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JIM Journal of Interdisciplinary Medicine

Aims and scope

The Journal of Interdisciplinary Medicine aims to publish top quality papers related to any fields of medicine that present an interdisciplinary dimension.

The journal will mainly focus on recent advances in the field of diagnosis and treatment of the most common situations encountered in the clinical or research practice. Interdisciplinary approaches will be extremely welcomed, presenting new advances in the approach of different pathologies from the perspective of various clinical fields.

The Journal of Interdisciplinary Medicine will publish high-quality basic and clinical research related to interdisciplinary medical fields, in a common approach that will integrate the clinical studies with the pre-clinical work dedicated to the discovery of new mechanisms involved in the development and progression of a large spectrum of diseases.

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Journal of Interdisciplinary Medicine

ORIGINAL RESEARCH

ORAL REHABILITATION // PERIODONTOLOGY

Drug-Induced Changes in the Gingival Tissue

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ABSTRACT

Introduction: Drug-induced gingivitis is caused by the administration of certain drugs such as hydantoin, calcium blockers, beta-blockers, cyclosporine, and oral contraceptives. The aim of this study was to evaluate the modifications linked to drug-induced gingivitis such as changes in color, volume, and consistency, and the clinical signs of periodontal disease. Materials and methods: The study was based on a questionnaire made up of 14 questions, formulated using colloquial language to increase addressability. Results: The most frequently used drugs were beta-blockers (37%), calcium channel blockers (33%), followed by anticonvulsants (18%), oral contraceptives (8%) and cyclosporine (4%). Color changes occurred in 81% of anticonvulsant treatments and 57% of oral contraceptives. Increases in the gingival volume were higher with anticonvulsants (73%) followed by cyclosporine (67%). Gingival consistency was higher with anticonvulsant treatments (90%), followed by calcium channel blockers (60%). Gingival changes and gingival bleeding during brushing were higher with anticonvulsant treatments, followed by beta-blocker medication. Spontaneous gingival bleeding had a higher prevalence in anticonvulsant treatments, followed by cyclosporine. Conclusions: The patients most affected by gingival enlargement were those under hydantoin treatment, followed by cyclosporine. Calcium channel blockers and beta-blockers had similar effects on gingival pathology. The intensity of the pathological changes that occurred secondary to the administration of these drugs was influenced by the dose, the duration of the treatment, and the association of several drugs. Early detection and management of gingival enlargement is important in order to allow patients to continue with their therapy, and also to increase their quality of life.

Keywords: gingival enlargement, hydantoin, calcium blockers, beta-blockers, cyclosporine, contraceptives

INTRODUCTION

Periodontal diseases include a large variety of conditions, some of which are induced by bacterial plaque, while others occur separately from biofilm build-up and may be modified or unaffected by it. The periodontal disease classification system of 1999 was the first to recognize the need to classify gingival diseases, but it had numerous flaws. This classification system did not define the state of periodontal

health, which is a critical factor in establishing the diagnosis of periodontal diseases. The description of gingivitis was excessively complex because it included both predisposing factors and factors that modify the evolution of the disease in the diagnosis. In 2017, a new classification was proposed that helps clinicians in establishing the diagnosis of periodontal diseases. New concepts, such as periodontal health status, were introduced, both histologically and clinically. Also, a reduced methodology was adopted, which helps to classify gingivitis in two major categories: gingivitis caused by the dental biofilm (due to dental biofilm only; facilitated by systemic or local risk factors; drug-induced gingival hypertrophy) and gingival conditions not caused by the dental biofilm (such as genetic/developmental conditions; specific infective disease; inflammatory and immune disorders; reactive processes, malignant, endocrinological and nutritional disorders, but also traumatic lesions and pigmentation).[1,2]

Nowadays, most people after a certain age receive a treatment that involves certain medication, which can have a multitude of adverse effects, with visible changes in the oral cavity. Drug-induced gingivitis is caused by the administration of drugs such as hydantoin, calcium blockers, beta-blockers, cyclosporine, and oral contraceptives.[3] Patients who have been prescribed both calcium antagonists and cyclosporine show excessive hypertrophy of the gingival tissue due to the combined effects of the two drugs.[4]

Hydantoin, used in the treatment of epilepsy, produces gingival hyperplasia in most patients, especially in children.[5] The association between hydantoin and gingival enlargement has been widely described. Other anticonvulsants, such as barbiturates, valproic acid, succinimides, and carbamazepine, may also induce gingival hyperplasia. However, the incidence of gingival hyperplasia associated with these agents is low compared to that of hydantoin-induced gingival enlargement. Of the 2 million patients taking hydantoin, approximately half had some degree of gingival hyperplasia, which may be related to the dosage, duration of treatment, and plasma levels of the drug.[6] Hydantoin hyperplasia also occurs in the absence of plaque and calculus in patients with good oral hygiene. The presence of bacterial plaque, however, causes increased inflammation, which also increases gingival hypertrophy and hyperplasia.

Calcium antagonists are a group of drugs used in the treatment of cardiovascular diseases that inhibit the influx of calcium ions through the cell membrane of cardiac cells and smooth muscles, blocking the intracellular mobilization of calcium. This leads to the dilation of coronary arteries and arterioles, thus improving the oxygenation of the heart muscle and reducing blood pressure by dilating peripheral vessels. Secondary to the administration of some of these drugs, gingival hyperplasia may occur.[7] The treatment of cardiovascular diseases with calcium channel inhibitors may have different effects in the oral cavity. It may restore cellular metabolism and stimulate cell proliferation in the gingiva. Histologically, calcium channel blocker-related gingival hyperplasia is characterized by an increase in the number of fibroblasts that closely resemble hydantoin-induced hyperplasia, a predominantly lymphocytic nonspecific inflammation. After a long-term treatment with amlodipine, mispositioned teeth were observed on both arches, which may lead to tooth extractions.[8] In the case of gingival hyperplasia caused by calcium antagonists, dental practitioners will not recommend stopping such a vital treatment, instead they will treat it with appropriate local therapy.[9]

Beta-blocker medication produces gingival enlargement in the lowest percentage of all antihypertensive medications. Research shows that some beta-blockers can still cause gingival hyperplasia, but with a very low prevalence rate of around 7.4%.[10]

Cyclosporine is an immunosuppressant administered to prevent the rejection of transplanted organs and for the treatment of autoimmune diseases. Gingival hyperplasia occurs in 30% of patients who receive this drug, more often in children.[11] Several techniques for gingival hyperplasia have been proposed, including dose reduction or substitution of medication, but also optimal oral hygiene programs and surgical treatment. Nevertheless, each of these approaches may have contraindications, and dose reduction or the use of alternative drugs is not possible in all situations. Other medicines may also have side effects. Surgery is only used for cosmetic reasons, and oral hygiene procedures can be used only for disease control in patients developing cyclosporine A-induced gingival hyperplasia but cannot inhibit its development.[12]

Oral contraceptives are used by approximately 50 million women worldwide. Numerous systemic and oral adverse reactions have been identified in patients who are under oral contraceptive treatment. Studies have found that the use of oral contraceptives is associated with a higher prevalence of gingival inflammation, attachment loss, and progression of periodontal disease.[13] Both estrogen and progesterone are known to cause increased gingival exudate, edema, and inflammation.[14] Women taking oral contraceptives for more than 1–2 years have been found to present gingival bleeding on probing, deeper periodontal pockets, and significant attachment loss. This indicates that the longer the duration of oral contraceptive use, the poorer the periodontal health status.

Due to the controversies surrounding the side effects of certain drugs on the gingival tissue and drug-induced gin-

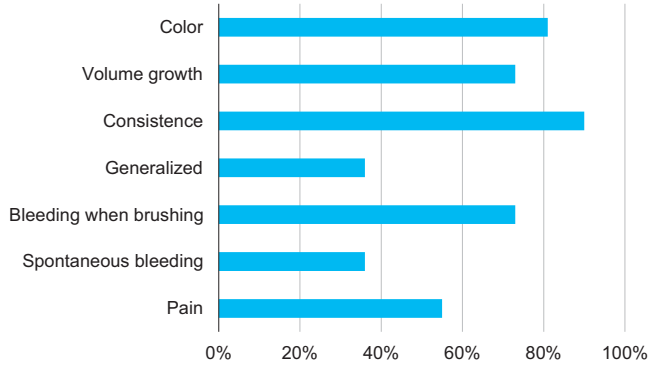

FIGURE 1. Gingival changes due to hidantoin

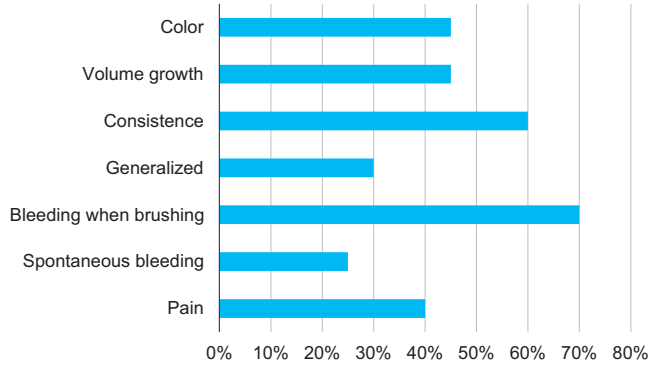

FIGURE 2. Gingival changes due to calcium blockers

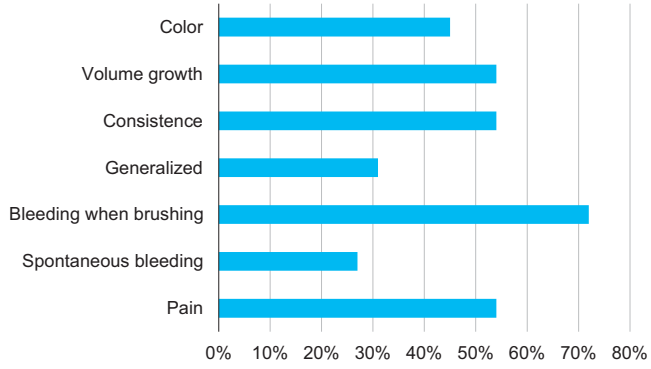

FIGURE 3. Gingival changes due to beta-blockers

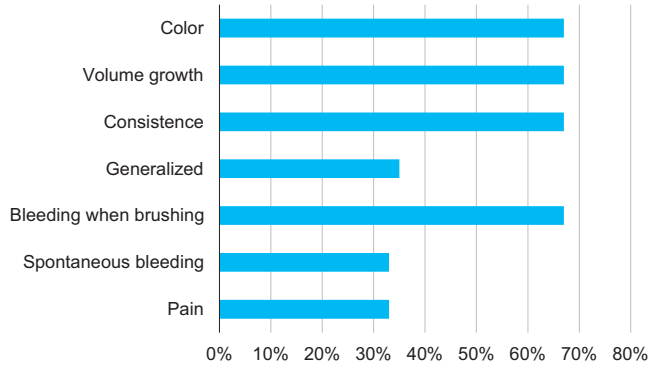

FIGURE 4. Gingival changes due to cyclosporine

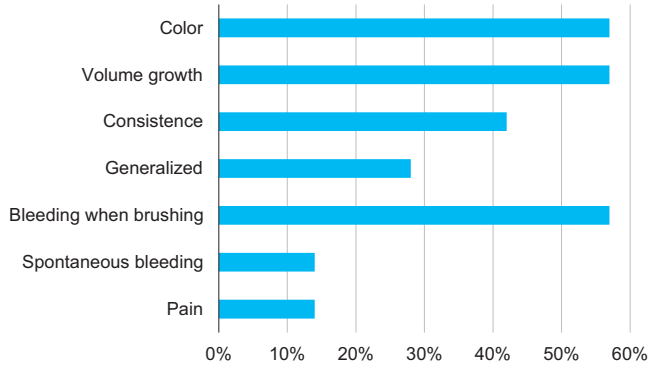

FIGURE 5. Gingival changes due to contraceptives

gival hyperplasia, we decided to evaluate the modifications linked to drug-induced gingivitis.

MATERIALS AND METHODS

The study took place between April 2020 and June 2021 at the Faculty of Dental Medicine of the "George Emil Palade" University of Medicine, Pharmacy, Science and Technology of Târgu Mureș, Romania. Due to the COVID-19 pandemic, our study was based on a questionnaire made up of 14 questions using colloquial language (for example: "increase in the volume of the gum" for gingival hypertrophy) to increase addressability. In the absence of a clinical examination, the questions were formulated according to the structure of an anamnestic questionnaire in order to guide the results toward formulating the most realistic conclusions possible regarding periodontal health. The first two questions referred to personal characteristics such as age and sex. Questions 3–7 referred to drug treatments that could induce changes in periodontal structures. Through questions 8–10, we wanted to detect the changes in color, volume, and consistency that appeared at a periodontal level. Questions 11–14 were related to the observation of relevant clinical signs that would suggest the installation of periodontal diseases: bleeding when brushing and the presence of gingival pain.

RESULTS

The majority of the patients were men (58.4%) aged between 50 and 69 years (68%). The most frequently used drugs were beta-blockers (37%), calcium channel blockers (33%), anticonvulsants (18%), oral contraceptives (8%), and cyclosporine (4%).

The changes that appeared in the gingival tissue due to the administration of these medications are presented in Figures 1–5. The most frequent changes in patients undergoing hydantoin treatment included changes in consistency, color, and also bleeding (Figure 1). For subjects treated with calcium channel blockers, the most frequent change was in consistency and bleeding while brushing (Figure 2), which was similar to those treated with beta-blockers (Figure 3). On the other hand, subjects undergoing treatment with cyclosporine more frequently presented changes in color and volume growth, but also changes in consistency and bleeding (Figure 4). The use of oral contraceptives triggered bleeding during brushing, changes in color and consistency (Figure 5).

DISCUSSION

The results of our study showed that color changes occurred in 81% of anticonvulsant treatments and 57% of oral contraceptives. Increases in the gingival volume were higher in patients receiving anticonvulsants, followed by cyclosporine. Gingival consistency was higher in subjects undergoing anticonvulsant treatments, followed by calcium channel blockers. Gingival changes and gingival bleeding during brushing were higher with anticonvulsant treatments, followed by beta-blocker medication. Spontaneous gingival bleeding had a higher prevalence in anticonvulsant treatments, followed by cyclosporine.

Many studies were conducted concerning the side effects of drugs on the gingival tissue. A retrospective study found only 147 cases of drug-induced gingival hyperplasia (0.04% of all cases). Patients were more frequently male (58.5%), aged between 40 and 69 years. The evolution was favorable in 47.5% of cases. The most common "suspected" drugs were calcium channel blockers (30.6%), followed by immunosuppressants (15.2%) and anticonvulsants (10.1%). Gingival hyperplasia has also been reported with less well-known periodontal drugs (mycophenolate mofetil, valproic acid, clarithromycin, ethinylestradiol, levonorgestrel, desogestrel etc.).[15]

Another study found that genetic factors and patient susceptibility are important for the etiopathogenesis of amlodipine-induced hyperplasia. Genetic predisposition may influence drug interactions, cells characteristics, plaque-induced inflammation, functional heterogeneity of gingival fibroblasts, collagenolytic activity, drug-receptor binding, collagen synthesis, and many other factors. Since most types of pharmacological agents involved in amlodipine-induced hyperplasia can have negative effects on the flux of calcium ions across cell membranes, it has been postulated that these agents can interfere with collagenase synthesis and function.[16] A recent in vitro study showed that treating human gingival fibroblasts with cyclosporine in relevant doses leads to significantly lower levels of MMP-1 and MMP-3 secretion. This will contribute to the accumulation of extracellular matrix components.[16]

Treatment with other antihypertensive medication, such as angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, and beta-blockers, produces changes at the gingival level less often compared to calcium channel blockers.[17,18] Therefore, in patients at risk for developing drug-induced gingivitis or those who already did, replacing calcium channel blockers with other antihypertensive drugs is a treatment option.[19]

Another study showed that drug-induced gingival hyperplasia occurs mainly in medical therapy with phenytoin, the antihypertensive drug nifedipine, and the immunosuppressant cyclosporine in 50% of the people who take this kind of medication. Gingival enlargement induced by drugs is an important oral health issue, particularly if insufficient attention is paid to oral hygiene by dentists or the patients themselves. This may occur due to a miscommunication between patients and physicians.[20]

Excessive gingival enlargement causes both physical and psychological suffering. Generally, the increase in gingival volume is limited, but severe cases can also occur when the gingival tissue completely covers the teeth, thus interfering with chewing and speaking. Gingival enlargement can also lead to depression and anxiety, especially when it causes esthetic problems, affecting the smile and facial expressions.[21]

CONCLUSIONS

The patients most affected by gingival enlargement are those under hydantoin treatment. After hydantoin, cyclosporine is the drug with the most adverse side effects on the periodontium. Calcium channel blockers and beta-blockers have similar effects on gingival pathology. The intensity of the pathological changes in the gingival tissue that occur secondary to the administration of these drugs is influenced by the dose, the duration of the treatment, and the association of several drugs. Early detection and management of gingival enlargement is important in order to allow patients to continue with their therapy, and also to increase their quality of life.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

REFERENCES

1. Caton JG, Armitage G, Berglundh T, et al. A new classification scheme for periodontal and peri-implant diseases and conditions – Introduction and key changes from the 1999 classification. *Journal of Clinical Periodontology*. 2018;89:1-8.
2. Chapple ILC, Mealey BL, Van Dyke TE, et al. Periodontal health and gingival diseases and conditions on an intact and a reduced periodontium: Consensus report of workgroup 1 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *J Clin Periodontol*. 2018;45:S68-S77.
3. Zhang R, Wu J, Zhu J, Wang X, Song J. Bibliometric analysis of research trends and characteristics of drug-induced gingival overgrowth. *Front Public Health*. 2022;10:979861.
4. Hughes FJ, Bartold PM. Periodontal complications of prescription and recreational drugs. *Periodontol 2000*. 2018;78:47-58.
5. Tungare S, Paranjpe AG. Drug Induced Gingival Overgrowth. 2022 Sep 19. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan.
6. Chacko LN, Abraham S. Phenytoin-induced gingival enlargement. *BMJ Case Rep*. 2014;2014:bcr2014204670.
7. Livada R, Shiloah J. Calcium channel blocker-induced gingival enlargement. *J Hum Hypertens*. 2014;28:10-14.
8. Quenela L, Keribinb P, Giranc G, Tessierd MH, Lesclouse P. Amlodipine-induced gingival enlargement: A case report. *Journal of Stomatology, Oral and Maxillofacial Surgery*. 2020;121:308-311.
9. Haruna H, Junko A, Yuuki H, et al. Drug-induced gingival hyperplasia: a retrospective study using spontaneous reporting system databases. *Journal of Pharmaceutical Health Care and Sciences*. 2017;3:19-25.
10. Syed AR, Omar BK, Bassel T, Dilshad U, Salah I. Propranolol-induced gingival hyperplasia with Nager syndrome: A rare adverse drug reaction. *Journal of Advanced Pharmaceutical Technology and Research*. 2016;7:64-68.
11. Chojnacka-Purpurowicz J, Wygonowska E, Placek W, Owczarczyk-Saczonek A. Cyclosporine-induced gingival overgrowth – Review. *Dermatol Ther*. 2022;35:e15912.
12. Claudio G, Giada B, Giuseppe Z, Carla MC. Gingival overgrowth induced by anticonvulsant drugs: A cross-sectional study on epileptic patients. *Journal of Periodontal Research*. 2020;57:363-369.
13. Heasman PA, Hughes FJ. Drugs, medications and periodontal disease. *Br Dent J*. 2014;217:411-419.
14. Markou E, Eleana B, Lazaros T, Antonios K. The influence of sex steroid hormones on gingiva of women. *Open Dent J*. 2009;3:114-119.
15. Emmanuelle BG, Haleh B, Jean-Louis M. Drug-induced gingival overgrowth: a study in the French Pharmacovigilance Database. *Journal of Clinical Periodontology*. 2012;39:513-518.
16. Lauritano D, Lucchese A, Di Stasio D, et al. Molecular Aspects of Drug-Induced Gingival Overgrowth: An In Vitro Study on Amlodipine and Gingival Fibroblasts. *Int J Mol Sci*. 2019;20:2047.
17. Bajkovec L, Mrzljak A, Likic R, Alajbeg I. Drug-induced gingival overgrowth in cardiovascular patients. *World J Cardiol*. 2021;13:68-75.
18. Ustaoğlu G, Erdal E, Karaş Z. Influence of different anti-hypertensive drugs on gingival overgrowth: A cross-sectional study in a Turkish population. *Oral Dis*. 2021;27:1313-1319.
19. Kamei H, Furui M, Matsubara T, Inagaki K. Gingival enlargement improvement following medication change from amlodipine to benidipine and periodontal therapy. *BMJ Case Rep*. 2022;15:e249879.
20. Trackman PC, Kantarci A. Molecular and Clinical Aspects of Drug-induced Gingival Overgrowth. *Journal of Dental Research*. 2015;94:540-54.
21. Debra F. Drug-Induced Gingival Overgrowth: More than a Cosmetic Issue. *Pharmacy Times*. 2015;81:7-14.

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ORIGINAL RESEARCH

NEUROLOGY // CLINICAL PHARMACOLOGY

Dual versus Monotherapy in the Prophylaxis of Acute and Chronic Migraine

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ABSTRACT

Background: Migraine, a primary headache disorder, is a debilitating condition with reduced productivity, increased disability, and a very high economic burden. The present study aimed to individualize the treatment protocols for episodic and chronic migraine in order to reduce the duration, frequency, and severity of attacks, as well as the disability associated with migraine by comparing monotherapy and dual therapy. **Materials and Methods:** We conducted a prospective observational study between February 2019 and July 2021. Patients were diagnosed with migraine based on simplified diagnostic criteria. Episodic migraine was present in 62% and chronic migraine in 38% of cases. Disability due to headache was assessed using the Migraine Disability Assessment Score (MIDAS) questionnaire. Prophylactic therapy was individualized, with 210 patients receiving monotherapy (propranolol, flunarizine, or valproic acid) and 190 patients receiving dual therapy (propranolol and flunarizine, or valproic acid and flunarizine). Disability at baseline was graded from I to IV, and improvement after treatment was graded as no recurrence of headache, grade I, grade II, and grade III. **Results:** After 2–3 months of therapy, we observed significant improvement in the form of reduction in the frequency of attacks and reduction of disability. Patients with grade II disability who received dual therapy showed 100% improvement with no recurrence of headaches. Treatment with valproic acid resulted in no recurrence in 100% of patients with grade I and 85.7% of patients with grade II disability scores. Significant improvement was observed in all grades of disability with dual therapy. **Conclusion:** Dual prophylactic therapy was more efficient than monotherapy in reducing the frequency, duration, and severity of symptoms in grade III and grade IV patients.

Keywords: Migraine Disability Assessment (MIDAS) score, monotherapy, dual therapy

INTRODUCTION

Migraine is a primary headache disorder and the second most common incapacitating and painful disorder in the world, affecting 6% of men and 15% of women.[1] The global prevalence of migraine is one in seven, and it is the seventh cause

of disability in the world.[2,3] Results from the International Burden of Migraine Study (IBMS) show that migraine-related disability has a high economic burden.[4] According to the International Classification of Headache Disorders, episodic migraine (EM) lasts <15 days per month, and chronic migraine (CM) lasts >15 days per month.[5] It has been estimated that about 2.5% of individuals with EM eventually progress to CM over time.[6]

The degree of disability at baseline and the subsequent response to treatment is usually determined with the Migraine Disability Assessment Score (MIDAS), a well-validated tool in the form of a questionnaire.[7] Management protocols involve a combination of non-pharmacological and pharmacotherapeutic interventions. The former includes lifestyle modification and avoidance of known trigger factors.[8,9] Pharmacological therapy includes abortive medications for acute attacks and prophylactic treatment for chronic migraineurs. Prophylaxis aims to reduce the severity, frequency, and duration of the attacks, thereby reducing the disability associated with the disease. Drugs used for prophylaxis include beta blockers such as propranolol, metoprolol, and nadolol; anticonvulsants such as valproic acid and topiramate; calcium channel blockers such as flunarizine; and antidepressants such as amitriptyline, dosulepin, venlafaxine, and desvenlafaxine.[10,11] Onabotulinum toxin A has recently been approved for migraine prophylaxis when headaches occur for more than 14 days a month. It is given every 12 weeks as multiple injections around the head and neck to try to dull future headache symptoms.[12]

The aim of this study was to explore the possibility to individualize the treatment protocols for episodic and chronic migraine in order to reduce the duration, severity, and frequency of attacks, as well as the disability associated with migraine by comparing monotherapy (propranolol, flunarizine, valproic acid) and dual therapy (propranolol and flunarizine, valproic acid and flunarizine).

MATERIALS AND METHOD

We carried out a prospective observational study between February 2019 and July 2021 on 400 patients in the outpatient neurology department of a tertiary care multispecialty teaching hospital, based on the simplified diagnostic criteria for migraine of the Headache Classification Committee of the International Headache Society, published in 2013. Written informed consent was obtained from all study participants, and the study was approved by the ethics committee of the institution where it was performed.

A standardized structured questionnaire was used to carry out the interview with regards to clinical symptom location, severity of pain, frequency of attacks, and the quality of headache. Comorbidities and migraine triggers were also assessed. These factors are both directly and indirectly related to the overall treatment response and the benefits of prophylactic treatment in migraine patients. Furthermore, a 5-item MIDAS questionnaire was filled out to assess the grade of disability associated with the migraine. The MIDAS scale quantifies the amount of disability and reduction in activity concerning school work, household work, employment etc. Greater disabilities are associated with higher scores. Scores were graded as grade I, grade II, grade III, grade IV, and Severe disability. Two groups of patients were selected randomly: the first one received monotherapy, and the second one received dual therapy as prophylactic treatment. Patients on monotherapy were randomly divided into 3 subgroups of 70 patients each. Each subgroup was put on beta blocker propranolol 20 mg/40 mg twice daily, cerebroselective calcium channel blocker flunarizine 10 mg once daily, and valproic acid/sodium valproate 250 mg/500 mg once daily, respectively. The other group of patients was put on prophylactic dual therapy for both episodic and chronic migraine and was subdivided into 2 subgroups of 95 patients each. One subgroup received a combination of propranolol 20 mg with flunarizine 10 mg, and the other received valproic acid 250 mg with flunarizine 10 mg. Patients were assessed before and after initiating prophylactic treatment, and disability at baseline was graded from I to IV. Likewise, improvement after treatment was graded as no recurrence of headache, grade I, grade II, and grade III. After 2–3 months of therapy, we observed improvement in the form of reduction in the frequency of attacks and reduction of disability. The MIDAS questionnaire was filled out again, to assess the improvement in the disability grades compared to the baseline MIDAS score.

The data was analyzed using Statistical Package for the Social Sciences software version 22 (SPSS Inc, Chicago, IL, USA). An independent t-test was used to compare the means of the groups, and a p value of less than 0.05 was considered significant.

RESULTS

Among the 400 patients with migraine, 72 (18%) were males and 328 (72%) females. The majority of patients were in the age group of 25–35 years (28%) followed by 36–45 years (25%). Two hundred ten (52.5%) patients were put on monotherapy and 190 (47.5%) on dual therapy.

Disability scores at baseline and their improvement after monotherapy with propranolol 20 mg/40 mg are present-

TABLE 1. Baseline disability scores and improvement after treatment with monotherapy (propranolol)

				Post-treatment improvement				Total	p value
				No recurrence	Grade I	Grade II	Grade III		
Propranolol 20 mg/ 40 mg BID	Disability at baseline	Grade I	N	10	0	–		10	>0.05
			% showing improvement	100.0%	0.0%	–	–	100.0%	
		Grade II	N	10	5	2	–	17	
			% showing improvement	58.8%	29.4%	11.7%	–	100.0%	
		Grade III	N	8	12	4	–	24	
			% showing improvement	33.3%	50.0%	16.6%	–	100.0%	
		Grade IV	N	3	13	2	1	19	
			% showing improvement	15.7%	68.4%	10.5%	5.2%	100.0%	
		Total	N	31	30	8	1	70	
			% showing improvement	44.28%	42.8%	11.42%	1.4	100.0%	

TABLE 2. Disability scores and improvement with monotherapy (flunarizine)

				Post-treatment improvement				Total	p value
				No recurrence	Grade I	Grade II	Grade III		
Flunarizine 10 mg	Disability at baseline	Grade I	N	10	0	0	0	10	>0.05
			% showing improvement	100.0%	0.0%	0.0%	0.0%	100.0%	
		Grade II	N	11	4	2	0	17	
			% showing improvement	64.0%	23.5%	11.76%	0.0%	100.0%	
		Grade III	N	6	15	1	2	24	
			% showing improvement	24.0%	62.5%	4.1%	8.3%	100.0%	
		Grade IV	N	3	13	2	1	19	
			% showing improvement	15.7%	78.9%	10.52%	5.2%	100.0%	
		Total	N	30	32	5	3	70	
			% showing improvement	42.8%	45.7%	7.1%	3.%	100.0%	

ed in Table 1. None of the patients with grade I scores had recurrence. Patients with grade II scores showed a 58.8% improvement with no recurrence. Those with grades III and IV showed little improvement. Clinical improvement after monotherapy with cerebroselective drug flunarizine 10 mg are presented in Table 2.

Prophylactic monotherapy with valproic acid 250 mg/500 mg led to a significant improvement in all grades of disability scores (Table 3). Grade I patients improved by 100%, and grade II patients showed no recurrence in 85.7% of cases. Grade III and grade IV patients improved to a disability score of grade I.

Improvement after dual therapy with propranolol and flunarizine are presented in Table 4, and the modifications of headache disability scores after dual therapy with valproic acid and flunarizine are presented in Table 5. We observed a reduction in disability scores from grade I and grade II at baseline to no recurrence of headache following dual prophylactic therapy ($p < 0.001$). Dual therapy has also reduced the disability scores of grade III and grade IV patients.

DISCUSSION

In the current study, participants who were administered propranolol 20 mg or 40 mg twice daily as monotherapy showed improvement from baseline disability and most patients did not report any recurrence during follow-up visits. Silberstein et al. conducted a similar study in which beta blockers propranolol (20–80 mg/day), timolol (10–15 mg twice daily), and metoprolol tartrate (50–200 mg/day) were effective in the prophylaxis of migraine as monotherapy.[13] These drugs are contraindicated in patients with bronchial asthma, congestive heart failure, dyslipidemia, and diabetes. Participants who were put on cerebroselective calcium channel blocker flunarizine as a prophy-

TABLE 3. Disability scores and improvement with monotherapy (valproic acid)

				Post-treatment improvement				Total	p value
				No recurrence	Grade I	Grade II	Grade III		
Valproic acid 250 mg/ 500 mg	Disability at baseline	Grade I	N	9	0	0	0	9	>0.05
			% showing improvement	100.0%	0.0%	0.0%	0.0%	100.0%	
		Grade II	N	18	3	0	0	21	
			% showing improvement	85.7%	14.3%	0.0%	0.0%	100.0%	
		Grade III	N	4	15	1	0	20	
			% showing improvement	20%	75%	5%	0.0%	100.0%	
		Grade IV	N	1	17	1	1	20	
			% showing improvement	5%	85%	5%	5%	100.0%	
		Total	N	32	35	2	1	70	
			% showing improvement	45.7%	50%	2.8%	1.4%	100.0%	

TABLE 4. Disability scores and improvement with dual therapy (propranolol 20 mg and flunarizine 10 mg)

				Post-treatment improvement				Total	p value
				No recurrence	Grade I	Grade II	Grade III		
Propranolol 20 mg and flunarizine 10 mg	Disability at baseline	Grade I	N	30	0	0	0	30	<0.001
			% showing improvement	100.0%	0.0%	0.0%	0.0%	100.0%	
		Grade II	N	25	0	0	0	25	
			% showing improvement	100.0%	0.0%	0.0%	0.0%	100.0%	
		Grade III	N	15	5	5	0	25	
			% showing improvement	60%	20.6%	20%	0.0%	100.0%	
		Grade IV	N	10	3	2	0	15	
			% showing improvement	66%	20%	13.3%	0.0%	100.0%	
		Total	N	80	8	7	0	95	
			% showing improvement	84.4%	88.4%	7.3%	0%	100.0%	

lactic medication for both episodic and chronic migraine showed complete symptomatic relief with no recurrence in 100% of cases with grade I disability, while 64% of patients had no recurrence who had initially grade II disability scores. The results suggest that flunarizine is a better prophylactic drug, especially for patients with grade I and grade II disability scores. The possible side effects, such as sedation, weight gain, and depression, may limit its use in some patients.

According to the 2022 guideline of the Scottish Intercollegiate Guidelines Network for the pharmacological management of migraine, sodium valproate is more effective than placebo for patients with episodic migraine and provides ≥50% reduction in headache frequency over a period of 2–3 months.[14] Being a teratogenic drug, it cannot be used as a first-line migraine prophylactic in women of childbearing age. Its efficiency is comparable to flunarizine 10 mg and propranolol 20 mg/40 mg.

Our study also showed that all patients with grade I disability scores had 100% improvement, with a reduction in headache frequency. Moreover, participants with grade III disability scores improved to a grade I score in 75% of cases. Linde et al. observed that sodium valproate was more effective than placebo as a prophylactic migraine medication, with a ≥50% reduction in headache frequency over a period of 2–8 months.[15] Possible side effects of valproic acid include alopecia, tremors, liver damage, and polycystic ovarian disease in girls, which can limit its use in the prophylaxis of episodic and chronic migraine.

Participants who received dual prophylactic medication (propranolol 20 mg + flunarizine 10 mg) had a significant reduction in their disability scores, as well as a decrease in the frequency of headaches. Participants with grade III and grade IV disability scores showed significant improvement, with no recurrence of symptoms. Our study also revealed that dual therapy with valproic acid 250 mg and flunarizine

TABLE 5. Disability scores and improvement with dual therapy (valproic acid 250 mg and flunarizine 10 mg)

				Post-treatment improvement				Total	p value
				No recurrence	Grade I	Grade II	Grade III		
Valproic acid 250 mg and flunarizine 10 mg	Disability at baseline	Grade I	N	25	0	0	0	25	<0.001
			% showing improvement	100.0%	0.0%	0.0%	0.0%	100.0%	
		Grade II	N	30	0	0	0	30	
			% showing improvement	100%	0.0%	0.0%	0.0%	100.0%	
		Grade III	N	15	10	0	0	25	
			% showing improvement	60%	40.0%	0.0%	0.0%	100.0%	
		Grade IV	N	5	10	0	0	15	
			% showing improvement	33.3%	66.6%	0.0%	0.0%	100.0%	
		Total	N	75	20	0	0	95	
			% showing improvement	78.9%	21.0%	0.0%	0.0%	100.0%	

10 mg showed excellent outcomes, as patients with grade III and grade IV disability scores showed no recurrence for a period of 3 months. The continuation of dual therapy has ameliorated the symptoms of both acute and chronic migraine, and improved the quality of life to a greater extent.

CONCLUSIONS

Patient-tailored migraine treatments need to be explored by evaluating the degree of attack frequency and calculating disability scores that account for the presence of medical or psychiatric comorbidities and associated trigger factors. In this study, dual therapy showed significant improvement and more tangible prognostic results than monotherapy, especially in patients with grade III and grade IV disability scores, as it markedly decreased the severity of pain, duration of headache, and frequency of attacks. A combination treatment with valproate and flunarizine can represent a better therapeutic armamentarium to tackle the disability associated with migraine, alleviate the pain, and improve the lives of migraine patients.

CONFLICT OF INTEREST

All authors declare no potential conflicts of interest.

REFERENCES

1. Peter JG, Neil H, Dennis LK, et al. Migraine and other Primary Headache Disorders. Principles of Internal Medicine. New York: Mc Graw Hill, 2016; p. 2586-2598.
2. Steiner TJ, Stovner LJ, Birbeck GL. Migraine: the seventh disabler. *Cephalalgia*. 2013;33:289-290.
3. Steiner TJ, Stovner LJ, Vos T. Migraine is the third cause of disability in under 50s. *J Headache Pain*. 2016;17:4.
4. Blumenfeld AM, Varon SF, Wilcox TK. HRQoL and resource use among chronic and episodic migraineures: results from the International Burden of Migraine Study (IBMS). *Cephalalgia*. 2011;31:301-315.
5. Headache Classification Committee of the International Headache society (IHS). The International Classification of Headache Disorders. *Cephalalgia*. 2013;33:629-808.
6. Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB. Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. *Headache*. 2008;48:1157-1168.
7. Stewart WF, Lipton RB, Whyte J, et al. An international study to assess reliability of the Migraine Disability Assessment (MIDAS) score. *Neurology*. 1999;53:988-994.
8. Kelman L. The triggers or precipitants of the acute migraine attack. *Cephalalgia*. 2007;27:394-402.
9. Banday MS, Wani M, Para BA, Qureshi S. Impact of trigger factors on clinical profile of migraine patients. *Int J Basic Clin Pharmacol*. 2020;9:1191.
10. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38:1–211.
11. Pooja Mohan Rao. Diagnosis and Treatment of Migraine. *Journal of Clinical Outcomes Management*. 2017;24:516-526.
12. Diener HC, Dodick DW, Aurora SK, et al. Onabotulinumtoxin A for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. *Cephalalgia*. 2010;30:804-814.
13. Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E. Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2012;78:1337-1345.
14. Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of migraine. Edinburgh: SIGN; 2022. https://www.sign.ac.uk/our-guidelines/pharmacological-management-of-migraine/ (15 February 2022)
15. Linde M, Mulleners WM, Chronicle EP, McCrory DC. Valproate (valproic acid or sodium valproate or a combination of the two) for the prophylaxis of episodic migraine in adults. *Cochrane Database Syst Rev*. 2013;6:CD010611.

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CASE REPORT

INTERNAL MEDICINE // TOXICOLOGY // INFECTIOUS DISEASES

Vitamin D Toxicity Due to Self-Medication During the COVID-19 Pandemic – a Case Report

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ABSTRACT

Introduction: During the COVID-19 pandemic, vitamin D was used along with vitamin C and zinc as a preventive and curative therapy against SARS-CoV-2 infection. Vitamin D toxicity, even if it is rare, occurs when serum concentrations exceed 150 ng/mL and is usually manifested by hypercalcemia phenomena. **Case report:** We hereby report a case of two twin sisters who self-medicated with vitamin D in a dose of 4 × 4,000 IU/day for almost 10 months as a method of 'protection' against COVID-19, influenced by mass media advertising. The patients presented to the emergency department with hypervitaminosis D-related symptoms such as hypertension, headache, nausea, vomiting, and diffuse abdominal pain. Laboratory investigations revealed high levels of vitamin D and calcium. **Conclusions:** Vitamin D toxicity can lead to difficulties in positive and differential diagnosis because of the multiple complications of hypercalcemia.

Keywords: vitamin D toxicity, hypercalcemia, SARS-CoV-2, self-medication

INTRODUCTION

Vitamin D is an important secosteroid hormone that plays a significant role in maintaining the normal balance of calcium and phosphorus (Figure 1).[1,2] In addition to its important role in calcium metabolism, vitamin D is known for its immunomodulatory effects, as it can modulate innate and adaptive responses.[3] During the COVID-19 pandemic, vitamin D was used along with vitamin C and zinc as preventive and curative therapy against SARS-CoV-2 infection.[4] Vitamin D deficiency is a worldwide public health problem and is defined as a level of less than 20 ng/mL (Table 1).[5] Vitamin D toxicity occurs when serum concentrations exceed 150 ng/mL and is usually manifested in the form of hypercalcemia phenomena (Table 2).[6]

We hereby report a case of hypercalcemia due to vitamin D overdose as a method of 'protection' against SARS-CoV-2 infection.

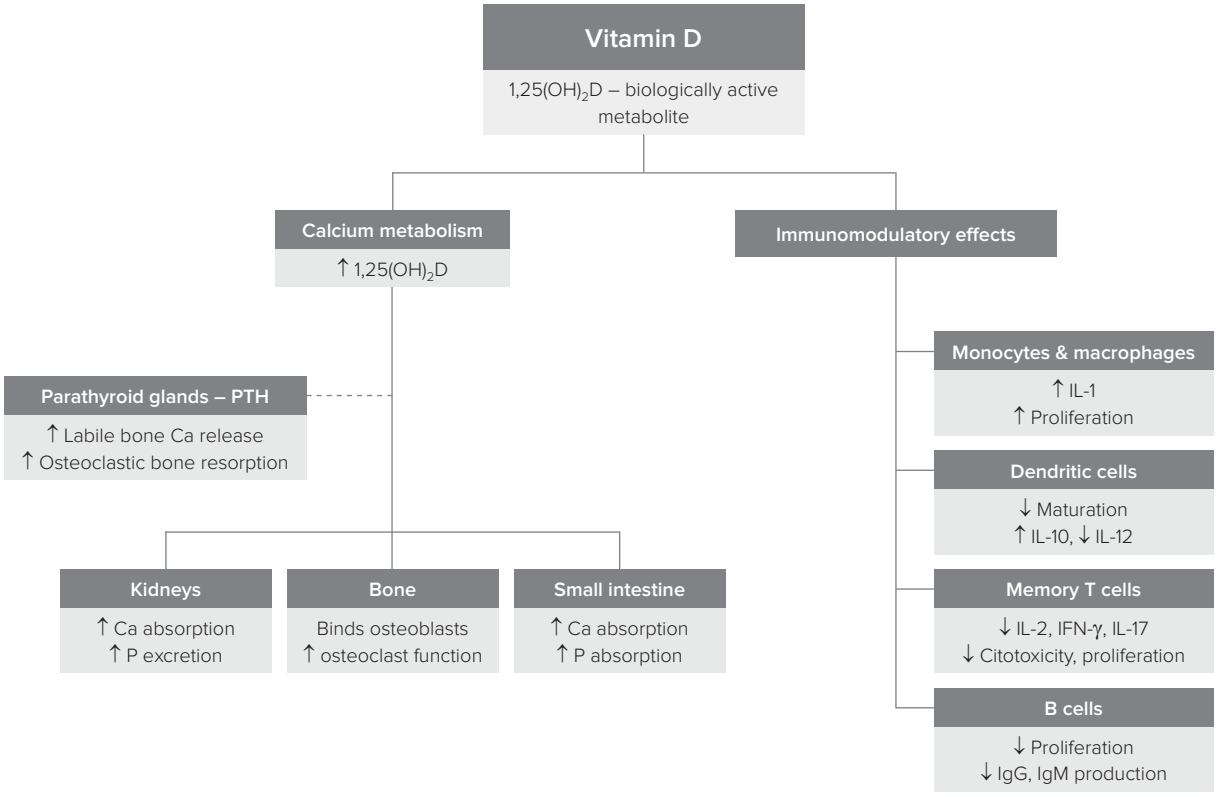

FIGURE 1. The role of vitamin D in calcium metabolism and its immunomodulatory effects[1,2]

Ca, calcium; P, phosphorus; IL-1, interleukin 1; IL-2, interleukin 2; IL-10, interleukin 10; IL-12, interleukin 12; IL-17, interleukin 17; IFN-γ, interferon gamma

CASE REPORT

In June 2022, two 27-year-old twin sisters with a history of borderline behavior disorder presented to the emergency department and were subsequently admitted to the Department of Internal Medicine for nausea, vomiting, headache, toothache, diffuse abdominal pain, constipation, fatigue, and hypertension over the past 3 weeks. The patients reported self-medication with vitamin D in a dose of 4 × 4,000 IU/day for almost 10 months as a method of 'protection' against COVID-19, influenced by mass media advertising.

TABLE 1. Diagnostic cut-off points for vitamin D concentrations[5]

Category	nmol/L	µg/L
Deficiency	<50	<20
Insufficiency	51–74	21–29
Sufficient	>75	>30
Excess	>250	>100
Intoxication	>375	>150

Laboratory investigations were performed in both patients. In one of them, they revealed the following pathological values: hemoglobin 11.6 g/L, creatinine 2.4 mg/dL, uric acid 12.7 mg/dL, vitamin D >150 µg/L, calcium 3.98 mmol/L, urine examination with 75 leukocytes/µL,

TABLE 2. Diagnostic cut-off points for vitamin D concentrations[5]

Category	Symptoms
Generalized	Fatigue Irritability
Gastrointestinal	Anorexia Constipation Nausea and vomiting
Musculoskeletal	Muscle weakness
Renal	Kidney stones Renal insufficiency
Central nervous system	Irritability Confusion Slurred speech Unstable gait
Metabolic	Dehydration Hypercalcemia

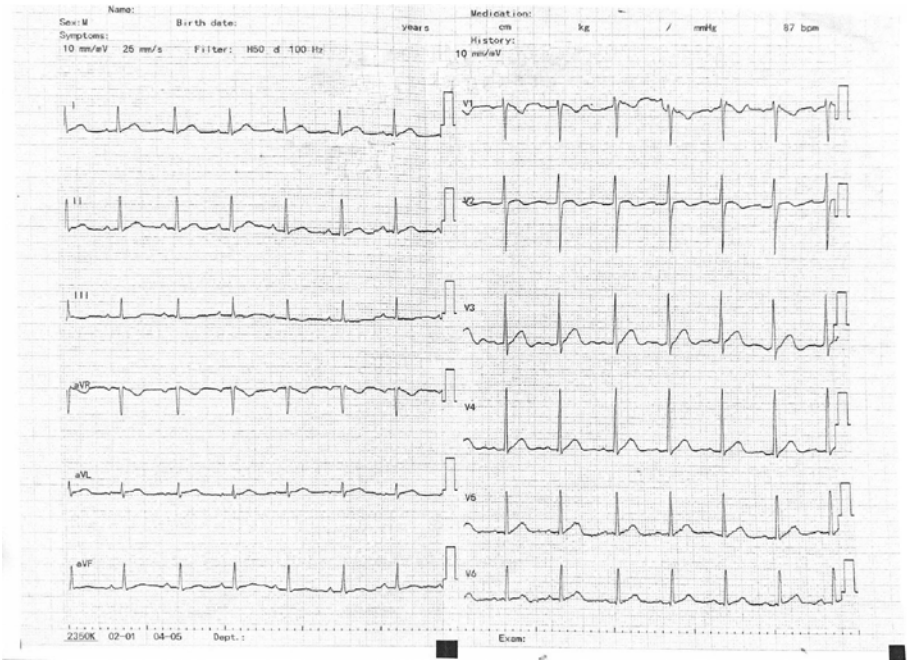

FIGURE 2. ECG of the first patient

negative nitrites. Laboratory examination of the other patient revealed the following pathological values: hemoglobin 11.5 g/L, creatinine 1.83 mg/dL, uric acid 11.3 mg/dL, vitamin D >150 μg/L, calcium 4.43 mmol/L, urine examination with 500 leukocytes/μL, negative nitrites. In both cases, the electrocardiograms (ECGs) showed ST-segment shortening (Figures 2 and 3). One day after admission, the laboratory tests were repeated and revealed a lower hemoglobin level – 9.7 g/L and 9.3 g/L – with no signs of bleeding. Gastroscopy was suggested, but the patients refused it. Parathyroid hormone or phosphorus levels were not determined in either case. Bacterial urine culture was negative in both cases. Ultrasonography of the abdomen showed decreased renal parenchymal index

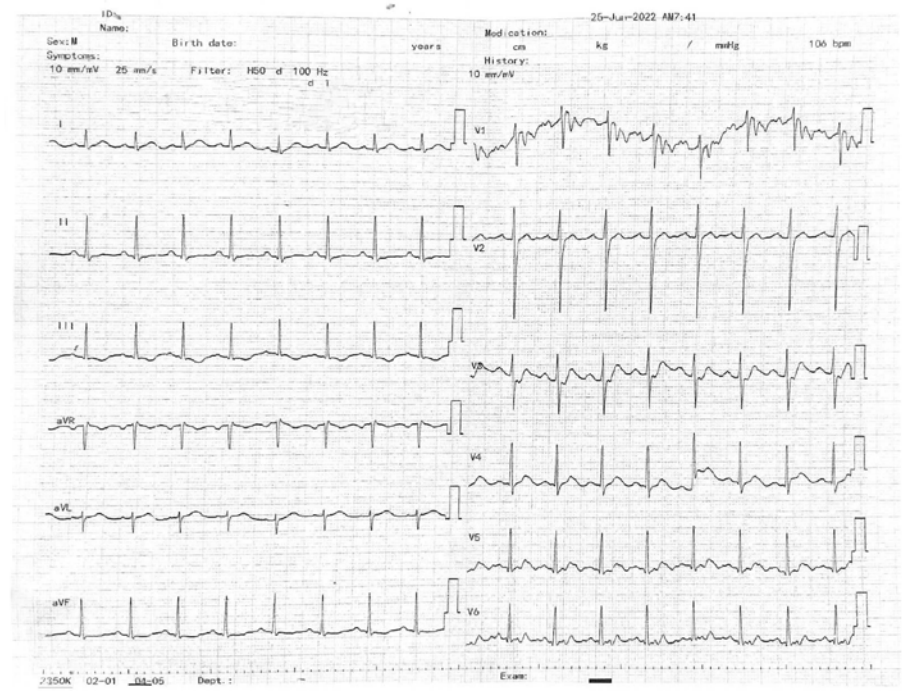

FIGURE 3. ECG of the second patient

and poor corticomedullary differentiation of the kidney in both cases.

During admission to the Department of Internal Medicine, the patients were treated with intravenous saline, diuretics, and oral antihypertensive therapy, with regular monitoring of hemogram, renal function, vitamin D, and calcium levels. Creatinine and uric acid showed normalized values after 11 days.

The patients were discharged after 12 days with a prescription for low-calcium diet and antihypertensive therapy, and were advised to maintain good fluid intake. They were also advised not to take vitamin D and not to expose themselves to the sun.

In November 2022, the patients presented for a follow-up. Vitamin D was still high in both cases (510 ng/mL and 490 ng/mL). The patients agreed to the publication of their clinical data and this case report.

DISCUSSION

In December 2019, the outbreak of SARS-CoV-2 began in Wuhan, China, and rapidly spread worldwide, resulting in a global health crisis with significant psychological and socioeconomic consequences.[4] Because it is a highly virulent virus that is primarily spread through contact and respiratory droplets, people had to make radical choices to protect themselves such as isolation, wearing face masks, social distancing in public, and using preventive medicine.[2] During the pandemic, as well as today, the mass media heavily advertised vitamin and mineral supplements. Out of general concern, people tend to overdose on these supplements without consulting a physician.

Vitamin D is a fat-soluble vitamin that plays an important role in calcium metabolism, as well as in innate and adaptive immunity.[3] Vitamin D receptors are known to be expressed on T cells, B cells, and antigen-presenting cells. Vitamin D modulates immune function through its action on dendritic cells and T cells, which are involved in reducing the inflammatory response and promoting viral defense.[7] In addition, vitamin D plays a variety of roles, including regulating the transcription of antimicrobial peptides in different cell lines, contributing to the differentiation of monocytes and macrophages, and suppressing the production of proinflammatory cytokines.[8] Tang *et al.* demonstrated that normal vitamin D levels are associated with lower levels of IL-1 and IL-6.[9] The pathophysiology of SARS-CoV-2 infection includes the overproduction of several proinflammatory cytokines such as IL-1, TNF, IL-6, IL-12, IL-17, GM-CSF, and IFN-γ, which may trigger the cytokine storm.[2,8] Furthermore, vitamin D receptors have been identified in epithelial cells of the human respiratory tract, having the ability to regulate local respiratory homeostasis by upregulating the expression of antimicrobial peptides or by influencing viral replication.[8] Akbar *et al.* performed a meta-analysis with 14 studies and 999,179 participants, which showed that low serum vitamin D levels were associated with higher rates of SARS-CoV-2 infection, severe courses, and mortality.[10]

According to Amos *et al.*, vitamin D is involved in zinc homeostasis, which plays an important role in reducing coronavirus replication.[11] During the pandemic, and even today, vitamin D, vitamin C, and zinc are used as preventive medicine and are considered 'immunity boosters' by the general population.[4] Because of the general concern and perhaps because of the intense advertising in the mass media, people started self-medication with vitamins without considering the toxicity risk. As in our case, patients overdosed on vitamin D under the influence of media advertising. Also, the fact that they did not need a doctor's prescription encouraged them to self-medicate without consulting a physician. On the other hand, prescription errors can also lead to vitamin D toxicity, often being seen in patients requiring high doses for the treatment of various conditions.

Hypercalcemia is defined as a total calcium level greater than 2.5 mmol/L and is considered a medical emergency when it exceeds 3.5 mmol/L.[12] It has many manifestations including neurologic, cardiac, renal, and gastrointestinal.[12,13] The etiology of hypercalcemia includes malignancy, hyperparathyroidism, or osteoporosis, but in rare cases, it may be due to excessive vitamin D intake.[1,2,13,14] In our case, hypercalcemia occurred due to excessive vitamin D intake over a long period of time (16,000 IU/day for almost 10 months). The main complications in our case were hypertension and acute kidney injury. Being a fat-soluble vitamin, vitamin D is excreted slowly, which is why both patients had high serum vitamin D levels at follow-up.

CONCLUSION

Vitamin D toxicity, although rare, can lead to difficulties in positive and differential diagnosis because of the multiple complications of hypercalcemia. One of the factors contributing to vitamin D overdose is probably the intense advertising in the media and the possibility of obtaining the vitamin without a doctor's prescription.

As outlined, vitamin D is involved in immunity in many ways and plays an important role in the prevention and cure of SARS-CoV-2 infections by lowering the rate of infection, improving the course, and reducing mortality.

CONFLICT OF INTEREST

Parts of the case have been reported at the 2023 National Congress of the Romanian Society of Internal Medicine.

REFERENCES

1. Chen L, Wen Y, Kuo C, Chen K. Calcium and Vitamin D Supplementation on Bone Health: Current Evidence and Recommendations. *Int J Gerontol*. 2014;8:183–188.
2. Rosas-Peralta M, Holick MF, Borrayo-Sánchez G. Dysfunctional immunometabolic effects of vitamin D deficiency, increased cardiometabolic risk. Potential epidemiological alert in America? *Endocrinol Diabetes Nutr*. 2014;64:162–173.
3. Amrein K, Scherkl M, Hoffmann M. Vitamin D Deficiency 2.0: An Update On The Current Status Worldwide. *Eur J Clin Nutr*. 2020;74:1498–1513.
4. Name JJ, Souza ACR, Vasconcelos AR, Prado PS, Pereira CPM. Zinc, Vitamin D and Vitamin C: Perspectives for COVID-19 With a Focus on Physical Tissue Barrier Integrity. *Front Nutr*. 2020;7:606398.
5. Taylor PN, Davies JS. A Review Of The Growing Risk Of Vitamin D Toxicity From Inappropriate Practice. *Br J Clin Pharmacol*. 2018;84:1121–1127.
6. Brant, J. Vitamin D In The Prevention Of Aromatase Inhibitor–Induced Musculoskeletal Symptoms: Is It Ready For Practice? *J Adv Pract Oncol*. 2012;3:245–248.
7. Sassi F, Tamone C, D'Amelio P. Vitamin D: Nutrient, Hormone, And Immunomodulator. *Nutrients*. 2018;10:1656.
8. Pinheiro MM, Fabbri A, Infante M. Cytokine Storm Modulation In COVID-19: A Proposed Role For Vitamin D And DPP-4 Inhibitor Combination Therapy (VIDPP-4i). *Immunotherapy*. 2021;13:753–765.
9. Tang J, Zhou R, Luger D. Calcitriol Suppresses Antiretinal Autoimmunity Through Inhibitory Effects On The Th17 Effector Response. *J Immunol*. 2009;182:4624–4632.
10. Akbar MR, Wibowo A, Pranata R, Setiabudiawan B. Low Serum 25 Hydroxyvitamin D (Vitamin D) Level Is Associated With Susceptibility To COVID-19, Severity, And Mortality: A Systematic Review And Meta-Analysis. *Front Nutr*. 2013;8:660420.
11. Amos A, Razzaque MS. Zinc And Its Role In Vitamin D Function. Current Research In Physiology. *Curr Res Physiol*. 2022;5:203–207.
12. Mahendra A. Hypercalcemia. https://emedicine.medscape.com/article/240681-overview (2 March 2023).
13. Tebben PJ, Singh RJ, Kumar R. Vitamin D-Mediated Hypercalcemia: Mechanisms, Diagnosis, And Treatment. *Endocr Rev*. 2016;37:521–547.
14. Asif A, Farooq N. Vitamin D Toxicity. [Updated 2022 Apr 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan. https://www.ncbi.nlm.nih.gov/books/NBK557876/ (28 April 2022)

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