

Evaluation of vitamin D prescribing and consumption in Türkiye

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ABSTRACT

Background and Aims: Vitamin D plays several roles in keeping the body's cells healthy and functioning the way they should. Most people do not get enough Vitamin D, so supplements are common. However, it is also possible for this vitamin to build up and reach toxic levels in the body. This study investigated the prescription of Vitamin D and Analogues in primary care and outpatient consumption in Türkiye between the years 2015- 2018. Also, the number of protocols created with Hypervitaminosis D was evaluated.

Methods: In this study, drug consumption data were evaluated by Prescription Information System (PIS) and ATC/DDD (Anatomical, Therapeutic and Chem- Defined Daily Dose) Methodology. Descriptive statistics were used for evaluation of the data, and numerical values were presented via tables and graphics. Statistical analysis of the data was performed using the SPSS 23 (Statistical Package for the Social Sciences) package program. The Chi-square test was used to evaluate the relationship between the variables, and the P value below 0.05 was accepted as a statistical significance.

Results: Between 2015 and 2018, a total of 11.874.898 prescriptions containing drugs with the A11CC (Vitamin D and Analogues) ATC code were created by family physicians. The total number and the percentage of prescriptions containing Vitamin D and Analogues increased over these years. There was a statistically significant difference between the number of prescriptions. While the percentage of prescriptions containing Vitamin D and Analogues was 0.89 in 2015, it was 3.38 in 2018. It was determined that the percentage of prescriptions increased over these years. The consumption of the drugs with the A11CC ATC code in outpatients increased over these years according to the ATC/DDD methodology.

Conclusion: The study showed that the prescription of preparations containing Vitamin D by family physicians increased significantly over the years and there was an increase in Vitamin D consumption in outpatients. In addition, it was shown that the number of protocols established for the diagnosis of Hypervitaminosis D increased over the years in Türkiye.

Keywords: Drug, drug consumption, rational drug use, Vitamin D, prescribing

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INTRODUCTION

The World Health Organization (WHO) defined a drug as a substance used to examine or change physiological systems or pathological conditions for the benefit of the living creature (Kayaalp, 2005).

Like the consumption of drugs, the unconscious consumption and abuse of drugs are as old as civilization. Drug abuse is the use of drugs outside of medical indications or in a way that does not comply with the cultural and social structure of that society (Vural, 2005).

All drugs are open to unnecessary, inappropriate and unconscious consumption, and undesirable effects can be observed even at treatment doses. One of the drugs thought to be used unconsciously in Türkiye is Vitamin D. Vitamin D is an important vitamin for almost all systems of our body (Kayaalp, 2005).

Vitamin D regulates calcium and phosphorus metabolism through especially three target organs, namely, kidney, bone and small intestines, maintains the body's Ca and P balance, and also has important effects on our body (Kayaalp, 2005; Holick, 2007). Vitamin D is a fat-soluble vitamin and is transported to the tissue level by binding to the carrier protein in the blood (Kayaalp, 2005; Holick, 2007; Holick, 2017; Osteoporoz ve Metabolik Kemik Hastalıkları Tanı ve Tedavi *Kılavuzu*, 2022).

Awareness of using Vitamin D has increased in recent years. Its use has become popular with the influence of media such as the internet, social media, television, radio and newspaper. It should not be forgotten that Vitamin D is also a drug, it is stored in the body by dissolving in fat and its use in high doses can cause toxic effects. The awareness, knowledge and conscience level of health professionals and the public should be increased about these issues. Like all drugs, great attention should be paid to the pharmaceutical form, frequency and dose of Vitamin D.

The aim of this article is to evaluate the prescription and consumption of Vitamin D in Türkiye. The situation assessment was made by evaluating Vitamin D prescribing in primary health care institutions in Türkiye through the Prescription Information System (PIS) and examining Vitamin D consumption in outpatients according to the ATC/DDD Methodology (Anatomical Therapeutic Chemical /Defined Daily Dose). In addition, the number of protocols created with the diagnoses of "Hypervitaminosis D", "Poisoning with Vitamins" and "Side Effects Caused by Vitamins" in health institutions in Türkiye were evaluated.

In Türkiye, oral solution, injection solution, oral drops, ampoule, tablet and capsule formulations containing "Vitamin D and its Analogues" are available (TİTCK SKRS E-Reçete İlaç ve Diğer Farmasötik Ürünler Listesi, 2022).

Vitamin D levels that can be consumed daily according to the age group are stated on the official website of the Turkish Medicines and Medical Devices Agency (TMMDA).

Although there is no consensus on the optimal level of Vitamin D as a result of the studies, in most guidelines, the Vitamin D level is defined as:

- Deficiency if it is <10 ng/ml (25 nmol/L),
- Insufficiency if it is between 10 - 20 ng/ml (25-50 nmol/L),
- Sufficient if it is >20 ng/ml (50 nmol/L) (Holick, 2009; Manson, Brannon, & Rosen, 2016; Pilz et al., 2019; Altieri et al., 2009; Sempos et al., 2018 Boullion & Carmet, 2018; Giustina et al., 2019; Lips et al., 2019; Dawson-Hughes, 2022).

According to the Turkish Society of Endocrinology and Metabolism Osteoporosis and Metabolic Bone Diseases Working Group, the Vitamin D level is:

- Insufficient if it is between 10-20 ng/ml (25-50 nmol/L),
- Deficient if it is <10 ng/ml (25 nmol/L),
- Sufficient for bone health if it is >20 ng/ml (50 nmol/L),
- Sufficient for its extra-bone effects if it is between 30-50 ng/ml (75-125 nmol/L) (TİTCK KÜB/KT Listesi 2022).

Vitamin D intoxication and hypervitaminosis D are different cases.

According to the related sources:

Serum 25-OH Vitamin D level:

- >100 ng/ml (250 nmol/L) is considered D hypervitaminosis.
- >150 ng/ml (375 nmol/L) is considered as Vitamin D intoxication (Giustina et al., 2019; Lips et al., 2019; Dawson-Hughes, 2022; Galior, Grebe & Singh, 2018; Osteoporoz ve Metabolik Kemik Hastalıkları Tanı ve Tedavi *Kılavuzu*, 2022).

According to the Endocrine Society serum 25-OH Vitamin D level >150 ng/L and calcium level >10.5 mg/dl are defined as Vitamin D intoxication (Dawson-Hughes, 2022).

With the increase in awareness about Vitamin D all over the world, the use of exogenous Vitamin D has increased, and there has been an increase in cases of hypervitaminosis D/Vitamin D intoxication (19-44). When the PIS data obtained from TMMDA are examined, it has been determined that there has been an increase in the cases of hypervitaminosis D in Türkiye over the years.

According to the the cases examined; The most common causes of irrational use of Vitamin D have been found to be:

- Vitamin D is not seen as a drug by the society,
- The perception that Vitamin D will not harm no matter what dose is used,
- Inappropriate doses of Vitamin D are usually given to the baby during infancy,
- Health professionals such as physicians, pharmacists, and nurses recommend to the parents that the baby should take

a high dose of Vitamin D, even though the baby is not diagnosed with Vitamin D deficiency and/or rickets,

- The parents want their babies to teethe early, accelerate bone development, walk early, and use inappropriate doses of Vitamin D on their babies, voluntarily, based on hearsay information,
- The desire of the elderly to consume high doses of Vitamin D without any recommendation,
- Consuming the ampoule form of Vitamin D although it is not needed,
- Consuming more ampoule forms than necessary,
- Oral consumption of the ampoule form,
- Long-term use of Vitamin D above the daily dose (Özkan, Hatun, & Bereket, 2012; Hossein-Nezhad & Holick, 2013; Urbańska, Łukaszkiwicz, Płudowski, & Jones, 2018; Ketha, Wadams, Lteif, & Singh, 2015; Belaidi et al., 2016; Garbim et al., 2017; Ertl et al., 2017; Scheelings, Slocombe, & Bayley, 2017; Sharma, Dutta, Sharma, & Gadpayle, 2017; Vincentis et al., 2021; De Paula et al., 2020; Bozacı, Avcı, Nalbant, Vasi, Soydan M., 2018; Balkan and Ünal, 2013; Yılmaz, Gül, Çakan, & Aydın, 2014; Uytun, Ertural, Baş, & Torun, 2014; Ünal et al., 2007; Taşkesen Gümüş & Katar, 2009; Yasar, Fırat, Özer, Özer, & Erdemir, 2011; Kara, Yıldırım Baş, & Öngel, 2012; Sarı, Bülbül, Benzer, Akçay, Özkul Sağlam, 2014; Türkmenoğlu et al., 2014; Uğur et al., 2016; Buluş, İnan, Demet, & Andiran, 2016; Aydın & Dokuzlar, 2018).

MATERIALS AND METHODS

Materials

In this study, the data was evaluated by both Prescription Information System (PIS) and ATC/DDD Methodology.

PIS is an electronic system managed by the Turkish Medicines and Medical Devices Agency of the Ministry of Health, which analyzes and evaluates the drugs prescribed by physicians, and enables them to follow up and inform the physicians about their own prescriptions

ATC/DDD Methodology is a drug classification system developed, managed and supported by WHO. The ATC/DDD is a unique methodology which allows the presentation and comparison of drug consumption statistics on national and international platforms. The differences such as amount, dose, duration, and population are eliminated with this methodology. The use of the ATC/DDD methodology in drug use research continues to become increasingly common around the world.

The ATC/DDD methodology is also an important comparison method used in drug consumption studies and is accepted worldwide. With this method, a defined daily dose is examined in proportion to the population, and thus, drug consumption comparisons can be made more concretely (Aksoy, Alkan, İşli, 2015; TİTCK Akılcı İlaç Kullanımı Web Sitesi 2022).

In this article, the consumption of Vitamin D and Analogues in outpatients in Türkiye was examined using the ATC/DDD methodology, which is a method recommended by WHO and

where comparisons can be made between data in national and international fields. A comparison of the consumption of Vitamin D and Analogues between 2015 and 2018 was made by calculating the "defined daily dose (DDD) per 1.000 people in a day".

A drug in the Vitamin D and Analogues group in the ATC classification system is in the main group A (Level 1) and has the code A11CC (WHO ATC/DD Index 2022).

Defined daily dose (DDD) expresses the average daily maintenance dose assumed to be used in adults for the main indication of a drug in the ATC system. DDD is a statistical measure of drug consumption determined by WHO and is used to standardize the comparison of drug use in different drugs or in different health care settings TİTCK Akılcı İlaç Kullanımı 2022).

DDD is based on main indication, maintenance dose and route of administration. DDD can only be assigned to drugs with an ATC code. DDD is a unit of measurement and does not need to reflect the daily dose recommended or prescribed by the doctor (TİTCK Akılcı İlaç Kullanımı Web Sitesi 2022).

Doses required for patients or patient groups are often different from DDD and vary according to individual characteristics such as age, body weight, and pharmacokinetic characteristics. When calculating DDD, it is assumed that the average weight of an adult is 70 kg. Except for some cases, DDD calculation is not made for pediatric drugs. DDD is not given for immune serums, vaccines, general and local anesthetics, topical preparations, antineoplastic drugs, allergen extracts, and contrast agents. Medication consumption, given as DDD units, gives a rough estimate of the amount of medication actually consumed and does not reflect the actual amount of medication consumed. DDD is a fixed unit of measurement independent of price and formulation. It offers researchers the opportunity to identify and compare drug consumption trends. $DDD \text{ amount} = \frac{[\text{"Number of boxes"} \times \text{"Number of tablets in box"} \times \text{"Tablet weight in grams"}]}{\text{"DDD value of drug in grams"}}$. "Defined daily dose per package (DPP)" can be calculated by "Package Content" / DDD formula (TİTCK Akılcı İlaç Kullanımı Web Sitesi 2022).

Method

Data usage permission was obtained from TMMDA for this article. In Türkiye, the prescribing of Vitamin D in primary health care institutions through the Prescription Information System and the consumption of Vitamin D in outpatients according to the ATC/DDD Methodology were examined and a situation assessment was made. In addition, the number of protocols created with the diagnosis of Hypervitaminosis D, Poisoning with vitamins and side effects caused by vitamins in Türkiye were evaluated. All prescriptions created electronically by family physicians and registered in PIS for the years 2015-2018 were examined retrospectively. Prescriptions containing the A11CC (Vitamin D and Analogues) ATC code were also evaluated. In this context, the data were obtained separately for each year. This manuscript does not contain information about dietary supplements.

Statistical evaluation of the data was made and the data was presented with tables and figures.

Descriptive statistics were used for evaluation of the data, and numerical values were presented via tables and graphics. Statistical analysis of the data was performed using the SPSS 23 (Statistical Package for the Social Sciences) package program. The Chi-square test was used to evaluate the relationship between the variables and the P value below 0.05 was accepted as statistical significance.

RESULTS

Between 2015 and 2018, a total of 561.269.736 prescriptions were created by family physicians. It was determined that the total number of prescriptions created by family physicians increased over the years. There was a statistically significant difference between the number of prescriptions over the years ($p < 0.05$).

Table 1. Number of prescriptions created by family physicians by years.

Year	Number of Prescriptions
2015	130.098.241
2016	134.235.120
2017	141.625.433
2018	155.310.942
Total	561.269.736
P	$p < 0.05$
χ^2	2.622.215.8

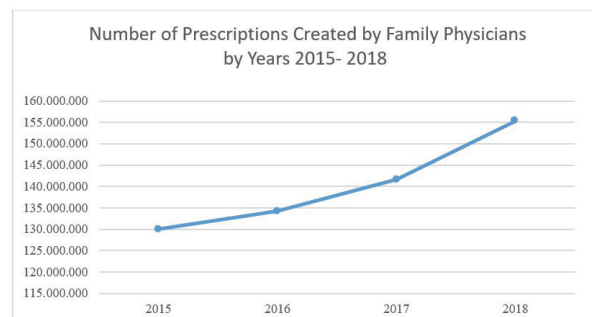


Figure 1. Number of Prescriptions Created by Family Physicians by Years.

Between 2015 and 2018, a total of 11.874.898 prescriptions containing drugs with the A11CC (Vitamin D and Analogues) ATC code were created by family physicians. It was determined that the total number of prescriptions containing A11CC (Vitamin D and Analogues) ATC-coded drugs created by family physicians increased over the years. It was seen that there was a statistically significant difference between the number of prescriptions over the years ($p < 0.05$).

While the percentage of prescriptions containing A11CC (Vitamin D and Analogues) ATC-coded drugs created by family physicians was 0.89 in 2015, it was 3.38 in 2018. It was determined that the percentage of prescriptions increased over the years.

Table 2. Number of prescriptions containing the drugs with A11CC (vitamin D and analogues) ATC code generated by family physicians by years.

Year	Number of Prescriptions
2015	1.163.954
2016	2.309.867
2017	3.149.651
2018	5.251.426
Total	11.874.898
P	$p < 0.05$
χ^2	3.009.626

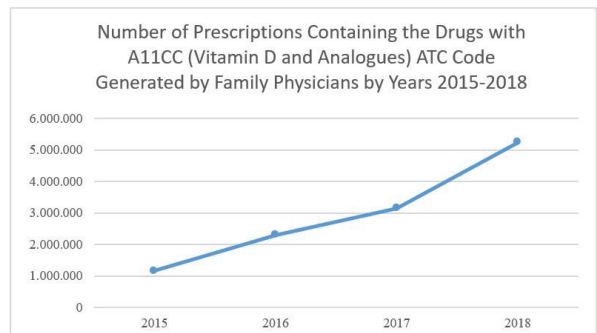


Figure 2. Number of Prescriptions Containing the Drugs with A11CC (Vitamin D and Analogues) ATC Code Generated by Family Physicians by Years.

The number of prescriptions containing A11CC ATC-coded medicines created by family physicians for the 0-2 age group between 2015 and 2018 constitutes only 5% of the total prescriptions.

Table 3. Percentage of prescriptions containing drugs with A11CC ATC code generated by family physicians by years.

Year	Percentage of Prescription
2015	0.89
2016	1.72
2017	2.22
2018	3.38

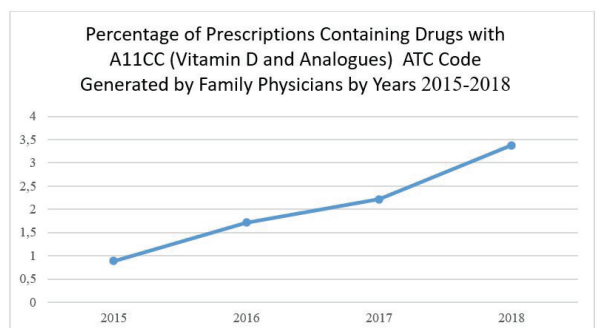


Figure 3. Percentage of Prescriptions Containing Drugs with A11CC ATC Code Generated by Family Physicians by Years.

A11CC (Vitamin D Analogues) ATC code in outpatients increased over the years according to the ATC/DDD methodology.

Table 4. Consumption of the drugs with A11CC ATC code in outpatients according to ATC/DDD methodology by years.

Year	DDD
2015	120.74
2016	163.65
2017	169.88
2018	201.7

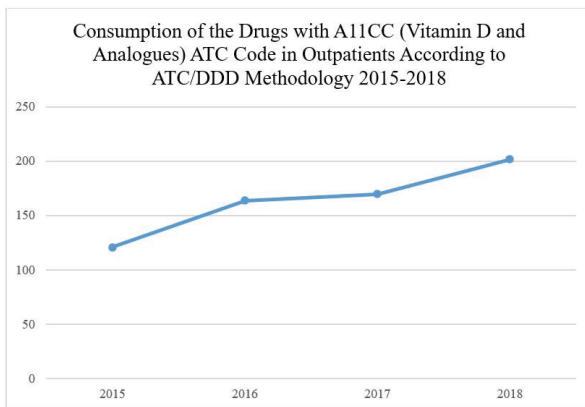


Figure 4. Percentage of Prescriptions Containing Drugs with A11CC ATC Code Generated by Family Physicians by Years.

Family physicians prescribed the drugs with the A11CC (Vitamin D and Analogues) ATC code for a total of 8.610.282 patients between 2015 and 2018. It was determined that there was an increase in the number of patients whose prescriptions contained the drugs with the A11CC ATC code over the years. It was found that the total number of patients increased over the years. It was seen that there was a statistically significant difference between the number of patients over the years ($p < 0.05$).

Table 5. Number of patients prescribed containing A11CC ATC-coded drugs by family physicians by years.

Year	Number of patients
2015	816.854
2016	1.655.771
2017	2.303.903
2018	3.833.754
Total	8.610.282
P	$p < 0.05$
χ^2	2.267.162.8

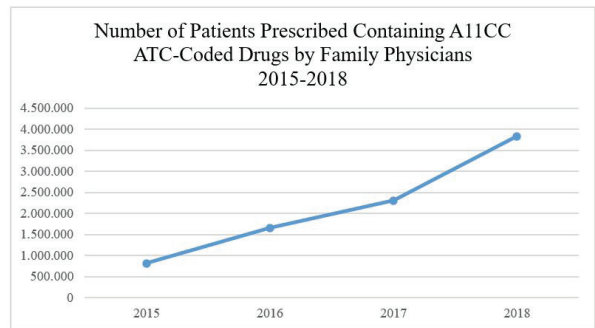


Figure 5. Number of Patients Prescribed Containing A11CC ATC-Coded Drugs by Family Physicians by Years.

A total of 4.029 protocols were created with the E67.3 ICD-10 diagnosis code (Hypervitaminosis D) between 2015 and 2018. It was seen that there was a statistically significant difference between the number of protocols over the years ($p < 0.05$).

Table 6. Number of protocols created with E67.3 ICD-10 diagnosis code by years.

Year	Number of Protocols
2015	580
2016	524
2017	1.260
2018	1.665
Total	4.029
P	$p < 0.05$
χ^2	906.0221

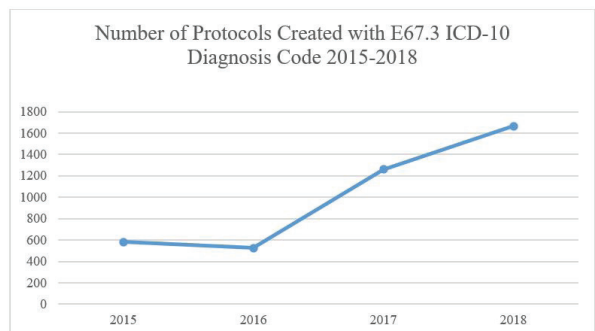


Figure 6. Number of Protocols Created with E67.3 ICD-10 Diagnosis Code by Years.

DISCUSSION

As a result of the data evaluation for the years 2015-2018 taken from TMMDA, it was determined that Vitamin D prescribing, consumption and cases of hypervitaminosis D increased significantly over the years in Türkiye. It can be concluded that hypervitaminosis D/Vitamin D intoxication develops as a result of false information and beliefs about Vitamin D insufficiency and its prevention.

According to the data evaluation of the years 2015-2018, it was determined that the total number of prescriptions and the number of prescriptions containing drugs with the A11CC ATC code created by family physicians increased significantly over the years. In addition, the percentage of prescriptions containing the drugs with the A11CC (Vitamin D and Analogues) ATC code has also displayed an increasing trend over the years. A11CC (Vitamin D and Its Analogues) ATC-coded Drugs were analyzed according to the ATC/DDD methodology, and it was determined that the consumption of Vitamin D in outpatients increased over the years.

In our study, it was determined that there was a significant increase in the number of patients who were prescribed A11CC (Vitamin D and Analogues) ATC-coded drugs by family physicians over the years.

One of the limitations of this study was that the prescription of the drugs containing Vitamin D and its Analogues was evaluated only among primary care physicians in this study. In addition, no evaluation was made about the usage of the prescribed drugs by the patients.

In order to prevent unconscious consumption of Vitamin D, there are some studies of TMMDA. "Dear Pharmacist's Letter", which is one of the documents sent directly to healthcare professionals by TMMDA and aims to ensure the safe and effective use of drugs, was published in 2016 and shared with relevant stakeholders. Information was given about the high number of cases of hypercalcemia and Vitamin D intoxication, especially in children, as a result of the selling without prescription and unconscious use of drugs containing high doses of Vitamin D in pharmacies. It was emphasized that maximum attention should be paid to the fact that drugs containing high doses of Vitamin D are sold by prescription in pharmacies (TITCK Eczacı Bilgilendirme Mektubu, 2016).

In 2020, an announcement about the use of preparations containing Vitamin D was shared with the public by TMMDA. In this announcement, it was stated that the indications, posology, warnings and precautions sections in the Summary of Product Characteristics (SPC) and Instructions for Use (IU) of drugs containing Vitamin D should be revised. The term "oral" cannot be used in the names of parenteral products containing Vitamin D and in SPC-IU information. It was denoted that these products should be regulated as indicated only in patients with gastrointestinal malabsorption in the case of Vitamin D deficiency in the "indications" section of these parenteral products. For orally taken products containing Vitamin D, the indication information should be arranged to show that the product is indicated for the treatment, maintenance and prophylaxis of Vitamin D deficiency. It was indicated that the doctor has to decide how to use the drug and that the drug must be used according to the doctor's recommendation in the SPC-IU information of all oral and parenterally administered products containing Vitamin D (TITCK, D Vitamini İçeren İlaçlar Hakkında Yazı, 2020).

CONCLUSION

In this study, a situation assessment was made by examining the prescribing of Vitamin D in primary health care institu-

tions through the Prescription Information System (PIS) and the consumption of Vitamin D in outpatients using the ATC/DDD Methodology in Türkiye. The study showed that the prescription of preparations containing Vitamin D by family physicians increased significantly over the years and there was an increase in Vitamin D consumption in outpatients. In addition, it was shown that the number of protocols established for the diagnosis of Hypervitaminosis D, Vitamin Poisoning increased over the years in Türkiye. It is obvious that Vitamin D is a very important vitamin for our body, and its deficiency causes serious problems. The effect of Vitamin D on many systems such as the skeletal, muscular, cardiovascular and immune systems has become more known in recent years. Awareness of the benefits of Vitamin D in healthcare professionals and the general public is increasing. It is thought that the popularization of Vitamin D in social media, TV, radio and newspaper leads to an increase in the irrational use of irrational Vitamin D and its unconscious consumption among the public.

"Dear Pharmacist's Letter" published by TMMDA in 2016 and shared with the relevant stakeholders, plus the writing shared with the public in 2020 regarding the use of preparations containing Vitamin D reveal the importance given to the rational use of Vitamin D.

According to the prescribing and consumption data, it was seen that the number of patients receiving Vitamin D supplementation was increasing.

It is thought that providing training to health professionals and the public about the use of Vitamin D will reduce the irrational and unnecessary use of Vitamin D and the risk of intoxication. Training and awareness activities can be organized in order to increase awareness among health professionals and the public. Health professionals and the public should be aware that unconscious and high-dose Vitamin D consumption may cause Vitamin D intoxication, and Vitamin D should be used in case its deficiency is detected by laboratory methods.

In our society, vitamins are not generally accepted as medicine. Therefore, it may be difficult to obtain a history of high-dose Vitamin D consumption in some patients. Anamnesis should be taken carefully in patients with hypercalcemia. There is a perception that vitamins are not drugs, and therefore excessive consumption is harmless. For this reason, when taking the patient's anamnesis, it should also be questioned whether there is a use of Vitamin D in addition to drug use.

The most important step in preventing Vitamin D intoxication is not starting the treatment with high-dose Vitamin D without proving Vitamin D deficiency with laboratory results. It is thought that using the drop form instead of the ampoule form in patients with Vitamin D deficiency will reduce the risk of toxicity. Appropriate dose treatment should be planned for patients and patients taking Vitamin D supplements should be followed closely.

In case of any adverse reaction to the drug, it is necessary for health professionals and patients to inform the health authority about it. Persons in the risk group in terms of Vitamin

D deficiency/insufficiency should be tested and, if necessary, replacement should be made in line according to the test results. The person should be evaluated according to age, body weight, and additional diseases, and a treatment plan should be created accordingly. The physician should decide how to use the preparations containing Vitamin D. It should be used according to the doctor's recommendation and under the advice of a pharmacist. It is recommended that patients receiving long-term treatment with high-dose Vitamin D be informed of the symptoms of a possible overdose. People who use Vitamin D should be told to what they should pay attention.

It is thought that raising awareness among health professionals and the public will make a great contribution to the rational use of Vitamin D-containing preparations.

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