

Vitamin D and vitamin B₁₂ profiles in children with primary nocturnal enuresis, an analytical cross-sectional study

Hoda Atef Abdelsattar Ibrahim, Shymaa Sobhy Menshawy, Fatma E. Hassan, Shirin M. El-Makawi, Omnia Raafat Amn, Nermeen Bastawy, Samar Saad, Shadia M.Hussein, Dina Mahmoud & Khaled Mohamed Abdelhamid ElKhashab

To cite this article: Hoda Atef Abdelsattar Ibrahim, Shymaa Sobhy Menshawy, Fatma E. Hassan, Shirin M. El-Makawi, Omnia Raafat Amn, Nermeen Bastawy, Samar Saad, Shadia M.Hussein, Dina Mahmoud & Khaled Mohamed Abdelhamid ElKhashab (2024) Vitamin D and vitamin B₁₂ profiles in children with primary nocturnal enuresis, an analytical cross-sectional study, *Annals of Medicine*, 56:1, 2352030, DOI: [10.1080/07853890.2024.2352030](https://doi.org/10.1080/07853890.2024.2352030)

To link to this article: <https://doi.org/10.1080/07853890.2024.2352030>



© 2024 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group



Published online: 10 Jun 2024.



Submit your article to this journal [↗](#)




View related articles [↗](#)



View Crossmark data [↗](#)

Vitamin D and vitamin B₁₂ profiles in children with primary nocturnal enuresis, an analytical cross-sectional study

Hoda Atef Abdelsattar Ibrahim^{a,b} , Shymaa Sobhy Menshawy^c, Fatma E. Hassan^{d,e}, Shirin M. El-Makawf^f, Omnia Raafat Amn^f, Nermeen Bastawy^d, Samar Saad^g, Shadia M.Husseini^h, Dina Mahmoud^g and Khaled Mohamed Abdelhamid ElKhashab^a

^aDepartment of Pediatrics, Faculty of Medicine, Cairo University, Giza, Egypt; ^bPediatric Clinical Nutrition Division, Department of Pediatrics, Faculty of Medicine, Cairo University, Giza, Egypt; ^cDepartment of Pediatrics, Faculty of Medicine, Menofia University, Menofia, Egypt; ^dDepartment of Medical Physiology, Kasr Alainy, Faculty of Medicine, Cairo University, Giza, Egypt; ^eDepartment of Physiology, Batterjee Medical College, Jeddah, Saudi Arabia; ^fDepartment of Psychiatry, Faculty of Medicine, Cairo University, Giza, Egypt; ^gDepartment of Chemical Pathology, Faculty of Medicine, Cairo University, Giza, Egypt; ^hDepartment of Chemistry, Ain Shams University, Cairo, Egypt

ABSTRACT

Purpose: To outline the prevalence of vitamin D and vitamin B₁₂ deficiencies in enuretic children. **Methods:** An analytical descriptive study was conducted on enuretic children who were followed up at the outpatient clinic for nocturnal enuresis at the Children's Hospital, Cairo University. Sociodemographic and clinical data were recorded. The levels of vitamin D and vitamin B₁₂ were assessed and correlated with the severity of enuresis.

Results: Two hundred and eighty-eight children were enrolled. Insufficiency of Vitamin D predominated ($n=139$; 48.3%). Vitamin D deficiency was present in 31.3%, $n=90$ and it was normal in 20.5%, $n=59$. Vitamin B₁₂ deficiency was observed in 25% of the studied children, $n=72$. The one-sample Wilcoxon signed-rank test was significant for both vitamins (P value =0.001). Vitamin D showed a stronger inverse correlation with the number of enuresis episodes per day than vitamin B₁₂ (-0.680 vs. -0.219 respectively). A cut-off of 13.7 ng/ml for vitamin D was detected, below which the child was predicted to have failed dry nights. Using multivariate logistic regression, higher vitamin D levels and behavioural treatment coexistence were significant protective factors for the absence of dry nights.

Conclusion: Low levels of vitamin D and B₁₂ were detected in children with primary nocturnal enuresis, which could be considered a burden on the clinical severity of enuresis.

KEY MESSAGES

- What is already known on this topic?
Children with Primary Nocturnal Enuresis may have vitamin D and vitamin B₁₂ abnormalities as deficiencies
- What does this study add?
Vitamin D insufficiency may be the most prevalent vitamin D abnormality in children with primary nocturnal enuresis. Vitamin D insufficiency may be more common in children with severe enuresis than vitamin B₁₂ deficiency.
- How might this study affect research, practice, or policy?
This study may invite further research to examine the possible use of vitamin D and vitamin B₁₂ as potential adjuvant therapies for children with Primary Nocturnal Enuresis.

ARTICLE HISTORY

Received 27 November 2023
Revised 9 April 2024
Accepted 22 April 2024



KEYWORDS

Vitamin D; vitamin B₁₂; enuresis; children; dry

Introduction

Primary Nocturnal Enuresis [PNE] is the most common voiding problem in children and is characterized by involuntary urination during the night after the age at which bladder control is expected. It has been

extensively studied because of its high prevalence. The causes of PNE, such as small bladder size, abnormal sleep patterns, increased urine production at night, and delayed development of the central nervous system, have been widely discussed but are not fully understood [1].

CONTACT Hoda Atef Abdelsattar Ibrahim  hodaibrahim424@cu.edu.eg, hodaibrahim424@gmail.com  Department of Pediatrics, Faculty of Medicine, Cairo University, Cairo 12613, Giza, Egypt.

This article is published in the PEDIATRICS SECTION OF ANNALS OF MEDICINE
© 2024 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited. The terms on which this article has been published allow the posting of the Accepted Manuscript in a repository by the author(s) or with their consent.

Vitamin D receptors can be found in various parts of the body, including the muscles, bladder, and skeletal and smooth muscles. Vitamin D is believed to play a role in several clinical conditions, such as asthma, respiratory tract infections, insulin problems, autoimmune disorders, metabolic syndrome, fertility, urinary tract infections, overactive bladder syndrome, chronic kidney diseases, and pelvic floor muscle disorders. Recent studies have suggested a potential link between vitamin D and lower urinary tract symptoms, although the results have been inconsistent [2]. Moreover, evidence from clinical studies suggests that vitamin D is involved in sleep regulation [3].

Vitamin B₁₂ may play an essential role in the development and maturation of the nervous system in children. Despite extensive research on PNE, many questions regarding its pathophysiology remain unanswered [4].

Our study aimed to outline the prevalence of vitamin D and B₁₂ abnormalities in enuretic children. Additionally, the link between the levels of both vitamins and the clinical severity of enuresis, which was represented by the number of enuresis episodes per day and the absence of dry nights, was another objective.

Materials and methods

This study enrolled 288 children diagnosed with primary nocturnal enuresis between January 2022 and June 2022. Face-to-face interviews with caregivers or parents were conducted using a structured questionnaire. The information collected included the child's age, gender, frequency of nighttime bedwetting, presence or absence of dry nights, and possible risk factors such as family troubles or psychiatric disorders.

Serum samples of the collected blood from all enuretic children were separated using tubes containing separating gel, centrifuged, and preserved at –20°C until laboratory assessments. We used the Electrochemiluminescence method to detect serum 25-hydroxyvitamin D and B₁₂ levels and correlated these results with the reference ranges.

For each child, a checklist was used to record their data [name, age, sex, serum vitamin D, and vitamin B₁₂]. All enrolled children with primary enuresis were diagnosed and confirmed to have no secondary causes or systemic causes as convulsions. Children who were 5 years or older than 5 years of age, who had at least 2 episodes of wet nights, never experienced nocturnal dryness for more than 6 consecutive months and with normal urine and stool analysis, normal lumbar x-ray were enrolled. Informed consent was obtained from all the caregivers or parents.

Control of potential bias

1. Children receiving vitamin D or vitamin B₁₂ supplementation were excluded from the study.
2. Children with secondary nocturnal enuresis by history; through which the child had a period of being dry and then beginning to wet, were excluded. Also, we excluded children with genetic causes through family history. Laboratory investigations as random blood sugar and kidney functions were applied to exclude other secondary causes such as Diabetes Mellites and renal compromise [5–6].
3. Sampling of the enrolled children was in one season which is the Spring (March to May) to exclude any bias resulting from seasonal variations in vitamin D levels

Operational definitions

1. Reference ranges for vitamin D and vitamin B₁₂ were used to outline the definitions for vitamin D and vitamin B₁₂ abnormalities [7–8].
2. Primary nocturnal enuresis is the involuntary passage of urine at night in children old enough to be expected to have bladder control. Enuresis is considered to be primary when bladder control has never been achieved and secondary when the incontinence reappears after at least six months of continence [9]. Children who have more than five episodes of wet nights are defined to have severe Primary nocturnal enuresis [10].

Sample size considerations

The primary objective of this study was to determine the prevalence of abnormally low 25-hydroxy vitamin D (25 [OH] D) levels among children with primary nocturnal enuresis. El-Baz et al. 2021 estimated that 46% of pediatric patients with primary nocturnal enuresis had low abnormal vitamin D levels [11].

By setting an acceptable margin of error of 0.06, and a confidence level of 95%, the minimum required sample size for the study was 266 patients using a Statulator calculator for estimating a single proportion. [12]. To enhance the precision of our findings and achieve a lower margin of error, we purposefully exceeded the calculated sample size in our study as much as it was possible.

Ethical considerations

After an adequate explanation of the study, written consent was obtained from all parents or caregivers of

the enrolled children. The study was revised and approved by the Scientific Ethical Research Committee of Cairo University (ethical clearance number: N-80-2021). This study was performed following the laws for human research, following the principles of the Declaration of Helsinki.

Statistical considerations

Statistical calculations were performed using SPSS version 27 and MedCalc software. Categorical variables were represented as frequency counts and percentages, while numerical variables were represented as medians and ranges, as most of the data were not normally distributed according to the Kolmogorov–Smirnov test. The one-sample Wilcoxon signed-rank test was applied to detect whether the median of the sample was equal to the known standard value (i.e. the reference value of vitamin D and vitamin B₁₂). Spearman's rank correlation was used to determine the possible correlation of vitamin D and B₁₂ levels with the number of enuresis episodes per day. Associations between categories of vitamin D levels and categories of dry nights were studied using the chi-square test. The receiver operator characteristic (ROC) curve was used to detect the cut-off value for vitamin D for predicting children with the absence of any dry nights. Multivariate logistic regression analysis was used to control for possible confounders.

Results

This study aimed to estimate the prevalence of vitamin D abnormalities as deficiencies in children with nocturnal enuresis and to assess the prevalence of vitamin B₁₂ deficiency. Figure 1 illustrates the

prevalence of abnormal levels of vitamin D and shows that insufficiency of vitamin D was predominant ($n=139$, 48.3%). Vitamin D deficiency was present in 31.3%, $n=90$ and it was normal in 20.5%, $n=59$). The figure also shows the prevalence of vitamin B₁₂ deficiencies (25%, $n=72$). To address if each of these results is different from the normal population, the one-sample Wilcoxon signed-rank test was applied using the normal levels of both vitamins as references. A significant difference was also observed ($p=0.001$).

However, within the children with nocturnal enuresis, vitamin D appears to be a stronger covariate with the number of nocturnal enuresis episodes per day than vitamin B₁₂ as shown in Table 1.

Table 2 presents the socio-demographic and clinical criteria. The median age of the children with nocturnal

Table 1. Spearman's rank correlation between the number of nocturnal enuresis episodes per day and both vitamin D and B₁₂.

Studied variables	Number of nocturnal enuresis per day	
	rho*	p value**
Vitamin D	-0.680	0.001**
Vitamin B 12	-0.219	0.001**

*Spearman's rank correlation coefficient.

**p value is significant if <0.05.

Table 2. Sociodemographic and clinical criteria of the study participants.

Numerical study variable	Median (IQR)	Min-Max
Age in years	9.3 (8)	5–13
Vitamin D	14.15(7.83)	3.54–68.21
Vitamin B12	403.7(202.3)	174–2000
Number of nocturnal enuresis per day	2(5)	1–6
Gender distribution, Total $n=288,100\%$		
Males	$N=142$	49.3%
Females	$N=146$	50.7%
Dry nights		
Absence of dry nights	$N=168$	58.3%
Presence of dry nights	$N=120$	41.7%

IQR: interquartile range; N: number.

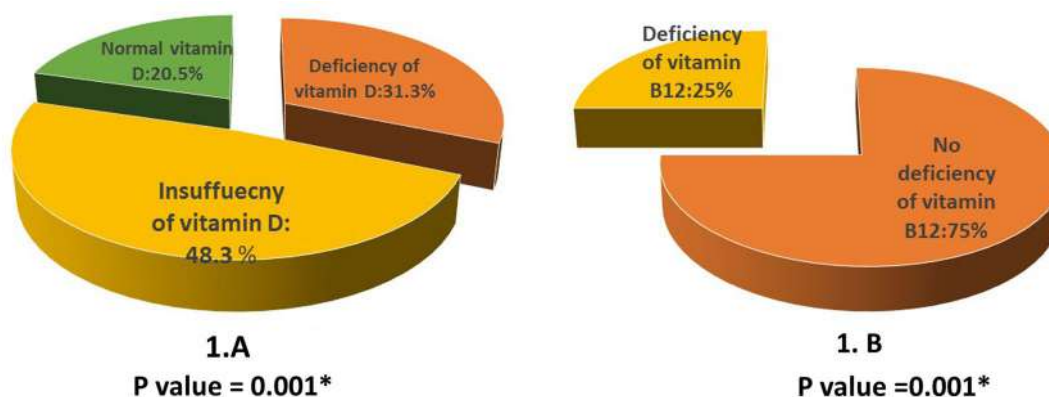


Figure 1. Distribution of levels of vitamin D(1.A) and vitamin B12(1.B) in our study. *p value of One-Sample Wilcoxon Signed Rank Test is significant.

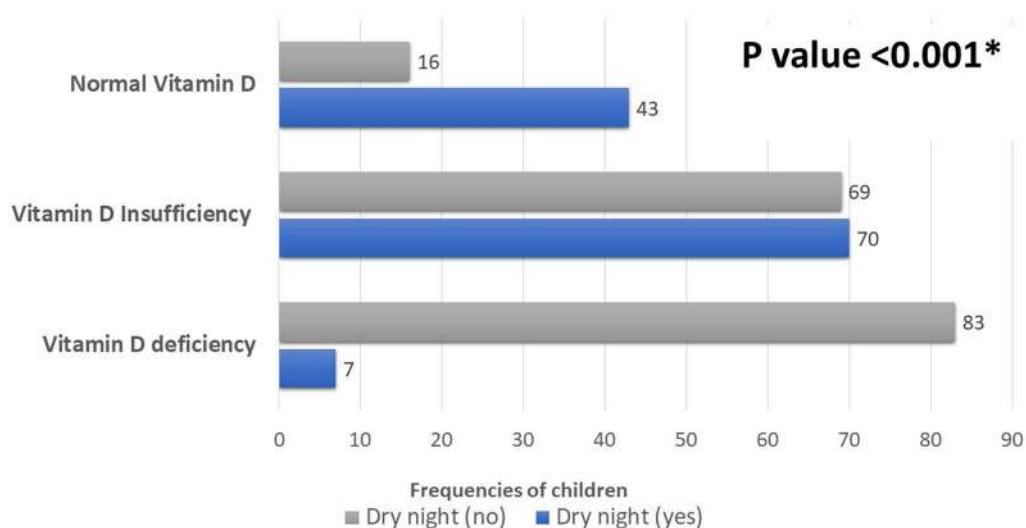


Figure 2. The distribution of absence and presence of dry nights through levels of vitamin D. * p value of Chi-squared test.

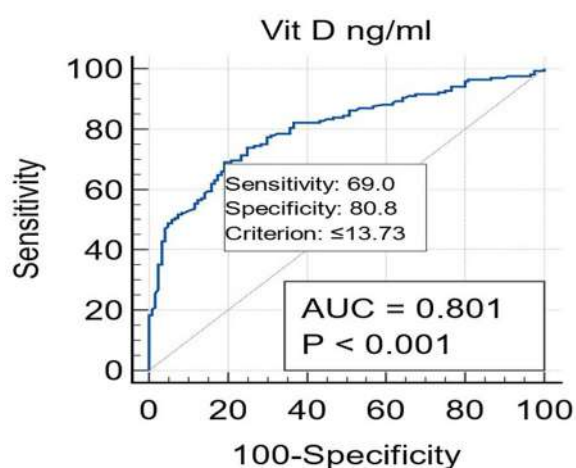


Figure 3. ROC curve of vitamin D level for absence of dry nights.

enuresis was 9.3 with female predominance. Nearly fifty-eight percent ($n=168$) of the study participants did not have dry nights.

As the vitamin D level was a strong covariate with the number of nocturnal enuresis, further analysis was performed in the absence and presence of dry nights. A significant association was observed (Figure 2). It seems that children who did not experience any dry nights had lower vitamin D levels.

Additionally, ROC analysis was carried out to outline the cut-off with the highest sensitivity and specificity for the absence of dry nights, and a cut-off of 13.7 with a considerable area under the curve was detected, as shown in Figure 3.

To control for possible confounders that could affect the predictive value of vitamin D in the absence of dry nights, a multiple logistic regression was performed. The vitamin D level was a significant predictive variable. Vitamin D levels seemed to be protective factors; the odds of the absence of any dry nights decreased

Table 3. Multivariate logistic regression for the absence of dry nights in children.

Independent variables	Univariate analysis		Multivariate analysis			
	p value	Unadjusted odds ratio	p value	Adjusted odds ratio	95% Confidence Interval for odds ratio	
					Lower	Upper
Vit D ng/ml	<0.001	0.840	<0.001	0.841	0.795	0.890
Vit B12 pg/ml	0.008	0.998	0.124	0.999	0.998	1
Gender (female)*	0.002	2.1	0.111	0.641	0.372	1.106
Age in years	0.396	0.954				
Behavioural treatment**(no)	0.015	1.08	0.012	0.492	0.283	0.855
Family disorders(yes)	0.235	1.34				
Psychiatric disorders*** (yes)	0.01	1.98	0.53	0.558	0.309	1.008

*Female gender is the reference, so the odds for the absence of dry nights decreased by 0.641 times in males compared to females.

**Absence of behavioural therapy is the reference. So, the odds of the absence of dry nights decreased in those children with behavioural therapies by 0.492 times compared to those without.

***The presence of any psychiatric disorder is the reference, so the odds of the absence of dry nights decreased in children without psychiatric disorders by 0.558 times compared to those children with.

N.B: p value is significant if <0.05 .

with higher levels of vitamin D (odds ratio =0.841, $p=0.001$), as shown in Table 3.

Discussion

Our study aimed to determine the prevalence of vitamin D and vitamin B₁₂ abnormalities in children with primary nocturnal enuresis. This study reports that vitamin D insufficiency could be a major risk factor for children with PNE because of the higher prevalence of vitamin D insufficiency in the enrolled children. Our report is very close to a previous report, in which a higher prevalence of vitamin D insufficiency and deficiency was detected [13]. Additionally, there was a strong inverse correlation between the number of nocturnal enuresis episodes per day and levels of vitamin D, a result that has been closely reported [13].

There are various explanations for the impact of vitamin D on bladder function. Vitamin D receptors, including those in the detrusor muscle and urothelium of the bladder, are found in both skeletal and smooth muscle cells. Vitamin D helps reduce bladder contractions by suppressing sensory signals during the bladder-filling phase. Insufficiency or deficiency of vitamin D can lead to uncontrolled bladder contractions. Additionally, vitamin D plays a role in bladder mucosal immunity by promoting cathelicidin production. Lack of vitamin D can increase the risk of recurrent urinary tract infections, leading to bladder dysfunction. Furthermore, low levels of vitamin D can affect the renal expression of endothelin-1 and decrease the activity of the epithelial sodium channel, potentially causing natriuresis [13–17].

Enuretic children who were capable of having some dry nights represented 41.7% of the study group. We were interested in defining the cut-off value for vitamin D, below which an enuretic child cannot have any dry nights. This cut-off was 13.7 ng/dl. Previous research has defined a higher cutoff value of 19 ng/dl, but this value was used to discriminate between enuretic and healthy children [11]. Therefore, it could be concluded that, with higher levels of vitamin D, the child's chance of being enuretic decreases.

Looking at the status of vitamin B₁₂, vitamin B₁₂ deficiency occurs in a considerable number of patients. New research in behavioural neuroscience has emphasized the importance of nutrition in brain development. These studies have shown that a lack of essential nutrients can have detrimental effects on children's cognitive abilities and motor neuron functions. Additionally, deficiencies in vitamin B₁₂ have been linked to behavioral changes, delayed puberty, and maturation of the central nervous system [18–20]. This could be the reason for the considerable prevalence of

vitamin B₁₂ deficiency in our enrolled patients, a result that was closely stated [21].

As part of the structured questionnaire, data regarding possible contributing factors for enuresis were gathered. Examples of these factors include the absence of behavioral treatment, the presence of family troubles, and the coexistence of psychiatric disorders.

To adjust the possible predictive value of vitamin D and vitamin B₁₂, all other possible contributing factors were studied *via* multiple logistic regression. It was found that higher levels of vitamin D and the co-existence of behavioral therapy were the only significant protective factors against severe enuresis, which was represented by the absence of dry nights. Behavioral interventions are the primary treatment approach for PNE. Vitamin D deficiency may be a potential cause of treatment failure [22]. Behavioural treatments for bedwetting are characterized as interventions that require the child to engage in conduct or activity that promotes night dryness, as well as techniques that reward that behavior [23]. Previous investigations have shown that vitamin D metabolites may cross the blood-brain barrier. Vitamin D has also been found in human CSF fluid. Therefore, it may play a role in the behavioural therapy [24].

Study recommendations

Our study recommends screening children with nocturnal enuresis for levels of vitamin D, as insufficiency of vitamin D predominated in our study, which may not have the clinical presentations of low vitamin D and might be bypassed. Furthermore, screening for vitamin B₁₂ deficiency should be considered.

Strength of the study

To the best of our knowledge, this is the first study to simultaneously investigate vitamin D and vitamin B₁₂ levels in children with PNE. Therefore, we outlined which of them was a stronger covariate for the severity of enuresis.

Limitations of the study

This is a cross-sectional study, meaning that no assumptions for etiology can be made. Only prevalence can be found from cross-sectional studies. To provide assumptions for etiology, cohort or case-control studies should be performed.

Conclusion

Through conducting this study, it was concluded that children with nocturnal enuresis suffered from low

levels of vitamin D and B₁₂ to some extent, which might have been a factor responsible for the sleep disorders and maturation delay, subsequently, for inducing the enuresis in children.

Acknowledgment

Thanks to the Research Committee of the Faculty of Medicine, Cairo University for helping make the kits of the required labs available

Authors' contributions

Hoda Atef Abdelsattar Ibrahim: conceptualization, data collection/curation, formal statistical analysis, arranging diagnostic investigations, project methodology, project administration, data validation and interpretation, visualization, supervision, literature review, manuscript drafting/writing, and editing; Shymaa Sobhy Menshawy: literature review, reviewing and editing; Fatma E. Hassan: literature review, reviewing and editing; Shirin M. El-Makawi: reviewing and resources; Omnia Raafat Amn: supervision and resources; Nermeen Bastawy: data collection and project methodology; Samar Saad, Shadia M. Hussein and Dina Mahmoud: delivering diagnostic investigations and their interpretation; Khaled Mohamed Abdelhamid ElKhashab: reviewing and supervision.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

No funding was received

ORCID

Hoda Atef Abdelsattar Ibrahim  <http://orcid.org/0000-0001-5399-8861>

Data availability statement

Raw data are available with the corresponding author upon reasonable request.

References

- [1] Altunoluk B, Davutoglu M, Garipardic M, et al. Decreased vitamin b(12) levels in children with nocturnal enuresis. *ISRN Urol.* 2012;2012:1. doi: [10.5402/2012/789706](https://doi.org/10.5402/2012/789706).
- [2] Cediell G, Pacheco-Acosta J, CastiUo-Durdn C. Vitamin D deficiency in pediatric clinical practice. *Arch Argent Pediatr.* 2018;116(1):e75-81-8. doi: [10.5546/aap.2018.eng.e75](https://doi.org/10.5546/aap.2018.eng.e75).
- [3] Gominak SC, Stumpf WE. The world epidemic of sleep disorders is linked to vitamin D deficiency. *Med Hypotheses.* 2012;79(2):132-135. doi: [10.1016/j.mehy.2012.03.031](https://doi.org/10.1016/j.mehy.2012.03.031).
- [4] Allen LH, Rosado JL, Casterline JE, et al. Vitamin B-12 deficiency and malabsorption are highly prevalent in rural Mexican communities. *Am J Clin Nutr.* 1995;62(5):1013-1019. doi: [10.1093/ajcn/62.5.1013](https://doi.org/10.1093/ajcn/62.5.1013).
- [5] Gomez Rincon M, Leslie SW, Lotfollahzadeh S. (2024). Nocturnal enuresis. In: *StatPearls. Treasure Island (FL): StatPearls Publishing; Available from: https://www.ncbi.nlm.nih.gov/books/NBK545181/*
- [6] von Gontard A, Schaumburg H, Hollmann E, et al. The genetics of enuresis: a review. *J Urol.* 2001;166(6):2438-2443. PMID: 11696807. doi: [10.1097/00005392-200112000-00117](https://doi.org/10.1097/00005392-200112000-00117).
- [7] Yeşiltepe Mutlu G, Hatun Ş. Use of vitamin D in children and adults: frequently asked questions. *J Clin Res Pediatr Endocrinol.* 2018;10(4):301-306. doi: [10.4274/jcrpe.0012](https://doi.org/10.4274/jcrpe.0012).
- [8] Ras RM, Aulesa C, Ortega JJ. Valores de referencia de la vitamina B12 en sangre en una población de niños y una de adultos con el método IMxRB12. Reference values for vitamin B12 in blood in a population of children and one of adults using the IMxRB12 method. *Sangre.* 1994;39(1):29-34.
- [9] Management of primary nocturnal enuresis. *Paediatr Child Health.* 2005;10(10):611-614. doi: [10.1093/pch/10.10.611](https://doi.org/10.1093/pch/10.10.611). PMID: 19668675; PMCID: PMC2722619.
- [10] Ma Y, Liu X, Shen Y. Behavioral factors for predicting severity of enuresis and treatment responses in different compliance groups receiving behavioral therapy. *Pak J Med Sci.* 2017;33(4):953-958. doi: [10.12669/pjms.334.12922](https://doi.org/10.12669/pjms.334.12922).
- [11] El-Baz FM, Abdelsayed MGR, Abdel-Hafeez AS, et al. Decreased vitamin D levels in children with primary mono-symptomatic nocturnal enuresis. *Egypt J Med Hum Genet.* 2021;22(1):71. doi: [10.1186/s43042-021-00191-8](https://doi.org/10.1186/s43042-021-00191-8).
- [12] Dhand NK, Khatkar MS. Statulator: an online statistical calculator. Sample size calculator for estimating a single proportion. 2014; Accessed 17 November 2023 at <http://statulator.com/SampleSize/ss1P.html>
- [13] Siroosbakht S. Are vitamin D levels linked to primary monosymptomatic nocturnal enuresis in children? Six years of experience about a controversy in medicine. A case-control study. *Iran J Pediatr.* 2023;33(3):e133755. doi: [10.5812/ijp-133755](https://doi.org/10.5812/ijp-133755).
- [14] Baer R, Tene L, Weintraub AY, et al. The effect of vitamin D deficiency and supplementation on urinary incontinence: scoping review. *Int Urogynecol J.* 2022;33(5):1083-1090. doi: [10.1007/s00192-021-04963-z](https://doi.org/10.1007/s00192-021-04963-z).
- [15] Shapiro B, Redman TL, Zvara P. Effects of vitamin D analog on bladder function and sensory signaling in animal models of cystitis. *Urology.* 2013;81(2):466 e1-7-466.e7. doi: [10.1016/j.urology.2012.10.027](https://doi.org/10.1016/j.urology.2012.10.027).
- [16] Hanna-Mitchell AT, Robinson D, Cardozo L, et al. Do we need to know more about the effects of hormones on lower urinary tract dysfunction? ICI-RS 2014. *Neurourol Urodyn.* 2016;35(2):299-303. doi: [10.1002/nau.22809](https://doi.org/10.1002/nau.22809).

- [17] Tokonami N, Cheval L, Monnay I, et al. Endothelin-1 mediates natriuresis but not polyuria during vitamin D-induced acute hypercalcaemia. *J Physiol.* 2017;595(8):2535–2550. doi: [10.1113/JP273610](https://doi.org/10.1113/JP273610).
- [18] Albayrak S, Zengin K, Tanik S, et al. Vitamin B12, folate and iron levels in primary nocturnal enuresis. *Pak J Med Sci.* 2015;31(1):87–90.
- [19] Keles A, Karakeci A, Onur R. Relationship between 25-hydroxyvitamin D, vitamin B12, folate and primer nocturnal enuresis (PNE) in five to thirteen year old children: a single center cohort study. *Eur Urol Suppl.* 2019;18(1):e923–e925. doi: [10.1016/s1569-9056\(19\)30673-6](https://doi.org/10.1016/s1569-9056(19)30673-6).
- [20] Black MM. Effects of vitamin B12 and folate deficiency on brain development in children. *Food Nutr Bull.* 2008;29(2 Suppl):S126–S31. doi: [10.1177/156482650802925117](https://doi.org/10.1177/156482650802925117).
- [21] Kompani F, Barati L, Mehrjerdian M, et al. Folic acid and vitamin B12 deficiency, two new findings in pediatric enuresis. *Iran J Pediatr.* 2023;33(2):e129308. doi: [10.5812/ijp-129308](https://doi.org/10.5812/ijp-129308).
- [22] Walker RA. Nocturnal enuresis. *Prim Care.* 2019;46(2):243–248. doi: [10.1016/j.pop.2019.02.005](https://doi.org/10.1016/j.pop.2019.02.005).
- [23] Caldwell PH, Nankivell G, Sureshkumar P. Simple behavioural interventions for nocturnal enuresis in children. *Cochrane Database Syst Rev.* 2013;19(7):CD003637. PMID: 23881652. doi: [10.1002/14651858.CD003637.pub3](https://doi.org/10.1002/14651858.CD003637.pub3).
- [24] Ucuz II, Dursun OB, Aydin N. The effects of vitamin D3 on brain development and autism. *Klinik Psikofarmakoloji Bülteni-Bull Clin Psychopharmacol.* 2015;25(3):302–311. doi: [10.5455/bcp.20141024012912](https://doi.org/10.5455/bcp.20141024012912).