

EVALUATION OF IMMUNOLOGICAL MARKER INTERLEUKIN-17 AMONG PATIENTS WITH DERMATOPHYTOSIS INFECTION

Emad Saud Obais^{1*}, Professor. Dr. Fadhil Sami Alammar², Professor. Dr. Angham Jasim Mohammed Ali³

^{1,3} Collage of Health and Medical Technology / Kufa, Al-Furat Al-Awsat Technical university, Iraq,
Email: angham.ali@atu.edu.iq

² Technical Institute/Kufa, Al-Furat Al-Awsat Technical university, Iraq, Email: zghair.fa@atu.edu.iq

*Corresponding Author:
emadsauod6@gmail.com

Abstract

This study was conducted to evaluate the immunological parameter IL-17 associated with development of dermatophyte infection.

The study was carried out in the period beginning of December 2022 to end of June 2023. This study has been done at the Al-Hilla Teaching Hospital, Dermatology Unit, Babylon Government; ages range between 1 to ≥ 50 years in male and female. During the study a total 90 clinical specimens (Skin scraping and 5ml of blood) were obtained from all participants (45 dermatophytosis cases and 45 controls). Blood samples (serum introduced for evaluation of concentration level of IL-17 by ELISA).

The ELISA was used to measure two types of cytokines (IL-17 and TNF- α), and it was observed a significant increase ($P \leq 0.0001$) of serum IL-17 in dermatophyte infected patients (35.015 ± 0.837 pg/ml) when compared with control subjects (6.481 ± 0.848 pg/ml).

The levels of IL-17 concentration in patients Infected with Dermatophyte Infection according to age groups appear non significant difference between age groups (P .value = 0.8780) and the highest concentration level of IL-17 appears with age group (31-40 years) and (41-50 years) and were (37.191 ± 2.806 Pg/ml) and (37.006 ± 0.934 Pg/ml) respectively while the lowest concentration level of IL-17 with (≤ 10 years) was (33.784 ± 4.756 Pg/ml). while in control group, appear non significant difference between age groups (P .value = 0.8991) and the highest concentration level of IL-17 appears with age group (51-60 years) and (≤ 10 years) and were (8.636 ± 2.300 Pg/ml) and (8.281 ± 1.352 Pg/ml) respectively while the lowest concentration level of IL-17 with (31-40 years) was (5.869 ± 1.002 Pg/ml).

In depending on Gender, in dermatophyte infected patients group, the results have shown the high concentration level of IL-17 appear in male was (35.950 ± 0.916 Pg/ml) other than female (33.255 ± 1.643 Pg/ml) with non significant difference (P .value= 0.1266) also in control group, the results have shown the high concentration level of IL-17 appears in male was (7.383 ± 0.911 Pg/ml) and the low concentration level appears in female and was (6.544 ± 0.957 Pg/ml), and this height also non significance (P .value= 0.5381).

The concentration level of IL-17 according to duration of infection in dermatophytosis patients, appear significant difference between groups (P .value ≤ 0.0001) and the highest concentration level of IL-17 appears with groups (> 2 years) and was (74.083 ± 9.807 Pg/ml), while the lowest concentration level of IL-17 with (≤ 6 month) and was (33.892 ± 2.890 Pg/ml).

INTRODUCTION

A dermatophyte infection, also known as dermatophytosis or tinea, refers to a group of fungal infections that can affect the skin, hair, and nails. Tinea is caused by the dermatophytes, which include the fungus of the genus *Trichophyton*, *Microsporum*, and *Epidermatophyton* (Kovitwanichkanont and Chong, 2019).

Many pathogens are known to contribute toward abnormal immune responses in genetically susceptible individuals through molecular mimicry, epitope spreading, bystander activation, or other mechanisms (Celestrino et al., 2021).

Acute dermatophytosis is associated with a Delayed-type hypersensitivity (DTH) skin response against them, while persistent disease corresponds to Type I hypersensitivity responses, to high levels of IgE and IgG4 antibodies, and to the production of Th2 cytokines by mononuclear leukocytes (Sardana et al., 2021).

Acquired resistance the efficient and protective response against dermatophytosis is a cell-mediated response of the DTH, characterized namely by the action of macrophages as effector cells, interferon- α secretion from type 1 T-helper lymphocytes and by some key cytokines like TNF- α (Vinh, 2023).

IL-17 is well known to mediate host defense against many of fungal infections in barrier tissues, in particular those caused by dermatophytosis. There is evidence that type 17 immunity is also essential for defense against dermatophytosis (Tangye and Puel, 2023).

Materials and Methods

Patients and Control Groups

A case control study has been conducted from beginning of December 2022 to end of June 2023. The blood samples have been taken from 100 participants (50 cases with dermatophytosis and 50 controls): 50 Iraqi Patients experiencing dermatophytosis who attended hospitals with consultations for dermatology diseases in Al-Hilla Teaching Hospital, dermatology Unit, Babylon province, and some of outpatients clinics. The laboratory findings as well as clinical examinations have indicated that the patients are experiencing dermatophytosis. Furthermore, information regarding all cases were recorded. Additionally, 50 control group was selected from the same place, but they suffer from diseases other than skin who have no history of dermatophytosis.

Blood Samples Collection

Five ml of venous blood were drawn from all participants, collected in gel tubes and EDTA tubes. The withdrawal of the blood sample was slow via the needle of syringe to prevent hemolysis. The samples were centrifuged at 3000 rpm for 10 min at room temperature. The serum was transferred to Eppendorf tubes after that stored at -20C to be used for Immunological investigations IL-17.

Ethical Approval

The participants in the study were notified about the study and a verbal agreement has been taken from each participant.

Test (IL-17) ELISA Kit

The level of IL-17 concentration in the serum of all samples from patients with dermatophytes infections and the control subjects was measured according to the manufacturer's instructions BT/China.

Result and Discussion

Interleukine-17

A. Levels of Interleukin-17 Concentration in Sera of Patients Infected with Dermatophyte Infection and Control Groups

Levels of serum IL-17 concentration were measured in the two study groups (Patients infected with dermatophyte infection and control subjects). Figure (1), shows a significant increase ($P \leq 0.0001$) of serum IL-17 in dermatophyte infected patients (35.015 ± 0.837 pg/ml) when compared with control subjects (6.481 ± 0.848 pg/ml).

The skin is the outermost layer of the body and is exposed to many environmental stimuli, which cause various inflammatory immune responses in the skin. Among them, fungi are common microorganisms that colonize the skin and cause cutaneous fungal diseases such as dermatophytosis. The skin exerts inflammatory responses to eliminate these fungi through the cooperation of skin-component immune cells. IL-17 producing cells are representative immune cells that play a vital role in anti-fungal action in the skin by producing antimicrobial peptides and facilitating neutrophil infiltration. However, the actual impact of IL-17-producing cells in cutaneous fungal infections remains unclear (Burstein et al., 2020).

IL-17 plays a vital role in host defense against dermatophytes microorganisms through the production of antimicrobial peptides to promote microbial homeostasis and neutrophil recruitment, consistently, dysfunction of IL-17 signaling is closely associated with increased morbidity during microbial infection. Predisposing host immune conditions, such as epithelial barrier disruption and cutaneous inflammation of the skin in atopic dermatitis, are closely related to the pathological function of commensal fungi-specific Th17 cells (Sawada et al., 2021).

Burstein et al., (2018) clearly identify IL-17 immunity as a key mechanism of host defense against the dermatophyte *Microsporum* species in patients. Thus, IL-17 is a more common mediator of antifungal immunity against fungal pathogens and its actions are not limited to protection against *Candida* as earlier work might have suggested. Whether IL-17 is also involved in host protection against other fungi in mammalian barrier tissues, such as the pathogenic dermatophyte *Trichophyton*.

Superficial dermatophytosis presents in the stratum corneum and cannot directly make contact with immune cells in the dermis. Therefore, some possible anti-fungal immune responses have been postulated. Patients suffered from superficial

skin infection with dermatophytes, mild inflammation in the skin was observed with a Th17-mediated immune response by Langerin+ cells (Sawada *et al.*, 2021).

The results of current study was compatible with results of some studies which mentioned that, there were an increased in IL-17 is observed in the peripheral blood and skin of patients with dermatophytosis (Sakuragi *et al.*, 2016; Goto *et al.*, 2019).

Also the results of our study were agree with results of Nawfal and Zghair, (2022), where they were proved that the distribution of IL-17 level means into controls and patients, IL-17 mean level control was the lower (53.92 ± 0.75), in compared to patients (83.47 ± 3.17), where the P-value was less than 0.05.

In addition, Tawfek *et al.*, (2016), proved that the serum IL-17 level was significantly increased in dermatophytosis patients compared with the healthy controls. Thus our results compatible with them.

In comparison with other studies, Tokura *et al.*, (2014) explained that, innate immune disrupted diseases, such as adult-T cell leukemia/lymphoma (ATLL), commonly exhibit superficial dermatophytosis among cutaneous mycotic infections.

The frequency of IL-17 in peripheral blood is reduced in patients with ATLL, indicating that the secretion of Th17-mediated antimicrobial peptides by keratinocytes when is reduced, leading to the frequent occurrences of dermatophytosis (Sawada *et al.*, 2021).

Burstein *et al.*, (2018) observed a selective induction of *Microsporium*-specific T helper (Th) type 17 cells after infection. They further showed that the IL-17 pathway was responsible for preventing uncontrolled fungal growth and overt inflammation in response to dermatophytosis.

IL-17 deficiency allows dermatophytes fungi to colonize the epidermis and exacerbate skin inflammation through an IFN- γ -mediated response. Dectin-1 and Dectin-2 deficiency result in inadequate production of inflammatory cytokines in response to *T. rubrum* infection and impair its elimination (Yoshikawa *et al.*, 2016).

In addition, patients lacking IL-1R show decreased IL-17 production in response to *T. rubrum*. STAT1 gain-of-function mutation also facilitates severe dermatophyte infection in the skin with impaired Th17 responses in the peripheral blood (Yoshikawa *et al.*, 2015).

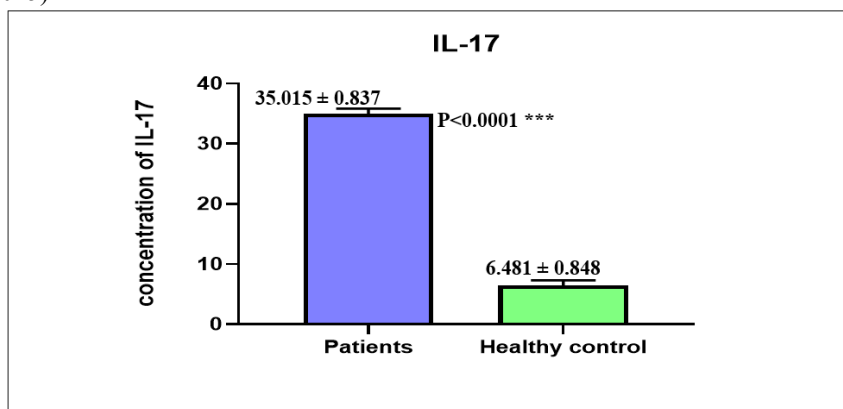


Figure (1): Levels of Interleukin-17 Concentration in Sera of Patients Infected with Dermatophyte Infection and Control Groups. ***($P \leq 0.05$) higher significant.

B. Levels of Interleukin-17 Concentration in Sera of Patients Infected with Dermatophyte Infection and Control Groups according to Age Groups and Gender

The results in table (1) shown in dermatophyte infected patients group, appear non significant difference between age groups (P .value = 0.8780) and the highest concentration level of IL-17 appears with age group (31-40 years) and (41-50 years) and were (37.191 ± 2.806 Pg/ml) and (37.006 ± 0.934 Pg/ml) respectively while the lowest concentration level of IL-17 with (≤ 10 years) was (33.784 ± 4.756 Pg/ml).

IL-17 concentrations level in dermatophyte infected patients group were (35.420 ± 1.808 Pg/ml , 34.862 ± 1.600 Pg/ml , 34.217 ± 1.390 Pg/ml) in age groups (10-20 years, 51-60 years, 21-30 years) respectively.

On the other side, the results of table (1) shown in control group, appear non significant difference between age groups (P .value = 00.8991) the highest concentration level of IL-17 appears with age group (51-60 years) and (≤ 10 years) and were (8.636 ± 2.300 Pg/ml) and (8.281 ± 1.352 Pg/ml) respectively while the lowest concentration level of IL-17 with (31-40 years) was (5.869 ± 1.002 Pg/ml).

IL-17 concentrations level in control group were (7.821 ± 1.785 Pg/ml, 6.813 ± 1.248 Pg/ml , 6.323 ± 2.071 Pg/ml) in age groups (41-50 years, 21-30 years, 10-20 years) respectively.

A close relationship between aging, inflammation, and dermatophyte fungi is widely accepted. Aging is accompanied by a progressive increase in pro-inflammatory cytokines, including interleukin 17 (IL-17), a key pro-inflammatory cytokine that becomes dysregulated with age. However, the contribution of IL-17 to age-related dermatophytosis remains unclear, but inflammation and immunity may a significant impact on the process of aging (Spielmann *et al.*, 2014).

Certain cytokines, such as IL-17 that produced from TH1 and TH17, have clearly emerged as key to promoting inflammaging. Moreover, inflammatory death of cutaneous cells due to exogenous factors such as dermatophytosis infection also promotes the progression of inflammaging. During aging, the imbalance between the increased production and decreased disposal via autophagy, mitophagy, and proteasome, stimulus the innate immune system and thereby triggers the body from a pre-inflammatory state towards a pro-inflammatory state (Mázló *et al.*, 20122).

IL-17 protect from uncontrolled fungal growth during dermatophytosis. IL-17 signaling suppresses type 1 immunity to *Microsporum*, relieving inhibition of fungal clearance (Sparber and LeibundGut-Landmann, 2018).

High rate of interleukin (IL-17) with fungal infections, IL-17 mediated immunity plays an important role in human defense against fungal dermatophytosis infections. People lacking the IL-17 receptor or IL-17's ability to secrete it are more susceptible to dermatophyte infection, however the temporarily blocking of IL-17 pathway during an infection in wild-type humans had no effect on fungal control (Nawfal and Zghair, 2022).

For fungal infections, it is thought that the IL-17 axis improves pathogen survival while simultaneously inducing chronic inflammation. IL-17, which is produced in large quantities at the site of infection, both inhibit antifungal effector activities of neutrophils and activate their inflammatory program (i.e., the production of metalloproteinases and oxidants) despite evidence that IL-17 contributes to neutrophil mobilization in disseminated dermatophytosis. Neutrophils and dendritic cells (DCs) may create more interleukin 23 because to fungal persistence in this environment, which aids in the maintenance of inflammation and increases the production of IL-17 (Nawfal and Zghair, 2022).

The results of current study were nearly compatible with results what was mentioned by Sharma and Nonzom, (2021), which discovered that IL-17 was significantly increased in dermatophytosis patients with age group (31-40 years) and this age group more prone to dermatophyte infections in contrast to other groups.

While Gupta *et al.*, (2015) said that the average age was higher in the infected group than in the uninfected group. The incidence of dermatophytosis increases with aging, thus, aging might contribute to the onset of dermatophyte fungal infections.

In depending on Gender, in dermatophyte infected patients group, the results have shown the high concentration level of IL-17 appear in male was (35.950 ± 0.916 Pg/ml) other than female (33.255 ± 1.643 Pg/ml) with non significant difference (P.value= 0.1266) also in control group , the results have shown the high concentration level of IL-17 appears in male was (7.383 ± 0.911 Pg/ml) and the low concentration level appears in female and was (6.544 ± 0.957 Pg/ml) , and this height also non significance (P.value= 0.5381).

To date, nearly no study has reported gender-specific effects related to a IL-17 cytokine and dermatophytosis.

In comparison with other studies, the interaction between gender and immunity is intriguing. Hormones such as prolactin, growth hormone, and insulin-like growth factor 1 are sexually dimorphic and have been implicated in the increased susceptibility of women to autoimmunity (Yu *et al.*, 2021).

Studies of multifactorial diseases that demonstrate differential susceptibilities between genders encounter confounding variables, such as lifestyle, socioeconomic status, environmental exposures, and genetic polymorphisms. Hence, experimental models with gender differences enable a more systematic study of the effects of gender on disease (Grover *et al.*, 2016).

Male with dermatophyte infection exhibit a greater activity of Treg cells than females, which served to dampen the inflammatory response and protect males disproportionately from disease. T cells isolated from male with dermatophytosis expressed elevated levels of peroxisome proliferator-activated receptor α mRNA, which inhibits the activity of NF- κ B. Peroxisome proliferator-activated receptor α expression is sensitive to androgens, which may partly explain why males are resistant to certain forms of autoimmune inflammation (Rai *et al.*, 2020).

Jaillon *et al.*, (2019) showed that males were more resistant to cutaneous fungi than females, perhaps implicating sexual dimorphism in innate immunity as well. In contrast, our data indicate that female suffered from dermatophytosis respond to infection but very little than male cells to inflammatory stimuli, including IL-17 (Table 4.5).

Although somewhat unexpected, this finding may indicate that the enhanced sensitivity of IL-17-deficient female compared to that of males lies not in the inherent response to IL-17 but the immunoregulatory mechanisms involved in suppressing IL-17 mediated inflammation. Indeed, abundant of immune-suppressive mechanisms are in place to limit Th17 development and IL-17 function, including IL-27, IL-2, and IL-10 (Choi *et al.*, 2021).

In our study not found large difference in concentration level of IL-17 between male and female in both groups (dermatophytosis patients and control). But in one studies shows that IL-17 deficiency lead to increased susceptibility to dermatophytosis infection in both males and females (Burstein *et al.*, 2018).

Table (1) Levels (Mean± S.D.) of Interleukin-17 (Pg/ml) in Sera of The Study Individuals according to Age groups and Gender

Clinical groups		Mean concentration± S.D IL-17 No. (Conc. Pg/ml)		P.value
		Pateints	control	
Age groups	≤ 10 y	33.784 ± 4.756	8.281 ± 1.352	0.0007 ***
	10-20 y	35.420 ± 1.808	6.323 ± 2.071	≤0.0001***
	21-30 y	34.217 ± 1.390	6.813 ± 1.248	≤0.0001***
	31-40 y	37.191 ± 2.806	5.869 ± 1.002	≤0.0001***
	41-50 y	37.006 ± 0.934	7.821 ± 1.785	≤0.0001***
	51-60 y	34.862 ± 1.600	8.636 ± 2.300	≤0.0001***
	P.value	0.8780 NS	0.8991 NS	
Gender	Female	33.255 ± 1.643	6.544 ± 0.957	≤0.0001 ***
	Male	35.950 ± 0.916	7.383 ± 0.911	≤0.0001 ***
	P value	0.1266 NS	0.5381 NS	

*** (P<0.05) higher significant, NS: Non Significant

C. Levels of Interleukin-17 Concentration in Sera of Dermatophytosis Patients group according to Duration of infection and Residence

The concentration level of IL-17 according to duration of infection in dermatophytosis patients as shown in table (2), appear significant difference between groups (P.value ≤ 0.0001) and the highest concentration level of IL-17 appears with groups (> 2 years) and was (74.083 \pm 9.807 Pg/ml), while the lowest concentration level of IL-17 with (≤ 6 month) and was (33.892 \pm 2.890 Pg/ml).

IL-17 concentrations level in other groups were (36.477 \pm 3.493 Pg/ml, 51.484 \pm 6.877 Pg/ml , 51.425 \pm 1.405 Pg/ml) in groups (≤ 1 year, ≤ 1.5 year, ≤ 2 years) respectively.

Dermatophytes have evolved a strategy of maintaining a low immunologic profile because of their superficial localization in the skin. Though they induce clinical signs, the immune response in their hosts is rather complex and poorly understood (Rai *et al.*, 2020). Gnat *et al.*, (2019) have described that pathogenic dermatophytes produce a highly polymorphic spectrum and host immune response which restrict the infection to superficial layers of skin, hair and nails. A severe inflammatory response in the host develops when it is not adapted than its natural host. Chronic infections in human are associated with anthropophilic species causing minimal inflammation, while zoophilic or geophilic species are highly inflammatory, though self-limiting. Several defense mechanisms develop against dermatophytes varying from innate to a more robust specific adaptive responses to prevent fungal invasion (Gupta *et al.*, 2023).

Numerous studies have shown that resolution of dermatophytosis is generally associated with the effective development of a delayed-type of hypersensitivity (DTH) reaction, while conversely, the persistent and chronic infection is associated with a poor DTH response (instead of a prominent type 1 hypersensitivity reaction). The humoral immunity to dermatophytosis, however, is not protective; cell-mediated immunity of the host is required for clinical recovery and protection from reinfection (Schmid-Wendtner *et al.*, 2007; Heinen *et al.*, 2017).

Expression of IL-17 as early as three days after a dermatophyte infection means that there is a rapid activation of IL-17 is reminiscent of the innate Th-17 responses against fungal infections rather than adaptive immune response (Sparber and LeibundGut-Landmann, 2019).

Recently, the importance and protective role of Th17 cells promoting the Th1 immune response and inhibiting the Th2 response has been discussed. IL-17 α aids in mobilization of neutrophils and stimulates defensins, thus resulting in rapid effective control of infections (Jartarkar *et al.*, 2021).

The earlier studies on cytokine profile at the dermatophyte infection site reveals TGF- β , IL-1 β , and IL-6, which are involved in the initiation and perpetuation of the Th17 pathway. Further, an increase in IL-22 mRNA was also observed, and both findings suggesting that the Th17 cell pathway may be involved in the immunopathogenesis of dermatophytic infections, therefore, the concentration of IL-17 increases gradually as the infection continues and reaches its peak gradually with increasing severity of dermatophytosis (Sardana *et al.*, 2021).

IL-17 plays an important role in the clearance of fungal infections, however, dysregulated production of IL-17 can result in excessive pro-inflammatory cytokine production and chronic inflammation, leading to tissue damage and the disease worsens (Omidian *et al.*, 2019).

The results of our study were compatible with results of Gnat *et al.*, (2019) where mentioned that the concentration level of IL-17 continues to be secreted as the infection continues and reaches its peak in chronic infection.

Recently, the focus has shifted to the Th17 cell pathway, which promotes the Th1-type immune responses and inhibits Th2-type responses. IL-17 has been shown to mobilize neutrophils and stimulate defensins' secretion, contributing to the rapid and effective control of infection as an innate response (Mills, 2023).

The study introduced by Hiruma *et al.*, (2021), demonstrated that IL-17 signaling may also have a role in inhibiting dermatophyte infections.

Rai *et al.*, (2020) Reported that dermatophyte infections have evolved in the past decade demonstrating a clinically problematic diversity due to increasing relapses, reinfections and chronicity with a duration lasting up to one years or more and is accompanied by a high continuous concentration in IL-17 and this was compatible with our results.

While there are some studies have linked levels of IL-17 in serum to dermatophytosis in an attempt to delve deeper into the division of Th17 responses and determine IL-17 in chronic recalcitrant dermatophytosis. They found that this interleukin keeps its secretion constant and continues to rise moderately even months to years after occurrence of the infection (Lacy *et al.*, 2022; Pendlebury *et al.*, 2023). Also this is consistent with what we found through the results of our current study.

Table (2) Levels (Mean \pm SEM) of Interleukin-17 (Pg/ml) in Sera of Dermatophytosis Patients group according to Duration of Infection

Duration of infection						
IL-17	≤ 6 Month Mean \pm SEM	≤ 1 year Mean \pm SEM	≤ 1.5 year Mean \pm SEM	≤ 2 years Mean \pm SEM	> 2 years Mean \pm SEM	P.value ≤ 0.0001 ***
Dermatophytosis Patient	33.892 \pm 2.890	36.477 \pm 3.493	51.484 \pm 6.877	51.425 \pm 1.405	74.083 \pm 9.807	
***($P \leq 0.05$) higher significant.						

In depending on residency, and as shown in Figure (2), in dermatophyte infected patients group, the results have shown the high concentration level of IL-17 appear in rural and was (35.803 \pm 0.945 Pg/ml) and the low concentration level appears in urban and was (33.770 \pm 1.551 Pg/ml), with non significant difference (P.value= 0.2409).

The complex interplay between agent, host and the environment plays a role in the pathogenesis of dermatophytosis. The predisposing factors in the host include immunocompromised states such as diabetes mellitus, lymphoma and chronic illnesses, which can lead to extensive, recurrent or recalcitrant dermatophytoses. Intertriginous areas including groin, axilla, inter-web spaces are more susceptible to infection due to excess sweating, rubbing and alkaline pH. Environmental factors which predispose people to higher chances of infection include high humidity, high temperature, increased urbanization, use of tight-fitting clothes and occlusive footwear. In most parts of the world, anthropophilic *T. rubrum* is the most common isolate, but it is being increasingly replaced by *T. interdigitale* and *T. mentagrophytes* complex in some geographical locations (Jartarkar *et al.*, 2021). *T. interdigitale* is responsible for mild and chronic infections (Ilkit and Durdu, 2015).

Variations in fungal virulence in various species of dermatophytes are likely to play a role in the recurrence or resistance of infections. A few clinical types like onychomycosis may have a genetic predisposition. Distal subungual onychomycosis may be inherited in an autosomal dominant fashion with incomplete or variable penetrance (Jartarkar *et al.*, 2021).

Dermatophytic infections is commonly spread in family members, especially in the case of *tinea capitis* and *tinea pedis* (Sharma and Nonzom, 2021). Therefore the prevalence of dermatophytes infection is more widespread in rural areas, and this depend on immunologically state for people, because it is known that residents of rural villages have a stronger immune system than city residents. This may be due to their constant exposure to different types of microbes, as well as the nature of their diet, exposure to the sun for long periods, and their continuous movement during the day. All of this plays a role in making their immunity better, so perhaps this is what made the level of IL-17 concentration is slightly higher than others.

The results of our study agree with results of Jha *et al.*, (2019), which mentioned that the level of IL-17 concentration is higher in rural residents than in urban residents with dermatophyte.

A study by Sharma *et al.*, (2021) which involved 247 families suffering from dermatophytosis and it has been reported that the patients living in rural areas show more frequency and higher level of IL-17 than the patients living in urban areas. This is consistent with the results of our presented study.

Our results also similar to results of Song *et al.*, (2023) which proved that IL-17 production has increased in the patient's with dermatophytosis who lived as farmer in a rural area of China other than who lived in urban.

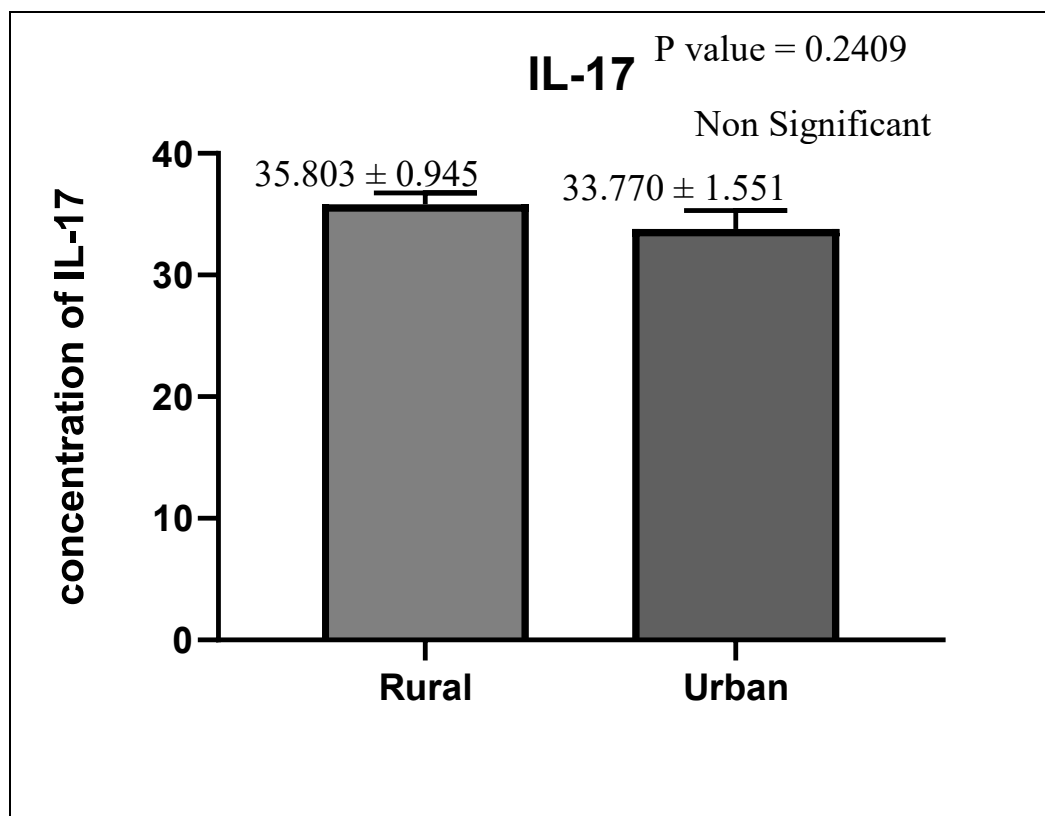


Figure (2): Levels of Interleukin-17 Concentration in Sera of Patients Infected with Dermatophyte Infection according to Residence.

References

[1]. Kovitwanichkanont, T., & Chong, A. H. (2019). Superficial fungal infections. Australian Journal of General Practice, 48(10), 706-711.
 [2]. Celestrino, G. A., Verrinder Veasey, J., Benard, G., & Sousa, M. G. T. (2021). Host immune responses in dermatophytes infection. Mycoses, 64(5), 477-483.
 [3]. Sardana, K., Gupta, A., & Mathachan, S. R. (2021). Immunopathogenesis of dermatophytoses and factors leading to recalcitrant infections. Indian dermatology online journal, 12(3), 389.

- [4]. Vinh, D. C. (2023). Of Mycelium and Men: Inherent Human Susceptibility to Fungal Diseases. *Pathogens*, 12(3), 456.
- [5]. Tangye, S. G., & Puel, A. (2023). The Th17/IL-17 axis and host defence against fungal infections. *The Journal of Allergy and Clinical Immunology: In Practice*.
- [6]. Burstein, V. L., Beccacece, I., Guasconi, L., Mena, C. J., Cervi, L., & Chiapello, L. S. (2020). Skin immunity to dermatophytes: From experimental infection models to human disease. *Frontiers in Immunology*, 11, 605644.
- [7]. Sawada, Y., Setoyama, A., Sakuragi, Y., Saito-Sasaki, N., Yoshioka, H., & Nakamura, M. (2021). The role of IL-17-producing cells in cutaneous fungal infections. *International Journal of Molecular Sciences*, 22(11), 5794.
- [8]. Burstein, V. L., Guasconi, L., Beccacece, I., Theumer, M. G., Mena, C., Prinz, I., ... & Chiapello, L. S. (2018). il-17-mediated immunity controls skin infection and t helper 1 response during experimental *Microsporum canis* dermatophytosis. *Journal of Investigative Dermatology*, 138(8), 1744-1753.
- [9]. Goto, Y., Suzuki, T., Suzuki, Y., Anzawa, K., Mochizuki, T., Tamura, T., ... & Tokura, Y. (2019). Trichophyton tonsurans-induced kerion celsi with decreased defensin expression and paradoxically increased interleukin-17A production. *The Journal of Dermatology*, 46(9), 794-797.
- [10]. Sakuragi, Y., Sawada, Y., Hara, Y., Ohmori, S., Omoto, D., Haruyama, S., ... & Nakamura, M. (2016). Increased circulating Th17 cell in a patient with tinea capitis caused by *Microsporum canis*. *Allergology International*, 65(2), 215-216.
- [11]. Nawfal, B. N., & Zghair, F. S. (2022). Study of immune response of immune mediator interleukin (17 and 23) against dermatophytes infection. *Journal of Algebraic Statistics*, 13(2), 2358-2365.
- [12]. Tawfek, A. R. K., Shafik, A. O., & Yousef, S. A. (2016). IL-17 Assay in Adult T-cell leukemia/lymphoma Patients with Dermatophytosis. *The Egyptian Journal of Medical Microbiology (EJMM)*, 24(2).
- [13]. Tokura, Y., Sawada, Y., & Shimauchi, T. (2014). Skin manifestations of adult T-cell leukemia/lymphoma: clinical, cytological and immunological features. *The Journal of dermatology*, 41(1), 19-25.
- [14]. Yoshikawa, F. S. Y., Ferreira, L. G., & de Almeida, S. R. (2015). IL-1 signaling inhibits *Trichophyton rubrum* conidia development and modulates the IL-17 response in vivo. *Virulence*, 6(5), 449-457.
- [15]. Yoshikawa, F. S., Yabe, R., Iwakura, Y., De Almeida, S. R., & Saijo, S. (2016). Dectin-1 and Dectin-2 promote control of the fungal pathogen *Trichophyton rubrum* independently of IL-17 and adaptive immunity in experimental deep dermatophytosis. *Innate immunity*, 22(5), 316-324.
- [16]. Spielmann, G., Bigley, A. B., & LaVoy, E. C. and Richard J. Simpson (2014). *Immunology of Aging*, 369.
- [17]. Mázló, A., Jenéi, V., Burai, S., Molnár, T., Bácsi, A., & Koncz, G. (2022). Types of necroinflammation, the effect of cell death modalities on sterile inflammation. *Cell Death & Disease*, 13(5), 423.
- [18]. Sharma, B., & Nonzom, S. (2021). Superficial mycoses, a matter of concern: Global and Indian scenario-an updated analysis. *Mycoses*, 64(8), 890-908.
- [19]. Sparber, F., & LeibundGut-Landmann, S. (2018). IL-17 takes center stage in dermatophytosis. *Journal of Investigative Dermatology*, 138(8), 1691-1693.
- [20]. Gupta, A. K., Daigle, D., & Foley, K. A. (2015). The prevalence of culture-confirmed toenail onychomycosis in at-risk patient populations. *Journal of the European Academy of Dermatology and Venereology*, 29(6), 1039-1044.
- [21]. Yu, P., Chen, Y., Ge, C., & Wang, H. (2021). Sexual dimorphism in placental development and its contribution to health and diseases. *Critical Reviews in Toxicology*, 51(6), 555-570.
- [22]. Rai, G., Das, S., Ansari, M. A., Singh, P. K., Pandhi, D., Tigga, R. A., ... & Dar, S. A. (2020). The interplay among Th17 and T regulatory cells in the immune dysregulation of chronic dermatophytic infection. *Microbial pathogenesis*, 139, 103921.
- [23]. Grover, V., Jain, A., Kapoor, A., Malhotra, R., & Singh Chahal, G. (2016). The gender bender effect in periodontal immune response. *Endocrine, Metabolic & Immune Disorders-Drug Targets (Formerly Current Drug Targets-Immune, Endocrine & Metabolic Disorders)*, 16(1), 12-20.
- [24]. Jaillon, S., Berthenet, K., & Garlanda, C. (2019). Sexual dimorphism in innate immunity. *Clinical reviews in allergy & immunology*, 56, 308-321.
- [25]. Choi, J. K., Yu, C. R., Bing, S. J., Jittayasothorn, Y., Mattapallil, M. J., Kang, M., ... & Egwuagu, C. E. (2021). IL-27-producing B-1a cells suppress neuroinflammation and CNS autoimmune diseases. *Proceedings of the National Academy of Sciences*, 118(47), e2109548118.
- [26]. Gupta, A. K., Cooper, E. A., Wang, T., Lincoln, S. A., & Bakotic, W. L. (2023). Single-Point Nail Sampling to Diagnose Onychomycosis Caused by Non-Dermatophyte Molds: Utility of Polymerase Chain Reaction (PCR) and Histopathology. *Journal of Fungi*, 9(6), 671.
- [27]. Gnat, S., Nowakiewicz, A., Łagowski, D., & Zięba, P. (2019). Host-and pathogen-dependent susceptibility and predisposition to dermatophytosis. *Journal of medical microbiology*, 68(6), 823-836.
- [28]. Schmid-Wendtner, M. H., & Korting, H. C. (2007). Effective treatment for dermatophytoses of the foot: effect on restoration of depressed cell-mediated immunity. *Journal of the European Academy of Dermatology and Venereology*, 21(8), 1013-1018.
- [29]. Heinen, M. P., Cambier, L., Fievez, L., & Mignon, B. (2017). Are Th17 cells playing a role in immunity to dermatophytosis?. *Mycopathologia*, 182, 251-261.
- [30]. Jartarkar, S. R., Patil, A., Goldust, Y., Cockerell, C. J., Schwartz, R. A., Grabbe, S., & Goldust, M. (2021). Pathogenesis, immunology and management of dermatophytosis. *Journal of Fungi*, 8(1), 39.
- [31]. Omidian, Z., Ahmed, R., Giwa, A., Donner, T., & Hamad, A. R. A. (2019). IL-17 and limits of success. *Cellular immunology*, 339, 33-40.

- [32]. Mills, K. H. (2023). IL-17 and IL-17-producing cells in protection versus pathology. *Nature Reviews Immunology*, 23(1), 38-54.
- [33]. Hiruma, J., Harada, K., Hirayama, M., Egusa, C., Tobita, R., Masuda-Kuroki, K., ... & Okubo, Y. (2021). Blockade of the IL-17 signaling pathway increased susceptibility of psoriasis patients to superficial fungal infections. *Journal of Dermatological Science*, 101(2), 145-146.
- [34]. Lacy, F., del Mar Melendez-Gonzalez, M., & Sayed, C. J. (2022). *Dermatologic Conditions. Reichel's Care of the Elderly: Clinical Aspects of Aging*, 457.
- [35]. Pendlebury, G. A., Oro, P., Ludlow, K., Merideth, D., Haynes, W., Shrivastava, V., & Ludlow, K. S. (2023). Relevant Dermatoses Among US Military Service Members: An Operational Review of Management Strategies and Telemedicine Utilization. *Cureus*, 15(1).