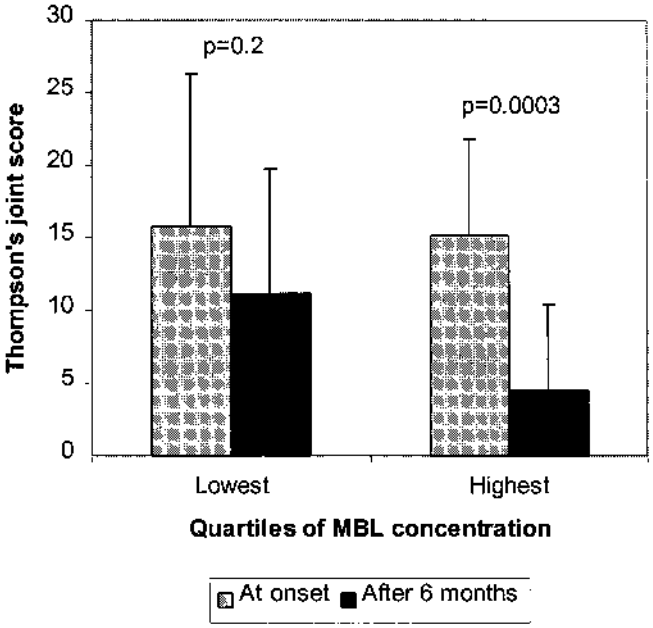

Figure 2. Thompson joint score (tenderness and joint swelling) at study entry and after 6 months in patients with low and high MBL concentration. Improvement in patients with high MBL was highly significant, but not in those with low MBL, and patients with low MBL showed significantly less improvement than those with high concentration of MBL (p = 0.03).

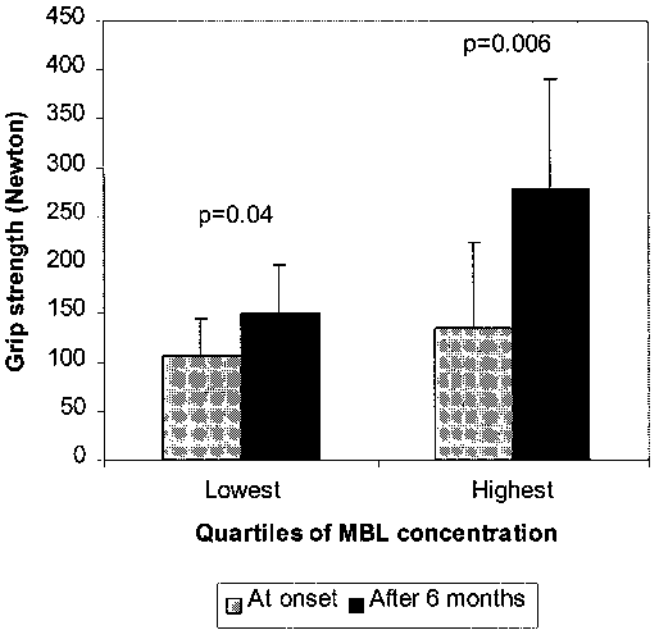

Figure 3. Grip strength at study entry and after 6 months in patients with low and high MBL concentration. Patients with low MBL showed significantly less improvement than those with high concentration of MBL (p = 0.004). Grip strength measurements were not available for 6 patients at onset due to instrument failure.

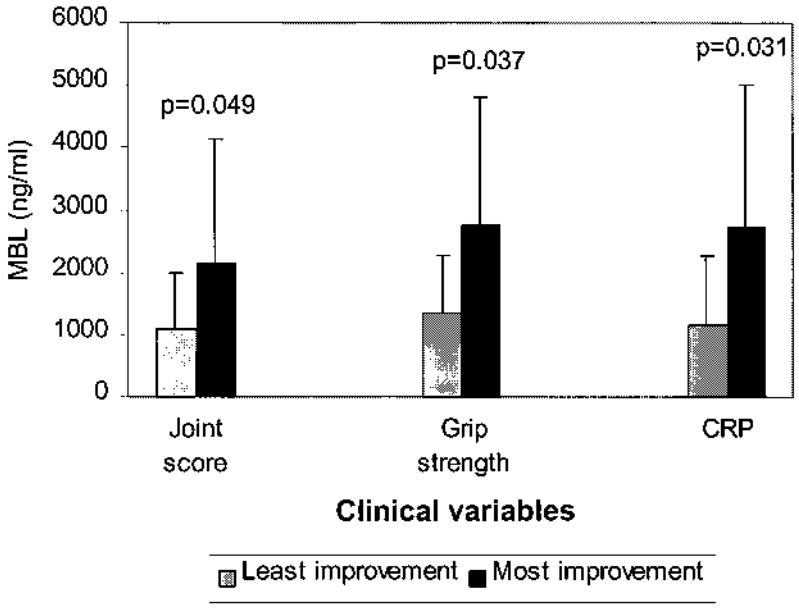

Figure 4. Comparison of initial MBL levels in patients who showed the least (lowest quartile) and most (highest quartile) clinical improvement at 6 month followup. Patients who showed the least clinical improvement had significantly lower MBL levels when they entered the study.

showed the least clinical improvement (lowest 25th percentile) had lower MBL levels when they entered the study than those who improved most (Figure 4), and Pearson correlation analysis showed that this also applied to the group as a whole (data not shown). Thus, the lower the MBL concentration, the less was the response to therapy.

RF measurements at disease onset. Patients with low MBL were significantly more often positive for IgA RF or combined IgM/IgA RF at study entry (Table 3). However, such associations were only borderline significant for IgM RF alone and not when RF was measured by agglutination (RAPA), which preferentially detects IgM RF (Table 3).

MBL concentrations and clinical variables in advanced RA. There was a negative correlation between MBL concentration and standardized radiographic score ($p = 0.036$, $r = -0.3$), and those patients who had radiographic score > 100, indicating severe joint damage, had lower MBL than the remaining patients ($p = 0.016$) (data not shown). No significant correlation was found between low MBL concentration and elevated RF in this group, although trends similar to the early RA group could be seen. However, in this group there was a significant positive correlation between MBL concentration and CRP ($p = 0.007$, $r = 0.3$) and grip strength ($p = 0.04$, $r = 0.3$) but not with the Thompson joint score.

MBL concentration and age at disease onset. In the early RA group there was no significant association between age at disease onset and MBL concentration. However, women with low MBL, in both the early and advanced groups, tended to have earlier disease onset, whereas the opposite applied to men (Table 4).

DISCUSSION

To our knowledge this is the first prospective study of serum MBL concentrations in patients with early RA. Previous studies have been either cross sectional or retrospective, involving patients with advanced disease[16-19,21], and the analyses have in most instances been based on the patients' MBL genotypes rather than actual MBL concentration in serum[18,19,21]. However, the concentration and functional activity of MBL in serum can vary markedly between indi-

Table 3. Percentage of RF positive patients with early RA according to MBL concentrations at study entry.

Patient Groups According to RF Status*	Low MBL, Lowest 25th Percentile	Higher MBL, Above Lowest 25th Percentile	p	RR	95% CI
Agglutination (RAPA) positive (%)	10/16 (63)	19/46 (41)	0.16	1.9	0.79–4.6
IgA RF positive (%)	11/16 (69)	16/47 (34)	**0.02**	**2.9**	**1.2–7.4**
IgM RF positive (%)	10/16 (63)	17/47 (36)	0.08	2.2	0.92–5.4
IgM + IgA RF positive (%)	10/16 (63)	14/47 (30)	**0.035**	**2.7**	**1.1–6.5**

*RF isotypes for 2 patients and RAPA measurement for 3 patients were not available.

Table 4. MBL concentration and age at disease onset.

Average Age of Men and Women, yrs	MBL Concentration Lowest 25th Percentile	Highest 25th Percentile	p
Women	49	58	0.26
Men	64	53	0.18
p	0.06	0.52	

viduals carrying the same genotype, although remaining markedly stable for each individual measured repeatedly[16,17], even over a period of several years (T. Vikingsdottir, *et al,* unpublished data). It should be noted in this context that *in vitro* studies have indicated that MBL may not be effective in activating the complement system at a concentration below 400 ng/ml[29].

Our findings indicate that low MBL may influence disease progress at a very early stage and that measurement of MBL concentration can be used as a prognostic marker. Because the patients were initially evaluated before the progress of their disease was influenced by disease modifying drugs, it was possible to analyze their response to such treatment in the context of their MBL levels. Patients with low MBL were more resistant to treatment than patients with high MBL concentration, and low MBL was also associated with radiological joint damage in both early and advanced RA. It is unlikely that low MBL in patients with RA is secondary to increased consumption because their MBL levels were stable over a period of 6–12 months regardless of changes in their disease activity.

Thus, our findings confirm and extend previous reports on an association between low MBL and disease activity in RA[16-18]. On the other hand, our results do not confirm unequivocally that patients with low MBL develop RA at a younger age than those with normal MBL levels[16,21], but we did observe such a trend in the women we studied, while the reverse was true for men. Neither did we confirm that RA patients have lower MBL than healthy controls[16,17], and this applied to both the patients with early disease and those with longstanding and advanced disease. Three other studies also failed to confirm such an association[18-20]. It is possible that this discrepancy is due to methodological or ethnic differences. Therefore, our findings do not support the simple notion that RA may be triggered by microorganism(s) that are particularly susceptible to MBL mediated defence mechanisms.

However, RA is a complex and multifactorial disease. It is possible that relatively high concentration of MBL could help to suppress microorganism(s) that may be involved in the pathogenesis of RA. Another and not mutually exclusive possibility is that MBL may facilitate the clearance of immune complexes from the rheumatoid joint. This might explain the association between low MBL and RF positivity, as immune complexes are known to stimulate the production of RF. MBL deficiency could therefore result in defective clearance of immune complexes and give rise to more severe disease outcome. Indeed, abnormal exposure of N-acetyl glucosamine has been found in IgG from patients with RA[30] and MBL has a high affinity to this sugar[1,2]. It has been shown that MBL binds to RA associated IgG (IgG-G0). Further, similar concentrations of MBL have been measured in the synovial fluid and serum of RA patients[31]. It is therefore possible that high concentration of MBL may promote inflammatory activity[21], but our findings do not support this.

Previous studies have not found an association between low MBL and elevated RF as measured by agglutination[16,17], and our findings agree with this. However, the relationship between low MBL and elevated RF was significant for those RF isotypes (IgM and IgA RF) that have the highest specificity for RA[32], and especially for IgA RF, which has been associated with poor prognosis in RA[33-36], but it is not possible on the basis of available data to corroborate a causal relationship between these phenomena.

We conclude that MBL may have a protective role in the pathogenesis of RA, and that measurement of MBL at an early stage of the disease can help to identify patients with RA who require aggressive and sometimes expensive treatment.

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