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Original Article

# The Relationship Between Pain and Vitamin D in Parkinson's Disease

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## ABSTRACT

**Objective:** Pain is one of the most common non-motor symptoms in patients with Parkinson's disease, and sometimes the complaint of refractory pain adversely affects the quality of life. The relationship between vitamin D and many types of pain, especially musculoskeletal pain, has been emphasized in different studies.

**Methods:** The demographic data of 43 idiopathic Parkinson's patients who were above stage 3 according to the Hoehn and Yahr scale, with MMSE 25 and above, not diagnosed with dementia, and without any disease and drug use affecting the vitamin D level, the UPDRS motor subscale, the nonmotor symptom scale and the shortened geriatric depression scale, were recorded. The relationship between vitamin D level and pain was evaluated.

**Results:** Of the patients included in the study, 24 were male and 19 were female. The mean age of the patients was 61.9 (±9.84) years. The mean disease duration was 3.9 years; the mean UPDRS motor score was 18.3 (±7.6). According to the nonmotor symptom scale, the patients scored 10.2 (±5.3) out of 30. 60.5% of the patients had pain complaints. No significant relationship was found between pain and vitamin D level, age, disease duration, UPDRS, drug dose, nonmotor symptom score, GDS, ($p>0.05$). A significant difference was found between the levodopa doses of patients aged 60 years and younger, with and without pain ($p=0.04$). Patients with pain had higher levodopa doses than those without pain. A significant positive correlation was found between the presence of pain and UPDRS in patients over 60 years ($p=0.035$).

**Conclusion:** As a result of the study, no relationship was found between pain and vitamin D levels. In larger patient populations, it was considered to be important to examine the relationship between pain and Vitamin D levels by identifying pain subtypes.

## INTRODUCTION

Parkinson's disease (PD) is a prevalent neurodegenerative disease characterized by tremor, rigidity, bradykinesia, and postural instability.[1] Non-motor symptoms such as pain, dementia, sleep disorders, anxiety, and depression are common among Parkinson's patients.[2] Especially pain complaints comprise a condition that may emerge at any stage of the disease as a result of various causes, and that adversely affects the patient's quality of life.[3] The pain complaints of Parkinson's patients are mainly classified into two categories, namely PD-related pain and non-PD-related pain. While PD-related pain is further divided into the three subgroups as fluctuation-related pain, dyskinesia-induced pain, and central pain; non-PD-related pain is divided into the subgroups of pain related to the musculoskeletal system, peripheral pain or central neuropathic pain.[4,5] Various studies found a correlation between many pain types, particularly pain associated with the musculoskeletal system, and vitamin D levels.[6] It was demonstrated that vitamin D replacement could have favourable effects on pain complaints, especially in pain associated with the musculoskeletal system. It is believed that vitamin D deficiency may cause disruption in bone mineralization, proximal muscle weakness, and myopathy-induced pain.[7] Identifying whether there is a correlation between the pain complaints identified in Parkinson's patients and vitamin D levels will prove very important in planning the treatment of such patients, and clarifying the etiology of pain. In this study, it was planned to examine the correlation between pain complaints and vitamin D levels in Parkinson's patients.

## MATERIALS AND METHODS

43 patients followed up with the diagnosis of idiopathic PD in the movement disorders outpatient clinic between 2017 and 2018 were included in our study. Patients with obesi-

ty, chronic liver disease, chronic kidney insufficiency, diabetes, thyroid disease, bone fracture or using medication that affects the metabolism of vitamin D were excluded from the study. Moreover, patients with dementia having a Mini-Mental State Examination (MMSE) score of less than 24 and the patients who are over stage 3 according to the Hoehn-Yahr Scale[8] were excluded from the study. The study was planned as a cross-sectional-type descriptive study; all participants provided written informed consent and the study was approved by the local ethics committee (2017/514/104/8-28.03.2017).

The patients' demographic data including age, gender, and duration of disease were recorded, and they were asked if they had any pain complaints within the last month. Also, the Unified Parkinson's Disease Rating Scale (UPDRS) motor subscale, the non-motor symptom scale[9,10] and the geriatric depression scale (GDS) short form, the validity and reliability of the Turkish language-version of which was approved in 2003, were used on the patients, and patients scoring 5 and above were considered to have depression.[11] The levodopa-equivalent dose used by the patients was calculated.[12] The patients having pain complaints within the last month, and those with no pain complaints were compared.

The patients' vitamin D levels were measured using the Abbott Architect 25 OH Vitamin D test. This test is a competitive chemiluminescence microparticle immunoassay (CMIA). The method was standardized using NIST reference material. The LoQ of this method is 8.0 ng/ml for a concentration interval of 19.0–78.4 ng/ml, the intra-assay CVs are less than 3.7%, and the inter-assay CVs are less than 4.6%. The method is linear up to 165.5 ng/ml.

### Statistical method

SPSS 15.0 package software was used in evaluating the data. For significance, the p-value had to be below 0.05. In the study, mean and standard deviation (SD) values were given for the measurement values. The categorical variables (group, gender) were given as percentage values. To identify the difference between variables, the T-test was used when parametric requirements were met, the Mann-Whitney U test was used in independent groups when parametric requirements were not met, and the Chi-Square Test was used to compare the categorical variables.

## RESULTS

43 idiopathic Parkinson's patients meeting the criteria of the United Kingdom Parkinson's Disease Society Brain Bank (UKPDSBB)[13] clinical diagnostic scale were included in the study. Of the patients participating in the study, 24 were male and 19 female. The patients' mean age was 61.9±9.84 years. The mean vitamin D levels of the patients were found to be 20.5±18.4 ng/ml, and 30 patients had vitamin D levels of less than 20 ng/ml. The demographic and clinical data of the patients have been summarised in Table 1.

**Table 1.** Demographic and clinical data on Parkinson's patients

| n=43 | Mean |
|---|---|
| Age, mean±SD | 61.9 (±9.8) |
| Gender, n (%) | |
| Female | 24 (55.8%) |
| Male | 19 (44.2%) |
| Disease duration (years) ±SD | 4.0 (±3.5) |
| UPDRS motor score±SD | 18.3 (±7.6) |
| Levodopa-equivalent dose (mg) ±SD | 527.7 (±276.2) |
| Nonmotor symptom score±SD | 10.2 (±5.3) |
| Vitamin D level (ng/ml) ±SD | 20.5 (±18.9) |
| GDS score±SD | 4.9 (±3.6) |

UPDRS: Unified Parkinson's Disease Rating Scale (UPDRS); GDS: Geriatric Depression Scale; SD: Standard deviation.

The patients were asked whether they had complaints of pain that would affect their daily lives in the last month. 26 of the patients (60.5%) gave a positive response.

No significant correlation ($p<0.05$) was found between the categorical variable of the presence of pain and the measurement values that are age, disease duration, vitamin D level, UPDRS motor subscale score, levodopa-equivalent dose, nonmotor symptom score, and GDS score (Table 2).

Considering that pain complaints may be related to different etiologies in young and elderly patients, the patients were divided into two groups as young and elderly patients according to the WHO definition of elderly. When only patients aged 60 years and younger were taken into consideration, no correlation was found between the presence of pain and the demographic and clinical characteristics of the patients. Meanwhile, a significant difference was found in the presence of pain in the levodopa doses of the patient group under 60 years of age ($p=0.04$). The patients with pain had a higher levodopa dose than those without pain. In patients over 60, a significant difference was found between the presence of pain and the UPDRS motor subscale score, which constitutes the measurement values, and the level of pain was found to be higher in those with a higher UPDRS motor subscale score.

No significant difference was found between male and female patients in terms of severity of pain ($p=0.05$) (Table 3).

## DISCUSSION

Pain is an important non-motor symptom seen in almost half of all Parkinson's patients, and although the motor complaints of patients may sometimes respond to drug treatment, persistent pain complaints has an adverse impact on their quality of life.[14–16] In a study carried out in Turkish Parkinson's patients, the prevalence of pain was reported to be 64.9%.[17] In the literature, the prevalence of pain in PD varies between 40 to 85%.[18] In our study, 60,5% of the patients complained of pain.

**Table 2.** Difference between the presence of pain and clinical and demographic variables

| | Pain (+) (n=26) | Pain (-) (n=17) | p-value |
|---|---|---|---|
| Age | 62.61±10.59 | 60.82±8.77 | 0.62 |
| Disease duration (years) | 4.26±3.39 | 3.52 ±3.74 | 0.32 |
| Unified Parkinson's Disease Rating Scale motor score | 20.11±8.09 | 15.58±5.96 | 0.06 |
| Levodopa-equivalent dose (mg) | 574.69±284.42 | 460.12±257.63 | 0.14 |
| Nonmotor symptom score | 10.96±5.52 | 9.00±4.79 | 0.27 |
| Geriatric Depression Scale score | 5.84±3.83 | 3.52±2.71 | 0.056 |
| Vitamin D levels (ng/ml) | 20.11±18.79 | 21.12±19.73 | 0.69 |

**Table 3a.** Difference between the presence of pain and clinical variables in patients under 60 years of age

| | Pain (+) (n=17) | Pain (-) (n=7) | p-value |
|---|---|---|---|
| Age | 53.61±4.5 | 54±4.21 | 0.814 |
| Disease duration (years) | 3.34±2.74 | 2.66±2.54 | 0.563 |
| Unified Parkinson's Disease Rating Scale motor score | 18.92±8.25 | 17.33±5.26 | 0.640 |
| Levodopa-equivalent dose (mg) | 567±262.56 | 362.25±221.18 | 0.040* |
| Nonmotor symptom score | 10.61±5.56 | 7.55±4.71 | 0.228 |
| Geriatric Depression Scale score | 6.15±4.07 | 2.88±1.96 | 0.054 |
| Vitamin D levels (ng/ml) | 24.03±23.95 | 16.58±6.36 | 0.570 |

**Table 3b.** The difference between the presence of pain and clinical variables in patients over 60 years of age

| | Pain (+) (n=9) | Pain (-) (n=10) | p-value |
|---|---|---|---|
| Age | 71.61±6.18 | 68.50±5.34 | 0.229 |
| Disease duration (years) | 5.19±3.82 | 4.50±4.75 | 0.509 |
| Unified Parkinson's Disease Rating Scale motor score | 21.30±8.8 | 13.62±6.43 | 0.035* |
| Levodopa-equivalent dose (mg) | 580.61±310.67 | 558±267.24 | 0.717 |
| Nonmotor symptom score | 11.30±5.69 | 10.62±4.62 | 0.771 |
| Geriatric Depression Scale score | 5.53±3.71 | 4.25±3.37 | 0.421 |
| Vitamin D levels (ng/ml) | 16.18±11.35 | 28.49±26.96 | 0.261 |

Examining the pain complaints in patients with PD etiologically, the pain related to the musculoskeletal system is found to rbe in the first place.[16–18] The role of vitamin D deficiency in the musculoskeletal pain is controversial. [19] Vitamin D is common in the body; firstly, the vitamin D receptor and 1a-hydroxylase [the enzyme that converts 25 (OH) D to 1.25 (OH) 2 D3 that is activated through hydroxylation] are found in both the brain and in muscles in humans. Secondly, vitamin D has immunomodulating properties that reduce proinflammatory cytokines and increase anti-inflammatory cytokines. Thirdly, it has been suggested that vitamin D deficiency increases skeletal muscle hypersensitivity in severe pain complaints.[19] Since there are studies showing a significant decrease in the pain scores with vitamin D supplementation, especially in the treatment of musculoskeletal pain,[6] compared to placebo, we also aimed to investigate whether there was a relationship between vitamin D levels and pain complaints in Parkinson's patients.

Our study demonstrated that there was no correlation between pain and vitamin D levels. Although we were not able to compare our results due to the lack of studies examining the relationship between vitamin D levels and Parkinson's disease in the literature, we explained our results with the fact that the pain complaints observed in Parkinson's patients differed depending on peripheral and central causes.[19] For this reason, it is thought that studies investigating the correlation between pain and vitamin D levels by identifying the pain subtypes in larger patient groups would answer questions on this subject.

In a study investigating whether vitamin D levels have an impact on Parkinson's symptoms other than pain, it was demonstrated that vitamin D supplements had a favourable effect on motor symptoms. However, its effect on non-motor symptoms and pain was not examined.[20] Peterson et al.[21] reported a correlation between vitamin D levels, and balance and the severity of Parkinson's disease.

More detailed studies should be conducted on the clinical the features of Parkinson's disease and vitamin D levels. Considering that pain related to the musculoskeletal system may be seen more frequently in elderly patients and re-examining the pain complaints after the patients were grouped as under 60 years of age and above, the prevalence of pain complaint was found to be higher in the group under 60 years of age, especially in patients with a higher levodopa-equivalent dose, however, no correlation was found between vitamin D levels and pain complaints. It was also noted that complaints on depression was rather high in these patients. It was reported in the study carried out by Marsala et al.[22] that, UPDRS motor scores and levodopa-equivalent doses were higher in Parkinson's patients with pain complaints.

In the examinations conducted after the patients were grouped according to age, the fact that pain was found to be associated with the levodopa-equivalent dose in the group under 60 years of age and with the UPDRS motor score in the group over 60 years of age group was tried to be explained by the fact that patients with higher dopaminergic loss in Parkinson's disease, who require higher-dose treatment, have pain complaints, and that patients in the early stages of pain complaints have more resistant non-motor findings despite their lower UPDRS scores because they respond better to the drug.Pain is a non-motor finding from the early stages of Parkinson's disease; in a study conducted on 433 Parkinson's patients, it was determined that 21% of the patients had non-motor symptoms quite prominently in the prodromal period, and the most frequently observed non-motor symptom among these was pain.[23] According to the Braak hypothesis, due to rostrocaudal progression in Parkinson's disease,pathology occurs in the brain stem regions containing the locus ceruleus and the raphe nucleus at an earlier stage than in the substantia nigra.[24,25] A study revealed that 30% of Parkinson's patients with of pain responded to dopaminergic treatment.[26] At this point, it may also be considered that the pain complaint observed during the treatment of Parkinson's patients may be caused by the early involvement of pathways involving neurotransmitter systems other than dopaminergic pathways.

## CONCLUSION

No significant correlation was found between the pain complaints and vitamin D levels in the patient group examined in our study. The fact that pain complaints were related to the levodopa equivalent dose in the group under 60 years old in subgroup analyses suggested that pain is an important problem that occurs in the early stages in correlation with the severity of the disease and persists despite the high-dose medication therapy. The lack of pain subtyping in patients describing the pain in the study, the lack of quantitative pain scales developed 'when evaluating pain in Parkinson's patients, and the lack of detailed evaluation of pain characteristics, and a small patient group are the limitations of this study. In order to investigate the relationship between pain and vitamin D levels, it is recommended to conduct more comprehensive studies that separate patient groups according to their age and determine pain subtypes.

### Ethics Committee Approval

This study approved by the Kartal Dr. Lutfi Kirdar Training and Research Hospital Clinical Research Ethics Committee (Date: 28.03.2017, Decision No: 2017/514/104/8).

### Informed Consent

Retrospective study.

### Peer-review

Internally peer-reviewed.

### Authorship Contributions

Concept: İ.G.A., B.Ö.B., A.B., N.P., R.I.; Design: İ.G.A., B.Ö.B., A.B., N.P., R.I.; Supervision: İ.G.A., B.Ö.B., A.B., N.P., R.I.; Fundings: İ.G.A., B.Ö.B., A.B., N.P., R.I.; Materials: İ.G.A., B.Ö.B., A.B., N.P., R.I.; Data: İ.G.A., B.Ö.B., A.B., N.P., R.I.; Analysis: İ.G.A., B.Ö.B., A.B., N.P., R.I.; Literature search: İ.G.A., B.Ö.B., A.B., N.P., R.I.; Writing: İ.G.A., B.Ö.B., A.B., N.P., R.I.; Critical revision: İ.G.A., B.Ö.B., A.B., N.P., R.I.

### Conflict of Interest

None declared.

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## Parkinson Hastalığında Ağrı ve D Vitamini İlişkisi

**Amaç:** Parkinson hastalarında en sık görülen nonmotor semptomlardan biri ağrıdır ve bazen dirençli ağrı yakınması yaşam kalitesini olumsuz etkilemektedir. Özellikle kas iskelet sistemi ile ilgili ağrılar olmak üzere pek çok ağrı tipi ile D vitamini arasında ilişki olduğu farklı çalışmalarda vurgulanmıştır.

**Gereç ve Yöntem:** Hoehn-Yahr skalasına göre evre 3'ün üstünde olan, mini mental durum testi (MMSE) 25 ve üstünde olup demans tanısı olmayan, D vitamini düzeyini etkileyecek hastalığı ve ilaç kullanımı olmayan 43 idiyopatik Parkinson hastasının demografik verileri, Bileşik Parkinson Hastalığı Değerlendirme Ölçeği (BPHDÖ) (UPDRS) motor alt skalası, nonmotor semptom skalası ve kısaltılmış geriyatrik depresyon ölçeği (GDÖ) kaydedilerek D vitamini düzeyi ile ağrı yakınması arasındaki ilişki değerlendirilmiştir.

**Bulgular:** Çalışmaya katılan hastaların 24'ü erkek 19'u kadındır. Hastaların yaş ortalaması 61.9 (±9.84) olarak belirlenmiştir. Ortalama hastalık süresi 3.9 yıl; UPDRS motor skor ortalaması 18.3 (±7.6) bulunmuştur. Nonmotor semptom skalasına göre yapılan değerlendirmede hastalar 30 üzerinden 10.2 (±5.3) puan almışlardır. Hastaların %60.5'inde ağrı yakınması olduğu görülmüştür. Ağrı varlığı ile D vitamini düzeyi, yaş, hastalık süresi, UPDRS, ilaç dozu, nonmotor semptom skoru, GDÖ, arasında anlamlı ilişki ($p>0.05$) bulunamamıştır. İlaç dozu açısından 60 yaş ve altındaki hasta grubunda ağrısı olan ve olmayan hastaların levodopa dozları arasında anlamlı fark bulunmuştur ($p=0.04$). Ağrısı olanların levodopa dozları olmayanlara göre yüksek bulunmuştur. Altmış yaş üstündeki hastalarda ağrı varlığı ile UPDRS arasında anlamlı pozitif ilişki bulunmuştur ($p=0.035$).

**Sonuç:** Çalışmanın sonucunda ağrı ile D vitamini düzeyleri arasında ilişki tespit edilmedi. Daha büyük hasta gruplarında ağrı alt tiplerini belirleyerek ağrı ile D vitamini düzeyleri arasındaki ilişkinin incelenmesinin önemli olduğu düşünülmüştür.

**Anahtar Sözcükler:** Ağrı; D vitamini; Parkinson hastalığı.