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# Mannose-Binding Lectin Serum Levels in Patients With Candiduria

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**Abstract**

**Background:** *Candida* species are normal mycoflora of human body which are capable to cause urinary tract infection (UTI). Mannose-binding lectin (MBL) is a kind of innate immune system and decreasing plasma levels of MBL may disrupt the natural immune response and increase susceptibility to infections.

**Objectives:** The aim of the present study was to assess MBL in the serum of patients with candiduria and compare them with control.

**Patients and Methods:** The blood and urine samples were collected from 335 patients (hospitalized in Golestan hospital, Ahvaz) using standard methods and the growing colonies on CHROMagar were identified using routine diagnostic tests. MBL activity in the serum of 45 patients with candiduria and 45 controls was measured using Eastbiopharm enzyme-linked immunosorbent assay (ELISA) kit.

**Results:** In this study, 45 (13.4 %) urine samples were positive for *Candida* species (17 males and 28 females). The most common isolated yeast was *Candida albicans* (34%), followed by *C. glabrata* (32.1%), *C. tropicalis* (9.4%), other *Candida* species (22.6%), and *Rhodotorula* species (1.9%). The mean serum levels of MBL were 0.85 ± 0.01 ng/mL and 1.02 ± 0.03 ng/mL among candiduric patients and controls, respectively, and there was no significant difference between the two groups (P = 0.6).

**Conclusions:** Our results showed that there was no significant relationship between MBL serum levels and candiduria.

*Keywords:* Candiduria, Mannose-Binding Lectin, *Candida*

## 1. Background

The immune system is the most important part of the human body to defend the host against microorganisms. Complement as an important component of the innate immune system against infections plays its role by three molecules including C1q, mannose-binding lectin (MBL) and C3, respectively in classical, lectin and alternative pathways (1). All three pathways converge at C3 and finally the membrane attack complex establishes and causes cell lysis. In the lectin pathway, MBL protein oligomers play a major role. MBL is a C-type serum protein circulating in humans and birds (2, 3), which is synthesized in the liver and is a dependent calcium (4, 5). This protein is able to recognize and bind to mannose, N-acetylglucosamine (6), peptidoglycan, and lipopolysaccharide (LPS) of microorganisms (7).

Sugar-binding proteins of MBL result in opsonization and activation of the complement of lectin pathway and clearance in the pathogen body. Reduced plasma levels of MBL may disrupt the natural immune response and increase susceptibility to infections (8). Generally, the MBL rate circulating in human serum is constant and ranges from 3 to 50 μg/mL (9). This difference in the normal and reduced plasma level of MBL in justified by three single nucleotide polymorphisms (SNPs) of Arg-52Cys (rs5030737), Gly54Asp (rs1800450) and Gly57Glu (rs1800451), which support MBL protein presence in the first exon of the MBL2 gene (9-11).

Many studies have reported that substitution at codon 54 is associated with lower MBL protein concentration in vagina and increased recurrent vulvovaginal candidiasis in females (6). Colodner et al. based on an in vitro model concluded that MBL was an important immune factor against *Candida albicans* in human (8). Urinary tract infection (UTI) is a serious infection in hospitalized patients. Diabetes, urinary catheter, female gender, drugs that suppress the immune system and genitourinary tuberculosis are the most important risk factors for candiduria (12). The majority of UTI cases are caused by bacteria whereas only 10% - 15 % of UTI causative agents are fungi (13). Reports have shown that UTI due to yeasts has increased in the recent decades (14). The most common yeast that infects the urinary and genital tracts in hospitalized patients worldwide is *Candida* (15). According to earlier articles, *C. albicans* is the predominant species in UTI of funguria and *C. glabrata* is the most frequent pathogen that mixes with *C. albicans* and less with other *Candida* species

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(16-18). There is little information in the literature on MBL serum levels in patients with candiduria. On the other hand, the association of MBL deficiency with abdominal *Candida* infection (19) and with vulvovaginal candidiasis (8, 20) is not yet clearly known.

## 2. Objectives

The aim of the present study was to assess MBL in the serum of patients with candiduria in two urology and internal medicine wards and compare them with non-candiduric patients.

## 3. Patients and Methods

This project was approved in the ethical committee of Ahvaz Jundishapur university of medical sciences (AJUMS; rec. 1392.259). All the patients or parents signed consent forms before sampling.

### 3.1. Urine Sample Culture and Yeasts Identification

In this study, 335 urine samples were collected from patients admitted to urology and internal medicine wards in Golestan hospital, affiliated to AJUMS, Iran. All the patients with urinary catheters were excluded from our study. At least 10 mL of the middle part of urines were collected in sterile urine bottles and transported quickly to the medical Mycology Laboratory, AJUMS, for mycological examinations. Urine sample bottles were shaken and then 10 μL of each uncentrifuged urine sample was spread on CHROMagar *Candida* plates (CHROMagar *Candida*®, France) (13). All the culture plates were incubated at 37°C and aerobic conditions. After 24 - 48 hours, not only positive cultures were counted and recorded based on colony colors, but also a direct slide was prepared and approved as yeast by microscopic examination. Finally, all the yeasts were identified using germ tube test, morphology on cornmeal agar medium (Difco, USA) with 1% Tween 80 (Merck, Germany), and growth at 45°C.

### 3.2. Blood Samples

Approximately, 2 mL peripheral blood sample was taken from each patient. The samples were centrifuged at 3000 rpm at room temperature; sera were separated and stored at -20°C until use.

### 3.3. Mannose-Binding Lectin Assay

In the present study, MBL serum concentrations were measured by an enzyme-linked immunosorbent assay (ELISA) technique using an ELISA kit (mannose-binding lectin, Eastbiopharm, USA) according to the manufacture's instruction. The kit allows testing of MBL in the range of 5 - 1500 ng/mL. Briefly, frozen sera samples were remove from freezer and put at room temperature for at least 30 minutes; 40 μL of each sample (serum) was added to each well in a 96-well microplate followed by 10 μL of MBL antibody and 50 μL of streptavidin- horseradish peroxidase (HRP). The microplate was covered with seal plate membrane, shaken, and incubated at 37°C for 60 minutes. The microplate was washed using washing buffer solution five times for removing unbound enzymes; 50 μL of each 3,3',5,5'-Tetramethylbenzidine (TMB) reagent (chromogenic reagent A and B) was added to wells, shaken, and then incubated at 37°C for 10 minutes. Finally, 50 μL of stop solution was added, mixed completely and then the optical density (OD) was read at 450 nm by an ELISA reader (Bio Lab, USA). According to the standard concentrations and the corresponding OD values, the linear regression equation of the standard curve was created and then according to the samples ODs, the concentration of each corresponding sample was calculated.

### 3.4. Statistical Analysis

In the present study, Mann-Whitney and chi-squared statistical tests were used for the analysis of the obtained data and $P < 0.5$ was calculated as the significance value.

## 4. Results

### 4.1. Patients' Results

In the present study, 335 patients were sampled; 196 (58.5%) patients were hospitalized at the internal medicine ward of which 123 (62.8%) were female and the rest were male. In addition, 139 (41.5%) patients were hospitalized at the urology ward, of which 108 (77.7%) were male and 31 (22.3%) were female. In the present study, 14 of 139 (10.1%) and 31 of 196 (15.8%) hospitalized patients at urology and internal medicine wards were positive for candiduria, respectively. Our study showed that totally 45 (13.4%) urine samples were *Candida* species, of which 14 (31.1 %) and 31 (68.9 %) were from urology and internal medicine wards, respectively. Males were accounted for 8 (57 %) positive cases at the urology ward, whereas 23 (74.2%) positive cases in the internal medicine ward were female. Polymicrobial species were also detected in 7 (15.6%) urine samples, five samples from the internal medicine ward (four females, one male) and two from the urology ward (one male and one female).

### 4.2. Culture Results

The results of urine cultures showed that the most common recovered species was *C. albicans* (18, 34.0%), followed by, *C. glabrata* (17, 32.1%), *C. tropicalis* (5, 9.4%), other *Candida* species (12, 22.6%), and *Rhodotorula* species (1, 1.9%). In addition, the results of colony counts of urine cultures showed that in 29 (54.7%) of the cases, the level of *Candida* in urine was higher than 103 CFU/mL (Table 1).

**Table 1.** The Details of Colony Counts of Urine Cultures in Candiduric Patients

| Organisms | Colony Counts [a] | | | | | Total |
|---|---|---|---|---|---|---|
| | 500 > | 501 - 1000 | 1001 - 5000 | 5001 - 10000 | 10000 < | |
| ***C. albicans*** | 7 (13.2) | 1 (1.9) | 2 (3.8) | 2 (3.8) | 6 (11.3) | 18 (34.0) |
| ***C. glabrata*** | 7 (13.2) | 3 (5.7) | 2 (3.8) | 2 (3.8) | 3 (5.7) | 17 (32.1) |
| ***C. tropicalis*** | 1 (1.9) | 0 | 0 | 0 | 4 (7.6) | 5 (9.4) |
| ***Candida* Sp.** | 2 (3.8) | 2 (3.8) | 2 (3.8) | 1 (1.9) | 5 (9.4) | 12 (22.6) |
| ***Rhodotorula* Sp.** | 1 (1.9) | 0 | 0 | 0 | 0 | 1 (1.9) |
| **Total** | 18 (34.0) | 6 (11.3) | 6 (11.3) | 5 (9.4) | 18 (34.0) | 53 (100) |

[a]Data are presented as No. (%).

**Table 2.** Mannose-Binding Lectin Serum Levels in Candiduric and Non-Candiduric Patients[a]

| MBL, ng/mL | Research Group | | | Control Group | | |
|---|---|---|---|---|---|---|
| | Male | Female | Total | Male | Female | Total |
| **< 50** | 0 | 5 (11.1) | 5 (11.1) | 2 (4.4) | 1 (2.2) | 3 (6.7) |
| **51 - 100** | 0 | 0 | 0 | 0 | 3 (6.7) | 3 (6.7) |
| **101 - 500** | 13 (28.9) | 21 (46.7) | 34 (75.6) | 9 (20.0) | 20 (44.4) | 29 (64.4) |
| **501 - 1000** | 2 (4.4) | 0 | 2 (4.4) | 2 (4.4) | 2 (4.4) | 4 (8.9) |
| **1001 - 1500** | 1 (2.2) | 3 (6.7) | 4 (8.9) | 3 (6.7) | 2 (4.4) | 5 (11.1) |
| **> 1500** | 0 | 0 | 0 | 0 | 1 (2.2) | 1 (2.2) |
| **Total** | 16 (35.6) | 29 (64.4) | 45 (100) | 16 (35.6) | 29 (64.4) | 45 (100) |

[a]Data are presented as No. (%).

### *4.3. The Results of Measuring Mannose-Binding Lectin*

A total of 90 hospitalized patients were selected, including 45 patients with candiduria (29 females and 16 males) as the case group and 45 patients without positive cultures (29 females and 16 males) as the control group. The mean levels of MBL were 0.85 ± 0.01 ng/mL and 1.02 ± 0.03 ng/mL among patients with candiduria and the control group, respectively and there was no significant difference between the two groups (P = 0.6) (Table 2). There was no statistical difference in the MBL serum levels between males and females using chi-squared tests (P = 0.6). Although, we could not find any significant difference (P = 0.8) between patients with candiduria and the control group (non-candiduric patients) in the urology ward, the statistical difference was significant (P = 0.2) between hospitalized patients with candiduria and controls in the internal medicine ward.

## 5. Discussion

Candiduria rarely occurs in the urinary tract in healthy individuals, but it is a current event in hospitalized patients due to several predisposing factors (21). Catheterization is one of the most important risk factors for candiduria in hospitalized patients (84.4%), although eliminate or changing the catheter can eradicate candiduria (15). Our results showed that the prevalence of candiduria among hospitalized patients in the internal medicine ward was 15.8%, whereas 10.1% of hospitalized patients in the urology ward had candiduria. Although several studies have shown that candiduria has been more prevalent among hospitalized patients, this prevalence has varied in hospital settings (13, 18). For example, it has been 5.2% in children ward (14), 15.6% in urology ward (22), and 43.1% in ICU ward (24). In addition, several epidemiological studies showed that candiduria was more common among females (15, 18, 21). Although *Candida* species are accounted as the most common UTI causes, several other yeasts and yeast-likes can cause UTI, such as *Saccharomyces cerevisiae*, *Trichosporon asahii*, *Blastoschizomyces capitatus*, *Cryptococcus neoformans*, *Rhodotorula*, and *Geotrichum* (13, 23-25). Our study showed that the most common isolate from patients with candiduria was *C. albicans* (34.0%), followed by *C. glabrata* (32.1%), *C. tropicalis* (9.4%) and other *Candida* species (22.6%). We also isolated a case of *Rhodotorula*.

Various factors such as galectin 3, toll-like receptors 2 and 4, DC-SIGN and membrane mannose receptor can be involved in the defense against pathogenic *C. albicans* (3). In addition, soluble lectin (such as MBL) enhances opsonization and phagocytosis of fungi, viruses, and bacte-

ria (19, 26). Several studies showed that 20% - 40% of the population had MBL deficiency due to variations in the MBL gene (8, 19). The reduction in the MBL level is closely associated with disease and some studies confirmed this association. For example, lower levels of MBL were associated with increase of infections due to Streptococcus pneumonia (27), dermatophytic infections (5), abdominal yeast infection (19), and recurrent *vulvovaginal candidiasis* (10). It was shown that MBL bound with several medically important yeasts (such as *C. albicans*, *C. parapsilosis* and acapsular *Cryptococcus neoformans*) via mannan and enhanced opsonophagocytosis by polymorphonuclear granulocytes (4). Nedovic et al. reviewed several published papers and found that the *B* allele of *MBL* gene polymorphism has the role in vulvovaginal candidiasis infections (20).

According to Miranda et al. MBL serum levels are classified as 0 - 500 ng/mL as low, 501-1000 ng/mL as medium, and > 1000 ng/mL as higher levels (29). In a study by Damiens et al. a serum level of 100 ng/mL was defined as the cut-off point for high MBL deficiency (3). On the other hand, van Till et al. showed that patients with MBL levels of < 500 ng/mL were 4.5 times more susceptible to abdominal yeast infection (19). Our study showed that 86.7% and 77.7% of cases and controls respectively had MBL deficiency with MBL levels of lower than 500 ng/mL. Our study showed that totally, there was no significant association between MBL and candiduria among hospitalized patients in urology and internal medicine wards (P = 0.6). However, a significant difference (P = 0.2) was found between MBL and candiduria among hospitalized patients in the internal medicine ward and control group.

Colodner et al. results showed that MBL serum levels were not associated with an increased risk for recurrent UTI in premenopausal women (8). On the other hand, some studies showed that MBL deficiency could be associated with recurrent vulvovaginitis (10, 29), candidemia (30) and *Candida* peritonitis (19). Our study limitations were the relatively small size of cases and controls and the unavailability of the genetic investigation of both patient and control groups. Our results showed that the reduction of MBL levels in the human body could not be a risk factor for candiduria. However, more studies could confirm our investigation.

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## Footnotes

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**Authors' Contribution:**Ali Zarei Mahmoudabadi contributed to project management, final approval of the study and final editing of the manuscript. Maryam Moslem contributed to all the steps of experimental work, data analysis, and manuscript draft preparation. Mahnaz Fatahinia contributed to data analysis and editing the manuscript draft. Alireza Kheradmand contributed to data collection and presenting patients for sampling.

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