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The role of anemia and vitamin D levels in acute and chronic telogen effluvium

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Aim: Telogen effluvium (TE) is an abnormality of hair cycling. Vitamin D promotes hair follicle differentiation. The importance of vitamin D in hair growth is evident in patients with hereditary vitamin D receptor deficiency. The role of vitamin D in the pathogenesis of TE has not been investigated before. We investigated the role of vitamin D, ferritin, and zinc in the pathogenesis of TE.

Materials and methods: We measured serum hemoglobin, ferritin, zinc, calcium, phosphate, parathormone, magnesium, 25 and 1,25-hydroxyvitamin D3, and bone alkaline phosphatase and thyroid stimulating hormone levels in 63 female patients and 50 control subjects. Twenty-nine of the TE patients were classified in the acute TE group and 34 were classified in the chronic TE groups.

Results: Ferritin (acute TE; 17.0 ± 12.8, chronic TE; 19.6 ± 15.2, control; 35.5 ± 31.8, $P < 0.001$) and hemoglobin (acute TE; 12.7 ± 1.7, chronic TE; 13.3 ± 1.0, control; 14.2 ± 1.2, $P < 0.0001$) levels were significantly lower in the TE group than in the control group. However, 25-hydroxyvitamin D3 levels were significantly higher in the TE group than in the control group (acute TE; 18.5 ± 9.2, chronic TE; 24.4 ± 11.2, control; 15.6 ± 15.8, $P < 0.01$). Vitamin D levels increased gradually from control groups to acute and chronic TE groups. However, active D vitamin levels (1,25-hydroxyvitamin D3) were similar.

Conclusion: Iron deficiency anemia seems to be the main triggering factor for the development of TE and the increase in serum 25-hydroxyvitamin D3 levels may be related to increased exposure to UV light due to TE.

Key words: Alopecia, hair disorder, telogen effluvium, vitamin D

Akut ve kronik telojen effluviumda anemi ve vitamin D seviyelerinin rolü

Amaç: Telojen effluvium (TE) bir saç siklus anomalisidir. Vitamin D kıl folikül farklılaşmasını destekler. Herediter vitamin D reseptör eksikliği olan hastalarda saç gelişiminde vitamin D'nin önemi açıkca görülmektedir. TE'nin patogenezinde vitamin D'nin rolü daha önce araştırılmamıştır. Biz TE'nin patogenenzinde vitamin D, ferritin ve çinkonun rolünü araştırmaktayız.

Yöntem ve gereç: 63 bayan hasta ve 50 kontrolde ferritin, çinko, kalsiyum, fosfat, parathormon, magnezyum, 25 ve 1,25 hidroksi vitamin D3 ve kemik alkalen fosfataz düzeyi ölçüldü. TE hastalarının 29'u akut, 34'ü kronik TE olarak sınıflandırıldı.

Bulgular: Ferritin (akut TE; 17,0 ± 12,8, kronik TE; 19,6 ± 15,2, kontrol; 35,5 ± 31,8, $P < 0,001$) ve hemoglobin (akut TE; 12,7 ± 1,7, kronik TE; 13,3 ± 1,0, kontrol; 14,2 ± 1,2, $p < 0,0001$) seviyeleri kontrol grubu ile karşılaştırıldığında TE grubunda belirgin olarak daha düşük bulundu. Buna rağmen 25-hidroksvitamin D3 seviyeleri TE grubunda kontrol grubuna göre belirgin olarak daha yüksek bulundu (akut TE; 18,5 ± 9,2, kronik TE; 24,4 ± 11,2, kontrol; 15,6 ± 15,8, P

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< 0,01).Vitamin D seviyeleri sırasıyla kontrol grubu, akut ve kronik TE gruplarında giderek artmaktaydı. Buna rağmen aktif vitamin D (1,25 -hidroksivitamin D3) seviyeleri benzerdi.

Sonuç: Demir eksikliği anemisi TE gelişiminde ana tetikleyici faktör olarak görülmektedir. 25- hidroksi vitamin D3 artışı da TE sonrası artan UV ışın maruziyetine bağlı olabilir.

Anahtar sözcükler: Alopesi, saç hastalığı, telojen effluvium, vitamin D

Introduction

Telogen effluvium (TE) is an abnormality of hair cycling that results in excessive loss of telogen hairs and is one of the most common causes of diffuse hair loss (1). TE may be caused by thyroid disease, drugs, and childbirth; however, in many cases etiology could not be found (1). TE can be classified into acute and chronic forms. Acute TE was first described as an acute onset scalp hair loss, 2-3 months after a triggering event, such as a high fever, or surgical trauma, sudden starvation, and hemorrhage (2,3). Severe iron-deficiency anemia and metabolic disturbances, such as liver disorders and chronic renal failure, are also known to cause sparse scalp hair (3,4). In about 33% of cases of acute TE, triggering pathological condition could not be identified and the functional mechanism of shedding is supposed to be secondary to an immediate anagen release (5). Chronic telogen effluvium (CTE) was defined as a primary idiopathic disease entity in 1996 (6). Women suffering from CTE present with an abrupt onset of generalized shedding of telogen hairs from the scalp, with or without an identifiable trigger, that persists for more than 6 months (7).

The main role of vitamin D until recent years was considered to regulate calcium and bone metabolism. However, 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] exerts many other important physiological effects, including immunoregulation and protection against UV radiation, infectious agents, oxidative stress, and cancer (8). Vitamin D promotes hair follicle differentiation, without affecting proliferation. The importance of vitamin D in hair growth is evident in patients with hereditary vitamin D receptor (VDR) deficiency (vitamin D-dependent rickets type II), who may suffer from alopecia (9). This role was also demonstrated by Vegesna et al. in nude mice, as application of vitamin D led to a dramatic stimulation of hair growth, associated with increased expression of several hair keratins (10).

Iron deficiency is one of the most common nutritional deficiencies that can be encountered in daily practice. In premenopausal women, the most common causes of iron deficiency anemia are menstrual blood loss and pregnancy (11). Hemoglobin concentration can be used for screening, whereas serum ferritin concentration can be used to confirm diagnosis of iron deficiency. Several studies have examined the relationship between iron deficiency and hair loss. Currently, there is insufficient evidence to recommend screening for iron deficiency in patients with hair loss on a routine basis and replacement of iron in the absence of iron deficiency anemia (12,13). There is also scarce information in literature about the relationship of the pathogenesis of TE with vitamin D and zinc deficiency. In this case-control study we aimed to investigate if there is any relationship between acute/chronic TE and anemia, zinc deficiency, and serum vitamin D levels.

Patients and methods

The study was performed in a case-control design. In order to minimize the effect of seasonal changes on vitamin D levels, the study was conducted in winter between November 2008 and March 2009. All of the patients enrolled in the study were living in Ankara (central Anatolia), where these months are considered to be winter, with little exposure to UV light. The study population consisted of 63 female patients with TE who had not previously received any treatment. Dermatological examinations of all patients were performed by the same dermatologist. A diagnosis of TE was considered when patients had increased shedding by history or physical examination that is performed by hair shedding continuing at a rate of 100/day, and the hair pull test that was positive (1,14). In chronic TE, as described by Whiting, women present with an abrupt onset of generalized shedding of telogen hairs from the scalp,

with or without an identifiable trigger, that persists more than 6 months (6). There is no frontoparietal hair loss with widening of the central part and these women characteristically present with a full, thick head of hair (15).

The patients diagnosed with female pattern hair loss (FPHL) were excluded from the study (16,17). In general, these women had widening of the midline hair part and preservation of the anterior hair line (17). In order to differentiate TE and FPHL, the subjects were examined with dermoscopy. No variation in shaft diameter is a characteristic of acute TE and no significant variation and no miniaturization are characteristics of chronic TE. Marked variation in shaft diameter and miniaturization of follicles are prominent features of FPHL (17).

Eligible subjects underwent a comprehensive medical assessment including documentation of the detailed history, physical examination, and measurement of the essential laboratory variables. Exclusion criteria were drug abuse, malignancy, hypercalcemia, hypocalcemia, hyperparathyroidism, functional renal or liver abnormalities, systemic lupus erythematosus, syphilis, and any condition causing fever. Patients who were on calcium-phosphorus modifying drugs were also excluded from the study. Fifty control subjects were chosen from patients who were referred to our clinic for the treatment of nevus and had no systemic disease and/or hair shedding. The Local Ethics Committee approved the study, and all patients gave informed consent.

Fasting blood samples were obtained by venipuncture of the large antecubital veins of the patients without stasis and after a 12-h fasting. The samples were then centrifuged immediately; the plasma was separated and stored at –80 °C. In order to avoid variation, all samples were studied on the same day and using the same kit. Serum 25-hydroxyvitamin D3 (25(OH)D3), 1,25(OH)2D3, and bone alkaline phosphatase (BAP) levels were measured by RIA. 25OH-VIT.D3-RIA-CT kit (Catalog No: KIP1961) and 1,25(OH)2-VIT.D3-RIA-CT kit (Catalog No: KIP1921, Biosource, Neville, Belgium) were used. BAP level was measured by Ostease IRMA kit (Immunotech, Beckman Coulter, Inc., Fullerton, CA, USA). Serum hemoglobin, ferritin, zinc, calcium, phosphate, parathormone, magnesium, and thyroid stimulating hormone (TSH) levels were measured by standard laboratory techniques.

Statistical analyses were performed with SPSS version 11.0 (SPSS Inc, Chicago, IL, USA). All numerical variables are expressed as the mean ± standard deviation (SD). Normality of data was analyzed using a Kolmogorov-Smirnov test and intergroup differences were analyzed and compared by means of the independent samples t test**.** We used one-way ANOVA to analyze intergroup differences of more than 2 groups and also used a Tukey test for post hoc analyses. In the case of nonhomogenic data, a Mann-Whitney U test was used to analyze intergroup differences. A Kruskal-Wallis test was performed for analyzing data of more than 2 groups with nonhomogenous variability. A chi-square test and regression analysis were used for defining risk factors for TE. A P value of less than 0.05 was considered statistically significant.

Results

The mean age was 29.1 ± 11.9 years in the TE group and 28.4 ± 9.4 years in the control group. Twenty-nine of the patients were classified as having acute TE and 34 as having chronic TE. Demographic and biochemical parameters are listed in Table 1. According to analyses comparing the control and TE groups of any stage, the TE group had significantly lower hemoglobin and ferritin, and higher 25(OH) D3 levels ($P < 0.0001$, 0.001, 0.01, respectively).

A comparison of the 3 groups with each other (no TE, acute TE, and chronic TE) also revealed that the acute TE group had the lowest hemoglobin (Table 2, Figure 1). Ferritin values of both chronic and acute TE groups were also lower compared to the control group but were similar with each other (Table 2). The chronic TE group had the highest serum levels of 25(OH)D3 (Table 2, Figure 2). Regression analysis revealed that the presence of anemia (Hb < 12 g/dL) was a significant risk factor for TE ($P < 0.02$, OR: 4.3, CI: 1.01-18.79). We also analyzed data after grouping patients according to being in the highest and lowest quadrants for hemoglobin, ferritin, 25(OH)D3, and 1,25(OH)2D3 values. According to these analyses, patients in the lowest hemoglobin and ferritin quadrants had higher risks for TE ($P < 0.001$, OR:

Table 1. Comparison of TE and control groups.

	TE group n: 63	Control group n: 50	P value
Age (years)	29.0 ± 11.9	28.4 ± 9.3	NS
Hemoglobin (g/dL)	12.9 ± 1.5	14.2 ± 1.2	< 0.0001
Ferritin (ng/mL)	18.4 ± 14.1	35.5 ± 31.8	< 0.001
Calcium (mg/dL)	9.7 ± 0.4	9.8 ± 0.3	NS
Phosphorus(mg/dL)	3.2 ± 0.4	3.3 ± 0.5	NS
iPTH (pg/ml)	59.2 ± 24.8	59.7 ± 31.2	NS
Magnesium (mmol/L)	0.7 ± 0.08	0.8 ± 0.07	NS
Alkalene Phosphatase (U/L)	10.2 ± 4.8	10.5 ± 4.9	NS
Zinc (µg/dL)	74.2 ± 10.8	73.5 ± 8.6	NS
TSH (mIU/L)	1.8 ± 1.0	1.8 ± 1.1	NS
25(OH)D3 (ng/mL)	21.7 ± 10.7	15.6 ± 15.8	< 0.01
1,25(OH)D3 (pg/mL)	21.9 ± 6.0	22.8 ± 5.2	NS

NS: non-significant
iPTH: intact parathyroid hormone
TSH: thyroid stimulating hormone
25(OH)D3: 25-hydroxyvitamin D3
1,25(OH)2D3: 1,25-dihydroxyvitamin D3

Table.2. Comparison of controls and acute and chronic TE groups.

	Acute TE group n: 29	Chronic TE group n: 34	Control group n: 50	P values
Age	26.9 ± 10.3	30.9 ± 12.9	28.4 ± 9.3	NS
Hemoglobin (g/dL)	12.7 ± 1.7	13.3 ± 1.0	14.2 ± 1.2	< 0.0001* < 0.01**
Ferritin (ng/mL)	17.0 ± 12.8	19.6 ± 15.2	35.5 ± 31.8	< 0.005* < 0.01**
Calcium (mg/dL)	9.7 ± 0.4	9.7 ± 0.3	9.8 ± 0.3	NS
Phosphorus (mg/dL)	3.2 ± 0.4	3.1 ± 0.5	3.3 ± 0.5	NS
iPTH (pg/mL)	62.4 ± 25.4	56.4 ± 24.3	59.7 ± 31.2	NS
Magnesium (mmol/L)	0.7 ± 0.07	0.8 ± 0.09	0.8 ± 0.07	NS
Alkalene Phosphatase (U/L)	11.0 ± 5.5	9.6 ± 4.1	10.5 ± 4.9	NS
Zinc (µg/dL)	75.0 ± 10.3	73.5 ± 11.2	73.5 ± 8.6	NS
TSH (mIU/L)	1.9 ± 1.3	1.7 ± .7	1.8 ± 1.1	NS
25(OH)D3 (ng/mL)	18.5 ± 9.2	24.4 ± 11.2	15.6 ± 15.8	< 0.05* < 0.01** < 0.05***
1,25(OH)D3 (pg/mL)	23.3 ± 4.8	20.8 ± 6.6	22.8 ± 5.2	NS

NS: non-significant
iPTH: intact parathyroid hormone
TSH: thyroid stimulating hormone
25(OH)D3: 25-hydroxyvitamin D3
1,25(OH)2D3: 1,25-dihydroxyvitamin D3
* P values for acute TE vs. control groups
** P values for chronic TE vs. control groups
*** P values for acute TE vs. chronic TE groups

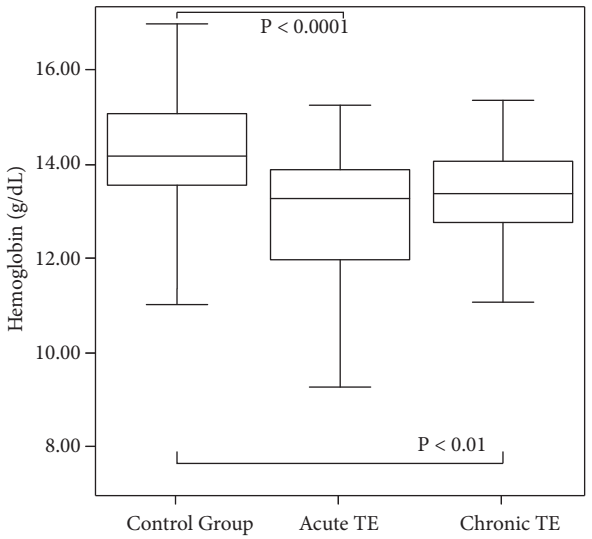

Figure 1. Hemoglobin levels in the control, acute TE, and chronic TE groups.

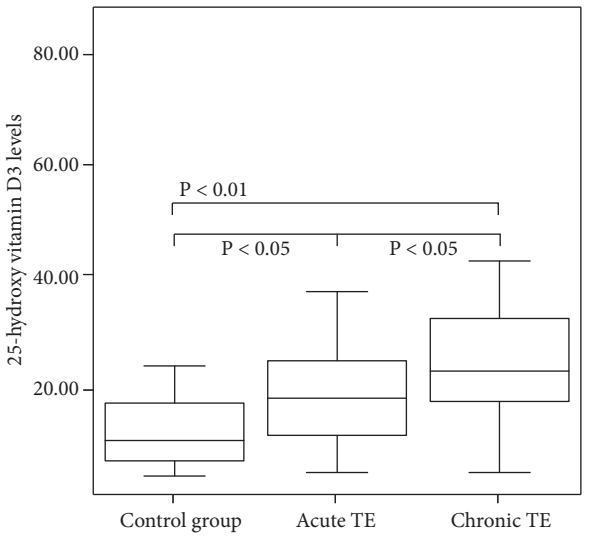

Figure 2. 25-Hydroxy vitamin D3 levels in the control, acute TE, and chronic TE groups.

2.7, CI: 1.47-5.23 and P < 0.02, OR: 1.9, CI: 1.06-3.48, respectively), while patients in the highest 25(OH) D3 quadrant had a significant risk compared to the lowest quadrant (P < 0.0001, OR: 3.1, CI: 1.54-6.59). No risk for 1,25(OH)2D3 levels was identified (Table 3). No risk factors specific just for acute or chronic TE could be identified. No significant differences for serum zinc levels could be identified in any stage of statistical analysis. We found no correlation between ferritin and parathormone, 25(OH)D3, 1,25(OH)2D3, and BAP levels. We stratified all of the study population into anemic and non-anemic groups. We found no statistical difference between these groups in terms of parathormone, 25(OH)D3, 1,25(OH)2D3, BAP, Ca, P, and Mg levels.

Discussion

Excessive telogen hair loss or TE is a problem that is commonly encountered by clinical dermatologists in daily practice. In nearly 33% of cases there is no identified etiological reason; however, in other patients usually a pathological condition could be identified as the underlying cause of TE. These causes vary from common and easily treatable hormonal or nutritional problems like thyroid metabolism defects or zinc deficiency to less common but severe systemic diseases like systemic lupus, chronic renal or liver failures, and malignancies or severe emotional stress. Presence of iron deficiency with or without anemia was also speculated as a cause of TE and some studies were conducted on this subject previously (1-5). According to our findings presence of anemia was an important risk factor for TE (P < 0.02, OR: 4.3) and both acute and chronic TE groups had significantly lower hemoglobin values compared to control patients (Table 2). Similarly we found that patients with acute or chronic TE had lower ferritin levels compared to the control group (Table 2). Being in the lowest hemoglobin and ferritin quadrants was

Table 3. Risk factors for Telogen effluvium.

	P-values	Odds ratio	95% CI
Presence of anemia	<0.02	4.3	1.01 – 18.79
Lowest Hb quadrant	<0.001	2.7	1.47 – 5.23
Lowest ferritin quadrant	<0.02	1.9	1.06 – 3.48
Highest 25(OH)D3 quadrant	<0.0001	3.1	1.54 – 6.59

also identified as a important risk factor for TE ($P < 0.001$, OR: 2.7 and $P < 0.02$, OR: 1.9, respectively). Acute TE patients also seem to have lower hemoglobin and ferritin values compared to chronic TE patients. However, these differences were not statistically significant (Table 2, Figure 1). Supporting our findings, Deloche et al. reported that a low iron store defined as low ferritin levels represents a risk factor for hair loss in non-menopausal women in a very large population of 5110 women aged between 35 and 60 years (18). Treatment of iron deficiency was also reported by some authors to decrease hair shed. In a prospective double-blind, placebo-controlled study Rushton et al. reported a group of 12 female subjects with chronic TE. In their study, 7 subjects received 72 mg iron and 1.5 g L-lysine daily for 6 months, whereas 5 subjects received placebo. Subjects receiving therapy experienced a 31% reduction in the amount of hair shed compared with a 9% increase in control subjects (19). Similarly in a prospective cohort study involving 22 female subjects with chronic TE who received 72 mg iron and 1.5 of L-lysine daily for 6 months, the mean percentage of hair in the telogen phase significantly decreased from 19.5% to 11.3% (15). However, there are also some studies that neglect iron deficiency anemia as a cause of TE. In one of these studies, Sinclair et al. reported a prospective cohort of 194 female subjects, presenting with diffuse telogen hair loss for 6 months or longer, and found that 12 (6%) had serum ferritin concentrations less than or equal to 20 ng/mL. Three of these 12 patients had chronic TE and they were treated with iron supplementation for 3 to 6 months until their serum ferritin concentrations rose above 20 ng/mL. However, no change in hair status after treatment was observed (7). Kantor et al. also reported that ferritin levels of patients with androgenetic alopecia and alopecia areata were significantly lower than in controls without hair loss; however, there is no difference between chronic TE patients and control subjects (14). Bregy and Trueb similarly reported that there is no association between serum ferritin levels >10 μg/L and hair loss activity in women (20). Authors who state that there is a link between iron deficiency and TE usually think that, in cases of low iron depots, hair follicles that have shed their hair at the end of telogen may temporarily fail to re-enter anagen, leading to a slow onset diffuse hair loss (5). The relationship between iron deficiency with no anemia or only mild anemia and chronic diffuse hair loss is, however, more complex and controversial (21).

Another commonly encountered problem that may cause anemia in women is zinc deficiency. There is also common belief that zinc deficiency is associated with hair loss (1,22,23). In the present study, we failed to find a significant difference in serum zinc levels of acute and chronic telogen effluvium groups compared to controls. However, there are also some contradictory reports that may support our findings, which also could not present any association between zinc deficiency and TE (23,24).

An interesting result that we found was increased 25(OH)D3 levels in patients with TE. Both acute and chronic TE patients had higher serum levels of 25(OH)D3 compared to control subjects (Table 2, Figure 2). Those having a serum level of 25(OH) D3 in the highest quadrant also had a significantly increased risk for TE compared to those in the lowest quadrant ($P < 0.0001$, OR: 3.1). We did not observe any statistically significant difference in the levels of calcium, phosphate, magnesium, bone alkaline phosphatase, 1,25(OH)2D3, or parathormone levels. It is well known that vitamin D has an important role in hair growth. Epidermis is the main site for synthesis of 25(OH)D3, mediated by sunlight (8). The epidermal keratinocytes, in addition to many other cells residing in the skin, have the required enzymes to metabolize vitamin D, and keratinocytes also contain the receptor for 1,25(OH)2D3 (25). The effects of 1,25(OH)2D3 on keratinocytes show a shift from the hyperproliferative cell compartment toward the differentiating cell compartment (26). Alopecia was noted in vitamin D receptor (VDR) knockout mice, and this is often, but not invariably, found in patients of some vitamin D-dependent rickets type II (VDDR-II) kindreds (27). Depending on these previous findings, one expects to observe decreased levels of 25(OH)D3 in patients with TE. However, this is not the case in our study and patients with chronic TE seem to have higher levels of 25(OH) D3 compared to both acute TE patients and control subjects. It seems that there is a trend of increase from control subjects to acute and chronic TE patients (Table 2, Figure 2). We think that this might

not be the cause but rather a secondary response to the development of TE. We do not know the reason for the increase in 25(OH)D3levels in TE patients. Telogen hair follicles do not show melanin synthesis in their undifferentiated melanocytes/melanoblasts, which may ultimately increase UV exposure and vitamin D synthesis in the skin (28).

In conclusion, iron deficiency anemia appears to be an important risk factor for development of TE in otherwise healthy female patients. We think that the increase in serum 25(OH)D3 levels is a compensatory response to TE and any possible effect of this increase should be assessed further by clinical and experimental studies.

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