



Serum vitamin B12, ferritin, and vitamin D levels in patients with seborrheic dermatitis: A case-control study

Seboreik dermatitli hastalarda serum vitamin B12, ferritin ve vitamin D düzeyleri: Bir olgu-kontrol çalışması

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Abstract

Background and Design: No evidence suggests that any micronutrients are associated with seborrheic dermatitis (SD). The etiopathogenesis of SD is attributed to excessive proliferation of *Malassezia* species in the skin, deterioration in epidermal barrier functions, and inflammation. Vitamin B12 affects the immune system. Moreover, the ferritin molecule can act as a proinflammatory cytokine and has immunomodulating effects. Vitamin D has immunomodulatory effects and affects the epidermal barrier. Therefore, we thought that low serum levels of these parameters might affect immune responses against *Malassezia* species that caused SD. The study aimed to compare the serum vitamin B12, ferritin, and vitamin D levels of patients with SD with healthy controls.

Materials and Methods: Patients aged 18-50 years who applied to the dermatology outpatient clinic and were found to have SD during dermatological examination were retrospectively reviewed. Serum vitamin B12, ferritin, and vitamin D levels of 63 patients with SD and 37 healthy controls were compared. Categorical variables were compared using chi-square analysis. Student's t-test was used to compare constant variables, and Pearson's correlation test was applied for the correlation analysis. $P<0.05$ was considered significant.

Results: No significant difference was found in the serum vitamin B12, ferritin, and vitamin D levels between the patient and control groups ($p=0.227$, $p=0.381$, $p=0.611$, respectively). In addition, no significant difference was found between the patient and control groups in terms of serum vitamin B12, ferritin, and vitamin D levels, which were categorized as deficient, insufficient, and adequate ($p=0.31$, $p=0.53$, and $p=0.80$, respectively).

Conclusion: Routine measurements of these values are not necessary, but since detected subclinical vitamin B12 deficiency was detected in the patient group, this should be investigated in prospective controlled studies with a large number of patients.

Keywords: Seborrheic dermatitis, vitamin D, vitamin B12, ferritin

Öz

Amaç: Herhangi bir mikro besin maddesinin seboreik dermatit (SD) ile ilişkili olduğuna dair kanıt yoktur. SD etiopatogenezinde deride *Malassezia* türlerinin aşırı çoğalması, epidermal bariyer işlevlerinde bozulma ve enflamasyon suçlanmaktadır. Vitamin B12'nin immün sistem üzerinde etkileri vardır. Ayrıca ferritin molekülü, immünomodülatör etkilere sahiptir. Vitamin D'nin hem immünomodülatör etkileri hem de epidermal bariyer üzerinde etkileri olduğu için, bu parametrelerin düşük serum düzeylerinin SD etiopatogenezinde suçlanan *Malassezia* türlerine karşı immün yanıtları etkileyebileceğini düşündük. Bunun için SD'li hastaların serum vitamin B12, ferritin ve vitamin D düzeylerini sağlıklı kontrollerle karşılaştırmayı amaçladık.

Gereç ve Yöntem: Hastanemiz dermatoloji polikliniğine başvuran ve dermatolojik muayenesinde SD saptanan 18-50 yaş arası hastalar retrospektif olarak incelendi. Altmış üç SD'li hasta ile otuz yedi sağlıklı kontrolün serum vitamin B12, ferritin ve vitamin D değerleri karşılaştırıldı. Kategorik değişkenler ki-kare analizi kullanılarak karşılaştırıldı. Sabit değişkenleri karşılaştırmak için Student's t-testi, korelasyon analizi için Pearson's korelasyon testi uygulandı. $P<0,05$ istatistiksel olarak anlamlı kabul edildi.

Bulgular: Hasta ve kontrol grupları arasında serum B12, ferritin ve D vitamini seviyeleri açısından istatistiksel olarak anlamlı fark yoktu (sırasıyla; $p=0,227$, $p=0,381$, $p=0,611$). Ayrıca hasta ve kontrol grupları arasında eksik, yetersiz ve yeterli olarak kategorize edilen serum vitamin B12, ferritin ve vitamin D düzeyleri açısından da istatistiksel olarak anlamlı fark yoktu (sırasıyla; $p=0,31$, $p=0,53$, $p=0,80$).

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Sonuç: Bu değerlere rutin olarak bakmak gerekli değildir, ancak hasta grubunda subklinik vitamin B12 eksikliği tespit edildiği için bu durumun çok hasta içeren ileriye dönük kontrollü çalışmalarla araştırılmasını öneriyoruz.

Anahtar Kelimeler: Seboreik dermatit, vitamin D, vitamin B12, ferritin

Introduction

Seborrheic dermatitis (SD) is a common chronic recurrent inflammatory skin disease characterized by redness, scaly patches, and dandruff on oily body areas such as the scalp, face, upper chest, and back¹. The incidence of SD in the normal population ranges from 1% to 3%, but in patients with acquired immune deficiency syndrome (AIDS) and Parkinson's disease, the incidence is much higher, ranging from 30% to 83 and 52-59%, respectively². The relationship between SD and many micronutrients such as essential fatty acids, vitamins, zinc, and iron has been speculated in many studies^{1,3-6}. However, studies on this subject are limited, and no evidence confirms that any micronutrients are associated with SD.

Malassezia yeasts have long been blamed for the etiopathogenesis of SD. The number of Malassezia yeast has been shown to correlate with the symptoms and severity of SD. Malassezia species activate the proinflammatory cytokine pathway, and the reduction in SD severity with antifungal treatment strengthens this relationship⁷.

The cellular immunity of the host is the main protective factor against fungal organisms. The incidence of SD increases in patients with AIDS and Parkinson's disease. The cellular immune response is impaired, especially in AIDS. There is evidence of immune system dysfunction in Parkinson's disease as well. Therefore, the frequent occurrence of SD in these diseases may be secondary to an impaired immune response against Malassezia yeasts^{8,9}.

Vitamin B12 (cobalamin) is an essential micronutrient that mainly plays a role in maintaining neuronal health and hematopoiesis and participates in oxidative stress processes¹⁰. Vitamin B12 deficiency inhibits nucleic acid formation, protein synthesis, and activation of immune cells, altering immune system responses by interfering with metabolic processes, including methylation cycles of amino acids¹¹.

Moreover, vitamin B12 deficiency has been reported in Parkinson's disease, parkinsonism secondary to neuroleptics, and human immunodeficiency virus (HIV) infection, which are common diseases with SD^{10,12,13}. We thought that there might be a possible vitamin B12 deficiency in patients with SD because vitamin B12 deficiency is seen in diseases where SD is common, and vitamin B12 can play a role in immune processes.

Ferritin is an intracellular protein that is mainly localized in the cell's cytoplasm but is found in smaller amounts in serum and biological fluids¹⁴. In addition to being a sizeable iron-storing molecule, ferritin is known to protect cells from the harmful effects of free iron and to have different functions, including immune regulation. It is one of the first discovered proteins involved in iron metabolism¹⁵.

We thought that high or low serum ferritin levels might be associated with SD. For example, high serum ferritin levels were suggested to be associated with inflammatory activity and may have a direct role in inflammation, and ferritin may act as a proinflammatory cytokine and have immunomodulatory effects¹⁶. Therefore, we thought that ferritin levels, an indicator of systemic inflammation, might be increased in SD, an inflammatory dermatosis.

Low ferritin level is also an indicator of iron deficiency. Iron is essential for lymphocytes in the proliferation of immune cells, producing a specific humoral and cellular immune response¹⁷.

Since cellular immunity plays a role in the immune response to Malassezia species that play a role in the etiopathogenesis of SD, we hypothesized that possible disruptions in the cellular immune response due to iron deficiency might contribute to SD development⁸.

Vitamin D is basically a hormone that regulates calcium homeostasis in the body. It is obtained from the diet or synthesized in the skin via ultraviolet B light. It also has essential roles in anti-inflammatory, immunomodulatory, keratinocyte growth, and differentiation processes^{18,19}.

Vitamin D has been shown to downregulate proinflammatory cytokine expression, have strengthening effects on the epidermal barrier, and regulate effects on keratinocyte proliferation. Therefore, vitamin D deficiency may play a role in the etiology of SD, in which proinflammatory cytokines are increased, and the epidermal barrier is disrupted^{7,20,21}.

Therefore, low serum levels of these parameters might contribute to SD etiopathogenesis by affecting immune responses or epidermal barrier functions to Malassezia species implicated in SD etiopathogenesis. Although SD is a common disease, no study has evaluated serum vitamin B12 and ferritin levels in patients with SD, but there was a study on vitamin D levels. In this study, we aimed to compare serum basic vitamin values and ferritin levels frequently used in our daily practice in patients with SD with healthy controls.

Materials and Methods

Study design

Between March 2019 and August 2020, records of 427 patients aged 18-50 years who applied to the dermatology outpatient clinic and were found to have SD in their dermatological examinations were retrospectively reviewed. Moreover, 63 patients with available results of parameters analyzed were included in the study. The test results of patients with ferritin, vitamin B12, and vitamin D blood tests were recorded. Data of the patients, such as age, sex, illness duration, and blood parameters, were transferred to the statistics program.

Patients with active infection indicators in their blood parameters (leukocytosis, high sedimentation rate, and high C-reactive protein levels), with a chronic systemic disease, and with missing blood tests, and with blood tests older than 1 month from the date of the application were excluded from the study.

Thirty-seven participants in the control group were selected from healthy hospital staff volunteers of similar age and sex who were tested for serum ferritin, vitamin B12, and vitamin D.

Serum vitamin B12 levels <160 ng/mL were considered deficient, 161-270 ng/mL insufficient, and 271-883 ng/mL sufficient¹⁰. In the central laboratory where the study was conducted, the normal reference range for ferritin levels was 22-274 ng/mL. Serum ferritin levels of <21 ng/mL were considered deficient, and values >275 ng/mL were considered

high. Serum 25 hydroxyvitamin D levels <20 ng/mL were considered deficient, 20-30 ng/mL insufficient, and 30-100 ng/mL sufficient¹⁹. Biochemical analyses were performed using ArchitectPlus, ci4100 (Abbott laboratories, North Chicago, IL, USA) device. The study protocol was approved by the Ethics Committee of Bezmialem Vakıf University (approval number: 54022451-050.05.04). Informed consent was obtained.

Statistical Analysis

Statistical analysis was performed on IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive data were expressed as number (n) and percentage (%), whereas other data were expressed as mean ± standard deviation. Categorical variables were compared using chi-square analysis. Student's t-test was used to compare normally distributed constant variables and the Mann-Whitney U test for non-normally distributed variables. Pearson's correlation test was applied for correlation analysis, and p<0.05 were considered significant.

Results

Of the patients, 28 (44.4%) were women, and 35 (55.6%) were men. The mean age of our patients was 32.17 (±8.13) years, and the mean disease duration was 31.8 (±26.13) months. Twenty participants in the control group were women (54.1%), and 17 (45.9%) were men, and the mean age was 31.86 (±9.86) years.

In the patient group, the mean serum vitamin D, vitamin B12, and serum ferritin levels were 19.50 (±8.93), 327.02 (±111.99), and 68.72 (±70.36), respectively. In the control group, the mean serum vitamin D, vitamin B12, and serum ferritin levels were 20.47 (±9.54), 356.46 (±124.97), and 81.93 (±75.41), respectively.

No correlation was found between disease duration and serum vitamin B12, ferritin, and vitamin D levels (p=0.25, 0.95, and 0.92, respectively). No significant difference was found in the serum vitamin B12, ferritin, and vitamin D levels between the patient and control groups (p=0.227, 0.381, and 0.61,1 respectively) (Table 1).

In the subgroup analysis, no significant difference was found between the patient and control groups regarding whether serum vitamin B12, ferritin, and vitamin D levels were low, normal, or high (p=0.31, 0.53, and 0.80, respectively) (Table 2).

In the patient group, serum vitamin B12 levels were deficient in 3.2%, insufficient in 33.3%, and sufficient in 63.5%. In the control group, no participants had vitamin B12 deficiency, whereas insufficient values were found in 24.3% and normal values in 75.7% of the patient group. Serum vitamin B12 levels were not below reference values in the control group. Subclinical vitamin B12 deficiency was detected in 33.3% of the patient group and 24.3% of the control group (Table 2). In the patient group, serum vitamin D levels were deficient in 55.6%, insufficient in 34.9%, and sufficient in 9.5%. In the control group, serum vitamin D levels were deficient in 48.6%, insufficient in 40.5%, and sufficient in 10.7%. No significant difference was found in the serum vitamin B12 and vitamin D levels between male and female patients in both groups (p=0.984, 0.572 respectively), but were significantly lower in women (p<0.001). In the subgroup analysis, no significant difference was noted in the serum ferritin levels between male and female patients in both groups, but the serum ferritin levels were lower in women in the patient group (64.2%) than in women in the control group (40%) (p=0.482 and 0.096, respectively) (Table 2).

Discussion

Excessive proliferation of *Malassezia* species in the skin, deterioration in epidermal barrier functions, and inflammation are involved in the etiopathogenesis of SD⁷. Vitamin B12 has effects on the immune system. The ferritin molecule can also act as a proinflammatory cytokine and has immunomodulating effects. Vitamin D has immunomodulatory effects and affects the epidermal barrier^{11,16,19}. Therefore, low serum levels of these parameters might alter immune responses against *Malassezia* species that caused SD.

SD is more common in men than in women and peaks in their forties. It can be classified as infantile period and adult-onset SD when sebaceous gland activity is both increased²². Similarly, in our study, the proportion of male patients (55.6%) was higher, and the mean age of the patients was 32.17 (±8.13) years.

Vitamin B12 is an essential vitamin for neuronal health and hematopoiesis. Clinical vitamin B12 deficiency is a rare condition that causes myeloneuropathy or megaloblastic anemia. Subclinical vitamin B12 deficiency could damage macromolecules such as nucleic acids, proteins, and lipids in tissues without apparent symptoms. When the

Table 1. Demographic data and statistics

| | | Groups | | |
|----------------------------------|--------------------|--------------------------|------------------|---|
| | | Patients with SD, (n=63) | Controls, (n=37) | Test value |
| Age | Median (min.-max.) | 33 (18-50) | 31 (18-50) | t=0.17 p=0.381 ^a |
| | Mean ± SD | 32.17±8.13 | 31.86±9.86 | |
| Sex | Female | 28 (44.4%) | 20 (54.1%) | χ ² =0.862 p=0.353 ^b |
| | Male | 35 (55.6%) | 17 (45.9%) | |
| Serum vitamin B12 levels (ng/mL) | Median (min.-max.) | 305 (125-590) | 335 (185-722) | t=-1.216 p=0.227 ^a |
| | Mean ± SD | 327.02±111.99 | 356.46±124.97 | |
| Serum ferritin levels (ng/mL) | Median (min.-max.) | 45.4 (1-342) | 47 (4.1-263) | t=-0.880 p=0.381 ^a |
| | Mean ± SD | 68.72±70.36 | 81.93±75.41 | |
| Serum vitamin D levels (ng/mL) | Median (min.-max.) | 18.8 (4.8-44) | 21 (3-44.6) | t=-0.510 p=0.611 ^a |
| | Mean ± SD | 19.50±8.93 | 20.47±9.54 | |

^aStudent's t-test, ^bPearson's chi-square test, SD: Seborrheic dermatitis, min.: Minimum, max.: Maximum

Table 2. Subgroup analysis data

| Groups | | | | |
|--------------------------|----------------------|-----------------------------|---------------------|-------------------------------|
| Subgroups | Serum value, (ng/mL) | Patient with SD, (n=63) (%) | Control, (n=37) (%) | Test value (p) |
| Serum vitamin B12 levels | 0-160 | 2 (3.2) | 0 | $\chi^2=2.314$ $p=0.314^b$ |
| | 161-270 | 21 (33.3) | 9 (24.3) | |
| | 271-883 | 40 (63.5) | 28 (75.7) | |
| Serum ferritin levels | 0-21 | 18 (28.6) | 8 (21.6) | $\chi^2=1.253$ $p=0.534^b$ |
| | 22-274 | 44 (69.8) | 29 (78.4) | |
| | ≥ 275 | 1 (1.6%) | 0 | |
| Serum vitamin D levels | 0-20 | 35 (55.6) | 18 (48.6) | $\chi^2=0.447$ $p=0.800^b$ |
| | 21-30 | 22 (34.9) | 15 (40.5) | |
| | 31-100 | 6 (9.5) | 4 (10.7) | |

^bPearson's chi-square test, SD: Seborrheic dermatitis

serum vitamin B12 level is around 161-271 ng/mL, subclinical B12 deficiency is mentioned. Subclinical vitamin B12 deficiency has been reported in diseases where SD is common, such as Parkinson's disease and HIV infection^{10,13}.

In our study, no significant difference was found in the serum vitamin B12 levels between the patient and control groups ($p=0.227$). In addition, 33% of the patients had subclinical vitamin B12 deficiency, whereas this rate was 24% in the control group. Although not significantly related, subclinical vitamin B12 deficiency may trigger SD development.

Ferritin is used as a marker of inflammation and iron status in the body. A low ferritin level is usually associated with iron deficiency²³. We did not find high ferritin values in our patients that suggest hyperinflammation. To our knowledge, no study has evaluated serum ferritin levels in patients with SD. There are few studies in which high iron levels were measured in serum and hair samples of patients with SD^{5,6}.

Moreover, no significant difference was found between the patient and control groups in terms of serum ferritin levels. Serum ferritin levels were not low in any of the male patients in the both groups. This finding is also supported by previous studies that serum ferritin levels are higher in the male population than in female patients²³. However, the serum ferritin level was low in 64.2% of the women in the patient group and 40% of the women in the control group. Perhaps, iron deficiency may facilitate SD occurrence in women.

In addition, the spontaneous resolution of SD during summer and the therapeutic efficacy of topical vitamin D analogs suggest that vitamin D may play a role in the etiopathogenesis of SD²⁴. Vitamin D receptors in keratinocytes inhibit the proliferation of keratinocytes and stimulate the differentiation of epidermal cells. Vitamin D also downregulates the expression and production of proinflammatory cytokines such as tumor necrosis factor-alpha and interleukin-1 β (IL-1 β), IL-6, and IL-8, which are found to be increased in the skin of patients with SD^{4,7,21}.

The loss of barrier functions of the skin is one of the conditions that play a role in the pathogenesis of SD other than Malassezia species. Vitamin D interacts with innate immune defenses by stimulating filaggrin synthesis, which is expressed by keratinocytes and plays an essential role in the formation of the skin barrier. The effects of vitamin D on both immune system functions and the effects on functions of some microorganisms such as Staphylococcus and Malassezia species

blamed in eczema exacerbations, are also discussed. Patients with low serum vitamin D levels have a higher positive immunoglobulin E rate against Malassezia^{7,20}.

Contrary to other studies, we could not find a significant difference in serum vitamin D levels between the patient and control groups in our study^{4,24}. In the patient group, serum vitamin D values levels were deficient in 55.6%, insufficient in 34.9%, and sufficient in 9.5%. In the control group, serum vitamin D levels were deficient in 48.6%, inadequate in 40.5%, and adequate in 10.7%. This result suggests that serum vitamin D levels may be low in the general population.

Study Limitations

The study is limited by the small size of the study group, retrospective design, and non-evaluation of seasonal variables that may affect vitamin D levels.

Conclusion

In our study, we did not find any significant difference in the serum vitamin B12, ferritin, and vitamin D levels between the patient and control groups. This suggests that many factors play a role in the pathogenesis of SD, and genetic and epigenetic changes may contribute to this.

In the patient group, we found subclinical vitamin B12 deficiency in all sexes and low serum ferritin levels in women. Therefore, all patients with SD should be examined for serum vitamin B12 levels, and women with SD should be examined for iron deficiency anemia.

Given the small number of patients and the retrospective design, we recommend conducting prospective studies with a large number of patients to achieve more accurate results.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Bezmi Alem Vakıf University (approval number: 54022451-050.05.04).

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.G., Concept: S.G., H.G., Design: S.G., Data Collection or Processing: S.G., Analysis or Interpretation: H.G., Literature Search: S.G., H.G., Writing: S.G., H.G.

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