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Comparison of the Effect of Secondary Hyperparathyroidism Due to Vitamin D Deficiency on Bone with The Healthy Control Group

D Vitamini Eksikliğine Bağlı Sekonder Hiperparatiroidizmin Kemik Üzerindeki Etkisinin Sağlıklı Kontrol Grubu ile Karşılaştırılması

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Abstract

Aim In healthy individuals, to demonstrate that adequate vitamin D status protects against osteoporosis by improving bone mineral density and reducing the risk of fractures.

Material and Method Fifty patients with high parathyroid hormone secondary to low vitamin D level and 50 patients with normal parathyroid hormones were included in the study as the control group.

Results Of the 50 patients with secondary hyperparathyroidism due to vitamin D deficiency included in the study, 45 (90%) were female and 5 (10%) were male. In the control group with normal parathyroid hormone, 44 (88%) were female and 6% (12%) were male. The median age in the hyperparathyroid group was 70.5 (66-73) and in the parathyroid hormone normal group it was 71 (69-73). This median mean age was significant (p=0.004).
In the group with secondary hyperparathyroidism; The median PTH value was 99.5 (66-205.9) and 49.8 (27-61.5) in the control group, with a significant difference (p<0.001). While 25-Hydroxy Vitamin D level was 10.73 (4.64-34.1) in the group with normal parathyroid hormone level, it was 18.63 (6.21-65.1). This created a significant difference in both groups (p<0.001). According to the results of bone densitometry in the hyperparathyroidic and control groups. no significant difference was found between bone mineral density (BMD). 0.92 (0.66-1134), 0.93 (0.75 – 1293), (p=0.095).
However, for the femur, the results in T and Z scores were significant (p=0.027- p=0.027), whereas for the supine (spine), no significant difference was observed between the T and Z scores (p=0.358- p=0.265).

Conclusion Especially when the vitamin D level falls below 10 ng/mL, PTH begins to respond. Beyond these observations, a normal serum 25 (OH) D concentration is particularly important in preventing femur fractures, but its significance for vertebral fractures is unclear.

Keywords Osteoporosis, secondary hyperparathyroidism, vitamin D

Özet

Amaç *Sağlıklı bireylerde yeterli D vitamini durumunun, kemik mineral yoğunluğunu iyileştirerek ve kırık riskini azaltarak, osteoporoza karşı koruduğunu göstermektir.*

Gereç ve Yöntem *D vitamin seviyesi düşüklüğüne sekonder, paratiroid hormonu yüksek 50 hasta ile paratiroid hormonları normal olan, 50 hasta kontrol grubu olarak çalışmaya dahil edildi.*

Bulgular *Çalışmaya dahil edilen D vitamin eksikliğine bağlı sekonder hiperparatiroidizmli 50 hastanın,45'i (%90) kadın, 5'i (%10) erkekti. Paratiroid hormonu normal olan kontrol grubunda ise, 44'ü (%88) kadın, 6'sı (%12) erkekti Hiperparatiroidik grupta median yaş ortalaması 70,5 (66-73), paratiroid hormonu normal grupta ise 71 (69-73) idi. Bu median yaş ortalaması anlamlıydı (p=0,004).*
Sekonder hiperparatirodizmli grupta; PTH median değeri 99,5 (66-205,9), kontrol grubunda ise 49,8 (27-61,5) olup anlamlı fark gözlendi (p<0,001). 25-Hydroxy Vitamin D seviyesi 10,73 (4,64-34,1) iken, paratiroid hormon seviyesi normal olan grupta 18,63 (6,21-65,1) idi. Bu da her iki grupta anlamlı fark oluşturdu (p<0,001). Hiperparatiroidik ve kontrol grubunda çekilen kemik dansitometresi sonuçlarına göre. kemik mineral yoğunluğu (BMD) arasında anlamlı fark saptanmadı. 0,92 (0,66-1134), 0,93 (0,75-1293), (p=0,095).
Buna rağmen femur için, T ve Z scorlarındaki sonuç anlamlı iken (p=0,027- p=0,027), supin (omurga) için T ve Z scorları arasında anlamlı fark gözlenmedi (p=0,358- p=0,265).

Sonuç *Özellikle D vitamin seviyesi 10 ng/mLnin altına indiğinde PTH cevap vermeye başlamaktadır. Bu gözlemlerin ötesinde, serum 25 (OH) D konsantrasyonunun normal seviyede olması özellikle femur kırıklarından korumada önemli iken, vertebra kırıkları için önemi belirsizdir.*

Anahtar Kelimeler *Osteoporoz, sekonder hiperparatiroidizm, D vitamini*

INTRODUCTION

Little is known about the relationship between vitamin D deficiency and skeletal structure in patients with primary and secondary hyperparathyroidism (SHPT). Although there is evidence of changes in bone structure in the Asian population where 25-hydroxyvitamin D [25 (OH) D] deficiency is common, detailed studies are needed.

Osteomalacia occurs when combined with low dietary calcium and vitamin D levels. Maximum bone structure and strength; It is obtained by taking sufficient calcium in the diet, along with normal vitamin D levels. The biological activity of each of the bone major cell types (osteoblasts, osteoclasts and osteocytes) is compatible with adequate circulating 25-OH vitamin D levels.[1]

Available data suggest that vitamin D deficiency contributes to the etiology of at least two metabolic bone diseases, osteomalacia and osteoporosis. Numerous clinical data show that an adequate vitamin D status, represented by serum 25-hydroxyvitamin D concentration, protects against osteoporosis by improving bone mineral density and reducing the risk of fracture.[2]

As reported in meta-analyses on vitamin D, baseline 25-hydroxyvitamin D has no effect on bone density or fracture risk when >40 nmol/L.[3,4]

Parathyroid hormone (PTH) concentrations and vitamin D are routinely measured in the diagnosis and treatment of bone and kidney diseases. However, in healthy individuals whose vitamin D deficiency has not been evaluated, the median PTH values depending on vitamin D levels vary.[5]
In the department of breast-endorine surgery; In some patients who applied to the outpatient clinic with complaints of weakness, fatigue and bone pain, it has been drawing our attention for many years that the high level of parathyroid hormone is related to vitamin D deficiency. The effects on bone structure were investigated by comparing this patient group with the control group with normal parathyroid hormone. For this, help was received from the Physiotherapy and Rehabilitation department.

The aim of this study; It is the comparison of T and Z scores measured by bone densitometry in cases with SHPT due to vitamin D deficiency with a healthy control group with normal parathyroid hormone level and no disease.

MATERIAL and METHOD

After the approval of Sakarya University Ethics Committee, patients who developed secondary hyperparathyroidism due to vitamin D deficiency between January 2018 and July 2022 were retrospectively analyzed. Fifty patients with high parathyroid hormone secondary to low vitamin D levels and 50 healthy individuals with normal parathyroid hormones were included in the study as the control group. Vitamin D levels in the control group were not required to be in the normal range.

Study groups were randomly selected from among patients. At the same time, calcium (Ca) values of each patient in the study and control groups, T and Z scores and Bone Mineral Density (BMD) were compared in bone densitometry, femur and supine positions.

Vitamin D level; Values >40 ng/mL (>100 nmol/L) were considered normal. Values with a vitamin D level between 20 and 40 ng/mL (50-100 nmol/L) indicate the onset of vitamin D deficiency. Vitamin D deficiency was considered when the concentration was between 10–20 ng/mL (25–50 nmol/L) and values less than 10 ng/mL (<25 nmol/L).

In the study, the lower and upper limits of hospital laboratory normal values were considered as 8.8-10.6 mg/dL for Calcium (Ca), and 15-65 pg/mL for PTH. In bone densitometry; Those with a T femur score >-1.0 are considered normal. A T score between -1.0/-2.5 indicates osteopenia, and those below -2.5 indicate osteoporosis. The Z score, on the other hand, is compared to normal people of the same age, sex, weight and race as the individual. If it is above

-2.0, it means that it is in the expected range for age, and below -2.0 indicates that it is below the expected range for age. Bone Mineral Density (BMD); It determines the quantitative ratio of the mineral part such as calcium and phosphorus in the bone structure.

In the study; According to the laboratory results of the patients who applied to the outpatient clinic with complaints of weakness, fatigue and bone pain, individuals who were definitely known to have high parathyroid hormone levels due to vitamin D deficiency and who did not have any kidney, liver and bone disease were included. Those with a diagnosed disease were excluded from the study.

Statistical Analysis

Descriptive analyses were performed to provide information on the general characteristics of the study population. Kolmogorov-Smirnov test was used to evaluate whether the distributions of numerical variables were normal. Accordingly, the independent sample t-test or the Mann-Whitney U tests were used to compare the numeric variables between groups. The numeric variables were presented as mean ± standard deviation or median [minumum - maximum]. Categorical variables were compared by the Chi-Square test. Categorical variables were presented as a count and percentage. A p-value <0.05 was considered significant. Analyses were performed using SPSS statistical software (IBM SPSS Statistics, Version 23.0. Armonk, NY: IBM Corp.)

RESULTS

Of the 50 patients with secondary hyperparathyroidism due to vitamin D deficiency included in the study, 45 (90%) were female and 5 (10%) were male. In the control group with normal parathyroid hormone, 44 (88%) were female and 6% (12%) were male (Figure 1).

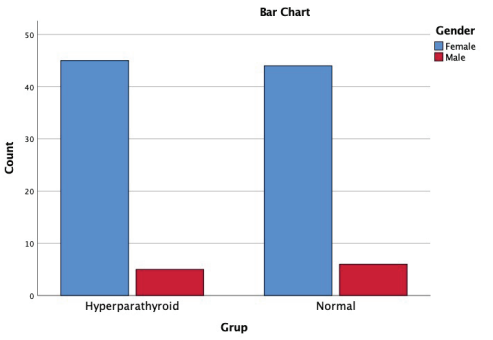

Figure 1. Demographic ratios of the hyperparathyroid group and the normal group

There was no significant difference between the two groups in terms of gender (p=0.749). The median mean age was 70.5 (66-73) in the hyperparathyroidic group and 71 (69-73) in the parathyroid hormone-normal group. This median mean age was significant (p= 0.004) (Table1).

Table 1. The relationship between sex and average age.

		Hyperparathyroid	Normal	p value
Gender	Male	5 (10%)	6 (12%)	0.749*
	Female	45 (90%)	44 (88%)	
Age		70.5 (66-73)	71 (69-73)	0.004**

* Chi-Square test, ** Mann Whitney-U test

In the group with secondary hyperparathyroidism; The median PTH value was 99.5 (66-205.9) and 49.8 (27-61.5) in the control group, with a significant difference (p<0.001). While 25-Hydroxy Vitamin D level was 10.73 (4.64-34.1) in the group with normal parathyroid hormone level, it was 18.63 (6.21-65.1). This created a significant difference in both groups (p<0.001).
Calcium level was 9.42∓0.42 in the secondary hyperparathyroidism group and 9.6∓0.41 in the normal group and was significant (p=0.007).

According to the results of bone densitometry in the hyperparathyroidic and control groups. no significant difference was found between bone mineral density (BMD). 0.92 (0.66-134), 0.93 (0.75-1293), (p=0.095).

However, for the femur, the results in T and Z scores were significant (p=0.027- p=0.027), while for the supine (spine), no significant difference was observed between the T and Z scores (p=0.358- p=0.265) (Table 2).

Table: 2 The relationship between PTH, Ca,25(OH)D and bone densitometry values of hyperparathyroid and normal groups.

	Hyperparathyroid	Normal	p value
PTH Value	99.5 (66.0 – 205.9)	49.8 (27.0 – 61.5)	<0.001*
25-Hydroxy Vitamin D	10.73 (4.64-34.1)	18.63 (6.21-65.1)	<0.001*
Calcium	9.42∓0.42	9.6∓0.41	0.007**
BMD	0.92 (0.66 – 1134)	0.93 (0.75 – 1293)	0.095*
T score femur	-0.94∓0.86	-0.52∓0.87	0.027**
T score supin	-2.0 (-3.3 – 1.40)	-1.65 (-4.1 – 3.2)	0.358*
Z score F	0.09∓ 0.89	0.52∓0.90	0.027**
Z score S	-0.1 (-1.4 – 3.40)	0.25 (-2.1 – 5.2)	0.265*
* Mann Whitney-U test, ** Independent samples t-test			

DISCUSSION

Maximum bone structure and strength depends on adequate vitamin D and a positive calcium balance. This is consistent with the 25 hydroxy vitamin D level. Osteoblasts; They have the ability to metabolize 25 hydroxy vitamin D [25-OH D] to 1.25 hydroxy vitamin D [1.25 (OH)2 D] to increase bone mineralization by osteocytes, as well as reduce bone resorption by osteoclasts. Numerous clinical data show that serum 25 (OH) vitamin D status protects against osteoporosis by improving bone mineral density and reducing the risk of fractures. Interestingly, adequate serum 1.25 (OH) 2D concentrations do not reduce the risk of fracture.[2]

In this study; In the group with low vitamin D, the significance of T and Z scores in the femur scan was not seen in the supine position. Therefore, we can say that the fracture risk for the "femur" increases relatively. However, it is difficult to explain the lack of difference for "supin".

There is no clear consensus when it comes to diagnosing vitamin D deficiency and determining exactly what level it is. Traditionally, vitamin D values below 5-7 ng/mL cause osteomalacia, values below 10–12 ng/mL lead to secondary hyperparathyroidism and osteoporosis, and levels above 18–20 ng/mL are considered normal.[6]

In our study, we observed that 25-OH vitamin D levels were below 7 ng/mL in most of the individuals with increased PTH levels, consistent with the literature.

The prevalence of vitamin D deficiency in the European elderly population was 36% of men and 47% of women. Surprisingly, most southern countries showed the lowest levels.[7]

In this study, vitamin D deficiency was observed in approximately 88-90% female and 10-12% male individuals, although the patient group was a very small series, mostly elderly. These percentages will likely vary in populations of all age groups and in large case series.

According to the balance between PTH and 25-hydroxyvitamin D obtained from different studies, the 25-hydroxyvitamin D concentration required for elderly people to have a normal PTH level should be 40 ng/mL.[8,9]

In clinical studies, vitamin D supplementation did not improve bone density, except in groups with 25-OH D <30 nmol/L. Vitamin D and calcium have different biological functions, so the need for supplementation, safety, and efficacy must be evaluated for each individually.

Meta-analyses of the effect of vitamin D supplements on bone density show no clinically relevant benefit.[10,11] However, two recent studies have shown that individuals with late winter 25-OH D levels <30 nmol/L have sustained bone loss of 1% per year when treated with placebo, and this loss is prevented by vitamin D.[12,13] However, when 25-hydroxyvitamin D >30 nmol/L, supplementation is ineffective.

A meta-analysis of studies supplementing with vitamin D alone found no effect on total fracture risk and hip fracture.[3,14]

Kanno et al.[15] reported that low vitamin D levels are more determinant in femur fractures than vertebral fractures. They emphasized that the secondary parathyroid hormone elevation was more common in those with vertebral fractures.

Although the statistical difference between T and Z scores in the "supin" and "femur" fractions was significant in our study, it is obvious that long-term vitamin D deficiency will lead to osteoporosis in some individuals. It would be pointless to generalize this situation to the entire population.

Vitamin D deficiency (25-hydroxyvitamin D <25 nmol/L) accelerates bone loss and may result in osteomalacia. Therefore, people with clinical risk factors for vitamin D deficiency (e.g. minimal sunlight exposure such as frail elderly and veiled, dark-skinned people living at high latitudes) should receive vitamin D replacement. Typically calciferol 400-1000 IU/day, but administration of supplements at weekly or monthly intervals may also be safe, effective and more convenient for patients.[16]

Vitamin D supplements appear to increase muscle strength (more so in individuals with baseline 25-hydroxyvitamin D levels <30 nmol/L), but not muscle strength or mass.[17]

In our study, serious improvements were detected with depot and intermittent daily treatments, especially in individuals with complaints of weakness and fatigue.

Sayed-Hassan et al.[18] reported that they could not find a significant relationship between 25-OH D and bone mineral density in the hip or lumbar spine.

In our study, no significant relationship was found in the secondary hyperparathyroidism patients and the control group.

CONCLUSION

The results of the findings were inconsistent when PTH and vitamin D were compared alone or in combination with calcium. Especially when the vitamin D level falls below 7 ng/mL, PTH begins to respond. Beyond these observations, a serum 25(OH)D concentration at a normal level is particularly important in protecting against femoral fractures, but its significance for vertebral fractures is unclear. Based on the available evidence regarding vitamin D supplementation, calcium intake, or a combination of both nutrients, it is difficult to make any concrete statements.

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Ethical Approval

Sakarya University Faculty of Medicine Ethics Committee and following the Declaration of Helsinki (decision no: E-71522473-050.01.04-224500-59, date: 27.02.2023).

Peer-review

Externally and internally peer-reviewed.

Authorship Contributions

Concept: H.D., E.G., Design: H.D., C.C., R.Ç., Data Collection or Processing: B.U.A., A.T.H., Analysis or Interpretation: E.G., Literature Search: H.D., C.C., Writing: H.D, C.C.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Informed Consent

Retrospective study

Limitations of study

This study was conducted in a single center and with a small number of patients.

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