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Insulin Resistance, Calcium, C-Reactive Protein, and Hormonal Parameters Associated with Vitamin D Deficiency in Hyperprolactinemic Women

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ABSTRACT

Background & Objective: Hyperprolactinemia is a common endocrine disorder characterized by elevated serum prolactin levels, which can result in menstrual irregularities, galactorrhea, infertility, and hypogonadism in women. Beyond its well-known reproductive consequences, emerging evidence suggests that hyperprolactinemia may also be associated with significant metabolic and inflammatory alterations. This study aimed to investigate the relationship between vitamin D (Vit D) deficiency and hormonal (follicle-stimulating hormone [FSH], estradiol, thyroid-stimulating hormone [TSH], triiodothyronine [T3], thyroxine [T4]) and biochemical parameters (insulin resistance, calcium, and C-reactive protein [CRP]) in women with hyperprolactinemia.

Materials & Methods: The study included 40 women aged 30–40 years, divided into two groups: 20 women with hyperprolactinemia and 20 healthy controls. Hormonal and biochemical parameters were measured in both groups, and comparisons were made to assess the effect of vitamin D deficiency.

Results: FSH levels increased in the hyperprolactinemia group but were not statistically significant, while estradiol showed a significant increase ($P \leq 0.01$). TSH and T4 levels were also significantly elevated ($P \leq 0.01$), whereas T3 increased significantly ($P \leq 0.05$) compared with the control group. Insulin resistance ($P \leq 0.05$) and CRP ($P \leq 0.01$) were significantly higher in the hyperprolactinemic group. Serum calcium levels decreased significantly ($P \leq 0.05$) compared with the control group.

Conclusion: Vitamin D deficiency in hyperprolactinemic women may be associated with various hormonal and metabolic disturbances. These include alteration of reproductive and thyroid hormone levels and elevation of inflammatory markers, suggesting that vitamin D deficiency may contribute to broader endocrine and biochemical dysregulation.

Keywords: Vitamin D Deficiency, Hyperprolactinemia, Insulin Resistance, CRP, Calcium

1. Introduction

Vitamin D deficiency is a global health problem that has reached pandemic proportions, documented across different age groups and ethnicities, affecting approximately 24%–49% of the global population (1). Vitamin D deficiency has been shown to be associated with increased mortality risk (2). It is also associated with secondary hyperparathyroidism, which contributes to bone loss and fracture risk among severely vitamin D deficient individuals (3).

In addition, vitamin D has potent immunomodulatory effects and plays important roles in the pathogenesis of autoimmune diseases (4). Vitamin D deficiency is particularly prevalent during women's reproductive years. It has been linked to disruptions of steroidogenesis and reproductive disorders such as premenstrual syndrome, dysmenorrhea, early menarche, and adverse fertility outcomes including polycystic ovarian syndrome (PCOS) and hypogonadism (5), in addition to lower clinical pregnancy rates (6).

Hyperprolactinemia (HPL) is a condition characterized by elevated serum prolactin levels, usually due to pituitary disorders, affecting both sexes and associated with impaired sexual and reproductive function (7). Multiple physiological, pathological (tumor and non-tumor related), and pharmacological factors contribute to the development of HPL (8, 9).

Furthermore, HPL may cause detrimental hormonal and reproductive consequences, including hypogonadotropic hypogonadism, irregular menstrual cycles (oligo-amenorrhea or polymenorrhea), galactorrhea, secondary amenorrhea, hirsutism in women, gynecomastia in men, and decreased fertility and libido in both sexes (10).

Previous studies have demonstrated that vitamin D deficiency is highly prevalent among women with hyperprolactinemia. It has been suggested that vitamin D ameliorates the association between insulin resistance and elevated prolactin levels in hyperprolactinemic patients (11-13). Moreover, vitamin D supplementation has been shown to reduce prolactin levels by enhancing calcium absorption in hyperprolactinemic rats (14).

The aim of this study was to investigate the role of vitamin D deficiency and its relationship with selected hormonal (FSH, estradiol, TSH, T3, and T4) and biochemical parameters (insulin resistance, CRP, and calcium) in hyperprolactinemic women.

2. Materials and Methods

This study was conducted in several health centers in Maysan Province, Iraq, between December 2023 and February 2024. A total of 40 women aged 30–40 years were enrolled and divided into two groups (20 per group): a control group (healthy women) and a hyperprolactinemia group (women with vitamin D deficiency). All participants were examined by a specialist physician and diagnosed with vitamin D deficiency and hyperprolactinemia according to serum 25(OH)D3 levels <20.0 ng/mL and prolactin levels >25 ng/mL, respectively (7). Women with chronic diseases, tumors, or those receiving hormonal treatments were excluded.

2.1 Sample Collection

Between 9:00 and 11:00 a.m., during the follicular phase of the menstrual cycle (days 8–10), 8–10 mL of venous blood was drawn from each participant. The blood was left at room temperature for 15 minutes to allow coagulation, centrifuged at 3000 rpm for 5 minutes, and the serum was separated and stored until analysis.

2.2 Data Collection and Laboratory Tests

Serum FSH, estradiol, TSH, T3, and T4 concentrations were measured using the VIDAS automated immunoassay system (BioMérieux, France) with corresponding commercial kits (BioMérieux, France). Serum CRP was determined using a Mindray BS-200 analyzer (Mindray, China) with CRP reagent kits (Mindray, China). Serum calcium concentrations were analyzed using the BioSystems A-15 analyzer (BioSystems, Spain) with corresponding reagent kits (BioSystems, Spain).

The reference ranges were as follows: FSH: 3.0–12.0 mIU/mL, Estradiol: 18–147 pg/mL, TSH: 0.25–5 µU/mL, T3: 0.9–2.3 nmol/L, T4: 60–120 nmol/L, CRP: 0–5 mg/L, and Calcium: 8.6–10.3 mg/dL. Insulin resistance was estimated using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), calculated as: HOMA-IR = [Fasting insulin (µU/mL) × Fasting glucose (mg/dL)] ÷ 405.

2.3 Statistical Analysis

Data were analyzed using one-way t-tests. Statistical significance was considered at $P \leq 0.05$ and $P \leq 0.01$ (15).

3. Result

The mean serum FSH levels in hyperprolactinemic women were nonsignificantly higher compared with controls (5.52 ± 0.78 mIU/mL vs. 5.48 ± 0.50 mIU/mL, $P > 0.05$). Estradiol concentrations were significantly elevated in the hyperprolactinemia group (88.95 ± 8.22 pg/mL) compared with controls (59.60 ± 5.82 pg/mL, $P < 0.01$). Prolactin levels were also markedly higher in hyperprolactinemic women (49.31 ± 4.32 ng/mL) than in controls (14.75 ± 1.21 ng/mL, $P < 0.01$). In addition, mean TSH and T4 concentrations were significantly higher in the hyperprolactinemia group (2.05 ± 0.17 µU/mL vs. 1.67 ± 0.18 µU/mL; 89.45 ± 4.43 ng/dL vs. 82.7 ± 4.79 ng/dL, $P < 0.01$). T3 levels were also significantly increased (1.62 ± 0.111 ng/dL vs. 1.54 ± 0.119 ng/dL, $P < 0.05$) (Table1).

The mean insulin resistance was significantly higher in hyperprolactinemic women compared with controls (4.49 ± 0.46 vs. 3.27 ± 0.59, $P < 0.01$). Serum CRP concentrations were significantly elevated in hyperprolactinemic women (3.54 ± 0.56 mg/dL) compared with controls (1.50 ± 0.31 mg/dL, $P < 0.01$). Serum calcium concentrations were significantly lower in hyperprolactinemic women (9.05 ± 0.18 mg/dL) compared with controls (9.25 ± 0.37 mg/dL, $P < 0.05$) (Table2).

Table 1. Vitamin D and hormonal changes during hyperprolactinemia.

Parameters	Hyperprolactinemia	Control	P-Value
FSH (mlU/ml)	5.52 ±0.78	5.48 ±0.50	0.4239
Estradiol (pg/ml)	88.95 ±8.22	59.60 ± 5.82	*P* <0.00001
Prolactin (ng/ml)	49.31 ±4.32	14.75 ± 1.21	*P* <0.00001
TSH (µUl/ml)	2.05 ± 0.17	1.67 ± 0.18	*P* <0.00001
T3 (ng/dl)	1.62 ± 0.111	1.54 ± 0.119	0.0168
T4 (ng/dl)	89.45 ± 4.43	82.7 ± 4.79	0.000019

Table 2. Insulin resistance, CRP and calcium changes during hyperprolactinemia.

Parameters	Hyperprolactinemia	Control	P-Value
Insulin Resistance	4.49 ± 0.46	3.27 ± 0.59	*P* <0.00001
CRP (mg/dl)	3.54±0.56	1.50±0.31	*P* <0.00001
Calcium (ng/ml)	9.05 ± 0.18	9.25 ± 0.37	0.01709

4. Discussions

Hyperprolactinemia may contribute to vitamin D deficiency through the influence of elevated prolactin on the steps of vitamin D synthesis, as reported by Amanzholkyzy et al **(12)** and Krysiak et al **(16)**, who found that vitamin D deficiency is associated with elevated prolactin levels in adolescent girls. This may be explained by the impact of hyperprolactinemia on circulating 25-hydroxyvitamin D, the precursor of active vitamin D synthesis.

In the present study, FSH concentrations were slightly increased, which may be attributed to vitamin D deficiency affecting ovarian function. Vitamin D plays a role in both FSH synthesis and receptor regulation. However, elevated prolactin inhibits gonadotropin-releasing hormone, which can reduce FSH secretion. Previous findings by Merhi et al **(17)** suggested that vitamin D alters anti-Müllerian hormone (AMH) signaling and steroidogenesis, with low vitamin D being associated with elevated FSH, a biomarker of diminished ovarian reserve and accelerated ovarian aging **(18)**. Bakare et al **(19)** and others **(20, 21)** confirmed that persistent hyperprolactinemia disrupts hypothalamic regulation of FSH and LH secretion.

The significant increase in estradiol observed in this study may also be linked to vitamin D deficiency, which affects estradiol synthesis and receptor expression. Vitamin D has been reported to attenuate estradiol signaling by downregulating estrogen receptor expression in breast cancer cells **(22)**. Elevated estradiol may, in turn, stimulate prolactin secretion through inhibition of dopamine production, as demonstrated by MohanKumar et al **(23)**.

The increases in TSH, T3, and T4 observed here are consistent with the regulatory effects of vitamin D on the hypothalamic-pituitary-thyroid axis. Vitamin D receptors are expressed in pituitary thyrotropes and thyroid cells **(24)**. While Amanzholkyzy et al **(11)** reported low T4 in vitamin D-deficient adolescents, other studies **(25, 26)** have shown strong associations between prolactin and thyroid hormones, possibly mediated through thyrotropin-releasing hormone (TRH).

Insulin resistance was significantly increased in hyperprolactinemic women, which may be related to both vitamin D deficiency and elevated prolactin. Vitamin D modulates insulin secretion in pancreatic β-cells through vitamin D response elements in the insulin gene promoter **(11)**. Prior studies **(27)** have consistently reported negative associations between vitamin D deficiency and insulin sensitivity.

CRP levels were significantly higher in hyperprolactinemic women, reflecting both vitamin D deficiency and prolactin's role as a pro-inflammatory mediator. Vitamin D supplementation has been shown to reduce CRP levels **(28)**, while prolactin itself has been described as a pro-inflammatory cytokine **(29)**. Elevated CRP in hyperprolactinemia has been reported in other studies **(30, 31)**.

Finally, the observed reduction in serum calcium in hyperprolactinemic women reflects the essential role of vitamin D in calcium absorption and homeostasis. Several studies support the role of vitamin D deficiency in impaired calcium absorption and mineral balance **(32, 33)**.

5. Conclusion

In conclusion, our findings highlight a close relationship between vitamin D deficiency and elevated prolactin secretion. Vitamin D deficiency may disrupt both the hypothalamic-pituitary-ovarian and hypothalamic-pituitary-thyroid axes, contributing to reproductive and endocrine dysfunction. Moreover, vitamin D deficiency exacerbates metabolic disturbances, particularly insulin resistance, and worsens the inflammatory state of hyperprolactinemia, which itself represents a low-grade inflammatory condition. Finally, impaired calcium absorption further reflects the systemic consequences of vitamin D deficiency. These results suggest that vitamin D deficiency contributes to broad hormonal, metabolic, and inflammatory dysregulation in hyperprolactinemic women.

6. Declarations

6.1 Acknowledgments

None.

6.2 Ethical Considerations

Ethical approval for this study was obtained from the Knowledge Management Division, Training and Human Development Center, Misan Health Directorate, Ministry of Health, Republic of Iraq (Approval No. 6; Date: January 4, 2024).

6.3 Authors' Contributions

All authors were equally involved in the study design, sample collection, laboratory work, data analysis, and the writing and interpretation of the results.

6.4 Conflict of Interest

The authors declare that they have no conflict of interest.

6.5 Fund or Financial Support

This study was self-funded by the authors.

6.6 Using Artificial Intelligence Tools (AI Tools)

The authors declare that they did not use the artificial intelligence.

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