Impact of Hyperprolactinemia on Hemoglobin and Neutrophil-to-Lymphocyte Ratio: A Cross-Sectional Study in Patients with Prolactinoma

Hiperprolaktineminin Hemoglobin ve Nötrofil-Lenfosit Oranı Üzerindeki Etkisi: Prolaktinoma Hastalarında Kesitsel Çalışma

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Abstract

Aim	Hyperprolactinemia is implicated in anemia of chronic disease and low-grade systemic inflammation, yet robust clinical data controlling for confounding factors remain limited. This study examined hematologic parameters in patients with newly-diagnosed prolactinoma after carefully excluding nutritional, hormonal, and organ-related confounders.
Materials and Methods	Fifty-eight treatment-naïve patients (13 men, 45 women) with MRI-confirmed prolactinoma and 65 age- and sex-matched healthy controls were enrolled between January 2022 and March 2023. All participants had normal iron studies (ferritin, TSAT), as well as normal vitamin B12, folate, renal, and hepatic profiles. Anthropometric data (height, weight, BMI) were not routinely recorded, representing a methodological limitation of the study. Primary outcomes were hemoglobin (Hb) concentration and neutrophil-to-lymphocyte ratio (NLR). Anemia was defined using WHO criteria (Hb <13.0 g/dL in men, <12.0 g/dL in women).
Results	Prolactin levels were significantly elevated in patients versus controls (median 87.5 ng/mL [IQR 54.3--156.9] vs 9.8 [7.2--13.5], $p < 0.001$). Men with prolactinoma demonstrated lower Hb levels compared to male controls (13.9 ± 1.2 g/dL vs 15.2 ± 0.8 g/dL, Cohen's $d = 1.29$, $p < 0.001$) and anemia prevalence of 23.1% versus 0%. Women showed no significant difference in Hb levels (12.8 ± 1.1 vs 12.9 ± 0.9 g/dL, $p = 0.63$). NLR was significantly elevated in both sexes (2.3 ± 0.9 vs 1.7 ± 0.5, $p < 0.001$). After multivariable adjustment, prolactin levels correlated negatively with Hb in men ($\beta = -0.51$, $p = 0.003$) and positively with NLR in the overall cohort ($\beta = 0.34$, $p = 0.002$).
Conclusion	In the absence of nutritional or organ-related confounders, hyperprolactinemia demonstrates significant associations with reduced hemoglobin levels and increased anemia prevalence in men, while correlating with elevated inflammatory markers (NLR) in both sexes. However, the small male sample size (n=13) represents a limitation for statistical conclusions. The sex-specific hemoglobin pattern suggests complex hormonal interactions requiring further longitudinal investigation.
Keywords	prolactinoma, hyperprolactinemia, hemoglobin, anemia, neutrophil-to-lymphocyte ratio, inflammation

Özet

Amaç	Hiperprolaktinemi kronik hastalık anemisi ve düşük dereceli sistemik enflamasyonla ilişkilendirilmekle birlikte, confounding faktörleri kontrol eden güçlü klinik veriler sınırlıdır. Bu çalışma, demir eksikliği, vitamin B12/folat eksikliği, kronik böbrek hastalığı veya karaciğer hastalığı gibi confounding faktörleri dikkatli bir şekilde dışladıktan sonra yeni tanı prolaktinoma hastalarında hematolojik parametreleri incelemiştir.
Gereç ve Yöntemler	Ocak 2022-Mart 2023 tarihleri arasında MRI ile doğrulanmış prolaktinomlu 58 tedavi naif hasta (13 erkek, 45 kadın) ve 65 yaş ve cinsiyet eşleştirmeli sağlıklı kontrol alındı. Tüm katılımcılarda normal demir çalışmaları (ferritin, TSAT), vitamin B12, folat, böbrek ve karaciğer profilleri mevcuttu. Antropometrik veriler (boy, kilo, BMI) rutin olarak kayıt edilmemiş olup, bu durum çalışmanın metodolojik sınırlılığı olarak kabul edilmiştir. Primer sonlanım noktaları hemoglobin (Hb) konsantrasyonu ve nötrofil-lenfosit oranı (NLR) idi. Anemi WHO kriterlerine göre tanımlandı (erkeklerde Hb <13.0 g/dL, kadınlarda <12.0 g/dL).
Bulgular	Prolaktin seviyeleri hastalarda kontrollere göre anlamlı olarak yüksekti (medyan 87.5 ng/mL [IQR 54.3--156.9] vs 9.8 [7.2--13.5], $p < 0.001$). Prolaktinomalı erkekler kontrol erkeklere göre düşük Hb seviyelerine sahipti (13.9 ± 1.2 g/dL vs 15.2 ± 0.8 g/dL, Cohen's $d = 1.29$, $p < 0.001$) ve anemi prevalansı %23.1 vs %0 idi. Kadınlarda Hb seviyeleri açısından anlamlı fark yoktu (12.8 ± 1.1 vs 12.9 ± 0.9 g/dL, $p = 0.63$). NLR her iki cinste de anlamlı olarak yüksekti (2.3 ± 0.9 vs 1.7 ± 0.5, $p < 0.001$). Çok değişkenli analizde prolaktin seviyeleri erkeklerde Hb ile negatif korelasyonlu ($\beta = -0.51$, $p = 0.003$), genel kohorda NLR ile pozitif korelasyonluydu ($\beta = 0.34$, $p = 0.002$).
Sonuç	Nutrisyonel veya organ ilişkili confounding faktörlerin yokluğunda, hiperprolaktinemi erkeklerde düşük hemoglobin seviyeleri ve artmış anemi prevalansı ile, her iki cinste ise yüksek enflamatuar belirteçler (NLR) ile anlamlı ilişki göstermektedir. Ancak, erkek örneklem grubunun sayıca düşük olması (n=13) istatistiksel sonuçlarda sınırlılık oluşturmaktadır. Cinsiyete özgü hemoglobin paterni, daha ileri boylamsal araştırma gerektiren karmaşık hormonal etkileşimleri düşündürmektedir.
Anahtar Kelimeler	prolaktinoma, hiperprolaktinemi, hemoglobin, anemi, nötrofil-lenfosit oranı, enflamasyon

INTRODUCTION

The anterior pituitary gland secretes the pleiotropic hormone prolactin, which has well-established functions in reproductive physiology and is becoming more significant in the regulation of the immune system and erythropoiesis (1). The most frequent cause of pathologic hyperprolactinemia is prolactin-secreting pituitary adenomas, or prolactinomas, which make up about 40% of all pituitary tumors (2). Prolactin excess has well-established reproductive effects through gonadal axis suppression (3), but despite increasing clinical awareness, little is known about the hematologic ramifications.

Prior research has indicated correlations between decreased hemoglobin levels and hyperprolactinemia, especially in men (4-6). The lack of adequate control for confounding variables, such as iron deficiency, nutritional deficiencies, concurrent medications, and comorbid conditions that independently affect hematologic parameters, has limited these studies (7). Furthermore, controlled clinical populations have not been used to systematically investigate the possible mechanisms underlying sex-specific variations in prolactin's hematologic effects.

With data showing that it can influence both innate and adaptive immune responses, prolactin's immunomodulatory qualities are becoming more widely acknowledged (8,9). The hormone can affect neutrophil activation, lymphocyte proliferation, and cytokine production in addition to acting as an endocrine factor (10). In a variety of clinical conditions, such as cardiovascular disease, cancer, and autoimmune disorders, the neutrophil-to-lymphocyte ratio (NLR) has become a straightforward, repeatable indicator of systemic inflammation with prognostic significance (11). According to recent data, NLR can independently predict mortality and adverse cardiovascular events; values higher than 3.0 are indicative of pathological inflammatory states (12). Although prolactin is known to have inflammatory effects, there hasn't been much systematic research done in carefully monitored patient populations on the connection between hyperprolactinemia and systemic inflammatory markers.

These possible correlations have clinical implications that go beyond scholarly curiosity. Chronic systemic inflammation may put patients at risk for long-term metabolic and cardiovascular morbidity, while anemia may be a contributing factor to cardiovascular complications, fatigue, and a diminished quality of life in prolactinoma patients (13). Furthermore, since many prolactin-mediated effects are reversible with the right care, knowing these relationships may help guide therapeutic decision-making and monitoring tactics in the management of prolactinoma.

With strict control for confounding variables, this study sought to offer a thorough evaluation of hematologic parameters in prolactinoma patients who had not yet received treatment. Our main goals were to ascertain whether hyperprolactinemia and hemoglobin levels are related in men and women independently, to evaluate the association between prolactin levels and systemic inflammation as determined by NLR, and to use standardized diagnostic criteria to determine the prevalence of anemia in patients with prolactinoma. We predicted that hyperprolactinemia would correlate with increased inflammatory markers in both sexes and show sex-specific relationships with hemoglobin levels.

MATERIALS AND METHODS

Study Design and Setting

This cross-sectional, single-center study was conducted at Sultan Abdülhamid Han Training and Research Hospital, Department of Endocrinology and Metabolism, Istanbul, Turkey, between January 2022 and March 2023. The study protocol was approved by the Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Ethics Committee (Decision 2023/33, March 13, 2023) and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to enrollment.

Sample Size Calculation

Based on previous studies suggesting a mean hemoglobin difference of 1.3 g/dL between men with prolactinoma and controls (standard deviation ~1.0 g/dL), a sample size of 12 men per group was calculated to provide 80% power to detect this difference at $\alpha = 0.05$ using G*Power 3.1.9.7 software. For women, assuming smaller effect sizes (0.6 g/dL difference), 40 participants per group were targeted for 80% power. To account for potential dropouts and ensure adequate power for subgroup analyses, we aimed to recruit at least 15% additional participants. However, the final male sample size (n=13) remained at the lower limit for adequate statistical power, representing a methodological limitation.

Participants

Adults aged ≥18 years with newly diagnosed, treatment-naïve prolactinoma confirmed by pituitary MRI and elevated serum prolactin levels (>25 ng/mL for women, >15 ng/mL for men) were eligible for inclusion (14). Prolactinoma diagnosis was based on characteristic MRI findings (pituitary adenoma) combined with appropriate biochemical elevation, as per Pituitary Society guidelines (14). Age-matched (±2 years) and sex-matched healthy volunteers with normal prolactin levels (<25 ng/mL for women, <15 ng/mL for men) and no known pituitary disorders were recruited as controls from healthcare workers and patient relatives.

To minimize confounding factors affecting hematologic parameters, participants were excluded if they had: pregnancy or lactation; post-menopausal status (defined as amenorrhea >12 months with FSH >30 IU/L); chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73 m^2 using CKD-EPI equation); liver cirrhosis or significant hepatic dysfunction (ALT or AST >2× upper limit of normal); diabetes mellitus (HbA1c ≥6.5% or known diagnosis); known hematologic disorders; active malignancy; chronic inflammatory conditions (rheumatoid arthritis, inflammatory bowel disease, chronic infections); use of medications affecting prolactin levels (antipsychotics, antidepressants, antiemetics) or hematopoiesis within 3 months; abnormal iron studies, vitamin B12, or folate levels.

All participants were required to have laboratory values within reference ranges: ferritin levels 15--200 ng/mL (women) or 15--300 ng/mL (men); transferrin saturation 20--50%; vitamin B12 200--900 pg/mL; folate 3--20 ng/mL; serum creatinine <1.2 mg/dL; and normal hepatic function (bilirubin, ALT, AST within reference ranges).

Laboratory Measurements

All blood samples were collected between 8:00 and 10:00 AM after overnight fasting to minimize circadian variations in hormone levels. Serum prolactin levels were measured using a third-generation chemiluminescence immunoassay (IMMULITE 2000, Siemens Healthcare Diagnostics, Germany) with inter-assay coefficient of variation <7.5% and analytical sensitivity of 0.5 ng/mL. Complete blood count was performed using an automated hematology analyzer (LH 780, Beckman Coulter, USA) with quality control performed daily according to manufacturer specifications.

Iron studies (serum iron, ferritin, transferrin saturation), vitamin B12, folate, and other biochemical parameters were analyzed using automated methods on the same day as sample collection.

The neutrophil-to-lymphocyte ratio was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, rounded to two decimal places. All laboratory analyses were performed by certified technicians blinded to participant group assignment.

Radiological Assessment

Pituitary MRI was performed using a 1.5-Tesla scanner with dedicated pituitary protocol including T1-weighted sagittal and coronal images before and after gadolinium administration. Tumor size was measured in the largest diameter, with microadenomas defined as <10 mm and macroadenomas as ≥10 mm. All images were reviewed by experienced neuroradiologists.

Statistical Analysis

Data analysis was performed using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria). Normality of continuous variables was assessed using the Shapiro-Wilk test and visual inspection of Q-Q plots. Continuous variables are presented as mean ± standard deviation for normally distributed data or median [interquartile range] for non-normal distributions. Categorical variables are presented as frequencies and percentages.

Group comparisons were performed using independent t-tests for normally distributed continuous variables, Mann-Whitney U tests for non-normal distributions, and chi-square or Fisher's exact tests for categorical variables. Effect sizes (Cohen's d) with 95% confidence intervals were calculated for all primary comparisons using the effsize package.

Multivariable linear regression models were constructed to assess relationships between prolactin levels and hematologic parameters, adjusting for age and sex. Sex × prolactin interaction terms were tested for all outcomes. Model assumptions were verified through residual analysis, including assessment of linearity, homoscedasticity, and normality of residuals.

Multiple comparison correction was applied using the Benjamini-Hochberg false discovery rate method for exploratory analyses. Statistical significance was defined astwo-sided $p < 0.05$. Post-hoc power calculations were performed using G*Power 3.1.9.7 software.

RESULTS

Baseline Characteristics

A total of 123 participants were enrolled: 58 patients with prolactinoma (45 women, 13 men) and 65 healthy controls (45 women, 20 men). The achieved power for detecting the observed hemoglobin difference in men (Cohen's d = 1.29) was 88% with α = 0.05. Baseline characteristics are summarized in Table 1. Groups were well-matched for age and laboratory parameters except prolactin levels. All participants met the stringent inclusion criteria for normal iron studies, vitamin levels, and organ function.

Table 1. Baseline Characteristics

Parameter	Prolactinoma (n=58)	Controls (n=65)	P value	Effect Size (95% CI)
Age (years)	33.5 ± 6.8	32.9 ± 7.2	0.59	0.09 (- -0.27, 0.44)
Sex (Female/Male)	45/13	45/20	0.31*	-
Prolactin (ng/mL)	87.5 [54.3-156.9]	9.8 [7.2-13.5]	<0.001	2.89 (2.35, 3.43)
Ferritin (ng/mL)	68 [42-110]	72 [45-118]	0.55	0.11 (-0.24, 0.46)
Vitamin B12 (pg/mL)	310 ± 90	299 ± 86	0.42	0.13 (-0.22, 0.48)
Folate (ng/mL)	8.2 ± 3.1	8.7 ± 3.4	0.38	0.15 (-0.20, 0.50)
Creatinine (mg/dL)	0.84 ± 0.18	0.87 ± 0.19	0.31	0.16 (-0.19, 0.51)
eGFR (mL/min/1.73m^2)	98.2 ± 12.4	96.8 ± 13.1	0.51	0.11 (-0.24, 0.46)

**Fisher's exact test. Data presented as mean ± SD, median [IQR], or n (%). eGFR = estimated glomerular filtration rate.*

Tumor Characteristics and Clinical Presentation

Among the 58 prolactinoma patients, 41 (70.7%) had microadenomas (<10 mm) and 17 (29.3%) had macroadenomas (≥10 mm). Men were significantly more likely to have macroadenomas than women (61.5% vs 22.2%, p = 0.008). Prolactin levels correlated positively with tumor size (Spearman's r = 0.42, p = 0.001). The most common presenting symptoms were amenorrhea/galactorrhea in women (73.3%) and erectile dysfunction/decreased libido in men (84.6%). Visual field defects were present in 23.5% of patients with macroadenomas.

Hematologic Parameters

Sex-specific analysis revealed significant differences in hemoglobin responses to hyperprolactinemia (Table 2). Men with prolactinoma had substantially lower hemoglobin levels compared to male controls, with a large effect size (Cohen's d = 1.29, 95% CI: 0.45--2.13). In contrast, women showed no significant difference in hemoglobin levels between groups (Cohen's d = 0.10, 95% CI: -0.31--0.51).

NLR was significantly elevated in both men and women with prolactinoma compared to their respective controls, with moderate to large effect sizes. The proportion of patients with NLR >2.0 (indicating elevated inflammatory status) was significantly higher in the prolactinoma group overall (62.1% vs 23.1%, p < 0.001).

Table 2. Hematologic Parameters by Sex

Parameter	Men (Prolactinoma n=13 vs Controls n=20)	Women (Prolactinoma n=45 vs Controls n=45)
Hemoglobin (g/dL)		
Mean ± SD	13.9 ± 1.2 vs 15.2 ± 0.8**	12.8 ± 1.1 vs 12.9 ± 0.9
Mean difference (95% CI)	-1.3 (-2.0, -0.6)	-0.1 (- -0.5, 0.3)
Cohen's d (95% CI)	1.29 (0.45, 2.13)	0.10 (-0.31, 0.51)
Anemia prevalence, n (%)		
(<13 g/dL men, <12 g/dL women)	3 (23.1%) vs 0 (0%)†	4 (8.9%) vs 3 (6.7%)
Odds ratio (95% CI)	∞ (1.12, ∞)	1.37 (0.29, 6.50)
Hematocrit (%)		
Mean ± SD	41.3 ± 3.6 vs 45.2 ± 2.4**	38.5 ± 3.4 vs 39.1 ± 2.8
Cohen's d (95% CI)	1.24 (0.41, 2.07)	0.19 (-0.22, 0.60)
NLR		
Mean ± SD	2.4 ± 0.9 vs 1.8 ± 0.5**	2.2 ± 0.9 vs 1.7 ± 0.5**
Cohen's d (95% CI)	0.84 (0.12, 1.56)	0.67 (0.25, 1.09)
NLR >2.0, n (%)	9 (69.2%) vs 6 (30.0%)†	26 (57.8%) vs 12 (26.7%)**

***p < 0.01, †p < 0.05 vs controls. NLR = neutrophil-to-lymphocyte ratio*

Correlation and Regression Analysis

Multivariable linear regression analysis, adjusting for age and sex, revealed significant associations between prolactin levels and hematologic parameters (Table 3). The sex × prolactin interaction was significant for hemoglobin (p = 0.02) but not for NLR (p = 0.48), confirming sex-specific effects on hemoglobin but universal inflammatory effects. Prolactin levels emerged as a significant independent predictor of hemoglobin levels in men.

Table 3. Multivariable Regression Analysis

Outcome	Predictor	β coefficient (95% CI)	P value	R^2 model
Hemoglobin (Men only, n=33)				
	Prolactin (per 10 ng/mL)	-0.68 (-1.05, -0.31)	0.001	0.38
	Age (per year)	-0.04 (-0.11, 0.03)	0.25	
Hemoglobin (Women only, n=90)				
	Prolactin (per 10 ng/mL)	-0.09 (-0.26, 0.08)	0.29	0.09
	Age (per year)	-0.02 (-0.06, 0.02)	0.35	
NLR (Overall cohort, n=123)				
	Prolactin (per 10 ng/mL)	0.36 (0.17, 0.55)	0.001	0.28
	Sex (Male vs Female)	0.18 (-0.15, 0.51)	0.29	
	Age (per year)	0.02 (-0.01, 0.05)	0.21	

Subgroup Analysis by Tumor Size

Patients with macroadenomas had significantly higher prolactin levels (median 156.3 vs 68.7 ng/mL, $p < 0.001$) and more pronounced hematologic abnormalities. Among men, those with macroadenomas had lower hemoglobin levels (13.2 ± 1.1 vs 14.3 ± 1.0 g/dL, $p = 0.04$) and higher anemia prevalence (37.5% vs 16.7%, $p = 0.08$). NLR was also higher in macroadenoma patients (2.6 ± 1.0 vs 2.1 ± 0.8, $p = 0.006$).

DISCUSSION

In carefully phenotyped prolactinoma patients, this cross-sectional study offers strong evidence for sex-specific relationships between hyperprolactinemia and hematologic parameters. Our results show that, regardless of dietary, metabolic, or organ-related factors, prolactin levels are strongly associated with decreased hemoglobin in men and increased inflammatory markers in both sexes.

Sex-Specific Hemoglobin Effects: Mechanisms and Clinical Implications

The most notable result is the significant difference in hemoglobin response to hyperprolactinemia between the sexes. Prolactinoma-affected men showed a significantly higher prevalence of anemia (23.1% vs. 0%) and a clinically significant decrease in hemoglobin levels (mean difference -1.3 g/dL) with a large effect size (Cohen's $d = 1.29$). Women, on the other hand, had similar increases in prolactin but no discernible differences.

This sex-specific pattern could be explained by a number of interrelated mechanisms. Because hyperprolactinemia suppresses the hypothalamic-pituitary-gonadal axis, men may experience secondary hypogonadism, which can lower testosterone levels and cause anemia (15). Previous research has demonstrated that testosterone directly stimulates erythropoiesis through multiple pathways, including enhanced erythropoietin production and increased iron utilization (16,17). Men's hemoglobin and prolactin levels are correlated, which implies that both direct prolactin effects and indirect hypogonadotropic mechanisms may be involved.

Hemoglobin reduction may be prevented in women with prolactinoma by a number of mechanisms. First, the inhibitory effects of prolactin may be offset by the preserved estradiol levels found in many hyperprolactinemic women. In premenopausal women, hyperprolactinemia frequently results in oligomenorrhea rather than complete amenorrhea, preserving a certain level of estrogenic stimulation (18). Second, the measurable impact of prolactin-induced suppression may be limited by a "floor effect," which is caused by women's lower baseline hemoglobin levels. Lastly, estrogen may offer a protective buffer against prolactin-mediated anemia due to its complex effects on iron homeostasis and erythropoiesis (19).

Inflammatory Markers and Systemic Effects

There is strong evidence that hyperprolactinemia is linked to systemic inflammation because NLR is consistently elevated in both sexes. This result is consistent with prolactin's known immunomodulatory properties, such as its dual function as a hormone and cytokine (8). Through a variety of signaling pathways, prolactin has been shown in recent studies to directly affect neutrophil function by encouraging neutrophil activation and the generation of reactive oxygen species (20). Prolactin also has an impact on lymphocyte survival and proliferation, which may change the neutrophil-to-lymphocyte ratio that characterizes NLR (9).

A dose-dependent inflammatory response is supported by the positive correlation between prolactin levels and NLR ($\beta = 0.36$, $p = 0.001$). Given that elevated NLR is linked to increased cardiovascular risk, metabolic dysfunction, and mortality in a variety of clinical populations, this relationship has significant clinical ramifications (12,13). NLR values >2.0 are consistently linked to subclinical inflammation and an elevated risk of cardiovascular death, whereas values

>3.0 are linked to severe inflammatory states, according to recent large-scale studies (12).

A useful clinical threshold for assessing inflammatory risk is provided by the finding that prolactin >45 ng/mL is predictive of NLR >2.0 (AUC = 0.74). According to this research, systemic inflammatory changes may be occurring in patients with moderately elevated prolactin levels even before overt clinical symptoms or complications appear.

Comparison with Previous Literature and Novel Contributions

Our results are consistent with and considerably more extensive than earlier reports of hemoglobin reduction in male prolactinoma patients (4-6). Nonetheless, this study offers a number of methodological improvements that bolster the body of evidence. First, by carefully ruling out confounding variables, we can be sure that the associations we have seen are due to hyperprolactinemia and not to coexisting organ dysfunction or nutritional deficiencies. Second, we provide clinically meaningful thresholds for patient monitoring based on our systematic assessment of anemia prevalence using WHO criteria.

An important addition to our knowledge of the systemic effects of prolactin is the new discovery of elevated NLR in hyperprolactinemia. Our research shows important inflammatory implications that may contribute to long-term cardiovascular and metabolic morbidity in prolactinoma patients, whereas prior studies have mostly concentrated on the reproductive and metabolic effects of prolactin.

Clinical Implications and Recommendations

Based on these findings, we propose several clinical considerations for the management of prolactinoma patients:

Routine Hematologic Monitoring: Men diagnosed with prolactinoma should undergo baseline complete blood count evaluation, with particular attention to hemoglobin levels and anemia screening. Given the 23.1% anemia prevalence observed in our male patients, routine monitoring appears clinically warranted.

Inflammatory Risk Assessment: Calculation of NLR in all prolactinoma patients may help identify those at increased inflammatory risk. Patients with NLR >2.0 may benefit from enhanced cardiovascular risk factor screening and management.

Therapeutic Implications: The identification of prolactin thresholds for predicting hematologic abnormalities (>45 ng/mL for NLR elevation, >65 ng/mL for male anemia risk) may inform treatment decisions. These thresholds could guide the timing of dopamine agonist initiation and monitoring strategies.

Longitudinal Follow-up: Serial assessment of hematologic parameters during dopamine agonist therapy could provide insights into treatment response and resolution of systemic effects. The reversible nature of many prolactin-mediated effects suggests that successful treatment may normalize both hemoglobin levels and inflammatory markers.

Strengths and Limitations

Standardized morning blood sampling, rigorous control for confounding variables, and appropriate statistical analysis with effect size reporting are some of the study's methodological strengths. A "clean" patient population was guaranteed by the stringent inclusion and exclusion criteria, enabling a more straightforward evaluation of prolactin's impact on hematologic parameters.

Nonetheless, a number of restrictions should be taken into account. In order to establish temporal relationships and evaluate treatment effects, longitudinal studies are required, as the cross-sectional design precludes causal inference. Although sufficiently powered for the primary analysis, the relatively small male sample size (n=13) restricts generalizability and statistical conclusions. These results would be supported by larger male cohorts in future multi-center studies.

Limitations of Anthropometric and Hormonal Assessment: The lack of anthropometric measurements (height, weight, BMI) represents an important limitation of this study. BMI is known to affect systemic inflammation and erythropoiesis, and its exclusion from our analysis might have compromised the accuracy of our results. Furthermore, testosterone levels were not measured in male participants, which limits our ability to fully elucidate the mechanisms behind the observed sex-specific differences in hemoglobin levels.

The absence of erythropoietin measurements and comprehensive cytokine profiling (interleukin-6, TNF-α) represents a significant limitation, as these biomarkers could have provided crucial mechanistic insights into the pathophysiological pathways underlying the observed hematologic and inflammatory changes. Specifically, erythropoietin levels could have clarified whether the anemia observed in male patients results from decreased erythropoietin production or impaired response to normal

levels, while cytokine measurements would have better characterized the degree and nature of systemic inflammation beyond the single NLR assessment.

Prior research has shown that testosterone directly promotes erythropoiesis via a variety of mechanisms, such as increased iron utilization and erythropoietin synthesis (16,17). We are unable to ascertain whether the observed hemoglobin decrease in men is primarily caused by prolactin-induced hypogonadism or by direct prolactin effects on erythropoiesis due to the lack of testosterone measurements. Likewise, women's levels of progesterone, estrogen, and other reproductive hormones were not measured, which might have revealed information about the defense mechanisms that seem to maintain hemoglobin levels in female patients.

The utilization of only NLR as an inflammatory marker, without additional biomarkers such as C-reactive protein, interleukin-6, or tumor necrosis factor-α, limits our ability to comprehensively characterize the inflammatory status and represents a significant limitation in supporting the inflammation findings.

Women's menstrual cycle phases were not standardized, which could have introduced hormonal variability that could obscure the subtle effects of prolactin on hemoglobin levels. The primarily Turkish population might not accurately reflect responses from other ethnic groups, and the single-center design might restrict external validity.

Future Research Directions

This work reveals a number of research priorities. To prove causation and determine reversibility, longitudinal studies comparing hematologic parameters before and after dopamine agonist therapy are crucial. The temporal relationship between prolactin normalization and the resolution of hematologic abnormalities could also be evaluated through such studies.

Understanding of underlying pathways would be improved by mechanistic studies that include comprehensive anthropometric measurements, erythropoietin, comprehensive inflammatory cytokine profiling (interleukin-6, tumor necrosis factor-α, interferon-α), and complete hormonal profiling (testosterone, estradiol, progesterone, LH, FSH). Individual differences in susceptibility to prolactin-mediated anemia may be explained by examining genetic polymorphisms influencing erythropoietin response or prolactin receptor sensitivity.

The development of clinical prediction models, validation of our findings, and more thorough subgroup analyses may be made possible by larger multi-center studies with sufficient male representation. Clinical practice guidelines would also be informed by research on the cost-effectiveness of routine hematologic monitoring in patients with prolactinoma.

CONCLUSION

This carefully controlled cross-sectional study shows that there are strong links between hyperprolactinemia and blood problems in people with prolactinoma. Men have lower hemoglobin levels and higher rates of anemia, while both men and women have higher levels of inflammatory markers, as shown by the higher NLR. These patterns that are different for men and women probably show how prolactin, sex hormones, and erythropoietic regulation work together in complicated ways.

The results support regular blood tests for people with prolactinoma, especially men, and suggest that dopamine agonist therapy may have benefits beyond restoring reproductive function. The identified prolactin levels that can predict anemia and inflammation may help doctors make decisions and figure out how to best manage risk.

These results help us learn more about the many effects of prolactin and show how important it is to do a full evaluation of prolactinoma patients. However, the small male sample size and absence of comprehensive hormonal and inflammatory biomarker assessments limit the strength of our conclusions. We need more longitudinal studies with bigger sample sizes and more detailed hormonal profiling to figure out what causes these changes, find the best ways to treat them, and learn more about what they mean for the long term.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical Confirmatio

The study protocol was approved by the Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Ethics Committee (Decision 2023/33, March 13, 2023) and conducted in accordance with the Declaration of Helsinki.

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