Comparison of 25-hydroxyvitamin D levels in breast cancer patients and control group: a cross-sectional study

Comparação dos níveis de 25-hidroxivitamina D em pacientes com câncer de mama e no grupo de controle: um estudo transversal

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ABSTRACT
To assess serum vitamin D levels in patients with breast cancer and compare them against control patients without the disease, testing the hypothesis that patients with breast cancer have lower serum levels of the hormone than patients without the cancer. A total of 101 treatment-naïve patients diagnosed with breast cancer at the Mastology Outpatient Clinic of the Department of Obstetrics and Gynecology of the Irmandade da Santa Casa de São Paulo (ISCMSP), and 100 control patients without the disease at the Endocrinologic Gynecology Outpatient Clinic of the same institution were selected. Serum vitamin D levels for the two groups were compared. Mean serum vitamin D level was 23.85 ng/dL in the breast cancer group versus 28.19 ng/dL in the control group, where this difference proved statistically significant on Student’s t-test (p=0.002). Patient age was a confounding bias, where no correlation between serum level and age was evident on the scatter plot. Patients with breast cancer had lower serum Vitamin D levels than patients without the cancer. However, longitudinal studies should be conducted to determine whether a causal relationship exists between these variables.

Keywords: vitamin D, breast neoplasms, calcitriol, carcinogenesis, metabolism.

RESUMO
Avaliar os níveis séricos de vitamina D em pacientes com câncer de mama e compará-los com controles de pacientes sem a doença, testando a hipótese de que pacientes com câncer de mama apresentam níveis séricos do hormônio mais baixos do que pacientes sem a doença. Foram selecionadas 101 pacientes sem tratamento, diagnosticadas com câncer de mama no Ambulatório de Mastologia do Departamento de Obstetrícia e Ginecologia da Irmandade da Santa Casa de São Paulo (ISCMSP), e 100 pacientes controle sem a doença no Ambulatório de Ginecologia Endocrinológica da mesma instituição. Os níveis séricos de vitamina D dos dois grupos foram comparados. O nível médio de vitamina D no soro foi de 23,85 ng/dL no grupo
INTRODUCTION

Breast cancer is the second most common type of cancer worldwide and the most common type among women. Some theories suggest a link between polymorphism of the vitamin D receptor (VDR) and the occurrence and prognosis of breast cancer. Vitamin D encompasses a group of fat-soluble compounds that play a key role in calcium homeostasis and health of the musculoskeletal system. The vitamin exists in two forms: D3 (cholecalciferol), synthesized in the skin from pro-vitamin D (7-dehydrocholesterol) by the action of ultraviolet sun light; and D2 (ergocalciferol), synthesized from a fungi (ergosterol). In humans, most Vitamin D (80-90%) required by the body is derived from endogenous synthesis (Figure 1), whereas 10-20% is dietary. Main sources of D3 are oily cold-water fish (salmon, tuna) and of D2 are edible fungi.

When ingested, Vitamin D is absorbed in the small intestine and transported via chylomicrons to the liver (and likewise for the portion synthesized by the skin) and, in this first pass, 75% undergoes hydroxylation into the 25 group. The converted form is denoted 25-hydroxyvitamin D (calcidiol) and constitutes the predominant form of circulating VD. It has a half-life of three weeks and serves as a reliable marker of stores of the vitamin in the body. In the kidney, 25(OH) VD again undergoes hydroxylation and is converted into the metabolically active form 1-a,25-dihydroxy-vitamin D [1,25(OH)2D or calcitriol]. Although this is the active form, it does not serve as a measure of body stores because of its shorter half-life (of around 6 hours) and can appear normal in cases of vitamin D deficiency due to the stimulatory action of parathyroid hormone (PTH).

In the Brazilian population, it is assumed that vitamin D levels are adequate, given the country’s high UV index, where sufficient exposure to UVB rays preclude the need for dietary sources to attain a level of 25(OH)D within the normal range. However, these reference values vary widely among studies and lead to conflicting reports in the medical literature, hampering...
accurate determination of vitamin insufficiency. The American National Academy of Medicine establishes a level > 20 ng/dL as sufficient\(^5\).

The most active natural metabolite of vitamin D (1, 25-di-hydroxyvitamin D3), has been shown to regulate growth and differentiation of different cell types including cancerous cells. There is also evidence of its regulating effect on cell death, tumor invasion and angiogenesis in breast tumor cells. Most breast cancer cases are linked to mutations in the gene allele of the receptor of this vitamin\(^7,8\).

Some experimental studies support the hypothesis that the anti-cancer effects of vitamin D can be mediated through the estrogen pathway by down regulation of estrogen receptors, reducing the hormone’s action on cell growth. Skin exposure to sunlight, a diet rich in vitamin D or daily supplementation with 400 UI of the nutrient, are factors associated with a lower risk of breast cancer\(^7,9\).

The objective of this study was to assess serum vitamin D levels in patients with breast cancer and compare these against patients without the cancer, testing the hypothesis that patients with breast cancer have lower serum levels of the hormone than individuals without the disease.

**2 MATERIAL AND METHODS**

A cross-sectional study with a control group, approved by the Ethics Committee for Research in Humans of the Irmandade da Santa Casa de Misericórdia de São Paulo Hospital (CAAE permit no. 67138117.4.0000.5479), was conducted. A total of 101 treatment-naïve patients diagnosed with breast cancer at the Mastology Outpatient Clinic of the Department of Obstetrics and Gynecology of the Irmandade da Santa Casa de São Paulo (ISCMSP), and 100 control patients without the disease at the Endocrinologic Gynecology Outpatient Clinic of the same institution (visiting for routine follow-up or climacteric-related complaints) were selected. Both groups were tested to determine vitamin D levels and values compared. Patients gave consent for blood collection.

Exclusion criteria for patients in the breast cancer group were: women with metastatic disease confirmed on diagnosis, currently undergoing treatment, and pregnant or nursing. Exclusion criteria for the control group were: women with suspected or diagnosed malignant tumors, anemia, and pregnant or nursing. Data collection and statistical analyses were carried out between August 2014 and August 2020.
3 RESULTS

Age in the breast cancer group ranged from 21 to 88 years, with a mean of 54.55 years. In the control group, age ranged from 40 to 69 years, with a mean of 53.21 years. Mean serum vitamin D level in the cancer group was 23.85 ng/dL versus 28.19 ng/dL in the control group (Figure 1). No correlation between serum level and age was evident on the scatter plot (Figure 2).

Thus, the control group had, on average, higher vitamin D levels than the cancer group. Student’s t-test was applied to validate this information for the study population. Levene’s test showed equal variance between the groups (p= 0.171> 0.005), and therefore results in the first row of the table should be noted (Figure 4). The study revealed a significant difference (p= 0.002) in serum vitamin D levels between the case and control groups, where levels in controls were 4.34 ng/dL higher.

4 DISCUSSION

The statistically significant difference between the groups confirmed the initial hypothesis that there is an association between low serum vitamin D levels and breast cancer. However, the cross-sectional design of the study precludes the establishing of a cause-effect relationship between the variables investigated.

Patient age may constitute a confounding bias, given that serum levels in women tend to vary with age. Nevertheless, the table of age distribution reveals no statistical correlation between the age variable and vitamin levels measured.

The study is cross-sectional and therefore no causal relationship between the variables can be determined. Both the hypothesis that the neoplastic process reduced vitamin levels and that existing low level of the vitamin represents a risk factor for developing the disease in the women remain plausible.

5 CONCLUSION

The results confirmed the study hypothesis that patients with breast cancer have lower serum vitamin D levels than patients without the cancer. Longitudinal studies should be performed to determine whether a causal relationship exists between these variables.
ACKNOWLEDGEMENTS

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REFERENCES


ANNEXES

Figure 1. Mean serum Vitamin D levels

Source: Authors

Figure 2. Scatter plot showing absence of correlation between age and serum vitamin D level

Source: Authors
Table 1. Student’s t-test showing statistically significant difference in vitamin D levels between groups analyzed.

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Source: Authors