

# Prevalence of sensitization to *Malassezia* spp. in adults with atopic dermatitis and psoriasis and its correlation with disease severity.

Prevalência da sensibilização a *Malassezia* spp. em pacientes adultos portadores de dermatite atópica e psoríase e sua correlação com a gravidade das doenças

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## RESUMO

**Fundamentos:** Dermatite atópica (DA) e psoríase apresentam similaridades clínicas e fisiopatológicas. **Objetivos:** Avaliar a frequência da sensibilização a *Malassezia* spp. em adultos portadores de DA e psoríase e correlacionar à gravidade dos quadros clínicos. **Métodos:** De janeiro de 2016 a agosto de 2017, conduziu-se um estudo observacional em indivíduos adultos onde foram realizadas dosagem de IgE específica anti-*Malassezia* spp. e raspados das lesões para cultura micológica. Testes paramétricos ou não paramétricos foram utilizados para análise. **Resultados:** Nos 20 portadores de DA, a mediana da idade foi 29 anos. O valor médio do *Scoring Atopic Dermatitis* foi  $45,35 \pm 18,32$ . A mediana de IgE específica anti-*Malassezia* spp. foi 0,63 kU/l. *M. furfur* e *M. sympodialis* foram isolados. A análise de correlação não-paramétrica de *Spearman* não mostrou correlação entre a sensibilização à *Malassezia* spp. e a gravidade. Nos 36 pacientes com psoríase, foram obtidas as seguintes medianas: idade 61 anos, comprometimento de superfície corpórea 22% e IgE específica anti-*Malassezia* spp. 0,00 kU/l. Houve identificação de *M. furfur* e *Malassezia* spp. **Limitações do estudo:** O número reduzido de participantes dificultou a avaliação da sensibilização por IgE a *Malassezia* spp. Não houve uniformidade nos locais de coleta dos raspados cutâneos. Medicamentos tópicos não foram suspensos anteriormente ao exame micológico, prejudicando o isolamento dos fungos. **Conclusões:** Sensibilização a *Malassezia* spp. apenas ocorreu nos portadores de DA. O teste de IgE específica anti-*Malassezia* spp. não se mostrou um marcador de gravidade para a DA neste grupo.

**Palavras-chave:** Imunoglobulina E, *Malassezia*, Dermatite atópica, Dosagem.

## ABSTRACT

**Fundamentals:** Atopic Dermatitis (AD) and Psoriasis (PS) share clinical and physiopathological similarities. **Objective:** Determine the prevalence of sensitization to *Malassezia* spp. in adults with AD and PS and its correlation with disease severity. **Methods:** A cross-sectional study was carried out from January 2016 to August 2017 with adults. *Malassezia* spp.-specific IgE dosages were measured, and skin scrapings for fungal culture performed. Parametric or nonparametric tests were used for analysis. **Results:** Median age of the 20 participants with AD was 29 years old, and the mean SCORAD was  $45.35 \pm 18.32$ . *Malassezia* spp.-specific IgE median dosage was 0.63 kU/l. *M. furfur* and *M. sympodialis* were isolated. Spearman's nonparametric correlation analysis showed no correlation between sensitization to *Malassezia* spp. and disease severity. The median age of the 36 participants with PS was 61 years old, the median body surface area affected was 22%, and *Malassezia* spp.-specific IgE median dosage was 0.00 kU/l. *M. furfur* and *Malassezia* spp. were identified. **Study limitations:** Assessing the sensitization to *Malassezia* spp. was difficult due to the reduced number of participants in the study. Furthermore, there was no uniformity in the location to collect skin scrapings. The use of topical medication was not suspended before collecting skin specimens for mycological examination, therefore interfering with fungal isolation. **Conclusion:** Sensitization to *Malassezia* spp. was only detected in the AD sample. *Malassezia* spp.-specific IgE test did not prove to be a marker for disease severity in our AD sample.

**Keywords:** Immunoglobulin E, *Malassezia*, Atopic dermatitis, Dosage.

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## INTRODUCTION

Atopic Dermatitis (AD) and Psoriasis (PS), the most common inflammatory skin disorders, are characterized by erythematous scaly plaques with different aspects and localizations. Both diseases reveal barrier abnormalities; the entire terminal differentiation of the epidermis is defective in AD, but accelerated in PS. PS and AD result from T-cell mediated inflammatory mechanisms but displaying differing T-cell polarity. PS is nowadays considered to be driven by Type 17 T-cell, with auto-antigens as likely activators, and there is also activation of Th1 and Th22 T-cells into psoriatic lesions. In AD, Th2 and Th22 T-cells are commonly present and activated. Th2 cell cytokines, IL-4 and IL-13, incite increased levels of IgE as they regulate IgE class switching. Then, AD is frequently associated with allergies, which are lacking in PS due to the non-existence of Th2 cells. Hence, PS and AD display differing clinical, tissue, and molecular disease phenotypes, making them perceived as distinct diseases.<sup>1,2</sup>

Recent studies reported similarities in immune activation in PS and AD that can be observed mainly in children at early stages of the disease and people of Asian descent, as an overlap between the two conditions, and some authors call it PS dermatitis.<sup>3</sup> In those patients and in the intrinsic form, AD has plaque-type psoriasiform lesions; on the epidermis, there are marked acanthosis, parakeratosis, and neutrophil infiltration. The overlap with PS extends to the Th17 immune response aligned with Th2 and Th22 activation. Consequently, it has been presumed that AD, PS, and PS dermatitis might exist across a disease semi colon, i.e., each extreme is affected by the classic forms of AD and PS, and in the interval they overlap, as PS dermatitis.<sup>4,5</sup>

On the epidermis, CARD 14 protein, a major regulator of nuclear factor- $\kappa$ B (NF- $\kappa$ B), is responsible for the synthesis of mediators of the immune system (IS). Gain-of-function mutations of its gene are described in PS literature, aligned with the release of pathogenic inflammatory chemokines that attract neutrophils and both CD and T-cells, triggering and perpetuating the disease.<sup>6</sup>

However, loss-of-function mutations in CARD14 result in an unusually severe form of AD, with inferior production of antimicrobial peptides and recurrent infections.<sup>7</sup> The mutations reinforce the idea that both disorders exist across a spectrum but with distinct pathophysiologic mechanisms underlying AD and PS.

*Malassezia* spp., a member of the skin microflora, seems to be involved in skin disorders. In AD, the damaged epidermal barrier would allow the penetration of whole and fragmented cells. The fungus can also generate indoles that serve as potent ligands for the host aryl hydrocarbon receptor. Thereby, the yeast potentially modifies the function of all cells in the epidermis expressing this receptor. Hence, the yeast interaction with keratinocytes and immune cells may induce a pro-inflammatory immune response.<sup>8</sup>

Studies show that IgE sensitization to *Malassezia* spp. was present in two-thirds of the adults.<sup>9</sup> A study carried out in 2015 indicates that IgE sensitization to food and environmental allergens was tested in 132 children and 67 adults, investigating the severity of AD. Only *Malassezia* spp.-specific IgE was correlated to the severity of the disease, and it occurred exclusively in adults.<sup>10</sup> Cell fragments of *Malassezia* spp. topically applied to the skin of psoriatic patients induced new psoriatic plaques. *Malassezia* yeasts could invade epiderm and stress predisposed keratinocytes to the increased production of cathelicidin LL-37. Complexes formed from self-DNA, released by stressed keratinocytes, and LL-37 stimulate plasmacytoid dendritic cells to secrete IFN, driving T-cell activation and the production of cytokines found in PS, thus initiating and sustaining PS lesions.<sup>11</sup>

In both diseases, *Malassezia* spp. can create a pro-inflammatory immune response, so they may play a pathogenic role. To expand the knowledge on pathophysiology, this study investigates IgE sensitization to fungi of the genus *Malassezia* in AD and PS cases and, if present, the degree of sensitization would signal the severity of the diseases. If such correlation is proven, antifungals can be considered a promising course of treatment since immunobiologicals are effective but quite expensive.

## METHODS

From January 2016 to August 2017, individuals (male and female) over 18 years old who would meet the established clinical criteria for AD and PS were selected at the Immunology and Rheumatology Services at Hospital Clementino Fraga Filho (UFRJ). Venous blood samples were drawn for the *Malassezia* spp.-specific IgE dosage, using ImmunoCAP<sup>™</sup> Specific IgE code m227 size 10 Art.No.14-5321-01 Barcode BT16 Phadia<sup>®</sup> Laboratory Systems, which verifies the sensitization to fungi of the genus *Malassezia*. The reference values are: below 0.1 kU/l, no sensitization; from 0,1 to 0,7 kU/l, low sensitization; from 0.71 to 3.5 kU/l, mild sensitization; above 3.5 kU/l, high sensitization. Skin scrapings of the lesions were collected from the upper and lower limbs and also the trunk for isolation in the culture of *Malassezia* spp. and identification through phenotypic evidence: culture in modified Dixon, urease test, catalase reaction, esculin test, and Tween assimilation.<sup>12</sup>

The scraping analyses and the mycological analyses were carried out at the Mycology Laboratory at Instituto Nacional de Infectologia (Fiocruz). The clinical questionnaire included age, skin color/ethnicity, gender, Severity Scoring of Atopic Dermatitis Index (SCORAD)/Body Surface Area (BSA), comorbidities, treatment, total leukocyte and lymphocyte counts, and lymphocyte percentage. SCORAD was calculated using PO-Scorad. Total leukocyte count, total lymphocyte count, and lymphocyte percentage had their average range value established by the Clinical Analyses Laboratory of Hospital Clementino Fraga Filho.

Descriptive statistics analysis provided prevalence and distribution, summarized in the tables below. For inferential statistics, Mann-Whitney U Test or Chi-Square test was used. The significance determination criterion adopted was 5%. As for the AD group, Spearman's nonparametric correlation analysis was used to correlate *Malassezia* spp.-specific IgE to the SCORAD index.

## RESULTS:

Out of the 20 outpatients, the median age of the AD participants was 29 years old ( $Q_1$  21.00,

$Q_3$  47.50). As to ethnicity/skin color, nine (45%) declared to be white, six (30%) brown, and five (25%) black. There were 13 (65%) female participants and seven (35%) male ones. Mean SCORAD was  $45.35 \pm 18.32$ , minimum 9.50 e maximum 69.60. In the sample, severity distribution follows: mild (0 a 24), three (15%) patients; moderate (25 a 50), eight (40%) patients; severe (51 to 103), nine (45%) patients. Atopic comorbidities were more frequent: asthmatic bronchitis in ten (50%) individuals, allergic rhinitis in seven (35%), allergic rhinoconjunctivitis in six (30%), and food allergy in one (5%). Cyclosporine was the drug most commonly used, prescribed to nine (45%) patients. A total of seven (20%) patients also informed the use of prednisone. Leukocyte count and specific lymphocyte count and its percentage were within the normal range for 19 and 17 individuals, respectively. The median *Malassezia* spp.-specific IgE dosage was 0,63 kU/l (Table 1). The median *Malassezia* spp.-specific IgE dosage according to AD severity was: mild 0.00 kU/l, moderate 0.63 kU/l, severe 1.50 kU/l. Although the median values increased according to disease severity, Spearman's nonparametric correlation analysis showed no correlation ( $p=0.56$ ) between sensitization to *Malassezia* spp. and disease severity (SCORAD). Indeed, there was no significant correlation between sensitization to the fungus and the SCORAD, even among the nine (45%) carriers of the severe disease (SCORAD 51 to 103), for which we could observe a distribution (n) of sensitization degree to the fungi as inexistent (n = 2), mild (n = 2), moderate (n = 2), and severe (n = 3). *M. sympodialis* was identified in one female patient and *M. furfur* in one male patient.

Out of the 36 outpatients, the median age of the PS samples was 61 years old ( $Q_1$  47.50,  $Q_3$  67.00). White and brown were the most commonly declared skin colors/ ethnicities, 18 (50%) and 17 (47.2%) individuals, respectively, and only one (2.8%) declared to be black. Regarding gender, 19 (52.8%) were female and 17 (47.2%) male. Median BSA evaluated in 35 patients was 22% ( $Q_1$  7%,  $Q_3$  37%). Out of the 36 patients, 22 had BSA above 10%. Psoriatic arthritis was found in 20 (55.6%) patients, and frequent systemic diseases were: systemic arterial hypertension in nine (25%) patients, dyslipidemia in

three (8.3%), diabetes mellitus type II, metabolic syndrome and ischemic cardiomyopathy in two outpatients (5.6%) each, and claudication in one (2.8%). Methotrexate was the most common course of treatment, used in 20 patients (55.6%). Thirty-six patients (100%) had leukocyte count, and 34 (94.4%) patients had specific lymphocyte count (as well as its percentage) within the normal range. The *Malassezia* spp.- specific IgE dosage was not zero for two patients (5.6%), ranging 0.36 kU/l (BSA 9%) and 0.44 kU/l (BSA 22%), both considered discrepant, and median value was 0,00 kU/l (Table 2). It was not possible to conduct statistical analysis to correlate *Malassezia* spp.- specific IgE and BSA since the test results were nearly all negative. *M. furfur* was isolated in one patient, and in two other patients, we could identify only the genus *Malassezia*.

The difference regarding the continuous numeric variables *Malassezia* spp.- specific IgE marker and age ( $p=0.0001$ ) was statistically significant between AD and PS by the *Mann-Whitney* test. According to the Chi-squared test, the analyses of the prevalence per gender and skin color/ethnicity displayed that both diseases were significantly different considering skin/color ( $p<0.000001$ ) – only one patient in the PS sample declared to be black –, but statistically similar in gender ( $p=0.32$ ).

## DISCUSSION

Until recently, the fungi of the genus *Malassezia* were almost exclusively known for their role as commensal in the human microbiota and their association with different skin diseases such as seborrheic dermatitis, *Malassezia* folliculitis, psoriasis, and Pityriasis Versicolor. The cause of the latter is well established. And the yeast is also related to systemic infections in patients in a severe state of immunosuppression and parenteral nutrition with lipid supplementation via a central venous catheter. Epidemiological and experimental studies correlate them to AD<sup>9</sup> and PS<sup>13</sup> with the possibility of triggering and/or aggravating episodes. It was the study's goal to investigate this possibility.

The median age of the AD sample was 29 years old ( $Q_1$  21.00,  $Q_3$  47.50). AD was al-

most exclusively considered a childhood disease; however, over the past few decades, there has been an increase in the number of adults with AD.<sup>2</sup> The mean SCORAD was  $45.35 \pm 18.32$ , with 9.50 as minimum and 69.60 as maximum, signaling moderate severity cases also seen in other studies with adult carriers of the disease.<sup>14</sup> The comorbidities associated with AD were atopic.<sup>14</sup> In children, asthmatic bronchitis and allergic rhinitis are commonly associated with the disease, which configures an atopic march initiated by AD. The same profile of atopic diseases is common in adults.<sup>15</sup> The median of *Malassezia* spp.-specific IgE test specific was 0.63 kU/l ( $Q_1$  0.00,  $Q_3$  3.50), showing the mild sensitization degree (mild degree from 0.1 to 0.7 kU/l). A total of seven patients informed the use of prednisone, which inhibits IgE synthesis, indicating a possible explanation for the mild sensitization verified in the sample. Spearman's nonparametric correlation analysis applied to the *Malassezia* spp.- specific IgE marker and the SCORAD showed that, as for the participants with AD, there is no correlation between sensitization to *Malassezia* spp. and disease severity. The fungus isolation on a small scale might have been influenced by the fact that almost all patients used topical medication. This factor certainly affected the mycological test results, mainly the fungal culture results. The studies diverge when it comes to the isolated species in the AD; nevertheless, *M. sympodialis*<sup>16-17</sup> is the most frequently associated species with the disease, and it was found in one of the patients of this study.

Although the median age of the PS sample was 61 years old ( $Q_1$  47.50,  $Q_3$  67.00), the onset of psoriasis generally occurs before 40 years old. One black patient in the sample corroborates with the literature on the disease, stating that this condition is rare in black individuals.<sup>18</sup> The median BSA was 22% ( $Q_1$  7%,  $Q_3$  37%). A 10% increase was observed in 22 patients (61.1%) and rates over 10% (0.10) indicate severe cases. The hospital where the study was carried out is a tertiary care hospital of high complexity, and the Rheumatology Service is considered a reference center, hence the high percentage of severe cases. Psoriasis arthritis was found in 55.6% of the sample, and it is seronegative arthritis,

which occurs before, simultaneously, or after the disease onset. More severe cases are usually associated with arthritis.<sup>18</sup> Two young patients with arterial hypertension both had psoriasis arthritis and one of them also suffered from intermittent claudication. In both cases, PS seems to have had a primary role in such comorbidities, confirming its systemic aspect.<sup>6</sup> *Malassezia* spp.-specific IgE was not zero in only two patients. Th2 activation is largely lacking in psoriasis, so sensitization to fungi of the genus *Malassezia* was not found. *M. furfur*, the most frequent species associated with PS, was isolated in a female patient, and the genus *Malassezia* was found in two male patients.

Statistically significant differences between both diseases were expected regarding the continuous variables *Malassezia* spp.-specific IgE and age besides the discrete variable, ethnicity/skin color. Th2 response is a marker for AD, but it lacks in PS, but not in PS dermatitis, when Th2 response is present. In the AD sample, there were no children or people of Asian descent, and as total IgE was not measured, it was unattainable to identify patients with an intrinsic form. AD is still considered a childhood disease, as there is a remission rate of 60 to 70% of the cases identified before adolescence, whereas PS is more prevalent in adults. Afro-descendant individuals are rarely affected by PS.

As for the study limitations, it was difficult to assess the prevalence of sensitization of specific IgE to *Malassezia* spp. and its subsequent correlation to the severity of the diseases due to the very few participants in the study, mainly in the AD sample. Furthermore, there was no uniformity in the location to collect skin scrapings. They were distinct in each patient, and such areas were not discriminated or itemized. The samples were considered unique, labeled just as "collected from skin lesion", even though multiple areas were scraped. For ethical and medical reasons —since the cases could be aggravated —, topical medication was not suspended before collecting skin specimens for mycological examination, therefore interfering with the fungus isolation cultures. Such cultures were not adequately processed and individualized regarding the area where they were collected from, even though such methodology was proven relevant by a study in 2011, according to which

the microbiome mapping is different for each region of the body surface.<sup>19</sup> The specimens should have been collected from the locations where fungi are known to be colonized, mainly the scalp, even if lesions had not been present.

## CONCLUSION

Brazil is a tropical country with high temperatures and a lot of humidity, which are favorable conditions for colonization and infection by fungi of the genus *Malassezia*. If confirmed as a triggering factor of AD in adult carriers of the disease, *Malassezia* spp.-specific IgE dosage can be considered a severity marker of the disease, upon a correlation between the degree of sensitization and the severity of clinical findings. We suggest that the study be carried out with a larger number of participants, including other medical facilities, and, ideally, with patients without prior oral or topical treatment. If the correlation is confirmed, we can expect to see more studies that will expand our comprehension of the mechanism of action of *Malassezia* spp. in AD.

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**Contribuição específica de cada autor para o trabalho**

- Contribuição substancial no esboço do estudo ou na interpretação dos dados: Souto LA, Brito-Santos F, Almeida-Paes R, Lupi O
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**Fonte de apoio**

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**Table 1**

Description of numeric variables in AD samples

Variable	n	mean	SD	median	min.	max.	Q <sub>1</sub>	Q <sub>3</sub>
Age (years)	20	34.20	16.18	29.00	18.00	72.00	21.00	47.50
SCORAD	20	45.35	18.32	45.25	9.50	69.60	33.20	61.70
IgE (kU/L)	20	3.83	7.47	0.63	0.00	30.90	0.00	3.50
Leukocyte (cells/mm <sup>3</sup> )	19	8,028.95	2,318.37	7,400.00	5,000.00	13,900.00	6,400.00	9,300.00
Lymphocyte (cells/mm <sup>3</sup> )	17	1,970.71	632.71	1,944.00	900.00	3,597.00	1,670.00	2,304.00
Lymphocyte (%)	17	27	9	26	9	47	22	33

**SCORAD:** Severity Scoring of Atopic Dermatitis Index; **IgE:** Immunoglobulin E dosage to *Malassezia* spp.; **SD:** Standard Deviation; **Q<sub>1</sub>:** first quartile; **Q<sub>3</sub>:** third quartile

**Table 2**

Description of numeric variables in PS sample

Variable	n	mean	SD	median	min.	max.	Q <sub>1</sub>	Q <sub>3</sub>
Age (years)	36	57.89	13.80	61.00	28.00	81.00	47.50	67.00
BSA (%)	35	23	19	22	1	76	7	37
IgE (kU/L)	36	0.02	0.09	0.00	0.00	0.44	0.00	0.00
Leukocyte (cells/mm <sup>3</sup> )	36	8,265.83	2,755.85	7,650.00	4,500.00	15,500.00	6,600.00	9,250.00
Lymphocyte (cells/mm <sup>3</sup> )	34	1978.74	722.22	1907.00	522.00	4242.00	1462.00	2322.00
Lymphocyte (%)	34	25	9	27	6	42	17	31

**BSA:** Body Surface Area; **IgE:** Immunoglobulin E dosage to *Malassezia* spp.; **SD:** Standard Deviation; **Q<sub>1</sub>:** first quartile; **Q<sub>3</sub>:** third quartile