

Different Pain Types at Coccygodynia and its Relation with Vitamin D Level.

Emel Güler *, Hanzade Aybuke Unal

Received: 15 February 2023 / Accepted: 6 March 2023 / Published online: 20 July 2023

This article is published with open access at <https://journal.astes.org.al>

© The author(s) 2023. © The Albanian Journal of Trauma and Emergency Surgery is an Open Access Journal. All articles are distributed under the terms of the Creative Commons Attribution Non-Commercial License: <http://creativecommons.org/licenses/by-nc> which permits unrestricted non-commercial use, distribution, and reproduction in any medium provided the original work is properly cited.

Abstract

Background: Coccygodynia is a musculoskeletal disease that affects quality of life. The main complaint of coccygodynia is nociceptive and/or neuropathic pain. Vitamin D deficiency has been associated with the development of pain in various diseases.

Aims: In this study we aimed investigate the pain types (nociceptive, neuropathic, mixed) and the relationship between pain types and Vitamin D level in patients with coccygodynia.

Study design: Observational study

Materials and Methods: A total of 54 patients diagnosed with coccygodynia were included. Pain intensity, disability and pain type were evaluated by Visual Analogue Scale (VAS), the Oswestry Disability Index (ODI), and the PainDETECT questionnaire, respectively. All participants had their vitamin D levels measured.

Results: Neuropathic pain was detected in 27.8% of the patients with coccygodynia. Vitamin D was determined to be insufficient or deficient in 81.5% of the patients. A statistical significant correlation was found between neuropathic pain and prolongation of coccygodynia and increased ODI values ($p < 0.05$). The Vitamin D values were determined to show statistically similar distribution in the nociceptive, mixed type, and neuropathic pain groups ($p = 0.532$).

Conclusion: The frequency of neuropathic pain in coccygodynia increases with increasing disability and disease duration. Although vitamin deficiency or insufficiency is common in coccygodynia, it is not associated with the type of pain.

Keywords: Neuropathic pain, Nociceptive pain, Coccyx, Vitamin D deficiency

Introduction

Coccygodynia is a painful clinical condition felt in the coccyx region (tailbone), which increases after a certain period of sitting or standing. [1, 2] The most common cause of coccygodynia is trauma but it may also emerge as idiopathic. [1]

DeAndres et al stated that the type of pain in coccygodynia could be somatic, neuropathic, or mixed type. [3] The chronic inflammatory process that develops following mechanical injury causes a change in the response of neurons over time. [4]

Repeated nociceptive inputs can trigger a long-term increase in synaptic activity and excitability of neurons in the central nociceptive pathways. Neuropathic pain symptoms develop in this condition. [5]

In recent years, Vitamin D has been shown to be responsible for the neurological, hormonal, and immunological effects in the formation of pain, and therefore has an important role in chronic pain. [6] Vitamin D deficiency has been associated with several musculoskeletal pain disorders and neuropathic pain syndromes. [7, 8]

To the best of our knowledge, there are no studies yet that have investigated the role of Vitamin D deficiency in coccygodynia.

Original article, no submission or publication in advance or in parallel

* **Corresponding author:**
Emel Güler MD
✉ dremelguler@gmail.com

Department of Physical Medicine and Rehabilitation, Division of Pain Medicine, Sivas Cumhuriyet University, Ankara, TURKEY

The objective of this study investigate the pain types (nociceptive, neuropathic, mixed), and the relationship between between pain types and vitamin D level in patients with coccygodynia.

Material and Methods

This prospective, cross-sectional study included patients diagnosed with coccygodynia who were consecutively admitted to a Sivas Cumhuriyet University Hospital Physical Medicine and Rehabilitation outpatient clinic between August and December 2021. The diagnosis of coccygodynia was made by a senior consultant based on a thorough medical history, clinical examination, and imaging procedures. Inclusion criteria were patient age in the range of 18- 70 years with coccygodynia, measurement of vitamin 25 (OH) D level and agreement to participate in the study. Exclusion criteria were defined as [1] presence of known polyneuropathy, [2] Diagnoses of diabetes mellitus, renal failure, thyroid disease that may lead to the development of neuropathic pain [3] taking vitamin D replacement therapy, [4] use of any medication that could affect neuropathic pain (such as duloxetine, pregabalin, gabapentin and tramadol), and [5] having received an injection or physical therapy for the treatment of coccygodynia in the last 3 months (Figure I).

A record was made for each patient of age, gender, body mass index (BMI), duration of symptoms, etiology of coccygodynia, pain severity, pain type. BMI was calculated as body weight (kg) divided by squared height (m²).

Serum 25-hydroxyvitamin (25-OHD) levels were measured by using a commercially available

chemiluminescence Immunoassay Kit. Patients were classified as having vitamin D deficiency with 25 (OH) D level of ≤ 20 ng/mL, vitamin D insufficiency with a level of 21–29 ng/ mL, or normal vitamin D with a level of ≥ 30 ng/ mL. [9]

The patients were assessed using a Visual Analogue Scale (VAS), the Oswestry Disability Index (ODI), and the PainDETECT questionnaire.

VAS: The intensity of pain of patients was assessed using the VAS pain score (0–10 cm, with higher scores indicating more pain). Patients' pain intensity at night, pain at rest and pain in active motion were questioned.

ODI: The ODI is used to determine functional level, and comprises 10 items measuring pain severity, personal care, rising from a seated position, walking, sitting, standing, social life, sleep, travel and the degree of pain. The maximum score is 50 points with higher total points indicating a higher level of disability. The total points are converted to a percentage value representing the disability percentage. Validity and reliability studies of the ODI in Turkish were conducted by *Yakut et al.* [10]

PainDETECT: This scale is used to evaluate the presence of nociceptive, neuropathic and mixed type pain. [11] A total score of <12 points is accepted as nociceptive pain with no presence of neuropathic pain. A total score of 13-18 points is indecisive and accepted as mixed type, in which there is a neuropathic component, and when the scores is ≥ 19 points, it is accepted that there is a neuropathic pain component. Validity and reliability studies of the questionnaire in Turkish were conducted by *Alkan et al.* [12]

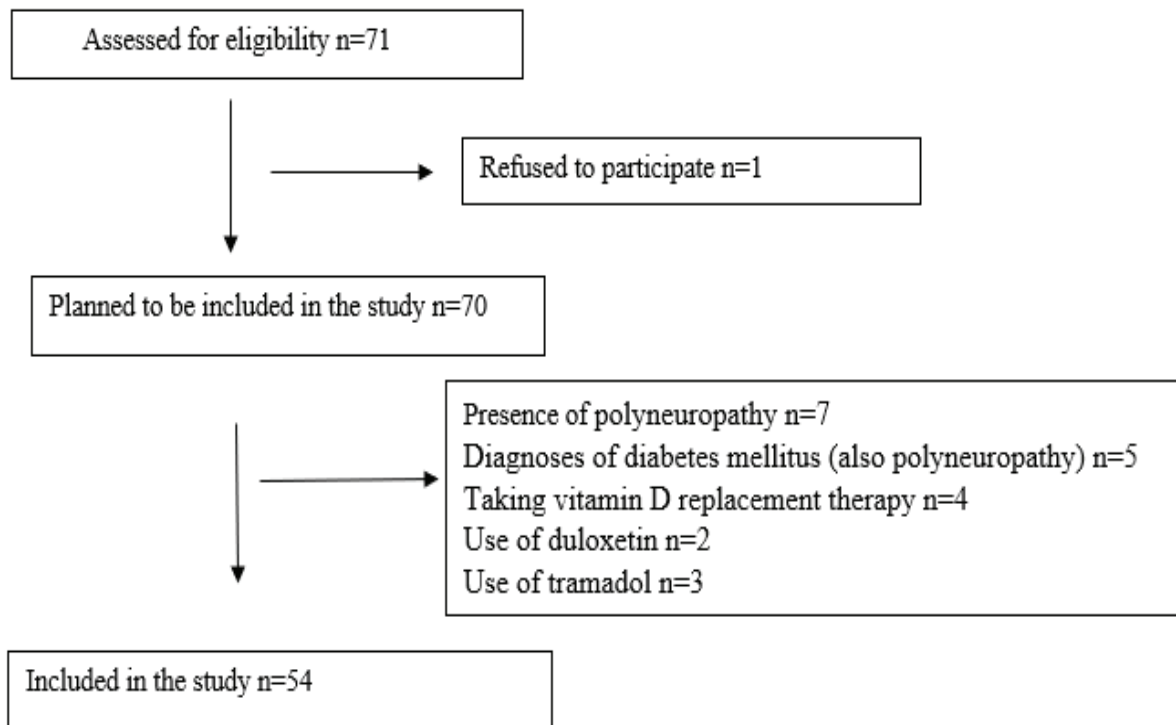


Figure I. Flow diagram of the treatment of coccygodynia

Statistical Analysis

Data obtained in the study were analyzed statistically using IBM SPSS Statistics Standard Concurrent User Vn. 26 software (IBM Corp., Armonk, NY, USA). Descriptive statistics were stated as number (n) and percentage (%) for categorical variables and as mean \pm standard deviation (SD), median, minimum and maximum, and interquartile range (IQR) values for continuous variables. The normal distribution of numerical variables was assessed with the *Shapiro Wilk test*. In the comparisons between the groups, One-Way Variance analysis was applied to variables with normal distribution and *Kruskal-Wallis analysis* was applied to variables not showing normal distribution. When a difference was found between groups as a result of *Kruskal-Wallis analysis*, the *Dunn-Bonferroni test* was used as a multiple comparison test. Relationships between categorical variables were compared with the Pearson Chi-square test exact method. When significance was determined in the Chi-square test, subgroup analyses were made with the *Bonferroni corrected Paired Ratio z test*.

A value of $p < 0.05$ was accepted as statistically significant.

Ethical Consideration

Study procedures were in accordance with the ethical standards of the responsible committee on human experimentation. The study was approved by Sivas Cumhuriyet University Ethics Committee. (2021-06/20) and Helsinki Declaration was taken into consideration. All participants underwent structured interviews and provided written informed consent to participate in this study.

Results

A total of 54 patients were included in the study. Table 1 shows the demographic and clinical characteristics of the patients. In all the patients, coccygodynia was determined as idiopathic or to have developed secondary to trauma. When classified according to BMI, 1 (1.9%) patient was classified as underweight (< 18.5), 10 (18.5%) as healthy weight (18.5-24.9), 24 (44.4%) as overweight (25-29.9), 15 (27.8%) as obese (30-39.9) and 4 (7.4%) as morbidly obese.

The median VAS values were determined as 4.0 (0.0-10.0) when active, 8.0 (4.0-10.0) at rest, and 5.0 (0.0-10.0) at night. The duration of sitting of the patients was determined to be mean 10.0 mins (range, 0-120 mins). According to the PainDETECT classification, neuropathic pain was determined in 15 (27.8%) patients and not in 24 (44.4%) patients. The type of pain was uncertain in 15 (27.8%) patients. The Vitamin D level was determined to be normal in 10 (18.5%) patients, insufficient in 11 (20.4%), and deficient in 33 (61.1%).

The relationships between the variables and the pain types according to the painDETECT scores are shown in

Female/male		47 (87.0)/7 (13.0)
Age, (years)		44.4 \pm 11.8
BMI, (kg/m ²)		29.05 \pm 5.56
Disease duration, (years)		12.8 \pm 11.4
VAS	Active	4.1 \pm 3.8
	Rest	8.1 \pm 1.7
	Night	4.1 \pm 3.7
Duration of sitting, (mins)		19.2 \pm 25.3
painDetect		14.7 \pm 6.7
ODI		42.5 \pm 18.3
25 (OH) D level (ng/mL)		20.51 \pm 13.04

Data presented as mean \pm standard deviation or number (%) BMI: Body mass index,

VAS: Visual Analogue Scale, ODI: Oswestry Disability Index

Table 1: Demographic and clinical characteristics of patients.

Table 2. No relationship was determined between age, BMI, gender, and the neuropathy status ($p=0.678$, $p=0.546$, $p=0.180$, respectively). A relationship was determined between the presence of neuropathic pain increasing the duration of coccygodynia and the ODI ($p < 0.05$). The VAS active values of patients with neuropathic pain were determined to be statistically significantly higher than those of patients with nociceptive pain and mixed type pain ($p < 0.05$). The relationship between neuropathic status and the VAS resting and VAS night values was not found to be statistically significant ($p=0.082$, $p=0.086$). The sitting duration of patients with neuropathic pain was determined to be significantly shorter ($p < 0.05$).

The Vitamin D values were determined to show statistically similar distribution in the nociceptive, mixed type, and neuropathic pain groups ($p=0.532$).

No statistically significant difference was found between the Vitamin D levels according to age, BMI, disease duration, VAS resting, VAS night, sitting duration and ODI values (Table 3).

The rate of Vitamin D insufficiency was found to be higher in male patients than in females.

Discussion

In this study, there was determined to be neuropathic pain in 27.8% of the patients with coccygodynia. Neuropathic pain was seen to be associated with increasing disability, disease duration, pain severity with activity, and shortened sitting duration. In 81.5% of the coccygodynia patients, 25 (OH) D vitamin was determined to be insufficient or deficient. Vitamin D insufficiency and deficiency were not correlated with pain type,

		Pain types			<i>p</i>
		Nociceptive (score ≤ 12)	Neuropathic (score ≥ 19)	Unclear (score 13-18)	
Female, <i>n</i> (%)*		19 (40.4)	15 (31.9)	13 (27.7)	0.180
Male, <i>n</i> (%)*		5 (71.4)	0 (0.0)	2 (28.6)	
Age, years, mean ± <i>sd</i>		46.1±12.3	43.7±12.4	42.7±11.1	0.678
BMI, kg/m² mean ± <i>sd</i>		29.72±5.27	29.28±5.87	27.72±5.83	0.546
Disease duration, <i>M</i>(<i>IQR</i>)		6.5 (8.5) ^a	20.0 (18.0) ^b	9,0 (14.0) ^{ab}	0.036
VAS <i>M</i> (<i>IQR</i>)	Active	8.0 (4.0) ^b	0,0 (5,0) ^a	8.0 (4.0) ^b	0.008
	Rest	9.0 (2.0)	9.0 (2.0)	9.0 (2.0)	0.082
	Night	6.0 (4.0)	0,0 (6.0)	6.0 (4.0)	0.086
Duration of sitting, <i>M</i> (<i>IQR</i>)		15.0 (20.0) ^a	5.0 (10.0) ^b	7.5 (9.0) ^b	0.010
ODI(%), <i>M</i> (<i>IQR</i>)		31.5 (28.8) ^a	60.0 (18.0) ^b	40.0 (23.0) ^{ab}	0.001
25 (OH) D, (ng/mL), <i>M</i> (<i>IQR</i>)		16.85 (13.20)	19.40 (23.90)	13.20 (17.6)	0.549
Vitamin D classification					
Deficiency		15 (62.5)	8 (53.3)	10 (66.7)	0.532
Insufficiency		6 (25.0)	2 (13.3)	3 (20.0)	
Normal		3 (12.5)	5 (33.3)	2 (13.3)	

sd: Standard deviation, *M*: Median, *IQR*: Interquartile range, ^a, ^b show differences between groups. Groups with the same letters are statistically similar.

BMI: Body mass index, VAS: Visual Analogue Scale, ODI: Oswestry Disability Index

Table 2: Comparison of patients with neuropathy status according to numeric variables

In the current study, females were predominant and more than half of the patients in the sample were obese. BMI is an important factor, and obesity is 3-fold more widespread in patients with coccygodynia than in the normal population. [13] Female dominance is connected to the more posterior localisation of the sacrum and coccyx in females, and being more exposed to trauma during childbirth. [3]

Neuropathic pain is defined by the IASP as pain related to a lesion of the somatosensory system or disease. [14]

Pain in coccygodynia develops from the nerve roots, plexus, and peripheral nerves associated with the coccyx, contractions of the muscles holding the tailbone, and injury

with tissue inflammation around the coccyx and coccygeal joints. [15]

The pathophysiology of pain in coccydynia is similar to that in musculoskeletal diseases. Although nociceptive pain is primarily seen in musculoskeletal diseases, it has been determined to be accompanied by neuropathic pain in recent years. [16]

In a study in which the LANSS neuropathic pain questionnaire was applied to patients with chronic musculoskeletal pain, neuropathic pain was determined in 13%. [17]

Peripheral sensitisation probably develops in

		25 (OH) D level			p
		deficiency	Insufficiency (21-29)	Normal (s ≥ 30)	
Female, n (%)*		30 (63.8)	7 (14.9) ^x	15 (31.9)	0.036
Male, n (%)*		3 (42.9)	4 (57.1) ^y	0 (0.0)	
Age, years, mean ± sd		42.3±12.4	48.1±12.9	47.4±6.9	0.271
BMI, kg/m² mean ± sd		29.9±5.6	28.3±2.5	26.8±7.2	0.285
Disease duration, M(IQR)		11.0 (20.0)	6.0 (6.0)	15.0 (18.0)	0.611
VAS M (IQR)	Active	4.0 (7.5)	3.0 (9.0)	4.5 (9.3)	0.718
	Rest	8.0 (3.0)	9.0 (3.0)	8.0 (3.3)	0.978
	Night	5.0 (7.0)	5.0 (6.0)	5.5 (8.3)	0.949
Duration of sitting, M (IQR)		10.0 (10.0)	10.0 (28.5)	12.5 (10.0)	0.572
ODI (%), M (IQR)		40.0 (22.5)	44.0 (38.0)	51.0 (44.0)	0.808

sd: Standard deviation, M: Median, IQR: Interquartile range; ^x, ^y: shows the statistical difference between female and men

BMI: Body mass index, VAS: Visual Analogue Scale, ODI: Oswestry Disability Index

Table 3: Comparison of patients by Vitamin D Level according to numeric variables

coccygodynia with continuous nociceptive stimulation originating from the coccyx and the muscles and joint holding the coccyx. Continuous nociceptor activation causes an increase in afferent stimuli of the dorsal horn of the spinal cord.

This process induces structural and functional changes throughout the spinal cord and more rostral structures, respectively, and ultimately leads to central sensitisation. [18]

As a result of peripheral and central sensitisation, neuropathic pain components are seen. [18, 19]

The frequency of neuropathic pain was 27.8% in our study. The ganglion impar that formed with the termination of the sympathetic chains in the sacral region is thought to have a role in the development of neuropathic pain in coccygodynia. [2, 3]

Sençan et al [4] reported that sympathetic hyperactivity was caused by chronic irritation of the coccygeal nerve associated with biomechanical changes of the coccyx, and the neuropathic pain in coccygodynia was reduced with ganglion impar block.

They reported that neuropathic pain was determined

with the LANSS questionnaire in 29 of 33 patients with coccygodynia. However, as the patient population in that study comprised cases who had not responded to conservative treatment and it was reported that this may not reflect the true incidence of neuropathic pain. [4]

The higher frequency of neuropathic pain in our study may be due to the fact that the patients did not respond to conservative treatment.

In recent studies, Vitamin D deficiency has been determined to be associated with the etiology of several different chronic painful conditions. [19] Although Vitamin D has been found to be lower in females in various musculoskeletal pain conditions, in the current study a higher rate of Vitamin D deficiency was determined in males. [20, 21]

The relationship between Vitamin D deficiency and symptom severity in chronic pain was determined by *von Kanel et al.* [22] However, the results of the current study showed no relationship between Vitamin D deficiency and pain severity and disability.

In experimental studies, cholecalciferol supplementation with created mononeuropathy was

determined to reduce mechanical hyperalgesia and cold allodynia. [8]

In another study of a rat model with neuropathic pain, cold allodynia and heat hyperalgesia were determined to be reduced with the application of Vitamin D3. [23] In the current study, no relationship was determined between Vitamin D deficiency and neuropathic pain in patients with coccygodynia.

Conclusion

In conclusion, nociceptive and neuropathic pain are seen in coccygodynia. The results of this study demonstrated that the presence of neuropathic pain is associated with disability, pain duration, pain severity with activity, and shortened sitting time in coccygodynia, but is not associated with the Vitamin D level. According to the data obtained in this study, the importance of the type of pain and independent evaluation of the Vitamin D level will be of guidance in providing the necessary medical treatments.

Acknowledgements

None

Conflict of Interest

The authors declare have no conflict of interest. This research received no specific grant.

Author contribution to the study

E. G (concept, design, supervision, resource, materials, data collection and/or processing, analysis and/or interpretation, literature search, writing, and critical reviewing).

H.A.Ü (literature search, writing)

References

- Patijn J, Janssen M, Hayek S, Mekhail N, Van Zundert J, van Kleef M. 14. Coccygodynia. *Pain Pract.* 2010; 10 (6): 554-9. doi: [10.1111/j.1533-2500.2010.00404.x](https://doi.org/10.1111/j.1533-2500.2010.00404.x)
- Sir E, Eksert S. Comparison of block and pulsed radiofrequency of the ganglion impar in coccygodynia. *Turk J Med Sci.* 2019; 49 (5): 1555-9. doi: [10.3906/sag-1906-51](https://doi.org/10.3906/sag-1906-51)
- De Andres J, Chaves S. Coccygodynia: a proposal for an algorithm for treatment. *J Pain.* 2003; 4 (5): 257-66. doi: [10.1016/s1526-5900\(03\)00620-5](https://doi.org/10.1016/s1526-5900(03)00620-5)
- Sencan S, Kenis-Coskun O, Demir FGU, Cuce I, Ercalik T, Gunduz OH. Ganglion Impar block improves neuropathic pain in coccygodynia: A preliminary report. *Neurol Neurochir Pol.* 2018; 52 (5): 612-7. doi: [10.1016/j.pjnns.2018.08.006](https://doi.org/10.1016/j.pjnns.2018.08.006)
- Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain.* 2011; 152 (3 Suppl): S2-S15. doi: [10.1016/j.pain.2010.09.030](https://doi.org/10.1016/j.pain.2010.09.030)
- Yesil H, Sungur U, Akdeniz S, Gurer G, Yalcin B, Dundar U. Association between serum vitamin D levels and neuropathic pain in rheumatoid arthritis patients: A cross-sectional study. *Int J Rheum Dis.* 2018; 21 (2): 431-9. doi: [10.1111/1756-185X.13160](https://doi.org/10.1111/1756-185X.13160)
- Knutsen KV, Madar AA, Brekke M, Meyer HE, Natvig B, Mdala I, et al. Effect of vitamin D on musculoskeletal pain and headache: A randomized, double-blind, placebo-controlled trial among adult ethnic minorities in Norway. *Pain.* 2014; 155 (12): 2591-8. doi: [10.1016/j.pain.2014.09.024](https://doi.org/10.1016/j.pain.2014.09.024)
- Poisbeau P, Aouad M, Gazzo G, Lacaud A, Kemmel V, Landel V, et al. Cholecalciferol (Vitamin D3) Reduces Rat Neuropathic Pain by Modulating Opioid Signaling. *Mol Neurobiol.* 2019; 56 (10): 7208-2. doi: [10.1007/s12035-019-1582-6](https://doi.org/10.1007/s12035-019-1582-6)
- Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2011; 96 (7): 1911-30. doi: [10.1210/jc.2011-0385](https://doi.org/10.1210/jc.2011-0385)
- Yakut E, Duger T, Oksuz C, Yorukan S, Ureten K, Turan D, et al. Validation of the Turkish version of the Oswestry Disability Index for patients with low back pain. *Spine (Phila Pa 1976).* 2004; 29 (5): 581-5; discussion 5. doi: [10.1097/01.brs.0000113869.13209.03](https://doi.org/10.1097/01.brs.0000113869.13209.03)
- Freyhagen R, Baron R, Gockel U, Tolle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin.* 2006; 22 (10): 1911-20. doi: [10.1185/030079906X132488](https://doi.org/10.1185/030079906X132488)
- Alkan H, Ardic F, Erdogan C, Sahin F, Sarsan A, Findikoglu G. Turkish version of the painDETECT questionnaire in the assessment of neuropathic pain: a validity and reliability study. *Pain Med.* 2013; 14 (12): 1933-43. doi: [10.1111/pme.12222](https://doi.org/10.1111/pme.12222)
- Patel R, Appannagari A, Whang PG. Coccydynia. *Curr Rev Musculoskelet Med.* 2008; 1 (3-4): 223-6. doi: [10.1007/s12178-008-9028-1](https://doi.org/10.1007/s12178-008-9028-1)
- IASP I, International Association for the Study of Pain (IASP) Taxonomy. <http://www.iasp-pain.org> Taxonomy; 2012. (Accessed on 7.1.2022)
- Nathan ST, Fisher BE, Roberts CS. Coccydynia: a review of pathoanatomy, aetiology, treatment and outcome. *J Bone Joint Surg Br.* 2010; 92 (12): 1622-7. doi: [10.1302/0301-620X.92B12.25486](https://doi.org/10.1302/0301-620X.92B12.25486)
- Trouvin AP, Perrot S. Pain in osteoarthritis. Implications for optimal management. *Joint Bone Spine.* 2018; 85 (4): 429-34. doi: [10.1016/j.jbspin.2017.08.002](https://doi.org/10.1016/j.jbspin.2017.08.002)
- Giske L, Bautz-Holter E, Sandvik L, Roe C. Relationship between pain and neuropathic symptoms in chronic musculoskeletal pain. *Pain Med.* 2009; 10 (5): 910-7. doi: [10.1111/j.1526-4637.2009.00622.x](https://doi.org/10.1111/j.1526-4637.2009.00622.x)
- Levesque A, Riant T, Ploteau S, Rigaud J, Labat JJ, Convergences PPN. Clinical Criteria of Central Sensitization in Chronic Pelvic and Perineal Pain (Convergences PP Criteria): Elaboration of a Clinical Evaluation Tool Based on Formal Expert Consensus. *Pain Med.* 2018; 19 (10): 2009-15. doi: [10.1093/pm/pny030](https://doi.org/10.1093/pm/pny030)
- Baron R. Peripheral neuropathic pain: from mechanisms to symptoms. *Clin J Pain.* 2000; 16 (2 Suppl): S12-20. doi: [10.1097/00002508-200006001-00004](https://doi.org/10.1097/00002508-200006001-00004)

19. de Oliveira DL, Hirotsu C, Tufik S, Andersen ML. The interfaces between vitamin D, sleep and pain. *J Endocrinol.* 2017; 234 (1): R23-R36. doi: [10.1530/JOE-16-0514](https://doi.org/10.1530/JOE-16-0514)
20. Knutsen KV, Brekke M, Gjelstad S, Lagerlov P. Vitamin D status in patients with musculoskeletal pain, fatigue and headache: a cross-sectional descriptive study in a multi-ethnic general practice in Norway. *Scand J Prim Health Care.* 2010; 28 (3): 166-71. doi: [10.3109/02813432.2010.505407](https://doi.org/10.3109/02813432.2010.505407)
21. Çidem M, Kara S, Sarı H, Özkaya M, Karacan İ. Yaygın kas-iskelet ağrısı olan hastalarda D vitamini eksikliği prevalansı ve risk faktörleri. *Journal of Clinical & Experimental Investigations.* 2013; 4 (4): 488-91. doi: [10.5799/ahinjs.01.2013.04.0330](https://doi.org/10.5799/ahinjs.01.2013.04.0330)
22. von Kanel R, Muller-Hartmannsgruber V, Kokinogenis G, Egloff N. Vitamin D and central hypersensitivity in patients with chronic pain. *Pain Med.* 2014; 15 (9): 1609-18. doi: [10.1111/pme.12454](https://doi.org/10.1111/pme.12454)
23. Banafshe HR, Khoshnoud MJ, Abed A, Saghazadeh M, Mesdaghinia A. Vitamin D supplementation attenuates the behavioral scores of neuropathic pain in rats. *Nutr Neurosci.* 2019; 22 (10): 700-5. doi: [10.1080/1028415X.2018.1435485](https://doi.org/10.1080/1028415X.2018.1435485)