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ORIGINAL RESEARCH

Vitamin D Deficiency: A New and Unexpected Concern in Men's Health Status

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Abstract: **Introduction:** Vitamin D deficiency represents a significant public health concern associated with various acute and chronic diseases. Emerging evidence suggests that vitamin D may influence iron metabolism and erythropoiesis through multiple pathways. This study aimed to investigate the relationship between vitamin D status, gender differences, and hematological parameters in an Iranian population. **Methods:** This cross-sectional study included 275 participants (95 men, 180 women) aged 18-70 years. Exclusion criteria comprised chronic diseases, malignancies, and use of iron/vitamin D supplements. Comprehensive hematological and biochemical analyses were performed using standardized methods, including HPLC for vitamin D quantification. **Results:** Mean vitamin D levels were significantly lower in men compared to women (26.53 ± 11.14 vs 30.51 ± 14.43 nmol/L). Vitamin D deficiency was more prevalent in men (63.4%) than in women (50%). A paradoxical inverse relationship was observed between vitamin D status and hemoglobin levels, with deficient individuals showing higher hemoglobin concentrations (13.68 ± 1.53 vs 13.19 ± 0.62 g/dL). No significant associations were found between vitamin D levels and conventional iron status markers. **Conclusion:** Our findings reveal a higher prevalence of vitamin D deficiency in men compared to women, challenging conventional assumptions about gender distribution of vitamin D status. The unexpected inverse relationship between vitamin D and hemoglobin levels suggests complex physiological interactions that warrant further investigation. These results highlight vitamin D deficiency as an emerging concern in men's health that requires greater clinical attention.

Keywords: Vitamin D Deficiency, Gender Differences, Hematological Parameters, Iron Metabolism, Men's Health

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1. Introduction

Vitamin D, a fat-soluble hormone, has traditionally been recognized for its crucial role in calcium homeostasis and bone metabolism (1). However, accumulating evidence over the past decade has revealed its extensive pleiotropic effects, including immunomodulation, anti-inflammatory properties, and potential involvement in hematopoiesis (2). The discovery of vitamin D receptors (VDR) in various tissues, including bone marrow and immune cells, has expanded our understanding of its extra-skeletal functions (3).

The global burden of vitamin D deficiency remains substantial, affecting approximately 40-90% of various populations worldwide (4). While traditionally considered more prevalent in women because of factors such as clothing practices, pregnancy, and lactation, recent epidemiological studies have reported shifting patterns, with increasing deficiency rates observed in male populations (5). This changing epidemiology warrants renewed investigation into gender-specific risk factors and consequences.

The association between vitamin D status and hematological parameters has attracted growing attention in recent years. Experimental evidence suggests that calcitriol, the biologically active form of vitamin D, plays a regulatory role in the hepcidin–ferroportin axis, thereby influencing iron availability for erythropoiesis (6). Furthermore, vitamin D has been shown to regulate inflammatory cytokines that may indirectly affect erythrocyte production and survival (7). Despite these mechanistic insights, clinical studies have yielded conflicting results regarding the association between vitamin D status and iron metabolism markers.

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Iron deficiency anemia (IDA) is the most common nutritional disorder globally, affecting nearly 1.5 billion people worldwide (8). The complex interplay between micronutrient deficiencies represents an important area of investigation, particularly in regions with high prevalence of both vitamin D deficiency and anemia. Previous studies examining the vitamin D-iron relationship have produced inconsistent findings, with some reporting positive correlations (9; 10) while others found no significant associations (11).

We aimed to investigate the gender-specific patterns of vitamin D status and its relationship with hematological parameters in a well-characterized Iranian population from Golestan Province.

2. Materials and Methods

2.1. Study Design and Population

This cross-sectional study was conducted between March 2022 and February 2023 at the Kavosh Laboratory in Golestan Province, northern Iran. The study initially enrolled 270 participants, with final analysis including 275 individuals after quality control procedures. The cohort comprised 95 men (34.5%) and 180 women (65.5%), aged 18-70 years.

2.2. Inclusion and Exclusion Criteria

Participants were eligible if they were between 18-70 years of age. Exclusion criteria included: evidence of chronic inflammatory conditions (elevated CRP >5 mg/L or ESR >20 mm/hr for men, >30 mm/hr for women); ferritin levels above the normal range (300 ng/mL); diagnosed malignancies; current use of iron or vitamin D supplements; and pregnancy or lactation in female participants.

2.3. Laboratory Assessments

Blood samples were collected after an overnight fast and analyzed using standardized protocols: Complete blood count (CBC) was performed using the Orfee cell counter (Orphee Medical, Switzerland), Vitamin D levels were quantified using high-performance liquid chromatography (HPLC) with the Agilent system (Agilent Technologies, USA). Ferritin levels were assessed using the Immulite 1000 immunoassay system (Siemens Healthineers, Germany), ESR was measured using the Vision C ESR Analyzer (ALIFAX, Italy), CRP and other biochemical tests were performed using the Mindray BS-800 analyzer (Mindray Bio-Medical Electronics, China) with diagnostic kits from Biorex Fars Company (Iran).

2.4. Statistical Analysis

Data were analyzed using SPSS software version 26 (IBM Corp., Armonk, NY). Continuous variables were expressed as mean ± standard deviation and categorical variables as frequencies and percentages. Independent t-tests were used for comparing means between groups, while Pearson correlation coefficients were calculated to assess relationships between continuous variables. Chi-square tests were employed for categorical variables. A p-value ≤ 0.05 was considered statistically significant.

2.5. Ethical Considerations

The study was approved by the Ethics Committee of Golestan University of Medical Sciences (Ethics Code: IR.GOUMS.1403.195). All participants provided written informed consent after being thoroughly informed about the study objectives and procedures.

3. Results

3.1. Study Population Characteristics

The final analysis included 275 participants with a mean age of 42.45 ± 16.92 years. The gender distribution showed comparable age between men (42.08 ± 17.83 years) and women (42.64 ± 16.47 years, p=0.795), ensuring valid gender-based comparisons (Table 1).

3.2. Gender-Based Differences in Hematologic and Vitamin D Levels

Significant gender-based disparities were observed across multiple parameters. Male participants demonstrated higher erythrocyte parameters, including RBC counts (5.14 ± 0.62 vs 4.63 ± 0.52 million/μL, p<0.001) and hemoglobin levels (14.40 ± 1.37 vs 12.87 ± 1.11 g/dL, p<0.001). Iron storage capacity, reflected by ferritin levels, was substantially higher in males (145.50 ± 125.73 vs 62.10 ± 56.04 ng/mL, p<0.001). Conversely, females exhibited significantly higher vitamin D levels (30.51 ± 14.43 vs 26.53 ± 11.14 nmol/L, p=0.020) and platelet counts (244.56 ± 54.01 vs 217.05 ± 49.18, p<0.001).

3.3. Vitamin D Status and Hematological Parameters

Using the 30 nmol/L cutoff for vitamin D deficiency, we identified a paradoxical relationship with hemoglobin levels. Participants with vitamin D deficiency demonstrated significantly higher hemoglobin levels compared to those with sufficient vitamin D status (13.68 ± 1.53 vs 13.19 ± 0.62 g/dL, p=0.006). This unexpected inverse relationship persisted despite no significant differences in iron metabolism parameters between vitamin D groups (Table 2).

3.4. Gender-Stratified Vitamin D Deficiency Analysis

Vitamin D deficiency showed a distinct gender-specific pattern, with higher prevalence in males (63.4%) compared to females (50%). Gender-stratified analysis revealed that among male participants, those with vitamin D deficiency

had significantly lower hemoglobin levels (14.12 ± 1.37 vs 14.84 ± 1.38 g/dL, p=0.020) and MCHC values (33.23 ± 0.77 vs 33.79 ± 0.79 g/dL, p=0.002) compared to their vitamin D sufficient counterparts. In contrast, female participants showed no significant differences in these parameters based on vitamin D status (Table 3).

3.5. Vitamin D Levels by Anemia and Iron Status

No significant differences in vitamin D levels were observed between anemic and non-anemic participants when analyzed by gender. Similarly, vitamin D levels showed no significant association with conventional markers of iron status. Participants with low ferritin levels (<30 ng/mL) showed comparable vitamin D levels to those with normal ferritin (29.7 ± 12.7 vs 30.7 ± 13.8 nmol/L, p=0.325), and no significant difference was observed between participants with low versus normal serum iron levels (28.7 ± 7.1 vs 30.8 ± 7.7 nmol/L, p=0.356).

3.6. Correlation Analysis

Vitamin D levels demonstrated significant positive correlations with age (r=0.27, p<0.001) and female gender (r=0.14, p<0.005), while showing a weak but significant inverse correlation with hemoglobin levels (r=-0.17, p<0.005). Gender-stratified analysis revealed that in female participants, vitamin D maintained a significant positive correlation with age (p<0.001), whereas in male participants, no significant correlations were observed between vitamin D and hematological parameters.

4. Discussion

This study elucidates complex relationships between gender, vitamin D status, and hematological parameters. Our findings confirm established physiological differences while revealing a novel, gender-specific interaction between vitamin D and erythropoiesis. The observed gender disparities in hematologic indices are consistent with well-documented physiological norms. The significantly higher hemoglobin, RBC count, ferritin, and serum iron levels in males are primarily attributed to the stimulatory effects of androgens on erythropoiesis and the iron losses associated with menstruation in pre-menopausal females (12; 13). Conversely, the higher platelet count in females aligns with previous reports, though the underlying mechanisms remain partially elucidated (14).

A central and unexpected finding of our investigation was the inverse association between vitamin D sufficiency and hemoglobin levels at the population level. This appears to contradict some studies that suggest a positive role for vitamin D in erythropoiesis (15). However, this paradoxical relationship was clarified through gender-stratified analysis. The association was significant only in males, where vitamin D-deficient individuals had lower hemoglobin and MCHC levels. This suggests that the relationship between vitamin D and hemoglobin is modulated by gender, a critical nuance that may explain inconsistencies in the literature. One plausible explanation is a gender-dimorphic interaction between vitamin D and sex hormones, particularly testosterone, which is a potent erythropoietic stimulant (12). Vitamin D sufficiency may potentiate the erythropoietic effects of androgens, a hypothesis that requires further mechanistic investigation.

A salient finding of the present investigation is the significantly higher prevalence of vitamin D deficiency observed among male participants (63.4%) compared to females (50%), which is consistent with their lower mean serum vitamin D concentrations. The etiology of this gender disparity is likely multifactorial, encompassing physiological, behavioral, and biochemical determinants.

From a physiological perspective, the larger body surface area and greater lean body mass characteristic of males may create a larger volume of distribution for vitamin D. This can result in a lower serum concentration of 25(OH)D for an equivalent synthetic or dietary dose, a phenomenon supported by observed inverse correlations between lean mass and vitamin D status (16). Behaviorally, males demonstrate a markedly lower propensity for dietary supplement utilization, including vitamin D, which is a significant modifier of nutritional status (17). Concurrently, while sun exposure patterns are complex, gender-specific differences in occupational and recreational sun exposure, as well as in the consistent use of sunscreen, are significant contributing factors (18).

Furthermore, emerging evidence suggests a potential endocrine interplay, wherein androgens may modulate vitamin D metabolism. Certain studies posit that testosterone may upregulate the catabolism of 25(OH)D via induction of the 24-hydroxylase enzyme (CYP24A1), thereby accelerating its clearance (19). The sequestration of vitamin D in adipose tissue also presents a gender-specific dynamic; the higher average adiposity in females may provide a reservoir that buffers against seasonal fluctuations, a buffer less pronounced in males (20).

5. Conclusion

The higher prevalence of vitamin D deficiency observed in the male cohort highlights the need to reconsider public health screening guidelines to explicitly recognize males as a vulnerable population. This disparity likely reflects a combination of factors, including greater volume of distribution, sex-specific behavioral patterns, and differences in endocrine regulation. Future longitudinal studies incorporat-

ing objective measures of body composition, sun exposure, and sex steroid hormones are needed to clarify the underlying biological and behavioral mechanisms. Collectively, these findings position vitamin D deficiency as an emerging concern in men's health that warrants increased clinical and public health attention.

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Table 1: Demographic and Baseline Characteristics by Gender

Parameter	Male (n=95)	Female (n=180)	p-value
Age (years)	42.08 ± 17.83	42.64 ± 16.47	0.795
Hemoglobin (g/dL)	14.40 ± 1.37	12.87 ± 1.11	<0.001
Vitamin D (nmol/L)	26.53 ± 11.14	30.51 ± 14.43	0.020
RBC (million/μL)	5.14 ± 0.62	4.63 ± 0.52	<0.001
Ferritin (ng/mL)	145.50 ± 125.73	62.10 ± 56.04	<0.001
Iron (μg/dL)	86.31 ± 20.75	74.49 ± 21.00	<0.001
TIBC (μg/dL)	334.11 ± 48.99	343.12 ± 60.81	0.213
Platelet ($\times 10^3/\mu$L)	217.05 ± 49.18	244.56 ± 54.01	<0.001

Table 2: Comparison of Hematologic Indices by Vitamin D Status

Parameter	Vitamin D Deficient (n=147)	Vitamin D Sufficient (n=123)	p-value
Hemoglobin (g/dL)	13.68 ± 1.53	13.19 ± 0.62	0.006
RBC (million/μL)	4.84 ± 0.59	4.77 ± 0.65	0.415
MCHC (g/dL)	33.41 ± 0.86	33.10 ± 0.86	0.004
Iron (μg/dL)	80.11 ± 21.80	76.00 ± 21.02	0.121
Ferritin (ng/mL)	91.50 ± 99.99	90.00 ± 88.58	0.899
TIBC (μg/dL)	342.56 ± 54.43	336.71 ± 60.88	0.406

Table 3: Hematologic Indices by Vitamin D Status, Stratified by Gender

Gender	Parameter	Vitamin D Deficient	Vitamin D Sufficient	p-value
Male	Hemoglobin (g/dL)	14.12 ± 1.37	14.84 ± 1.38	0.020
	MCHC (g/dL)	33.23 ± 0.77	33.79 ± 0.79	0.002
	Ferritin (ng/mL)	162.81 ± 131.83	132.54 ± 116.45	0.277
Female	Hemoglobin (g/dL)	12.94 ± 1.11	12.84 ± 1.19	0.547
	MCHC (g/dL)	33.13 ± 0.85	33.06 ± 0.88	0.584
	Ferritin (ng/mL)	54.10 ± 43.24	67.14 ± 66.05	0.119