ORIGINAL ARTICLE

Prevalence of Hypocalcemia and Vitamin D3 Deficiency among the Underprivileged Orphans of Azad Jammu and Kashmir, Pakistan

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ABSTRACT

Introduction: Rickets, an infantile condition stemming from hypocalcemia, is observed to be escalating among children. Vitamin D deficiency, deemed the primary cause of impaired calcium absorption from the gut, has been linked to the onset of hypocalcemia and subsequent rickets. Despite this, no prior investigations have scrutinized the prevalence of hypocalcemia among orphan children residing in urban settings in Pakistan. This study aims to evaluate the extent of calcium deficiency in orphaned children across various regions of Azad Jammu & Kashmir, Pakistan. **Methodology:** A screening study encompassed 544 underprivileged orphan children (300 males and 244 females) in Hattian Bala (Jhelum Valley), Kotli, Bagh, and district Bhimber, Azad Kashmir. Fasting blood samples were obtained, and serum calcium levels were assessed using the o-cresol-phthalein complexion color development method. Additionally, serum 1α,25-(OH)2D3 levels were assayed via the 1α,25-(OH)2D3 RIA method employing a kit from Mitsubishi Kagaku Bio-Clinical Labs, Inc., Japan. A comprehensive health examination conducted by a qualified physician aimed to identify other health concerns among the orphans. Statistical analyses were performed using GraphPad Prism (Version 7.04) software. **Results:** Among the total orphan population, 24.8% exhibited hypocalcemia, with a distribution of 56.3% females and 43.7% males. Vitamin D3 deficiency was observed in 5.3% of orphans, with a gender discrepancy of 27.6% males and 72.4% females. The mean age, calculated with a 95% Confidence Interval, was 12.0±0.3, with a standard deviation of 3.1. The age group of 5 to 9 years demonstrated the highest prevalence of both serum calcium (56.1%) and vitamin D3 (14.3%) deficiencies. A significant correlation ($p<0.0001$) between vitamin D3 deficiency and hypocalcemia was identified. District Kotli exhibited the highest prevalence of hypocalcemia, while district Hattian Bala (Jhelum Valley) showed a higher prevalence of low vitamin D3 levels. **Conclusion:** The underprivileged orphan population in Azad Kashmir, Pakistan, manifests low vitamin D3 levels, strongly associated with the prevalence of hypocalcemia. Notably, vitamin D3 insufficiency and hypocalcemia are more prevalent in the female population. To address this, the Government of Azad Jammu and Kashmir, Pakistan, is urged to institute policies providing sufficient and meaningful endowment funds for the state's orphans. Additionally, a national campaign should be initiated to raise awareness about malnutrition and the importance of a balanced diet.

Key Words: Hypocalcemia, Vitamin D Deficiency, Health of underprivileged orphans in AJ&K, Hypocalcemia among orphan children, Vitamin D associated hypocalcemia

INTRODUCTION

Hypocalcemia is a condition in which calcium levels drop from the normal range in the blood serum.[(1)] Normally the range is 2.1–2.6 mmol/L (8.8–10.7 mg/dl, 4.3–5.2 mEq/L) and if it decreases to 2.1 mmol/l hypocalcemia occurs. [(2, 4)] slight drop in Calcium level which develops slowly does not cause any symptom. [(2, 4)] Persistently low levels of body calcium cause numbness in various

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parts of the body, muscle spasms or cramps, seizures, confusion, and even cardiac arrest. [1, 2] Underactive thyroid gland (hypothyroidism) and deficiency of vitamin D are two major causes of hypocalcemia. [2] Other causes include kidney failure, pancreatic inflammation, calcium channel blocker overdose, rhabdomyolysis, tumor lysis syndrome (TLS), and medicines like bisphosphonates. [1] Hypocalcemia is a prevalent metabolic disorder with varying degrees of severity, ranging from asymptomatic in mild cases to life-threatening in severe instances. The regulation of serum calcium levels within the confined range of 2.1 to 2.6 mmol/L is overseen by three primary hormones: calcitonin, calcitriol (vitamin D), and parathyroid hormone (PTH). Approximately half of the total serum calcium is bound to proteins, with the remaining physiologically active fraction existing in the form of free ions. [5] One of the most common abnormalities of mineral metabolism seen in children is Hypocalcaemia. In children the lower calcium levels may occur as a result of various different etiologies. These include non-secretary or abnormal parathyroid gland, abnormal vitamin D metabolism and malfunctioning calcium-sensing receptor. [6] Calcium, constituting over 99 percent of the total body calcium, is primarily deposited in bones and teeth as calcium hydroxyapatite (Ca10[PO4]6[OH]2), reinforcing hard tissues. This allocation serves to fortify the skeletal structure. Beyond bones and teeth, calcium is distributed in the circulatory system, extracellular fluid, muscles, and various tissues, playing pivotal roles in functions such as the regulation of vascular contraction and vasodilation, normal muscle operation, nerve impulse transmission, cell signaling, and glandular secretion. The skeletal system serves as a central hub for meeting these essential metabolic demands, with calcium sourced through the intricate process of bone remodeling. [7] In the circulatory system, approximately half of the total calcium exists as free Ca++ ions, 40% is bound to proteins, predominantly albumin, and the remaining 10% is present in the form of complex anions like citrate. Of these forms, only plasma ionized calcium (iCa) holds biological activity, with its concentration meticulously regulated. The concentration of calcium in the body normally fluctuates with age, decreasing shortly after birth and recovering within a week. Notably, calcium levels are found to be elevated during infancy compared to childhood. [8]

In the extracellular environment, three fundamental regulators govern calcium levels: the calcium-sensing receptor (CaSR), parathyroid hormone (PTH), and calcitriol or vitamin D. When there is an inadequacy of ionized calcium (Cai) in the plasma, calcium-sensing receptors are activated, leading to the inhibition of parathyroid hormone (PTH) release. Conversely, when calcium concentrations are low, PTH is released into the bloodstream and transported to its targeted tissues, namely, the bone and kidney. [9] When this regimen is failed to maintained calcium inside the body other concerns are raised, possibly permanent causes of hypocalcemia. One of these disorders is the inherited hypoparathyroidism, which includes a number of abnormalities like absent parathyroid gland, a mutant gene coding for CaSR, defective Parathyroid hormone, or abnormal response to PTH. Chronic hypocalcemia can be grouped into two major categories: disorders relating to PTH and those which involves vitamin D. [8] Usually, Children living in orphanages often face nutritional deficiencies. [10]

There is a lack of management to control the orphan problem in Asia and Africa. [11] The practice to keep underprivileged children who have no guardian in orphanages has long been prevailing in socio-economically poor Asian countries. [12] In an ongoing study, Pakistan has been identified as the third-highest country in terms of hunger and under-five child mortality. The children in Pakistan face a multitude of challenges, including poverty, inadequate nutrition, substandard living conditions, infectious diseases, lack of education, and disrupted family structures, all of which can significantly impact their physical and mental well-being. [13] While there is no notable literature specifically quantifying hypocalcemia, reported instances of transient hypocalcemia after thyroidectomy range from 6.9% to 49%, and for permanent hypocalcemia, the range is between 0.4% to 33%. Generally, renal failure is recognized as the most prevalent cause of hypocalcemia, followed by factors such as vitamin D deficiency, magnesium deficiency, and acute pancreatitis. [14] To date, no study has specifically delved into the issue of hypocalcemia among urban orphanage children in Pakistan. The present study seeks to fill this research gap by investigating the prevalence of calcium and vitamin D3 deficiencies among orphaned children across various districts of Azad Jammu & Kashmir, Pakistan.

METHODOLOGY

A population of underprivileged orphans belonged from district Hattian Bala, district Kotli, district Bagh and district Bhimber of Azad Kashmir was selected for the present study. An extensive survey was organized across these four districts to find out underprivileged orphans. This survey was based upon the information about the mother's job, chronic disease in the family, earning hands, land and psychological support of society. The age groups included in these studies ranged from 5 years to 19 years. Orphans less than five years and more than Nineteen years of age were not included in this study. The size of this population was 544 including 300 males and 244 females.

Fasting blood samples were obtained through venipuncture using 5 ml syringes and immediately placed into gel tubes. After a 10-minute incubation period at room temperature, the tubes were centrifuged at 4000 rpm for five minutes. The resulting serum was carefully transferred to Eppendorf tubes and promptly stored in a refrigerator at -80℃ for further use.

Calcium levels were determined using the o-cresol-phthalein complex color development method [15] with the Centronic GmbH Company kit from Germany. The values presented below are in accordance with the CPC kit method.

Serum/Plasma	Mg/dl	mmol/l
2-12 months	8.4-10.8	2.1-2.7
1-4 years	8.4-10.4	2.1-2.6
5-20 years	9.2-11.0	2.3-2.7
21-50 years	8.8-10.2	2.2-2.5
>50 years	8.4-9.7	2.1-2.4

The serum 1α,25-(OH)2D3 level was assayed through 1α,25-(OH)2D3 RIA method using 1α,25-(OH)2D3 RIA kit of Mitsubishi Kagaku Bio-Clinical Labs, Inc., Japan. [16]

Expected declarations with values were the following:

Level	Description
< 20ng/ml	Deficiency
Between 20 to 30ng/ml	Insufficiency
Between 30 to 100ng/ml	Sufficiency
> 100ng/ml	Toxicity

Health examination was carried by an expert physician to find out other health issues of the orphans like previous medical history, any infection, rickets, physical health, vision-related issues, and BMI calculation. The data were used to statistical analysis to calculate the standard deviation and mean age, along with a 95% confidence interval. Additionally, a Chi-square test was employed to explore the relationship between vitamin D3 levels and serum calcium deficiency. All analyses were conducted using GraphPad Prism software (Version 7.04). Approval for the study was granted by the Directorate of Advanced Studies & Research (DAS&R), the body with the authority to approve research topics and address ethical considerations at the University of Azad Jammu and Kashmir, Muzaffarabad. Prior to sampling, each participant and their guardians provided a duly filled and signed participation consent. Confidentiality of all participant information was strictly maintained, and both laboratory testing and result provision were carried out without any cost to the participants.

RESULTS

In the present study, the total number of orphan participants was 544 including 300(55.2%) male and 244(44.8%) female individuals. All the participants were tested for serum calcium level and serum vitamin D3 level. We found 135 (24.8%) individuals with hypocalcemia and out of these 135 hypocalcemic participants 56.3% female population was found with low serum calcium as compared to 43.7% male population with low serum calcium level. Similarly, 29(5.3%) individuals were found with vitamin D3 deficiency including 08(27.6%) male and 21(72.4%) female population as shown in Table 1.

Table 1. Overall prevalence of hypocalcemia.

Total population		Hypocalcemic Individuals		Individuals with Vitamin D3 Deficiency	
544		135 (24.8%)		29 (5.3%)	
Male	**Female**	**Male**	**Female**	**Male**	**Female**
300 (55.2%)	244 (44.8%)	59 (43.7%)	76 (56.3%)	08 (27.6%)	21 (72.4%)

Table 2 shows the details about the prevalence of hypocalcemia and vitamin D3 deficiency regarding age. Standard deviation analyzed for the age of the total population was 3.1 and mean age with 95% Confidence Interval was found 12.0±0.3. The total population was divided into three age groups and the age group 5 to 9 years was found with the highest prevalence of both

serum calcium and vitamin D3 deficiency and the mean age of this age group was 7.7±0.3 with 95% Confidence Interval.

Table 2. Age-wise population distribution and prevalence of hypocalcemia.

Age Groups	No. of Individuals	Standard Deviation	Mean Age with 95% CI	No. of Hypocalcemic Individuals	Vitamin D3 Deficient Individuals
05-09	98	1.4	7.7±0.3	55(56.1%)	14(14.3%)
10-14	361	1.8	12.1±0.2	43(11.9%)	09(2.3%)
15-19	85	1.5	16.4±0.3	37(43.5%)	07(8.2%)
Total	544	3.1	12.0±0.3	135(24.8%)	29(5.3%)

In the present study, we screened total 544 individuals for both serum calcium level and vitamin D3 level and we found 135 individuals with low serum calcium and 29 with low vitamin D3 level. Out of 29 total vitamin D3 deficient orphans, 18 were hypocalcemic and 11 were non-hypocalcemic. We analyzed the data through two-sided Chi-square test at p-value <0.05 by using GraphPad Prism Version 5.00. We found the relationship significant with the p-value <0.0001. Table 3 shows that vitamin D3 deficiency is significantly associated with the low serum calcium level.

Table 3. The relationship between low serum calcium and vitamin D3 level.

Data analyzed	Vit.D3 Deficient	Non Vit.D3 Deficient	Total	Chi-square p-value	Significance (at p<0.05)
Hypocalcemic	18	117	135	0.0001	Yes
Non Hypocalcemic	11	398	409		
Total	29	515	544		

Table 4 shows the district wise prevalence of hypocalcemia and low vitamin D3 level in orphans with some associated health problems. 27.3% orphans were found with hypocalcemia and 2.4% orphans were found with low vitamin D3 level in district Bagh. Similarly, 14.4% orphans were found with hypocalcemia and 6.5% orphans were found with low vitamin D3 level in district Bhimber. In the district, Hattian Bala 42.3% orphans were found with hypocalcemia and 26.9% orphans were found with low vitamin D3 level.

The last district was district Kotli, Azad Kashmir Pakistan and we found 47.6% orphans with hypocalcemia and 14.3% orphans with low vitamin D3 level. Orphans with the highest percentile of vision abnormalities were found in district Kotli while we found only 02(0.4%) orphans with rickets from the total of 544 orphans. 01 was found in district Bagh and the other 01 was found in district Bhimber Azad Kashmir, Pakistan.

Table 4. Prevalence of hypocalcemia and low vitamin D3 level regarding to different districts

Districts	Total Orphans	Hypocalcemic Orphans	Orphans with low vitamin D3 level	Physically weak Orphans	Underweight Orphans	Orphans with Visual Abnormalities	Orphans with Rickets
Bagh	330	90(27.3%)	08(2.4%)	39(11.8%)	29(8.8%)	06(1.8%)	01(0.3%)
Bhimber	167	24(14.4%)	11(6.5%)	09(5.4%)	09(5.4%)	02(1.2%)	01(0.6%)
Hattian Bala (Jhelum Valley)	26	11(42.3%)	07(26.9%)	02(7.7%)	04(15.4%)	02(7.7%)	-
Kotli	21	10(47.6%)	03(14.3%)	10(47.6%)	03(14.3%)	03(14.3%)	-
Total	544	135(24.8%)	29(5.3%)	60(11%)	45(8.3%)	13(2.4%)	02(0.4%)

DISCUSSION

Lailou et al. [17] uncovered a staggering 97% prevalence of hypocalcemia among children below the age of 5 in Vietnam. In stark contrast, our investigation in Azad Kashmir, Pakistan, disclosed a hypocalcemia rate of 24.8% among orphaned children. This notable deviation in prevalence rates underscores the potential influence of diverse socio-economic backgrounds within the two studied populations. Turning to Isfahan City, Iran, the study by Hovsepian et al. [18] detected below-normal calcium levels in 66 out of 1,111 adults, a phenomenon attributed to possible vitamin D deficiency. In resonance with this, our study brought forth a significant correlation between hypocalcemia and vitamin D3 deficiency. It is crucial to note, however, that the focus of Hovsepian et al.'s [18] research was on adults, while our investigation centered on underprivileged orphans, thereby signaling the existence of distinct contextual nuances despite parallel findings. Existing reports point to a prevalence range of vitamin D deficiency among adults from 14-59%, with a more pronounced occurrence in Asian countries. [19, 20] Astonishingly, our study unveiled a 24.8% prevalence of hypocalcemia among orphans, aligning with the reported 14-59% hypocalcemia rates in Asian countries by Vander et al. [19] An intriguing revelation was the significantly elevated hypocalcemia rate of 56.1% among orphans aged 5-9 years, marking it as the highest prevalence across all age brackets.

In employing <30 ng/mL as the deficient range, our study identified 5.3% of orphans with vitamin D3 deficiency, a figure in stark contrast to the observations made by Mitchell et al. [25] Of note is the gender-based asymmetry, with a striking 72.4% prevalence of vitamin D3 deficiency in females compared to a markedly lower 27.6% in males. Contrasting with prior research reporting a 58% prevalence of hypocalcemia among children aged 0-4 years [26], our study shifted its focus to orphans aged 5-19 years. The findings revealed a 56.1% prevalence among those aged 5-9 years and an overall prevalence of 24.8%. This nuanced approach emphasizes the necessity of considering age-specific factors in evaluating hypocalcemia prevalence.

Moreover, diverging from known causes of hypocalcemia identified in a previous study [27], our findings accentuated a positive association between hypocalcemia and vitamin D3 levels. Furthermore, our study uncovered connections with other health issues among orphans, such as a 0.4% prevalence of rickets, 2.4% with visual abnormalities, 8.3% classified as underweight, and 11% experiencing physical weakness. While the precise causative factors remain elusive, it is plausible that the nutritional insufficiencies prevalent in our underprivileged orphan population contribute to these health disparities, underscoring the urgency of addressing nutritional imbalances. The higher prevalence of hypocalcemia among females also signals potential gender-based discrimination within the study area communities, adding a layer of social complexity to our findings.

CONCLUSION

The underserved orphan community in Azad Kashmir, Pakistan, exhibits low levels of vitamin D3, strongly associated with an increased prevalence of hypocalcemia. Notably, among females, there is a higher likelihood of widespread vitamin D3 insufficiency and hypocalcemia. To address this pressing issue, it is recommended that the Government of Azad Jammu and Kashmir, Pakistan, implement a comprehensive policy aimed at providing a substantial and beneficial endowment fund for the state's orphans. Furthermore, initiating a national campaign is advisable to enhance awareness regarding malnutrition and the importance of maintaining a balanced diet.

ACKNOWLEDGMENTS

We extend a sincere acknowledgment to the teachers and students of the Department of Biotechnology and the Department of Zoology at the University of Azad Jammu & Kashmir, Muzaffarabad, as well as the Hepatitis Society and Health Care Diagnostic & Research Centre in Muzaffarabad. Their active participation was integral to the success of this study. We would also like to express special gratitude to Human Appeal International (HAI) for their invaluable support in organizing screening camps, providing funding, and facilitating various aspects of the present study. Their contributions have significantly enriched the research process.

REFERENCES

1. Le-Mone, P., Burke, K., Dwyer, T., Levett-Jones, T., Moxham, L. and Reid-Searl, K., 2015. *Medical-surgical nursing*. Pearson Higher Education AU.
2. Nolan, J.P., Soar, J., Zideman, D.A., Biarent, D., Bossaert, L.L., Deakin, C., Koster, R.W., Wyllie, J. and Böttiger, B. European resuscitation council guidelines for resuscitation 2010 section 1. Executive summary. Resuscitation. 2010; 81(10), pp.1219-1276.
3. Pathy, M.J., Sinclair, A.J. and Morley, J.E. eds., 2006. Principles and practice of geriatric medicine. John Wiley & Sons.
4. Minisola, S., Pepe, J., Piemonte, S. and Cipriani, C. The diagnosis and management of hypercalcaemia. BMJ. 2015; 350(8011), p.h2723.

5. Fong, J. and Khan, A. Hypocalcemia: updates in diagnosis and management for primary care. Canadian family physician. 2012; 58(2), pp.158-162.
6. Shaw, N.J., 2015. A practical approach to hypocalcaemia in children. In *Calcium and Bone Disorders in Children and Adolescents* (Vol. 28, pp. 84-100). Karger Publishers.
7. Del Valle, H.B., Yaktine, A.L., Taylor, C.L. and Ross, A.C. eds., 2011. Dietary reference intakes for calcium and vitamin D. National Academies Press.
8. Zhou, P., Markowitz, M. and Adam, H.M. Hypocalcemia in infants and children. Pediatrics in review. 2009; 30(5): p.190.
9. Brini, M., Calì, T., Ottolini, D. and Carafoli, E. Intracellular calcium homeostasis and signaling. In Metallomics and the Cell. 2013; (pp. 119-168). Springer, Dordrecht.
10. Orphan Nutrition (2015). An initiative of a child's best start to improve nutrition and feeding of orphan children. Available from http:// www.orphannutrition.org/understanding malnutrition/causes-of-malnutrition-amongorphans/ [Retrieved 25 January 2015].
11. Orphan Hope international (2015). Facts & Statistics. Available from http://www. orphanhopeintl. org/facts-statistics [Retrieved 25 January 2015].
12. Mashkoor A. L. and Ganesan P. Health and nutritional status of orphan children's living in orphanages with special reference to the distric of Anantnag of Jammu and Kashmir. Inter J Indian Psychol. 2016; 3(2): 163-169.
13. Khattak, U.K., Iqbal, S.P. and Ghazanfar, H. The role of parents' literacy in malnutrition of children under the age of five years in a semi-urban community of pakistan: a case-control study. Cureus. 2016; 9(6); e1316.
14. Goyal A, Bhimji SS. Hypocalcemia. [Updated 2017 Apr 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2018 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430912.
15. Gitelman HJ. An improved automated procedure for the determination of calcium in biological specimens. Anal Biochem. 1967; 18:521-31.
16. Rieko Tanabe, Yuka Kawamura, Naoko Tsugawa, Mayu Haraikawa, Natsuko Sogabe, Toshio Okano, Takayuki Hosoi, Masae Goseki Sone. 2015. Effects of Fok-I polymorphism in vitamin D receptor gene on serum 25-hydroxyvitamin D, bone-specific alkaline phosphatase and calcaneal quantitative ultrasound parameters in young adults. Asia Pac J Clin Nutr. 2015; 24(2):329-335.
17. Laillou, A., Frank Wieringa, Thuy Nga Tran, Pham Thuy Van, Bach Mai Le, Sonia Fortin, Thi Hop Le, Regina Moench Pfanner, Jacques Berger. Hypovitaminosis D and mild hypocalcemia are highly prevalent in young Vietnamese children and women and related to low dietary intake. Plos one. 2013; 8:1-10.
18. Silva Hovsepian, Massoud Amini, Ashraf Aminorroaya, Peyvand Amini, Bijan Iraj. 2011. Prevalence of Vitamin D Deficiency among Adult Population of Isfahan City, Iran. J Health Popul Nutr. 2011; 29(2): 149–155.

19. Vander Wielen RP, Lowik MR, Vanden Berg H, de Groot LC, Haller J, Moreiras O, et al. Serum vitamin D concentrations among elderly people in Europe. Lancet. 1995; 346:207–10.
20. Souberbielle JC, Cormier C, Kindermans C, Gao P, Cantor F, Baulia EE, et al. 2001. Vitamin D status and redefining serum parathyroid hormone reference range in the elderly. J Clin Endocrinol Metab., 86:3086–90.
21. Omdahl JL, Garry PJ, Hunsaker LA, Hunt WC, Goodwin JS. Nutritional status in a healthy elderly population: vitamin D. Am J Clin Nutr. 1982; 36:1225–32.
22. Kinyamu HK, Gallagher JC, Balhorn KE, PetranicK KM, Rafferty KA. Serum vitamin D metabolites and calcium absorption in normal young and elderly free-living women and in women living in nursing homes. Am J Clin Nutr. 1997; 65:790–7.
23. Burnard B, Sloutskis D, Gianoli F, Cornuz J, Rickenbach M, Paccaud F, et al. Serum 25-hydroxyvitamin D: distribution and determinants in the Swiss population. Am J Clin Nutr. 1992; 56:537–42.
24. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone wloss and fractures and therapeutic implications. Endocr Rev. 2001; 22:477–501.
25. Deborah M. Mitchell., Maria P. Henao., Joel S. Finkelstein., Sherri-Ann M. Burnett-Bowie. 2012. PREVALENCE AND PREDICTORS OF VITAMIN D DEFICIENCY IN HEALTHY ADULTS. Endocr Pract., 18(6): 914–923.
26. BinMohanna MA, Raja'a YA, Saif GA. Prevalence of hypocalcemia in children examined for serum calcium in Sana'a, Yemen. Saudi Med J. 2005; 26(3): 457-9.
27. Desai TK, Carlson RW, Geheb MA. Prevalence and clinical implications of hypocalcemia in acutely ill patients in a medical intensive care setting. Am J Med. 1988; 84(2): 209-214.