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Cross Sectional Study

Relationship Interleukin-8 levels, Malassezia, and sebum fatty acids in dandruff severity

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ABSTRACT

Dandruff is one of the skin diseases that cause problems for patients with complaints of itching. Apart from feeling itchy, it also causes discomfort for patients. This study aims to examine Malassezia species in patients with dandruff by PCR-RT. This is a cross-sectional observational study with a sample size of 60 dandruff patients. Patients were divided into mild/moderate and severe severity based on Severity Dandruff Score. Malassezia species examination was performed by real-time polymerase chain reaction sequencing. Lipid types were determined by gas chromatography-mass spectrometry. IL-8 levels were examined using the Elisa method. The results showed 26 patients with mild-moderate dandruff and 34 with severe dandruff. M.restricta topped the list with 73.3%, followed by M.globosa (23.3%). The most common sebaceous lipid type was hexanediol acid (41.6%), followed by octadecanoic acid (31.7%). IL-8 levels were associated with the severity of dandruff, where in mild-moderate degree, there was an association of p=0.03, while in severe degree, there was a highly relevant association (p=0.00001). This study shows that elevated IL-8 levels are associated with the severity of dandruff. M.restricta is the most common cause of dandruff, while hexanediolic acid is the most common fatty acid that causes dandruff.

Keywords: Dandruff, GC-MS, Interleukin-8, Malassezia, RT-PCR

Introduction

Dandruff (*Pityriasis capitis*) is a problem in dermatology and venereology. It causes itching, the most common complaint felt by dandruff patients. Apart from causing itching, dandruff also causes psychological and aesthetic disorders and affects the patient's social quality of life. It is part of seborrheic dermatitis, but the two diseases differ in location and severity [1]. More than 50% of adults worldwide have suffered from dandruff in their lifetime [2]. The severity and clinical degree of dandruff sustained by a person varies. Men suffer from dandruff more than women, with a ratio of 3:2 [3]. *Malassezia fungus* is one of the microorganisms that cause dandruff, but the virulence factor of Malassezia is not known with certainty [4, 5]. Malassezia is a normal fungus on healthy human skin spread over several body parts [3]. From several studies conducted on cases of seborrheic dermatitis, *Malassezia restricta*, and *Malassezia globosa* are the two most common fungal species found and play the most role in the occurrence of the disease [6, 7]. Using the Polymerase Chain Reaction identification technique, *Malassezia sympodialis* and *Malassezia sloffiae* were most commonly found in these cases [8]. Apart from causing dandruff and seborrheic dermatitis, Malassezia species also cause skin diseases such as *Malassezia folliculitis* and *Pityriasis Versicolor*.

Differences in lipid levels on the body's surface also affect the type of Malassezia species. Most Malassezia have a dominant preference for depending on exogenous sources of fatty acids for nutritional needs. This occurs due to a lack of encoding genes for synthesizing fatty acids and metabolizing carbohydrates [9]. *Malassezia restricta* is more commonly found on the forehead and scalp, so this fungus is most often found in cases of dandruff and seborrheic dermatitis [6], while *Malassezia globosa* is more

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dominant on the chest and back, so it is often found in cases of *Pityriasis versicolor* [10]. IgG and IgM antibodies against Malassezia are detectable in most individuals, but healthy individuals are usually not as sensitive as atopic dermatitis patients [8]. Dandruff is often associated with the onset of puberty and concurrent with increased activity of the sebaceous glands of the scalp because all Malassezia species except M. pachydermatis require exogenous lipids as nutrition; they are often associated with sebum-rich areas of the skin, such as the scalp [11]. The interaction between Malassezia fungi, sebaceous gland lipids, and a person's immune mechanism will determine the change in the form of Malassezia, which was initially commensal to becoming a pathogen.

Malassezia can induce the production of proinflammatory cytokines released by keratinocyte cells[1]. If sebum production decreases, the lipid layer in the stratum corneum is affected, and the protective function of the lipid barrier may be disrupted [12]. Sebum nourishes Malassezia fungi, generally found in human sebum-rich areas, whose multiplication produces more fatty acids that disrupt the scalp's integrity and reduce the skin barrier [13]. Lipid metabolites (linoleic acid), lipase enzymes, and phospholipase enzymes induce skin inflammation and irritation. Lipase and phospholipase enzymes are considered the central virulence of Malassezia fungi [14]. The lipase enzymes produced by *Malassezia globos*a have significantly increased activity in the skin. The patient's head has been proven in patients suffering from seborrheic dermatitis [15]. Previous studies reported the expression of the lipase gene *Malassezia restricta* (MRE-0242). The gene is like LIP-1 in *Malassezia globose* [16]. Increased lipase and phospholipase secretion of Malassezia species in the skin can produce lipid metabolites in the form of indole compounds, which can damage the epidermis and activate local immune responses in seborrheic dermatitis and pityriasis versicolor [17]. Still, there is no data on these lipids' effect on dandruff.

The sensitization of Malassezia to human skin in activating the immune response can occur directly and indirectly. Malassezia stimulates an immunological response in the skin by activating dendritic cells and macrophages. Keratinocyte cells exposed to Malassezia produce cytokines and chemokines that play a role in inflammation and the severity of dandruff. Interleukin 8 (IL-8) produced by human keratinocyte cells in cases of seborrheic dermatitis exposed to Malassezia increased significantly compared to healthy people. In addition, keratinocytes also produce several other proinflammatory cytokines, such as IL-1, IL-6, IL-12, and TNFα [18, 19].

Intracellular signal recognition of human keratinocyte cells in response to exposure to Malassezia can be through signaling Toll-like receptor 2 (TLR2), C sky Lectin receptor (CLR), dectin and mingle, which belong to the glycoprotein group, which functions as a transmembrane surface receptor/Pattern Recognise Receptor (PRR) [20]. Toll-like receptors and CLRs are involved in the natural immune response against microorganisms. Toll-like receptors and C receptor lectins initiate signaling pathways that activate cytokines, chemokines, and antimicrobial peptides. Keratinocytes can express TLR1, TLR2, TLR3 and TLR5. Toll-like receptor two can recognize simple molecules (ligands) in fungi, namely zymosan [21, 22].

At this time, the species of Malassezia fungus, the levels of Interleukin-8, and the type of lipid that causes the severity of dandruff have not been identified. Therefore, this study was conducted to analyze the relationship between knowing levels of interleukin-8 and the severity of dandruff. This research is vital because dandruff treatment can be carried out properly by obtaining a relationship between these variables.

Materials and Methods

Samples collection

Samples were taken from dandruff patients who went to the Dermatology and Venereology Polyclinic at the Ahmad Muchtar Hospital, Bukittinggi, by scraping scales from the patient's scalp using a scalpel and a spirit comb. The samples were then inserted and stored in a 1.5 ml microtube until they were used.

Sampling

Samples were collected by scraping scales or scales from the patient's scalp using a scalpel and a spirit comb, then inserted and stored in a 1.5 ml microtube until use. Each sample will be separated into three microtubes, which will be used to identify Malassezia species, measure Interleukin-8 levels, and determine sebaceous lipid types.

Identification spesies malassezia

Dandruff samples were tested using the Alkaline Lysis method. The dandruff samples were centrifuged in PBS for 2 minutes. After removing the supernatant, 50 mM NaOH 180 µl was added to the dandruff pellets and vortexed. They were incubated at 95°C for 10 minutes. Add 20 µl Tris-HCl Ph 8.0, then vortex, centrifuge at 12,000 rpm for 5 minutes. Next, take the 0.5-2 µl supernatant for PCR and 100 µl transfer it to a new microtube. DNA isolation was carried out according to the kit procedure, which generally consisted of sample preparation, cell lysis, DNA binding, washing, and DNA elution. DNA extraction with enzyme polymerase using KOD Toyobo Fx Neo Japan Bio-Technology reagent.

The amplification steps were carried out as follows: 950C for 14 minutes (predenaturation) followed by 40 cycles at 94 °C for 45 seconds (denaturation), 55 °C for 45 seconds (annealing), 72 °C for 1-minute extension and 72 °C for 7 minutes final extension. The 580-bp chain associated with the 26S rDNA was electrophoresed with agarose gel, then restriction was carried out for 5 hours, and finally, the DNA fragments were visualized by electrophoresis in 1.5% agarose gel.

Measurement of interleukin-8 levels

The levels of interleukin-8 samples were tested using the Human IL-8 ELISA kit. Each sample was tested by calculating its absorption capacity at a wavelength of 450 nm using a multi-mode Microplate reader (Biorad). The results obtained are expressed in units of ng/l.

Lipid type testing

The type of sebaceous lipid was tested using the GCMS analysis. At the preparation stage, the sample was mixed with 2 ml of aqua and then bound using chloroform and methanol with a ratio of 1 2. Vortex for 2 minutes, add 2 ml of chloroform and 2.5 ml of aqua, vortex for 30 seconds, and centrifuge for 6 minutes. After that, the precise phase was discarded. It was put into the GCMS tool. The remaining extract was added to 2.5 ml of chloroform and incubated in the oven at 90 °C for 120 minutes. Added 1 ml of distilled water and 2 ml of extraction solution, then extracted with 2 ml of a mixture of hexa and chloroform with a ratio of 4:1. The top layer of this solution was taken with repetition up to 3 times. The results are read as a peaks diagram chromatogram GCMS solution [23-29].

Statistical analysis

Before carrying out the bivariate test, a normality test is carried out for numerical data. If the data is normally distributed, a parametric test can be carried out; if it is not normally distributed, then a transformation is carried out. After being transformed, the normality test was carried out again. A parametric test is carried out if it is usually distributed, but if it is still not normal, a non-parametric test is carried out. The Kruskal-Wallis and Mann-Whitney tests were carried out to see the relationship between variables.

Ethical clearance

This research has received ethical consideration and approval from the Research Ethics Committee Team of the Faculty of Medicine, Universitas Andalas, with registration number 109/KEP/FK/2020.

Results and Discussion

Identification of Malassezia species in dandruff patients

The type of Malassezia found in the examination above can be seen in **Table 1**.

Table 1. Results of the identification of Malassezia as a cause of dandruff in research subjects

No	Type	f	%
1	Malassezia globosa	14	23.3
2	Malassezia restricta	44	73.3
3	Malassezia furfur	1	1.67
4	Malassezia verfertilionis	1	1.67
	Total	60	100

Table 1 identified *Malassezia restricta* as the most common cause of dandruff in research subjects (73.3%).

In this study, it was found that the most common fungus, *Malassezia restricta*, was found, namely 44 (73.33%), followed by *Malassezia globosa* 14 (23.33%). *Malassezia vespertilionis* was also found, which is unusual on the scalp and has never been reported as a cause of dandruff. *Malassezia vespertilionis* is a species of yeast-like fungus that lives on the skin of bats. It was described as a new species in 2018. The holotype was obtained from skin swabs of the long-eared bat (*Myotis septentrionalis*) hibernating in Wisconsin, USA. The name vespertilionis uses the Latin vespertilio (bat) to refer to its host [30].

The results of this study are research conducted, who conducted a survey to identify Malassezia species in 21 dandruff patients using the PCR method. The results showed that there were ten species of Malassezia, with the most species being *M. sympodialis* (23.8%), *M. slooffiae* (9.5%), *M. furfur* (4.8%), *M. globosa* (4.8%), *M. restricta* and *M. sympodialis* (4.8%) [31]. In this research, no *Malassezia vespertilionis* species were found in all patients.

Sebaceous lipid types in dandruff patients

The results of research on sebaceous lipid types in research subjects can be seen in **Table 2**.

Table 2. Results of research on sebaceous lipid types in research subjects

No	Lipid Type	f	%
1	Octa decenoic acid	19	31.7
2	Benzenedicarboxylic acid	3	5
3	Hexa dioic acid	25	41.6
4	Hexa decanoic acid	7	11.7
5	Penta decanoid acid	1	1.7
6	Hepta decanoid acid	4	6.6
7	Tri decanoid acid	1	1.7
	Total	**60**	**100**

Table 2 shows that Hexa nediolic acid is the most common type of lipid (41.6%), followed by octadecenoic acid (31.7%) in dandruff patient study subjects.

The results of this study are also from a survey conducted by Honnavar *et al*. [32] in India on 200 patients with seborrheic dermatitis on the head. The results showed that *M. globosa* was found to be dominant at 36.2%, followed by *M. restricta* at 31.3%, *M. furfur* at 15.7%, and a mixture of *M. globosa* and *M. restricta* at 12% or *M. arunalokei* at 4.8%. Researchers [33] also conducted a study to identify Malassezia species in 57 dandruff patients, and the results showed that *M. sympodialis* (62.96%) was the most common Malassezia species, followed by *M.furfur* (25.93%) and *M.globosa* (11.11%).

Study to identify Malassezia species that can cause dandruff. This research was conducted on 145 patients with dandruff; then, samples were taken by scraping the scalp and cultured. Of the 145 patients, 90.3% showed positive results for Malassezia species, including M. *furfur* (70.2%) and *M. globosa* (51.9%) [34]. Revealed that *M. restricta* was the most common dandruff-causing species in North India at 37.8% and *M. furfur* at 46.4% in South India [35]. Using the PCR technique, Zaree *et al*. conducted a study to identify Malassezia species in 65 dandruff patients. The

results showed that 58.4% of M. restricta was predominantly on the scalp and 41.6% on *M. globose* [36].

Dandruff severity degree

According to Rogers *et al.*, 2003, the severity of dandruff is based on clinical symptoms. Based on this, the severity is divided into mild-moderate and severe.

1. Mild-moderate with a value of 0 to small with 4
2. Severe with a value of 4-5

The study results of dandruff's severity can be seen in **Table 3**.

Table 3. Results of research on the severity of dandruff

No	Degree of Severity	f	%
1	Mild-moderate	26	43
2	Severe	34	57
	Total	**60**	**100**

Table 3 shows the severity of dandruff, mild-moderate (43%) and severe (57%).

Distribution of lipid type examination

In this study, the most common type of lipid, hexanedioic acid (adipic acid), was found in 25 samples (41.6%). Hexanedioic acid is a dicarboxylic acid, one of the components that forms dandruff. Until now, there has been no relationship between the type of lipid and the degree of severity of dandruff a person suffers. Analyze the fat on the scalp of patients with dandruff (10 people) and patients without dandruff (10 people) or controls. This study used gas chromatography coupled with mass spectrometry. The results showed that Squalene, the main sebum component, was significantly more oxidized in dandruff-affected scalps and resulted in a much higher ratio of squalene monohydroperoxide (SQOOH). This was observed when comparing the dandruff-affected areas of dandruff patients with unaffected areas and control patients [11].

Previous research to detect lipid production by Malassezia using Nile red stain. The results showed that the average lipase synthesis rate increased by 30.7% and 29.8% in cells that were given *M. globosa* and *M. restricta* protein extracts, and *M. sympodialis* could increase lipase synthesis by 13.6% [7]. The results of another study by Lee *et al*. also showed *that M. restricta* could increase lipase synthesis. This study was conducted by taking swabs from the scalp and cheeks of 18 patients with seborrheic dermatitis and then analyzing them using the RT-PCR technique; the results showed that *M. restricta* increased lipase and phospholipase levels [14].

Correlation between IL-8 levels and the severity of dandruff in research subjects

The relationship between IL-8 levels and the severity of dandruff in research subjects can be seen in **Table 4**.

Table 4. The relationship between IL-8 levels and the severity of dandruff in the subjects study

No	Degree of Severity	F	IL-8 Levels	p
1	Mild-moderate	26	249.53±123.34	0.36
2	Severe	34	482.80±71.16	0.0001

Table 4 shows that in patients with mild-moderate degrees, there is no significant relationship with IL-8 levels (p=0.36); in patients with severe dandruff, there is a significant relationship with IL-8 levels (p=0.0001).

The relationship between interleukin 8 levels and the severity of dandruff

From the results of the ELISA examination, it was found that 26 samples had IL-8 levels below 400 ng/l, and 34 samples had IL-8 levels above 400 ng/l. IL-8 levels above 400 ng/l are categorized as high and vice versa. The average IL-8 level in severe dandruff was 484.27 ng/l, with a standard deviation of 70.64, while the IL-8 level in mild dandruff was 249.88, with a standard deviation of 123.76. The statistical test results obtained p = 0.05, meaning there was a significant difference in the average IL-8 level between mild and severe degrees of dandruff. The results of this study are also from a survey conducted by Honnavar *et al*. in India on 200 patients with seborrheic dermatitis on the head. The results showed that M. globosa was found to be dominant at 36.2%, followed by *M. restricta* at 31.3%, M. furfur at 15.7%, and mixed *M. globosa* dan *M. restricta* 12% or *M. arunalokei* at 4.8% [31]. Researchers [32] also conducted a study to identify Malassezia species in 57 dandruff patients, and the results showed that *M. sympodialis* (62.96%) was the most common Malassezia species, followed by *M.furfur* (25.93%) and *M.globosa* (11.11%).

The results of this study are based on research conducted, which showed that the concentration of IL-8 increased in all cultures treated with Malassezia species extracts. Cells treated with *M. globosa* extract showed the most significant increase, followed by *M. restricta*. In *M. globosa*, the concentration of IL-8 increased almost threefold, whereas in *M. restricta*, it caused a 2.77-fold increase. IL-8 production rate induced by *M. sympodialis, M. dermatis*, and *M. slooffiae* also increased significantly, respectively 2.58 times, 2.31 times, and 2.38 times compared to control [7]. This research is also supported by the results of previous research, which conducted a study to identify cytokine production by keratinocytes that Malassezia modulates. This study was undertaken to assess pro-inflammatory (IL-6, IL-8, IL-1a, and Tumor Necrosis Factor-α/TNF-α) and anti-inflammatory (IL-10) cytokines using enzyme-linked immunosorbent assays (ELISA) techniques [21]. The results showed that M. globosa acapsular caused a 66-fold increase in IL-8 production ($P < 0.001$), and M. furfura capsular caused a 38-fold increase in IL-6 production ($P < 0.001$), as well as an increase in IL-10 production. as much as 12 times.

Conclusion

From the study results, it can be concluded that *Malassezia restricta* is the most common species that causes dandruff, followed by *Malassezia globosa*. Hexa deconoid acid is the most common type of fat that causes dandruff, followed by Okta decenoid acid. There is a relationship between Interleukin-8 levels of dandruff severity, where in mild-moderate degrees, this relationship is not significant, but in severe degrees, this relationship is substantial. From this research, it is necessary to provide anti-inflammatory and anti-fungal drugs.

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