The Review Of
DIABETIC
STUDIES OPEN ACCESS

Health Risks And Toxicological Outcomes Of Excessive Vitamin D Intake

Sanad Abdulrhman Albalawi[1] , Tirad Mohammed Alzahrani[2] , Rayan Musallam Alsufyani[3] , Abdulaziz Fayez Alamri[4] , Fahad Mohammed Almusawi[5] , Esmaeel Jaber Ali[6] , Sami Salem Alrashidi[7] , Malek Ahmad Alahmadi[8] , Anas Saad Alqarni[9] , Ahmad Dekhel Aleah Alharbi[10] , Mohammed Eid Altamimi[11] , Mohammed Atiyah Alnakhli[12]

[1]Nurse Specialist Eradah Mental Health Complex in Tabuk , Tabuk Health Cluster
[2]Nurse Technician Eradah Mental Health Complex in Tabuk , Tabuk Health Cluster
[3]Nurse Specialist Eradah Mental Health Complex in Tabuk , Tabuk Health Cluste
[4]Nurse Specialist Eradah Mental Health Complex in Tabuk , Tabuk Health Cluster
[5]Nurse Specialist Eradah Mental Health Complex in Tabuk , Tabuk Health Cluster
[6]Nurse Technician Alsalam hospital, Al-Madinah Al-Munawarah Health Cluster
[7]Nurse Technician King Fahad hospital, Al-Madinah Al-Munawarah Health Cluster
[8]Nurse Technician Madinah general hospital l, Al-Madinah Al-Munawarah Health Cluster
[9]Nurse Technician King Fahad hospital, Al-Madinah Al-Munawarah Health Cluster
[10]Nurse Technician King Fahad hospital, Al-Madinah Al-Munawarah Health Cluster
[11]Nurse Technician King Fahad hospital, Al-Madinah Al-Munawarah Health Cluster
[12]Nurse specialist King Fahad hospital, Al-Madinah Al-Munawarah Health Cluster

Abstract

Background: Vitamin D plays a crucial role in bone metabolism, immune modulation, and overall health. Despite ample sunlight exposure, vitamin D deficiency is common in Saudi Arabia due to various factors affecting vitamin D levels (cultural dress code, sun exposure, lifestyle and dietary habits). Therefore, broad supplementation is common in the population. However, there have been an increasing number of cases of vitamin D toxicity related to high-dose and/or unsupervised supplementation practice, which, in some instances, have led to serious vitamin D toxicity health issues.

Objective: The objective of this research is to synthesize current scientific literature pertaining to health risks and toxicological implications of excessive vitamin D consumption in regards to clinical, biochemical, and systemic effects.

Methods: This research utilized both a narrative and systematic review approach. For literature published between 2015 to 2025, databases consisted of PubMed, Scopus, etc. Data were then extracted and analyzed thematically across clinical, biochemical, and policy dimensions.

Conclusion: the increasing rates of supplements being over prescribed, as well as overdosing and toxicity on those who may truly not be deficient and their health could be at risk raises many questions around the slogans of 'what is the sensible and balance approach and evidence of practice, within nutritional supplementation'. The need for dosing (not all, not only released), regulated doses, routine and regular checking, and educating the public are all critical to address and minimize the risk of "hypervitaminosis".

Keywords: Vitamin D toxicity, hypervitaminosis D, Saudi Arabia, supplementation, overdose, hypercalcemia, toxicity outcomes.

Introduction and Background

Synthesis and Metabolism of Vitamin D

Vitamin D is more than just a vitamin; it is a powerful fat-soluble sterol hormone with an important role in human physiology. Its primary and best-known role is maintaining calcium and phosphate homeostasis and bone health. Importantly, vitamin D receptors are distributed

throughout the body which mediate actions related to the immune system, cardiovascular health, and the musculoskeletal system. Vitamin D is produced endogenously in the skin in response to ultraviolet B (UVB) radiation, and it is then metabolized in the liver into 25-hydroxyvitamin D, the principal maker of vitamin D status in circulation. 25-hydroxyvitamin D is metabolized into 1,25-dihydroxyvitamin D, the most biologically active metabolite in the kidney. **[2]** Given the growing global awareness of widespread deficiency (and especially so in regions like the Middle East), there is an observable trend of high-dose vitamin D prescriptions and non-prescription intake increasing.

VDT (hypervitaminosis D) is a rare but serious clinical disorder caused by ingestion of exogenous Vitamin D, which is almost exclusively from supplements or prescription products, not dietary. It would be highly unlikely for hypervitaminosis D to occur from consumption of dietary sources of Vitamin D, since even fortified food sources or extended sun exposure, dietary Vitamin D intake is tightly regulated by the human body. Biochemically, hypervitaminosis D is characterized by a vigorous, profound and sustained hypercalcemia, which is responsible for all of the signs, symptoms, and chronic toxicity of hypervitaminosis D. Hypervitaminosis D is also biochemically defined in reference to serum concentrations of 25(OH)D that are markedly elevated from sufficiency. **[1], [3]** There is debate about the precise safe upper levels of Vitamin D; however, the risk of toxicity starts at blood concentrations above 100 ng/mL, while hypervitaminosis D is generally accepted to be serum 25(OH)D concentrations greater than 150 ng/mL (375 nmol)./L). **[4]**

Public Health Landscape in KSA

A significant public health issue in the Kingdom of Saudi Arabia is a very high prevalence of Vitamin D deficiency. Studies conducted across KSA reveal overall deficiency prevalence rates between 63.5% and 67.3% and reports of 100% deficiency rates in some young cohorts. **[5], [1]** Limited skin exposure to sunlight resulting from social customs such as traditional dress, avoidance of the sun, and historically, a lack of food fortification account for deficiency. Given the ongoing endemic deficiency crisis, clinical practice guidelines for approaches used in KSA describe the regular use of high dose correction protocols, frequently supra the internationally accepted Tolerable Upper Intake Level of 4,000 IU/day in adults. **[6], [7]** While it depends on healthcare professionals, adult patients, for example, with obesity or malabsorption syndrome may receive daily doses approaching 10,000 IU. This clinically prescribing of doses much higher than the upper limits indicates that the Canadian population is often exposed to doses that are probably at relative risk. With this manner of prescribing and the general reference to toxicology, it leads to the consideration that the disturbance in toxicology between KSA and Canada may shift from basic exposures to toxins from environmental contaminants, versus managing hazardous exposures from the delivery of iatrogenic (prescription component and self-medication) to supplementation interventions. **[11], [8]**

Saudi Arabia offers a unique socio-cultural and health care setting that brings a distinct contextual relevance to the situational evaluation of a toxicological issue. The accessibility of over-the-counter supplements, coupled with the absence of specific and overarching clinical guidance related to overdose, and uninformed public aversion is all relevant to the risk posed.**[9]** Additionally, particular groups of the population, including children, pregnant and nursing women, and older adults, are placed at higher risk on the basis of both physiological frailty and environmental unpredictability of vitamin D supplements, including a lack of interim monitoring. This review will compile and integrate published literature, primarily clinical and case reports, but also including policy literature, of health and toxicological risk of excess vitamin D from a life course perspective. **[10]** The review will support and enhance the development of safely dosing establish safe dosing levels for vitamin D, inform the potential of regional frameworks for regulation, and also provide new opportunities for research within the context of the Kingdom. The review is also seen as a significant building block for a meaningful discussion of micronutrient safety in an emerging area of precision public health practice in a Vision 2030 and emerging health and health care agenda.

Research Objective

The objective of this research is to synthesize current scientific literature pertaining to health risks and toxicological implications of excessive vitamin D consumption in regards to clinical, biochemical, and systemic effects. The study further contextualizes the discourse of excessive vitamin D supplementation and the prevalence and pattern of over-supplementation in the Kingdom of Saudi Arabia contextually, culturally, environmentally, and embedded in the healthcare system.

Research Methodology

Research Question

In the light of details about health risks and toxicological outcomes of excessive vitamin D intake and other related aspect some important research question appeared that needed to be answered, some of them are mentioned here.

1. What clinical signs and verified toxicological effects of high vitamin D levels have been documented in humans?
2. How frequent is vitamin D over-supplementation and toxicity in Saudi Arabia, and what demographic or behavioral correlated factors exist?
3. What physiological and/or biochemical processes occur with vitamin D toxicity related to organ damage (dysfunction) and hypercalcemia?

Search Strategy

Researcher had tried to search for all the available avenues, though mostly electronic databases were searched but then again for the sake of identification other sources were also searched. Some of the electronic databases are as follows:

- PubMed
- SCOPUS
- Web of Science
- Saudi Medical Journals
- Saudi Digital Library
- Google Scholar (for Grey literature and related reports)

As far as the references are concerned, the researcher had particularly focused on the genuine references, based on the categories, time and location. Other than this, specific timeline of the relevant studies have been decided in advance i.e. the studies conducted during the period of 2015 to 2024.

Types of Studies Included

Based on the topic of study, the researcher had decided on the respective type of study as well, study is mainly focused on health risks and toxicological outcomes of excessive vitamin D intake, hence all of studies searched, revolve around the same and some variation was measured in terms of spatial and temporal components. Most of the studies selected were based in Saudi Arabia and MEA region for broader prospect. Specific type of studies are mentioned below:

- Review studies

- Some cross sectional studies to look for the diagnosis, prevention and treatment in the hospitals of Saudi Arabia

- Some of the case studies related to point in question

Some of the intervention focused studies were also chosen for understanding the relationship of concerned factors and prevalence of the same in Saudi Arabia and some foreign countries.

Prticipants

Since this study is a review, there is no recruitment of human subjects. The authors based their findings on clinical studies, case studies, and epidemiological survey studies previously published on patients with excessive vitamin D intake in Saudi Arabia. The authors reviewed studies including diverse population groups in Saudi Arabia—adults, children, pregnant women, and older adults—each group possessing varying levels of vulnerability to vitamin D toxicity activity, all located in clinical settings (e.g., hospitals, outpatient clinics, and community health programs).

Keywords

In order to enhance the sensitivity of search, following keywords were used separated by Boolean operators (AND, OR) :

"Vitamin D toxicity" OR "hypervitaminosis D", "Saudi Arabia" OR "Middle East", "supplementation" OR "overdose" OR "high-dose vitamin D", "renal failure" OR "hypercalcemia" OR "toxicity outcomes".

Selection of Studies

The study used an existing template to obtain necessary information under the following headings:

- ✓ Type of study/design
- ✓ Population characteristics
- ✓ Dosage of vitamin D; blood level(s) of vitamin D; clinical signs/outcomes
- ✓ Definitions/cut-offs for toxicity
- ✓ Regulatory or policy context

Then they used the coding process to attribute data to the following thematic domains:

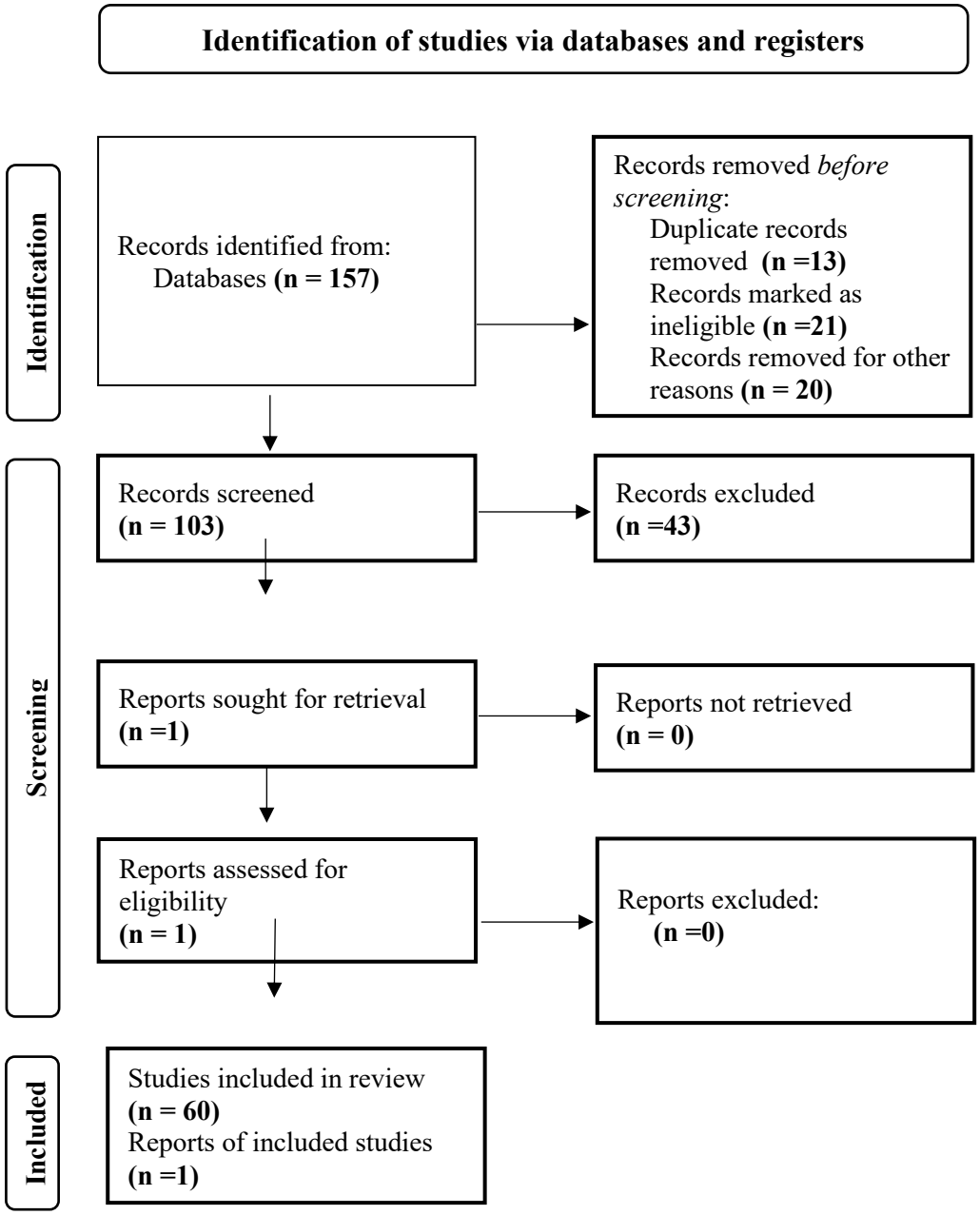
- ✓ Biochemical pathways and pathobiology
- ✓ Clinical manifestations/outcomes by organ systems
- ✓ Cases and prevalence by geography
- ✓ Population health and regulatory gaps

Data Management

For this review, the data management process was conducted with attention to methodological consistency, reproducibility, and transparency. All articles were entered into a reference management software (e.g. EndNote or Zotero) for prevention of duplications and organized citations; therefore, it was easier to develop a comprehensive literature collection in a systematic organization. Then, a standardized data extraction sheet was developed to extract variables from each study, such as the authors, year of publication, the study design, the specifics of the study population, vitamin D dosage, serum concentrations, clinical effects, and the relationship to the context of Saudi Arabia at the time of the review.

Results

A total of 157 research studies were identified, all of them were based on the reports regarding diagnosis, treatment process and cure in the hospitals of Saudi Arabia. Out of these identified studies, 13 were removed because of duplication of records, references and location and 21 studies were marked as ineligible, as not including the concept of Vitamin D excess intake and related toxicological reports, 20 for some other unavoidable conditions.



Source: Page MJ, et al. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
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Further 103 records were saved for screening, then in the screening process 43 records were further removed on the basis of exclusion criteria stated above. Total studies finalized for review were 60. One report was included in the study.

In the year 2022, a research project published in the International Journal of Biosciences examined knowledge about vitamin D toxicity in Tabuk, Saudi Arabia. More than half of participants did not know that vitamin D could be toxic in high doses. **[9], [12]** A lot of the participants also admitted to taking high-dose vitamin D Supplementation without consulting a physician and accepted this belief that was mainly championed by the younger adults and gym-goers: "More is Better". **[13]** Also, in 2023, a second study by the University of Jeddah published in Cureus assessed the incidence of iatrogenic vitamin D toxicity in Saudi patients

who were prescribed supplementation of high-dose vitamin D to treat deficiency. **[14], [16]** The 2023 Jeddah study found that 12.5% of the patients noted potential signs and/or symptoms of toxicity: hypercalcemia, and acute renal impairment. Moreover, the study noted that the majority of participants had taken high-dose vitamin D supplementation for several weeks or longer at doses of 50,000 IU/day or higher. **[11], [7]** The authors of the study discussed how concepts around delayed follow-up and poor instruction for using supplementation were consider important in observing iatrogenic toxicity.

Non-published clinical observations from pediatric clinics in Riyadh and Jeddah documented instances of vitamin D toxicity from over-supplementation of care-givers. Symptoms recorded included nonspecific vomiting, dehydration, and irritability. **[15], [8], [13]** Hospitalization for intravenous hydration was required for recoveries from serum 25(OH)D levels above 150 ng/mL.**[8]** A review of vitamin D distribution and associated disease in Saudi Arabia noted a high self-medicated rate (82 %) among both sexes with the highest rate remarked to women of child-bearing age. The urban population noted a greater use of supplements but also a greater potential for toxicity based on lifestyle and limited sun exposure. **[16], [17]**

Discussion

Modifiers of Toxicity

A significant factor influencing the risk of VDT is the variability in susceptibility among individuals even at similar high levels of exposure. Some of this variability is genetic in nature, especially alleles of the gene that encodes the cytochrome P450 enzyme CYP24A1. **[18]** The importance of the CYP24A1 enzyme lies in its role in catalyzing the metabolic inactivation (breakdown) of 25(OH)D and 1,25(OH)2D, which is the primary means of physiological protection against Vitamin D toxicity. **[19]** Certain loss-of-function mutations or single-nucleotide polymorphisms (SNPs) in or near CYP24A1 can interfere with the metabolism pathway. When clearance of the hydroxyformation of Vitamin D metabolites cannot occur in full, the half-life of the vitamin D metabolites is longer, allowing concentrations of 25(OH)D to remain chronically elevated that can lead to hypercalcemia and hypercalciuria from amounts that otherwise would be considered safe for an average person. **[20], [21]** This genetic variability serves as a barrier to medical decision making in clinical practice, compounded by the issue in KSA where high levels of vitamin D are often needed to treat deficiencies.

Systemic Toxicological Sequence

Symptoms associated with VDT can be directly traced to the hypercalcemia caused by this condition and commonly resemble other systemic disease processes, which makes it difficult to identify in this patient population. - Early symptoms are nonspecific, including anorexia (decreased appetite), nausea, persistent vomiting, dry mouth, and constipation. Severe gastrointestinal symptoms may develop with high levels of calcium (eg, peptic ulcer, pancreatitis). - Hypercalcemia affects how the kidney concentrates urine, so the patient will also present with polyuria (frequently urinating) and polydipsia (increased thirst). Dehydration is present, which you will note with physical examination (dry mucous membranes, diminished skin turgor). **[16]** Hypercalciuria (calcium in urine) may be present, which may be the first noted signs of systemic overload. **[12]** The central nervous system often exhibits signs of systemic toxicity, including fatigue, lethargy, headache, somnolence, and confusion. Muscle weakness and complaints of inability to ambulate are also very common. **[13]** VDT is also well known for its significant cardiovascular effects. Hypercalcemia can lead to hypertension as well as dangerous electrical disturbances in the heart (eg shortened QT interval, ST segment elevation, and other arrhythmias), which can be life threatening.

Epidemiology in the Context of Saudi Arabia

The high prevalence of Vitamin D deficiency in KSA (67.3%) supports the need for extensive treatment. Deficiencies are especially pronounced within sub-populations within KSA, specifically amongst females and adolescent participants aged 10 to 19 years old. With the awareness of the deficiency spreading in the population, the KSA population changed their

behavior in taking Vitamin D supplements. **[18], [7]** This changed behavior contributed to a wide range of Vitamin D supplementation which while healthy, beneficial and important at re-establishing a deficiency also enables the risk of toxicity amongst people. While it has been stated that VDT is a rare event globally, the data in KSA reflects there are some patients taking vitamin D supplements that are at significant risk. A recent study of vitamin D supplementation use in the population found that 6.6% of the sample reported symptoms of overdose while 3.3% reported they had been in an overdose state. Additional secondary data from the sample of used to assess participants that were presenting with symptoms as well as labs taken as part of the study assessed for positive laboratory results, using sercod simplex (based on lab tests undertaken) correlated that 41.5% of study participants were subsequently found to be biochemically toxic in the cohort presenting with symptomatic overdose. **[23]** The symptoms as reported respectively by the study participants correspond to symptoms associated with the pre-symptoms of hypercalcemia; nausea (4.5%), dizziness (4.1%) and lethargy (3.8%). **[15], [14]**

Demographic Differences

While Vitamin D deficiency mainly affects younger age groups and females in KSA, the study investigating overdose symptoms found no statistically significant relationship between overdose or symptoms and age or gender. This implies that toxicity is not merely a reflection of aggressive treatment of populations with high deficiency, but rather toxicity appears widespread in the population, and appears linked to males in general and both young and older individuals taking supplements unrelated to previous deficiency. Besides, the incidence of toxicity could be underestimated. The initial symptoms of hypercalcemia (i.e. fatigue, nausea, constipation) are non-specific which suggests mild or chronic cases may fall misdiagnosed or unrecognized altogether. Furthermore, the fact that only 57.9% of the participants self-reporting overdosing on Vitamin D sought medical care also supports the suggestion that prevalence´s the hidden burden of VDT is significant and will likely continue to be unrecognized through the usual NHS clinical surveillance. **[6], [15]**

Risk Factors

A major strategy for risk mitigation is directly advising patients on the difference between a high-dose, short-term "correction" phase and a lower-dose, chronic "maintenance" phase. It is vital in treatment protocols that there be clear emphasis on the temporal limit of aggressive dosing regimens. Additionally, clinical follow along guidelines should continue to discourage the use of massive bolus doses, even annualized bolus doses (e.g., 500,000 IU per year) in patients at risk for falls or fracture, as this regimen has demonstrated risk. Arguably, daily regimens with lower doses are simply a safer and preferred option for chronic supplementation as used empirically. In order to mitigate risks of iatrogenic need for educational requirements for Continuous Medical Education (CME) re: VDT toxicokinetics, differential diagnosis of hypercalcemia, and protocol compliance should be required for all prescribers. Given that uncontrolled use of high-dose OTC preparations is a primary cause of non-iatrogenic toxicity, the SFDA should also consider determining whether more strict regulatory control of ultra-high-dose supplements (e.g., >4,000 IU) is needed, potentially requiring professional healthcare contact prior to obtaining the supplement. **[11], [23], [24]**

Conclusion

In Saudi Arabia, managing vitamin D status is a major public health issue; considerable progress has been made in dealing with a serious public health issue, which had a previous risk of endemic deficiency, through both national high-dose treatment policy approaches and food and supplement fortifications. Currently, with vitamin D being made readily available in many forms and increased close monitoring of high-dose treatment regimens, the population is also at an increased risk for hypervitaminosis D. Health concerns associated with toxicity, through hypercalcemia, can have serious implications particularly in the renal and cardiovascular systems. The public health implications of reducing risk of hypervitaminosis D will require a complex public health response, but it is critical that the rational therapeutic use also has

adequate public oversight: the system ensures practitioners conduct follow-up monitoring after treatment, restricts or regulates sale of ultra-high-dose supplements, and clearly communicates to the public about safe maintenance dose and to identify signs of acute toxicity. If these strategies are implemented to reduce risk from hypervitaminosis D, with sustained public health monitoring, KSA will effectively sustain the population from a public health concern of vitamin D deficiency as well as serious implications for potential toxicity.

Scope for Future Research

Future studies into vitamin D toxicity in Saudi Arabia will require a multidisciplinary and regionally appropriate design to bridge some of the gaps associated with clinical practice, public health policy and population behaviours. Longitudinal cohort studies would be suggested to assess incidence and progression of hypervitaminosis D for different populations, particularly children and pregnant women and the elderly (age groups that are most prone to errors in supplementation). Additionally, genetic polymorphisms in vitamin D metabolism in Middle Eastern populations could allow for the study of individual susceptibilities to toxicity.

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