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CLINICAL RESEARCH

Undetectable mannose binding lectin (MBL) and low MBL concentrations are associated with an increased lifetime risk for urinary tract infections in females with autoimmune rheumatic disorders

[1,2]Jasjit Walia, [1]Paul S Noakes, [3]Sophie Coleman, [4]Monica Kemp, [5]Tracy Easter, [1,3,5]Graeme J Carroll

[1]School of Medicine, University of Notre Dame Australia, Fremantle; [2]South Western Sydney Local Health District, NSW; [3]ArthroCare, Mount Lawley; [4]Department of Clinical Immunology, PathWest Laboratory Medicine, Queen Elizabeth Medical Centre, Perth; [5]Department of Rheumatology, Fiona Stanley Hospital, Murdoch (all Western Australia except JW at New South Wales).

Abstract

Introduction: Urinary tract infections (UTI) are common in females with autoimmune diseases**.** Mannose binding lectin (MBL) is a component of the innate immune system and has been implicated in serious infections. A relationship between UTI frequency and MBL deficiency has not been conclusively established, but a recent study reported a possible association. Establishment of a relationship could alter the paradigm of prophylaxis and treatment of UTI in these patients.

Aim: To investigate the relationship between MBL deficiency (≤400 ng/mL) and lifetime risk for multiple (>5) UTI in females with diverse autoimmune rheumatic diseases. It was hypothesised that MBL deficiency confers increased risk for multiple lifetime UTIs.

Methods: A quantitative questionnaire was sent to 346 females with physician-diagnosed rheumatoid arthritis (RA), systemic lupus erythematosus, psoriatic arthritis, ankylosing spondylitis and others, based on autoimmunity, in whom pre-treatment MBL concentrations had been determined. Participants were not aware of their MBL status. Variables assessed were prescribed medications, smoking status, diabetes mellitus and total lifetime of self-reported UTI. Data were analysed in SPSS using a binomial logistic regression model.

Results: Analysable questionnaires were completed by 166 females (median age 66, range 22 to 93) of whom 116 had a diagnosis of RA (69.8%). Fifty participants (30%) were MBL deficient (≤400 ng/mL) and in 23 (13.8%) MBL was undetectable (≤56 ng/mL). Sixty-one (36.7%) had >5 lifetime UTI. MBL deficiency in patients with autoimmune rheumatic diseases was found to be associated with a high lifetime rate of multiple UTI (n >5, P <0.05) independent of potential confounding factors. A strong association was also identified when observed and expected frequencies for lifetime UTIs were compared by use of 2 x 2 contingency tables and Chi-squared testing (P < 0.001 for MBL <400 ng/mL and P<0.001 for undetectable MBL [<56ng/mL]).

Conclusion: In this questionnaire-based study, a relationship has been detected between self-reported lifetime UTIs and low or undetectable MBL concentrations. Due to the limitations associated with retrospective studies, the findings need to be confirmed prospectively and corroborated with microbiological and clinical outcome data.

Introduction

Rheumatoid arthritis (RA) is an auto-immune (AI) condition that can cause serious disablement and functional compromise. In RA, severe pain is reported 2.9 times more often, poorer health 3.3 times more often and psychological distress and decreased workforce participation 1.7 times more often, in comparison to the general population.[1] Furthermore, RA itself and diverse treatment regimens confer increased risk for major infections, including lower respiratory tract infections and urinary tract infections (UTIs). The latter accounts for about 10% of all serious infections in RA (defined as those requiring admission to hospital, intravenous antibiotics, or which cause death or serious disability). Overall, therapeutic interventions in RA are known to cause twice as many hospital admissions.[2]

Mannose Binding Lectin (MBL) is an important component of the innate immune system and is a member of the collectins family of molecules. MBL is produced in the liver and plays a major role in the identification of foreign microorganisms (bacteria, viruses, fungi and protozoa) through its lectin region.[3] The functions of MBL have been widely studied and can be summarised as[4] provision of immediate defence against infection by complement activation, promotion of complement-independent opsonophagocytosis, modulation of inflammation and promotion of apoptosis.

Germane to urinary tract infection susceptibility is the potential for MBL that is normally secreted to mucosal surfaces in general to be depleted at uro-genital mucosal surfaces in persons with low (≤400 ng/mL) or undetectable serum MBL (≤ 56ng/mL).[5] Although there is no data concerning uroepithelial secretion of MBL, evidence for the notion of reduced mucosal secretion has arisen from vulvovaginal lavage studies.[5] A 4-fold lower MBL concentration was noted in cervicovaginal lavage fluid from women who had recurrent vulvovaginal candidiasis. Similar reductions at uroepithelial surfaces could contribute to recurrent UTI.

Mutations in MBL and promoter polymorphisms may compromise the function of the MBL glycoprotein and give rise to differential concentrations with unpredictable consequences for host defence. MBL concentration and its effect on immunity has been widely studied in a variety of contexts. MBL deficiency was first identified as an opsonisation defect in children who presented with unexplained infections and failure to thrive.[6] This was further reinforced by the observation that MBL deficiency was associated with recurrent upper respiratory tract infections and meningococcal disease in children.[7]

Whilst there are several studies of MBL deficiency in healthy populations, there is relatively little research into the role that MBL plays in established autoimmune disease and in particular in regard to infection susceptibility, which is raised.

Systemic lupus erythematosus (SLE) patients who had MBL deficiency were found to be at increased risk for developing respiratory tract infections and arterial thrombosis in comparison to SLE patients with normal MBL concentrations.[8] Brazilian patients with MBL deficiency and RA were found to be at increased risk for pneumonia, UTIs, sepsis (septicaemia) and septic arthritis in comparison to RA patients without MBL deficiency.[9]

Previous research conducted in Western Australia found an association between the concentration of MBL and serious infections in patients with RA. The 7 year prospective study found that MBL deficiency was associated with a 5 times increased risk of developing serious infections.[10] The authors also noticed a relationship between increasing UTI frequencies and low MBL concentrations, however the question of whether a direct relationship between UTIs and MBL deficiency exists could not be answered. A further study of coexistent RA and bronchiectasis identified a significantly higher frequency of undetectable MBL in those RA patients with bronchiectasis in comparison to those without. Interestingly, in this cohort, undetectable MBL correlated with reduced long-term survival.[11]

This study extends the aforementioned findings and more directly analyses the relationship between MBL deficiency and lifetime UTI. The fundamental reason for further research in this field stems from the very large morbidity and mortality associated with autoimmune diseases and the added morbidity and mortality associated with serious infections. This added risk complicates the diseases and their treatment.

Methods

The study was in female participants with documented physician diagnosis of autoimmune disorders (rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis, ankylosing spondylitis and others) who were identified from the records of a private rheumatology clinic in Perth, Western Australia (Arthrocare, Mount Lawley). Participants were selected according to the criteria in Box 1. All patients were screened for immunodeficiency including MBL deficiency before introduction of immunosuppressants.

A quantitative questionnaire was sent to 346 female participants who were invited to complete the consent form and the questionnaire between May and August 2016. The inclusion criteria included a limitation to females, being the gender predominantly affected by autoimmune diseases and UTI.

Prior to a questionnaire being distributed to the study cohort, questionnaire validity and recall bias was examined using 100 randomly selected participants. The questionnaire was sent to these participants and then their results (the number of infections) were cross-referenced using medical records, their medical practitioner and pathology service results. Cronbach's alpha was used to test questionnaire validity. In this sample, it was found to be 0.8, which is considered to indicate acceptable validity.

The questionnaire requested the following information:

- Name and date of birth
- Main diagnosis (Table 1)
- Current medications
- Age at diagnosis
- Previous hospitalisations for infections and which type of infections
- Urinary tract, bladder or kidney infection
  - Total number of UTI
- Number of UTI that required antibiotic treatment.
- Confounding factors:
  - Diabetes mellitus (type 1 or 2)
  - Smoking (number of cigarettes/day)
  - Corticosteroid usage

The questionnaire required less than 10 minutes to complete. Participants were asked to return the questionnaire in a prepaid envelope. Returned questionnaires were stored in secure storage at the primary study centre in Mount Lawley. Participants who delayed returning the questionnaire and consent form were given a reminder phone call 4 weeks later, and those who declined to participate were removed from the database. The data was de-identified on coding.

Box 1. Inclusion and exclusion criteria

Inclusion criteria	Females over 18 years living in Western Australia
	Diagnosed autoimmune disease
	MBL concentrations measured
	Capable of giving consent
Exclusion criteria	Non-English speaking

After data collection was completed, MBL concentrations for each participant were linked to the corresponding clinical data in preparation for final data analysis.

A number of assumptions were made in this retrospective study, namely that all UTI numbers indicated by participants were correct and was the summation of kidney, bladder and urethral infections because it was too difficult for participants to distinguish between pyelonephritis, cystitis and urethritis. Hence in this study, the term urinary tract infection represents the summation of these three conditions.

Ethical approval was obtained from the University of Notre Dame Australia's Human Research Ethics Committee (UNDA HREC Reference number 016062F). The study received trial registration (ANZCTR Trial ID: ACTRN12616001076460)

MBL measurement

The concentration of oligomerized MBL in human serum was measured colorimetrically using the MBL Oligomer ELISA kit (Bioporto, Denmark). In summary, microwells coated with a monoclonal antibody against the MBL carbohydrate–binding domain were incubated with diluted patient serum. Bound MBL was detected with a biotinylated MBL antibody and developed using horseradish peroxidase-conjugated streptavidin tetramethylbenzidine substrate. The intensity of the coloured product is proportional to the concentration of MBL in the serum. The assay determines MBL concentrations and does not assess its function.[10] Mutations in MBL and promoter polymorphisms may compromise the function of the MBL glycoprotein. Persons with MBL concentrations <56 ng/mL were deemed to have undetectable MBL. Although MBL concentrations can vary over time and especially in conjunction with phenomena that induce an acute phase response when MBL tends to rise, whenever the concentrations are undetectable, they usually remain so when repeated.

Data analysis was carried out with Microsoft Excel and IBM's SPSSv24. Descriptive statistics are presented as medians and standard errors, whilst categorical variables are presented as percentages of the cohort. Using the final available sample size of 166 patients, a 95% confidence interval, p = 0.05, and effect size = 0.3, power was estimated to be 0.9999362.

Once data was de-identified, the patients were allocated into binary categories of MBL concentrations greater or less than or equal to 400 ng/ml. 400ng/mL was chosen as the primary limiting value because previous Australian studies have reported higher rates of infections and poorer outcomes (reduced survival) at MBL concentrations below that value.12 Undetectable MBL is a subgroup of the low MBL category but was studied alone in light of earlier studies demonstrating increased susceptibility to diverse infections in this sub-group of patients.[9-11]

A binomial logistic regression analysis was carried out placing the binary category of total UTI as the dependent variable, and smoking, diabetes mellitus, MBL concentration and treatment with methotrexate, etanercept, hydroxychloroquine, corticosteroids as the independent variables. The regression model was carried out in two steps with MBL added in the second step alone. Two by two contingency tables were constructed in order to analyse the number of UTI in relation to MBL deficiency (≤400 ng/ml) or non-detectability (<56 ng/ml) using chi-squared testing.

Results

Of the 346 mailed questionnaires, 174 were returned (50.6%). Of these, 8 were removed from data analysis due to incomplete data. Thus 166 responses were analysed. Rheumatoid arthritis accounted for 70% of participants (Table 1).

The median age was 66 y (range: 22 to 93 y) and 30% were MBL deficient. Sixty-two (37%) participants had greater than 5 UTI in their lifetime. Diabetics and smokers comprised only a small proportion of the participant cohort (11% and 5%, respectively). Methotrexate was the most frequent DMARD medication prescribed followed by corticosteroids, hydroxychloroquine and etanercept (Table 2).

Condition	n	%	Cumulative %
Rheumatoid arthritis	116	69.4	69.4
SLE	12	7.2	76.6
Psoriatic arthritis	13	7.8	84.4
Ankylosing spondylitis	13	7.8	92.2
Other*	12	7.8	100.0
Total	166	100.0	

Table 1. Frequency of diagnoses in the participant cohort. SLE = systemic lupus erythematosus. *Polymyalgia rheumatica, dermatomyositis and primary Sjögren's syndrome.

A logistic regression of increased lifetime risk of UTI expressed as a binary value greater than 5 or not against smoking, diabetes, medications (corticosteroids, hydroxychloroquine, methotrexate, etanercept) and MBL concentration as independent variables, using a modified stepwise analysis in which MBL concentration was added. The initial regression was not statistically significant, $\chi^2(7) = 12.370$, P >0.05 (Table 3, Step 1). After addition of MBL, two were statistically significant, MBL and etanercept (Table 3, Step 2).

Medication	n	Medication	n
Abatacept	11	Infliximab	2
Adalimumab	11	Leflunomide	15
Apremilast	1	Meloxicam	6
Azathioprine	1	Methotrexate	72
Celecoxib	7	Naproxen	2
Certolizumab	3	Paracetamol+ codeine	3
Diclofenac	2	Paracetamol	9
Etanercept	34	Prednisolone	41
Folate	46	Rituximab	8
Golimumab	10	Sulfasalazine	5
Hydroxy-chloroquine	38	Tramadol	2

Table 2 Medications in use by the study population. Total number of medications (329 is greater than the number of participants (166) because some patients were taking more than one medication.

Step 1: Smoking, diabetes and medications						
	B	S.E.	Wald	df	Sig.	Exp(B)
Smoking	0.51	0.76	0.45	1	.501	1.66
Diabetes	-0.02	0.52	0.002	1	.962	0.98
Corticosteroids	0.50	0.38	1.71	1	.190	1.65
HCQ	-0.51	0.42	1.48	1	.224	0.60
Methotrexate	-0.38	0.33	1.33	1	.249	0.68
Etanercept	-0.85	0.45	3.60	1	.058	0.43
Constant	-0.50	0.85	0.35	1	.556	0.61
Step 2: Smoking, diabetes, medications and MBL						
Smoking	0.49	0.766	0.40	1	.524	1.63
Diabetes	−0.05	0.520	0.01	1	.927	0.95
Corticosteroids	0.51	0.385	1.72	1	.189	1.66
HCQ	-0.56	0.426	1.72	1	.190	0.57
Methotrexate	-0.35	0.338	1.05	1	.306	0.71
Etanercept	-1.00	0.464	4.64	1	.031	0.37
MBL	-0.70	0.356	3.90	1	.048	0.49
Constant	0.03	0.893	0.001	1	.973	1.03

Table 3 Binomial logistic regression analysis before (Step 1, above) and after (Step 2, below) stepwise addition of MBL to the independent variables (smoking, diabetes and medications). HCQ = hydroxychloroquine.

The data showed that MBL deficient (≤400ng/mL) participants were 2.02 times more likely to have high rates of urinary tract infections in comparison to patients who were not MBL deficient. Participants not receiving etanercept were 2.72 times more likely to have high rates of UTI in comparison to patients receiving etanercept. The relevant 2 × 2 contingency tables are shown in Tables 4a and 4b.

A	MBL ≤400 ng/ml	MBL >400 ng/ml
≤5 UTI	36	126
>5 UTI	525	891

B	MBL ≤56ng/ml	MBL >56 ng/ml
≤5 UTI	7	155
>5 UTI	302	1114

Table 4a and 4b. 2 × 2 Contingency tables showing number of lifetime urinary tract infections according to two different critical values of MBL. For the critical value 400 ng/ml, χ^2 (1, N = 166) = 13.99 P <0.001; for 56 ng/ml, χ^2 (1, N = 166) = 26.69 P <0.001.

Discussion

In previous reports, MBL deficiency has been implicated in UTI in rheumatoid arthritis and ankylosing spondylitis.[9,10,13] In this study, MBL-deficient participants with several autoimmune diseases were found to be twice as likely to experience high rates of UTI compared to patients with normal MBL concentrations. Susceptibility was demonstrated for MBL <400 ng/mL (P <0.001) including undetectable MBL (P <0.001). The results also indicate that in such patients, MBL deficiency confers greater risk for UTI susceptibility than smoking, diabetes and immunosuppression (corticosteroids, hydroxychloroquine or methotrexate).

The total number of kidney, bladder and urethral or anatomically unspecified urinary tract infections was determined and then split into binary categories as follows: ≤5 or >5. Five was chosen arbitrarily to account for UTI that can result from normal phases throughout life i.e. in childhood, adolescence and pregnancy. Participants who were not sure of the number of UTIs were placed in the ≤5 UTIs category. Conversely, if patients replied to the number of kidney, bladder or urinary tract infections with "many or numerous" they were deemed to have had >5 infections. The researchers felt that this was an appropriate assumption given that many patients would begin to lose track of the exact number of infections once it became greater than 5.

Participants not taking etanercept were found to be almost 3 times more likely to have high UTI rates compared to those who were, suggesting a possible protective effect for etanercept. The apparent protective effect of etanercept was statistically significant (P <0.05), however this only occurred after the addition of MBL into the binomial logistic regression, as can be seen in Table 3 A and B. This occurred as a result of

the suppression effect whereby, in this analysis, MBL acted as an independent variable suppressor in order to increase the significance of etanercept. This finding was compared to other tumour necrosis factor (TNF) alpha inhibitors such as infliximab, adalimumab and certolizumab, which were not found to have a statistically significant effect on UTI frequency. The greater number of participants receiving etanercept however may have allowed a genuine protective effect of etanercept to be detected, as only small numbers of participants received other TNF inhibitors. The improved control of the RA conferred by etanercept may have facilitated improved mobility and /or improved urogenital hygiene, which in turn may have provided protection against UTI.

Somewhat surprisingly, no statistically significant relationship was found between UTI frequency and usage of corticosteroids. About a quarter of participants indicated that at the time they completed the questionnaire, they were receiving corticosteroids (n = 41).This finding contrasts with previous studies in which an association between higher rates of urinary tract infections and oral corticosteroid usage has been observed.[2] This discrepancy may be due to the design of our study, since lifetime UTIs were examined in relation to current medications only. Neither the current dosage, nor the cumulative dosage or duration of exposure to corticosteroids was ascertained.

The results of this study are supported by Nisihara *et al*, who found a relationship between MBL deficiency and UTIs in patients with RA in one cohort and between MBL deficiency and UTI in ankylosing spondylitis in a different cohort.[9] The smaller study populations as well as the different designs in the Nisihara studies and the use of different MBL cut-offs (RA, n = 60, 30 with and without MBL deficiency, and ankylosing spondylitis, n = 60, of whom 25 had MBL <100 ng/mL) limit comparison. Nevertheless, the findings in the current study accord with previous research, in which the use of synthetic disease-modifying anti-rheumatic drugs such as methotrexate and hydroxychloroquine were not found to be associated with any significant risk for high rates of UTI.[14] Taken together, the findings reported in the two studies by Nisihara *et al* plus results of an independent study of serious infections in RA and the findings reported in this study implicate MBL deficiency as an important risk factor for urinary tract infections in RA and (given the related pathologies) other autoimmune diseases.[9-11]

Strengths of this study include a relatively large sample, the moderately good return rate for questionnaire-based research and the inclusion of physician-diagnosed autoimmune diseases as opposed to self-reported disorders. Furthermore, the MBL assays were all performed by experienced medical scientists in a single laboratory, utilising robust and previously validated methodology.[10] In addition, MBL concentrations were determined *a priori*, that is, before commencement of the study, so that observations that emerged after the study was analysed were scientifically robust. Additionally, investigators were blinded to MBL concentrations until late in the data analysis after participants had been assigned to UTI frequency categories.

Like all retrospective studies, this study also has several weaknesses. Firstly, the tendency for recall bias in retrospective questionnaires may affect the validity of the data collected. For example, assessing lifetime risk with no proof of documented urinary tract infections relies on patients having sound knowledge and not over- or under- estimating the number of infections. Because the UTI could not be validated, microbiological data was unavailable and it was not possible to validate the reported infections or determine other questions such as whether MBL deficiency predisposes to any particular microbial infection or in any particular anatomical location. For example, no sub-analyses were possible for pyelonephritis for example, cystitis or urethritis. Also, the timing of the UTI in relation to diagnosis of autoimmune disease, whether hospitalization was required, treatment details, severity of infections, responses to treatment and concurrent MBL concentrations were not known. As this was a retrospective questionnaire-based study, the questionnaires were sent to potential participants known or thought to still be alive. Therefore, persons who had succumbed to UTI complicated by urosepsis were not included. Although overall corticosteroid usage was not shown to confer any significant risk for recurrent UTI (as defined in this study), we were unable to evaluate corticosteroid dosage and cumulative exposure as potential risk factors for incident UTI due to the nature of the study and in particular the questions utilised in the questionnaire. Since 95% of participants were Caucasian, the results may not apply to other ethnic groups. In addition, males with autoimmune disease were not studied.

One aspect of this study, not initially considered, is the level of hygiene amongst participants, some of whom had poor locomotor function. How this may have impacted UTI susceptibility is unclear. Thus, the capacity of patients with rheumatoid disease to maintain independence and personal hygiene was not addressed. Additionally, other comorbidities such as anatomical variations e.g. vesicoureteric reflux in childhood, neurological comorbidities and urinary continence impairment may have confounded lifetime urinary tract infection rates. The latter conditions however are unlikely to have been frequent amongst the total cohort.

Future studies could be designed prospectively and should enlist a more diverse and larger number of participants, for example from both tertiary hospitals and private clinics. Such inclusion may provide a more diverse population and a wider range of medications. Those admitted to hospital with urosepsis or in whom urosepsis developed, or who succumbed to infection need to be examined as important subsets affected by MBL concentrations. In a prospective study, UTI could be validated, microbiological data collected, the finding of a relationship between low MBL (≤400 ng/mL) and multiple UTI and the effect of different drug treatments may be more amenable to examination and comparison.

One way of achieving this would be to create a national or international register of autoimmune diseases.

In conclusion, low or undetectable concentrations of MBL (≤400 ng/mL) were found to be associated with high rates of lifetime UTI, in contrast to diabetes, smoking and medications such as corticosteroids and methotrexate, in patients with autoimmune disease. Additional findings include the apparent protective effect of etanercept for UTI, which at this point is unexplained and requires further examination. Should our findings be validated in a larger prospective study, it may be appropriate to re-examine the prevention and treatment paradigms for UTI in autoimmune diseases.

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Corresponding author: Dr Graeme J Carroll, ArthroCare, 19A Guildford Rd, Mount Lawley, Western Australia, 6050. Email: gjcarrollmd@gmail.com

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