The relationship between hand injuries due to occupational accidents and Vitamin D deficiency

Ali Sağlık, Tufan Akın Giray, Tarık Ocak

Istinye Universitesi, Emergency Medicine, Istanbul, İstanbul.

Abstract

Background: Bone fractures due to occupational accidents cause labor and cost losses in the world. Vitamin D deficiency is common in the world including industrialized countries. This study aimed to investigate the relationship between fracture and vitamin D levels in patients with wrist fractures due to occupational accidents.

Methods: This study was conducted in a study group consisting of patients who were admitted to the emergency department of a university hospital due to occupational accidents and were thought to have a fracture of the hand or wrist. Blood samples were analyzed biochemically and vitamin D levels were obtained.

Results: Vitamin D3 level was 16.3 ng/mL in patients with fractures and 21 ng/mL in patients without fractures, which was statistically significant (p<0.05). Vitamin D deficiency was found in %60.2 of patients with fractures, while vitamin D deficiency was found in %50.2 of patients with fractures and there was no statistical difference (p>0.112). Vitamin D deficiency was found in %39.8 of patients with hand injury without fracture, whereas vitamin D deficiency was not detected in %33 of patients with hand injury and the comparison was statistically significant (p<0.05)

Conclusion: There is insufficient data in the literature on the relationship between bone fractures and vitamin D levels and the vitamin D levels required to prevent bone fractures. In this study, a statistically significant difference was found between the vitamin D levels of patients with fractures and those of patients without fractures. This study is beneficial for the literature in this respect, but extensive studies on the relationship between vitamin D and fractures are needed.

Keywords: Hand injuries; hand fractures; occupational accidents; vitamin D

DOI: https://dx.doi.org/10.4314/ahs.v25i2.24

Cite as: Sağlık A, Giray TA, Ocak T. The relationship between hand injuries due to occupational accidents and Vitamin D deficiency. Afri Health Sci. 2025;25(2). 186-194. https://dx.doi.org/10.4314/ahs.v25i2.24

Introduction

The importance of occupational health and safety is rapidly increasing both in the world and in our country. Bone fractures are an important type of injuries caused by occupational accidents. Bone fractures occur when the human body is exposed to a high level of force. Unfortunately, it leads to labor and cost losses all over the world and in our country¹. Vitamin D maintains PTH levels at physiologically healthy levels, increases osteoblastic activity, and promotes bone mineralization, which in turn significantly reduces the risk of falls and fractures². There is evidence that patients with vitamin 25(OH)D3 levels

Corresponding author:

Tarık Ocak,

Istinye Universitesi, Emergency Medicine, Istanbul, İstanbul.

Email: drtarik1977@gmail.com

>30 ng/mL have a lower risk of fracture³. Vitamin D deficiency is now recognized as a global epidemic. Vitamin D deficiency and 20.7% of vitamin D insufficiency were found⁴.

This study aimed to obtain sociodemographic data on patients with wrist fractures due to occupational accidents and to investigate the relationship between characteristics and vitamin D levels.

Methods

This prospective study was conducted in the emergency department of a university hospital in the metropolitan area of Istanbul with approximately 43000 emergency patient admissions per year. Informed consent was obtained from all participants, and the study was monitored by the local ethical committee. The study group consisted of patients who presented to the emergency department for the first time as an occupational accident during



© 2025 Sağlık A et al. Licensee African Health Sciences. This is an Open Access article distributed under the terms of the Creative commons Attribution License (https://creative-commons.org/licenses/BY/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

the 3-year (2019-2021) study period and were thought to have a fracture of the hand and wrist by the emergency physician. Patients with multiple traumas, patients who refused to participate in the study, patients with sharps injuries, amputations, and burns, and patients younger than 16 years of age were excluded.

Many similar studies have been conducted to define vitamin D deficiency and insufficiency and to determine the normal range of 25(OH)D3 vitamin levels³. In the light of these studies, vitamin D deficiency was accepted if the 25(OH)D3 vitamin level was lower than 20 ng/mL, vitamin D insufficiency if the level was between 21 and 29 ng/mL, and adequate if the level was higher than 30 ng/mL³. Blood samples from the patients were transported to the hospital laboratory under appropriate conditions without waiting and the results were obtained by luminescence immunoassay on an Abbott Architect Autoanalyzer (GMI, Ramsey, USA) (reference values 30-80 ng/mL, deficiency <20 ng/mL).

Statistical Analysis

The study data were analyzed with MedCalc® Statistical Software version 22.006 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2023). Numeric data

were expressed as a median and interquartile ratio (IQR) and frequent variables as rates. Comparison of two independent groups with numeric data was performed by Mann Whitney U test, and the Chi-square test was used for categorical data. The normality analysis was conducted by the Kolmogorov-Smirnov test.

All the hypotheses were constructed as two-tailed and an alpha critical value of 0.05 was accepted as significant.

Results

The mean age of the 1168 patients who met the inclusion criteria was 38 years (min 16-max 77), 108 of them were female and 1060 of them were male, out of 3521 occupational accident cases admitted to our emergency department with hand injuries. Among the patients, 341 (29.2%) were smokers and the rest (N:827) were non-smokers. Among the patients who presented with hand injuries after occupational accidents, the most common type of occupational accident was cutting/piercing type injuries (N:1335). (Figure 1) Among these patients, the number of metal-machinery workers was 565, woodworkers 233, service personnel 125, textile workers 108, construction workers 74, and other workers 63. When the mechanisms of injury were analyzed, crush-type injuries were found to be the most common (N:883). (Table 1)

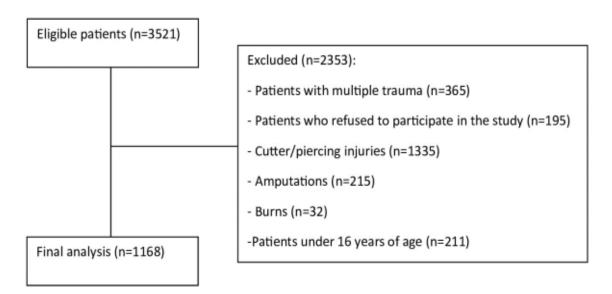


Figure 1: Patient flow chart

Table 1: Demographic variables of study patients

| Variable | N (%) | |
|-----------------------------------|---------------|--|
| Age, | | |
| Median (IQR) | 38 (29 to 45) | |
| M in-max | 16-77 | |
| Gender | | |
| Female | 108 (9.2) | |
| Male | 1060 (90.8) | |
| Smoking | | |
| Yes | 341 (29.2) | |
| No | 827 (70.8) | |
| Sectors of industry | | |
| M etal-machinery | 565 (48.4) | |
| Wood-furniture | 233 (19.9) | |
| Services | 125 (10.7) | |
| Textile | 108 (9.2) | |
| Construction | 74 (6.3) | |
| Other | 63 (5.4) | |
| Mechanisms of injury | | |
| Crush Injuries | 883 (75.6) | |
| Falls | 198 (17.0) | |
| Sprains | 39 (3.3) | |
| Involving more than one mechanism | 48 (4.1) | |

Abbreviations: IQR: interquartile range

In this study, the median 25(OH)D3 levels of women were 20.9 (IQR: 11.4-25.5) ng/mL and 18.7 (IQR: 11.5-25.5) ng/mL in men. 25(OH)D3 levels of the study patients are given in Table 2. The mean 25(OH)D3 levels of

all patients was 18.7 (IQR: 11.5-25.5) and 25(OH)D3 insufficiency was found in 86.9% (N:1015) of the patients, while 25(OH)D3 deficiency was found in 54.3% (N:634) of all patients.

Table 2: 25(OH)D3 levels of study patients

| Variable | N (%) | | |
|--------------------------|---------------------|--|--|
| Vitamin D3, median (IQR) | 18.7 (11.5 to 25.5) | | |
| Gender, median (IQR) | | | |
| Female | 20.9 (11.4-25.5) | | |
| Male | 18.7 (11.5-25.5) | | |
| Vit D insufficiency* | | | |
| Yes | 1015 (86.9) | | |
| No | 153 (13.1) | | |
| Vit D deficiency** | | | |
| Yes | 634 (54.3) | | |
| No | 534 (45.7) | | |

Abbreviations: IQR: interquartile range

Fractures were detected in 693 patients, of which 109 patients had forearm fractures, 12 patients had carpal bone fractures, 97 patients had metacarpal fractures, 422 patients had phalanx fractures and the remaining 53 patients had multiple fractures. Right-sided injuries (N:700) were frequently observed in the admitted patients, while left-sided injuries were observed in 450 patients and bi-

lateral injuries were observed in 18 patients. When finger injuries were analyzed, it was found that the second finger was the most common injury followed by the third finger. In cases with more than one finger injury, the 3rd and 4th finger injuries were frequently associated. While conservative treatment was generally applied to the injured patients, 43.1% (N:503) of the applicants underwent surgical procedures. (Table 3)

^{*}Vitamin D levels <30 ng/mL

^{**}Vitamin D levels <20 ng/mL

Table 3: Descriptive data of fractures identified in the study patients

| Variable | N (%) | | |
|---|------------------|--|--|
| Fracture | | | |
| Yes | 693 (59.3) | | |
| No | 475 (40.7) | | |
| Fractured Bone | | | |
| Forearm | 109 (15.7) | | |
| Carpal bones | 12 (1.7) | | |
| Metacarpus | 97 (14.1) | | |
| Phalanx | 422 (60.9) | | |
| More than one site Injury Site | 53 (7.6) | | |
| | 2 00 (50) | | |
| Right Site | 700 (60) | | |
| Left Site | 450 (38.5) | | |
| Bilateral Fracture Phalanx | 18 (1.5) | | |
| | | | |
| 1 st Phalanx | 67 (11.7) | | |
| 2 nd Phalanx | 118 (20.6) | | |
| 3 rd Phalanx | 113 (19.8) | | |
| 4 th Phalanx | 82 (14.3) | | |
| 5 th Phalanx | 87 (15.2) | | |
| 1 st and 2 nd Phalanx | 5 (0.9) | | |
| 1 st and 3 st Phalanx | 3 (0.5) | | |
| 2 nd and 3 nd Phalanx | 36 (6.3) | | |
| 3 rd and 4 th Phalanx | 32 (5.6) | | |
| 4 th and 5 th Phalanx | 17 (3) | | |
| 2 nd , 3 nd and 4 th Phalanx | 3 (0.5) | | |
| 3 rd , 4 th and 5 th Phalanx | 9 (1.6) | | |
| Treatment | | | |
| Conservative | 665 (56.9) | | |
| Surgical treatment | 503 (43.1) | | |

Vitamin D3 level was 16.3 ng/mL in patients with fractures and 21 ng/mL in patients without fractures, which was statistically significant (p<0.05). Vitamin D3 deficiency was found in 60.2% of the patients with fractures, while vitamin D3 deficiency was found in 50.2% of pa-

tients with no fractures and no statistically significant differences were found (p>0.112). Vitamin D3 insufficiency was found in 39.8% of patients with hand injury without fracture, whereas 33% did not have vitamin D3 deficiency and the comparison was significant (p<0.05). (Table 4) (Figure 2)

Table 4: Comparison of Vitamin D3 levels of study patients with and without fractures

| Variable | Patients with Fractures | Patients without Fractures | P Value |
|---|-------------------------|----------------------------------|------------|
| Vitamin D3 levels (ng/mL) | 16.3 (10.8 to 25.5) | 21 (20.1 to 21.7) | <0,00 |
| Vitamin D3 Insufficiency (<30 ng/mL), N (%) | | | |
| No | 82 (53.6) | 71 (46.4) | 0.112 |
| Yes | 611 (60.2) | 404 (39.8) | |
| Vit D3 Deficiency (<20 ng/mL), N (%) | | | |
| No | 268 (50.2) | 266 (49.8) | |
| Yes | 425 (67) | 209 (33) | |

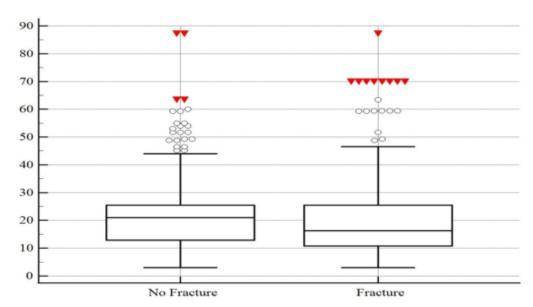


Figure 2: Vitamin D3 levels (ng/mL) of study patients with and without fracture

Discussion

The hand is recognized as the most utilized anatomical structure in the body, primarily due to its multifaceted capabilities, yet it is simultaneously highly prone to injuries. This vulnerability stems from its intricate anatomical composition, which includes 20 muscles, 27 bones, an extensive network of tendons, blood vessels, and nerves. A predominant factor contributing to hand injuries is in-

cidents occurring in occupational and sports settings^{5,6}. Data from a United States study indicates that 35.1% of workers experience job-related injuries annually, with approximately one million of these being hand-related injuries^{5,7-9}. The frequency of occupational traumatic hand injuries varies across different industries, with reported rates ranging from 4 to 11 injuries per 100 workers per year¹⁰. Notably, hand and finger injuries are the most

prevalent type of occupational injury recorded in emergency departments, constituting about 15% of total injuries. These injuries can range from minor lacerations and sprains to severe conditions resulting in disability or amputation^{11,12}.

The most frequently reported injuries treated in emergency settings are traumas involving the upper extremities, particularly the fingers and hands¹². Among these, hand fractures are the most common, occurring three times more often than distal radius fractures; globally, fractures of the hand, specifically metacarpal and phalanx fractures are the most widely occurring fracture types¹³. Work-related fractures have a notable incidence in the phalanges (15%), followed by foot bones (9%) and carpal bones (8%)^{12,14}. In our analysis, fractures were observed in 60.9% of cases within the phalanges, 15.7% in the forearm, 14.1% in the metacarpals, and 1.7% in the carpal bone, with 7.6% exhibiting fractures at multiple sites. Furthermore, research in Wasit Governorate corroborated the phalanges as the predominant fracture site¹⁵. Metacarpal fractures represent approximately 18-44% of all hand fractures recorded in the literature¹⁶. Studies conducted by Tayal et al. and Ghiya et al. revealed that 32% and 26% of hand fractures were attributed to phalanx injuries, while metacarpal injuries accounted for 68% and 74%, respectively^{11,17}. These findings underscore the variability in fracture incidence depending on the research context.

Vitamin D plays a critical role in maintaining calcium homeostasis and regulating skeletal health, primarily synthesized through skin exposure to sunlight or through dietary intake4. The metabolite 25(OH)D3 is employed as a standard marker for evaluating an individual's vitamin D status, with established thresholds categorizing levels <20 ng/mL as deficient, 21-29 ng/mL as insufficient, and >30 ng/mL as adequate³. Canadian studies have reported that 30-50% of individuals exhibit vitamin D deficiency, and similarly, data from 2001-2006 indicated that 33% of the US population was affected by this condition 18,19,20. Moreover, investigations into populations in India, Africa, Australia, Brazil, and Saudi Arabia have found significant vitamin D deficiency rates across adults and children alike^{3,21-25}. A systematic review encompassing 71 global studies identified occupational exposure as a significant determinant of vitamin D status, highlighting that indi-

viduals working indoors have a heightened risk of developing hypovitaminosis D compared to their outdoor counterparts²⁶. Further research demonstrated markedly lower serum vitamin D levels among shift workers in contrast to non-shift workers, with a particular study in Italy reporting levels of 16.3 ng/mL for shift workers versus 21.9 ng/mL for those working standard hours^{27,28}. In our analysis, despite the lack of regional studies linking vitamin D levels to occupational hand fractures, Uçar et al. reported that among adults presenting with non-specific complaints in Ankara, a significant proportion exhibited vitamin D deficiency (51.8%) and insufficiency (20.7%)4. Vitamin D levels are influenced by geographical location, lifestyle choices, dietary preferences, gender, and genetic predispositions. Collectively, this data indicates a widespread occurrence of vitamin D deficiency and insufficiency across diverse populations and age groups.

Globally, it is estimated that about one billion individuals experience insufficient or deficient levels of vitamin D²⁴. In our study population, the median 25(OH)D3 levels were documented at 20.9 ng/mL for women and 18.7 ng/mL for men, with an overall mean of 18.7 ng/mL. A concerning 86.9% and 54.3% of participants demonstrated vitamin D deficiency and insufficiency, respectively, findings that are consistent with existing literature. An analysis of vitamin D levels in those with fractures revealed an average of 16.3 ng/mL compared to 21 ng/mL in non-fractured counterparts, a difference deemed statistically significant.

Vitamin D deficiency predisposes individuals to secondary hyperparathyroidism, prompting increased bone resorption, thereby amplifying fracture risk⁴. In adults, insufficient 25(OH)D3 levels can lead to impaired mineralization of the collagen matrix, weakening structural integrity and elevating the fracture risk. However, the requisite vitamin D concentration for fracture prevention remains indeterminate²⁹. Research evaluating the impact of vitamin D supplementation on fracture susceptibility reveals mixed outcomes, with some reports indicating significant reductions in fracture incidence, while others do not. Notably, a meta-analysis encompassing over 30,000 subjects found that vitamin D supplementation at doses ≥792 IU/day resulted in a substantial reduction in fracture risk-30% for hip fractures and 14% for non-vertebral fractures³⁰.

Additionally, literature indicates that nearly half of patients treated for hand injuries after occupational accidents are smokers^{1,5,7}. Bhatti et al. highlighted that smoking among workers may contribute to diminished focus and increase susceptibility to injuries on the job⁵. Our own findings indicated that 29.2% of patients in our study were smokers—a considerably lower rate compared to other reports—potentially attributable to stringent anti-smoking regulations in our country, which have contributed to a decrease in smoking prevalence among younger populations.

Conclusions

Occupational accidents remain a major concern in developing countries and have serious public health consequences. Vitamin D deficiency is a common health problem worldwide, but there is a paucity of data in the literature on its association with bone fractures and the specific levels of vitamin D needed to prevent such fractures. Although additional and more extensive research is needed to better understand the link between vitamin D deficiency and fractures, our study provides valuable information in this regard.

The findings of our study emphasize the critical role of vitamin D supplementation, a balanced diet, regular physical activity and adequate sunlight exposure in promoting bone health. To address the high incidence of occupational fractures, we recommend regular screening of workers in high-risk sectors for vitamin D deficiency. Furthermore, occupational health policies should include targeted interventions such as vitamin D supplementation programs, educational campaigns on bone health and workplace strategies to reduce fracture risk. These measures can significantly contribute to reducing both the prevalence of vitamin D deficiency and the incidence of fractures among workers.

Limitations

When the sample size and the nature of the study are examined, the power analysis shows that the number of participants is sufficient and the study has the necessary power to detect the predetermined effect size. However, since the participants of our study included only cases in Istanbul province of Turkey, we believe that further studies with a large patient population are needed to determine the relationship between vitamin D levels and multifactorial causes such as ethnic, geographical, dietary

habits, duration of exposure to sunlight, comorbidities, medications and treatments.

References

- 1. El-Hadidy SS, El-Gilany AH, Nour K, Elsherbeny E, Hamied AHA. Occupational and non-occupational metacarpal bone fractures at the Mansoura University Emergency Hospital: A comparative study. *Toxicol Ind Health*. 2019;35(3):248-55.
- 2. Fidan F, Alkan BM, Tosun A. Çağın pandemisi: D vitamini eksikliği ve yetersizliği. *Türk Osteoporoz Dergisi*. 2014;20(2):71-4.
- 3. Wacker M, Holick MF. Vitamin D effects on skeletal and extraskeletal health and the need for supplementation. *Nutrients*. 2013;5(1):111-48.
- 4. Uçar F, Taşlıpınar MY, Soydaş AÖ, Özcan N. Ankara etlik ihtisas eğitim ve araştırma hastanesine başvuran hastalarda 25-OH Vitamin D düzeyleri. *Eur J Basic Med Sci.* 2012;2(1):12-5.
- 5. Bhatti DS, Ain NU, Fatima M. Occupational hand-related injuries at a major tertiary care burn and reconstructive center in Pakistan. *Cureus*. 2020;12(9):e10444.
- 6. Moellhoff N, Throner V, Frank K, Benne A, Coenen M, Giunta RE, et al. Epidemiology of hand injuries that presented to a tertiary care facility in Germany: a study including 435 patients. *Arch Orthop Trauma Surg.* 2023;143(3):1715-24.
- 7. Mostafa NS, Sayed AM, Osman AA. Work-related hand injuries treated at a tertiary care hospital. *J Egypt Public Health Assoc.* 2014;89(2):85-9.
- 8. Free H, Groenewold MR, Luckhaupt SE. Lifetime prevalence of self-reported work-related health problems among U.S. workers United States, 2018. *Morb Mortal Wkly Rep.* 2020;69(13):361-5.
- 9. Centers for Disease Control and Prevention (CDC). Nonfatal occupational injuries and illnesses treated in hospital emergency departments--United States, 1998. *Morb Mortal Wkly Rep.* 2001;50(16):313-7.
- 10. Sorock GS, Lombardi DA, Courtney TK, Cotnam JP, Mittleman MA. Epidemiology of occupational acute traumatic hand injuries: a literature review. *Saf Sci.* 2001;38(3):241-56.
- 11. Ghiya MN, Murty S, Shetty N, D'Cunha R. A descriptive study of hand injuries presenting to the adult emergency department of a tertiary care center in urban India. *J Emerg Trauma Shock*. 2017;10(1):19-25.
- 12. Serinken M, Karcioglu O, Sener S. Occupational hand

- injuries treated at a tertiary care facility in western Turkey. *Ind Health.* 2008;46(3):239-46.
- 13. Shrestha S, Tamrakar S, Banskota AK. Outline of Hand and Wrist Injuries Presenting to an Emergency of a Tertiary Care Centre in Nepal. *J Nepal Health Res Counc.* 2019;17(3):340-4.
- 14. Das B. Assessment of ergonomic exposure, work-related occupational injuries, and prevention: Child work in the brickfield industry in India. Toxicology and Industrial Health. 2021;37(8):481-495. doi:10.1177/07482337211025366.
- 15. Eliwy, A. S., Jafar, M. S., & Al-Najar, F. G. (2024). Pattern and Aetiology of Traumatic Hand Injury in Patients seen at Wasit Governorate. DOI: 10.13140/RG.2.2.20446.55361.
- 16. Kollitz KM, Hammert WC, Vedder NB, Huang JI. Metacarpal fractures: treatment and complications. *Hand*. 2014;9(1):16-23.
- 17. Tayal VS, Antoniazzi J, Pariyadath M, Norton HJ. Prospective use of ultrasound imaging to detect bony hand injuries in adults. *J Ultrasound Med.* 2007;26(9):1143-8.
- 18. Whiting SJ, Langlois KA, Vatanparast H, Greene-Finestone LS. The vitamin D status of Canadians relative to the 2011 Dietary Reference Intakes: an examination in children and adults with and without supplement use. *Am J Clin Nutr.* 2011;94(1):128-35.
- 19. Hanley DA, Cranney A, Jones G, Whiting SJ, Leslie WD, Cole DE, et al. Vitamin D in adult health and disease: a review and guideline statement from osteoporosis Canada. *CMAJ*. 2010;182(12):E610-8.
- 20. Looker AC, Johnson CL, Lacher DA, Pfeiffer CM, Schleicher RL, Sempos CT. Vitamin D status: United States, 2001-2006. NCHS Data Brief. 2011(59):1-8.
- 21. Sachan A, Gupta R, Das V, Agarwal A, Awasthi PK, Bhatia V. High prevalence of vitamin D deficiency among

- pregnant women and their newborns in northern India. *Am J Clin Nutr.* 2005;81(5):1060-4.
- 22. Prentice A, Schoenmakers I, Jones KS, Jarjou LM, Goldberg GR. Vitamin D Deficiency and Its Health Consequences in Africa. Clin Rev Bone Miner Metab. 2009;7(1):94-106.
- 23. Van der Mei IA, Ponsonby AL, Engelsen O, Pasco JA, McGrath JJ, Eyles DW, et al. The high prevalence of vitamin D insufficiency across Australian populations is only partly explained by season and latitude. Environ Health Perspect. 2007;115(8):1132-9.
- 24. Maeda SS, Kunii IS, Hayashi L, Lazaretti-Castro M. The effect of sun exposure on 25-hydroxyvitamin D concentrations in young healthy subjects living in the city of São Paulo, Brazil. *Braz J Med Biol Res.* 2007;40(12):1653-9. 25. Chaud Uçar, N., Grant, W. B., Peraita-Costa, I., & Morales Suarez-Varela, M. (2020). How 25 (OH) D levels during pregnancy affect prevalence of autism in children: systematic review. *Nutrients*, 12(8), 2311.
- 26. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. *Am J Clin Nutr.* 2008;87(4):1080s-6s.
- 27. Martelli M, Salvio G, Santarelli L, Bracci M. Shift work and serum vitamin d levels: A systematic review and meta-analysis. *Int J Environ Res Public Health*. 2022;19(15).
- 28. Romano A, Vigna L, Belluigi V, Conti DM, Barberi CE, Tomaino L, et al. Shift work and serum 25-OH vitamin D status among factory workers in Northern Italy: Cross-sectional study. *Chronobiol Int.* 2015;32(6):842-7.
- 29. Contreras JJ, Hiestand B, O'Neill JC, Schwartz R, Nadkarni M. Vitamin D deficiency in children with fractures. *Pediatr Emerg Care*. 2014;30(11):777-81.
- 30. Bischoff-Ferrari HA, Willett WC, Orav EJ, Lips P, Meunier PJ, Lyons RA, et al. A pooled analysis of vitamin D dose requirements for fracture prevention. *N Engl J Med.* 2012;367(1):40-9.