Analysis of Mannose-Binding Lectin Protein Levels and their MIC Profile in Patients with Dermatophytosis

Dear Editor,

Dermatophytosis, a superficial fungal infection affecting skin, hair, and nail, remains an unresolved public health problem globally. The geographical distribution of dermatophytes varies greatly depending on the socio-economic, hygienic, and environmental conditions of the population.[1,2] Combination of topical and systemic antifungals administered for a longer duration has become the rule of the day in the treatment of dermatophytosis of glabrous skin in the current scenario. Lack of compliance to treatment and general measures, inadequate duration of treatment and the emergence of drug resistance may delay recovery and cause relapses. Intake of antifungal drug for an appropriate duration is critical in order to achieve complete recovery and prevent treatment failure. In this study, we evaluated the minimum inhibitory concentration (MIC) of topical and systemic antifungal drugs against dermatophyte isolates collected from various parts of south India.

Mannose-binding lectin (MBL) is a subfamily of proteins known as calcium-dependent collagenous lectins (collectins); the members of this family contain collagenous regions and lectin domains.[3,4] Collectin gene is located on chromosome 10.[5] There are two MBL genes: MBL-1, which is a pseudogene, and MBL-2, which encodes the MBL-2 protein.[6] MBL is synthesized in the liver and acts as an acute-phase protein. It also acts as a kind of pattern recognition receptor.[6] Around 5%–7% of the world population has been affected with MBL deficiency. Three-point mutations on the gene of MBL-2 in codons 52, 54, 57 of the first exon of the MBL gene have been shown. These mutations cause amino acid substitutions and also impair the MBL function.[3,4] Studies have documented that MBL deficiency is consider to play a role in susceptibility to bacterial, viral, fungal and parasitic infections, and autoimmune disorders.[7,8] Recently, many researchers have been investigating MBL deficiency by studying individuals with recurrent infections and autoimmune disorders, but so far, comprehensive studies have not been conducted in relation to skin infections. As not much literature is available with regard to levels of MBL in patients with dermatophytosis, this study was taken up to evaluate the deficiency of MBL in these patients.

A cross-sectional study was conducted at the Department of Microbiology, during the period Jan 2016–Feb 2017 with 150 clinical dermatophyte isolates collected from three states in south India. The clinical details, susceptibility profile and MBL levels were noted and analyzed. The institutional ethical committee clearance was obtained for the study (IEC-NI/16/MAR/51/14).

Antifungal susceptibility testing was done according to the Clinical and Laboratory Standards Institute (CLSI)-M38-A2 guidelines using the broth microdilution method. Enzyme-linked immunosorbent assay (ELISA)-was performed using MBL Oligomer ELISA Kit (BIOPORTO Diagnostics) in micro wells coated with a monoclonal antibody against the MBL carbohydrate-binding domain and the reading was taken at 620 nm. MBL levels between 0.5-40 ng/ml was the normal range of calibration of this kit.

The patients most susceptible to dermatophyte infection were in the age group of 30–40 years, followed by those in the age group of 20–30 years which was similar to the other studies. As patients in these age groups are actively involved in outdoor activities with increased sweating and may be with compromised maintenance of hygiene, chances of contracting dermatophyte infection increase. In recent years in India, there has been an epidemiological shift of dermatophytes causing infection of the skin, from *Trichophyton rubrum* to *Trichophyton mentagrophytes*, which has emerged as the predominant organism. In this study, *T. mentagrophytes* complex (58%) was the most common organism isolated followed by *T.rubrum (40%).*

MICs for *Trichophyton mentagrophytes* ATCC 4439 were within the established range [Table 1]. Both *T.mentagrophytes* complex and *T.rubrum* had an MIC range from 0.06 to 8 μg/mL for terbinafine. Higher MICs were seen for *T.mentagrophytes*. MIC range of griseofulvin was 0.06–16 μg/mL with the majority of the isolates having 0.5 μg/mL. MIC value for both itraconazole (<0.06 μg/mL) and voriconazole (0.125 μg/mL) had low range, except two isolates of *T.rubrum* that had 16 μg/mL and 4 μg/mL respectively. Luliconazole, sertaconazole and fenticonazole had low range (0.06) μg/mL. MIC Fluconazole was less active, exhibiting the MIC range of (2–64 μg/mL). Similarly, a higher MIC range (4->64 μg/mL) for amphotericin B was seen for all the isolates [Table 2].This study points to a rising proportion of strains of *T.mentagrophytes* complex with the change in the MIC pattern for terbinafine and griseofulvin.

MBL in deramatophytosis

MBL deficiency appears to play a role in recurrent skin infections. The MBL and Mannose binding lectin -associated serine proteases (MASP) seem to play a role in limiting the disease by helping in clearing the apoptotic skin cells, promoting opsonophagocytosis of the invading pathogens, and hence controlling the spread. As per definition, MBL deficiency has been considered as values less than 1000 ng/mL. However, some authors have

taken even 500 ng/mL as cut-off.[8] In this study., levels of MBL ranged from 20 ng/ml to 40 ng/ml among the patients [Table 1]. Among the 150 isolates, 60 and 41 had high MIC for Terbinafine and griseofulvin respectively Hence, their MIC values were compared with MBL values which is shown in [Figures 1 and 2]. MBL levels ranged from 20-30 ng/ml in majority of the patients infected by these strains. (Terbinafine: 86%, Griseofulvin: 73%).

Though MBL levels were low in the study population other factors related to host immunity like defects in classical complement, humoral immunity, or phagocytic pathway have to be explored. Hence further large -scale studies need to be done to evaluate the role of MBL as a major risk factor for dermatophytosis.

Limitations

The sample size is too small to comment on the role of MBL. Evaluation of MBL levels in healthy controls would have thrown more light for better understanding. Clinical response in patients whose isolates were analyzed *in vitro* sensitivity of the antifungals was not evaluated.

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Conflicts of interest

There are no conflicts of interest.

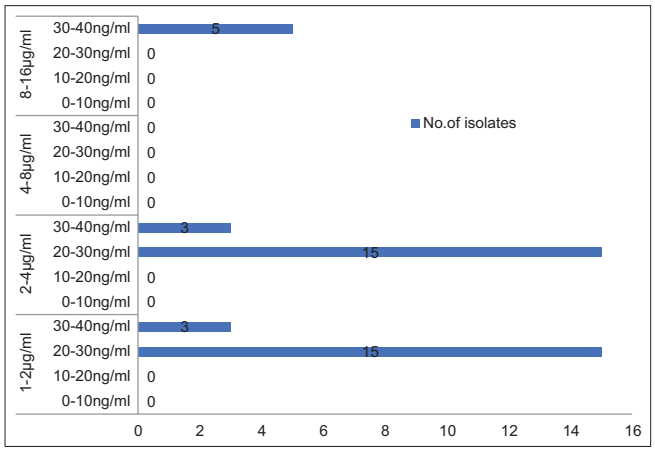

Figure 1: Correlation of Griesofulvin MIC and MBL values

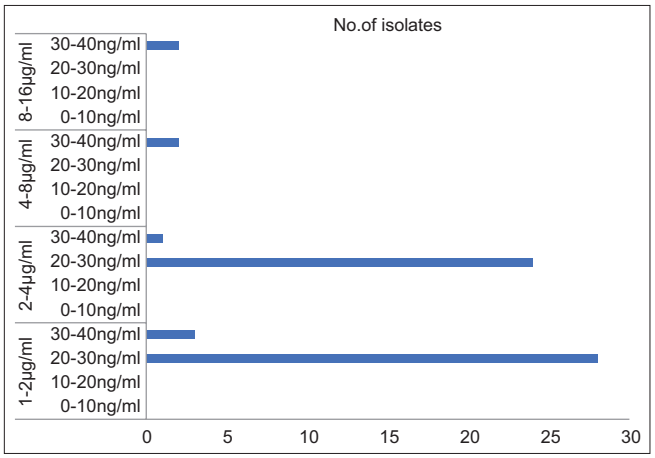

Figure 2: Correlation of Terbinafine MIC and MBL Values

Table 1: Distribution of mannose binding lectin range among different dermatophyte species

Dermatophyte species	0-10 ng/mL	10-20 ng/mL	20-30 ng/mL	30-40 ng/mL
Trichophyton mentagrophyte (*n*=78)	25	9	35	9
Trichophyton rubrum (*n*=70)	17	15	30	8
Epidermophyton floccosum (*n*=1)	-	1	-	-
Microsporum nannum (*n*=1)	-	1	-	-

Table 2: MIC range of the conventional and newer antifungal agents against isolates of dermatophytes

Drugs tested (range of concentration in µg/mL)	*Trichophyton mentagrophyte* (*n*=78) µg/mL	*Trichophyton rubrum* (*n*=70) µg/mL	*Epidermophyton floccosum* (*n*=1) µg/mL	*Microsoprum nanum* (*n*=1) µg/mL
Amphotericin B (64-0.25)	4->64	4->64	4	4
Fluconazole (64-0.25)	2-64	2-64	2	>64
Itraconazole (16-0.06)	0.06-1	0.06-16	8	0.06
Voriconazole (32-0.125)	0.125-4	0.06-4	0.125	0.5
Griseofulvin (16-0.06)	0.06-4	0.125-16	0.25	0.5
Terbinafine (16-0.06)	0.06-8	0.06-2	0.06	0.06
Sertaconazole (16-0.06)	0.06-4	0.06	0.06	0.06
Luliconazole (16-0.06)	0.06	0.06	0.06	0.06
Fenticonazole (16-0.06)	0.06	0.06	0.06	0.06

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