The growing interest in vitamin D is positively related to that of its kidney complications and is negatively related to that of bone benefit: an analysis based on Google Trends

Marco Zaffanello Sr, Franco Antoniazzi Sr, Giorgio Piacentini Sr

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Marco Zaffanello SrMD, PhD, ; Franco Antoniazzi Sr; Giorgio Piacentini SrMD,

Corresponding Author:
Marco Zaffanello SrMD, PhD,
Phone: +39045 8127126
Email: marco.zaffanello@univr.it

Abstract

Background: The benefits of vitamin D relate to muscle strength, cardiovascular health, and prevents osteoporosis.

Objective: This study aimed to explore trends of global interest on vitamin D, hypercalcaemia, adverse kidney effects (stones and kidney failure) and osteoporosis

Methods: An electronic search was conducted with Google Trends, limiting searches based on the "health" criterion.

Results: Worldwide interest in vitamin D3 (cholecalciferol), vitamin D2 (ergocalciferol or calciferol), kidney stones and kidney failure is progressively growing over time. On the other hand, vitamin D was found to be negatively correlated with hypercalcaemia and bone density. Another result of our analysis is the distribution of the popularity of searches across countries. In particular, the global popularity for vitamin D3 seems higher than that of vitamin D2 and also shows different geographical preferences. The growing interest in vitamin D parallels that of kidney stones and kidney failure, while decreasing popularity has been noted for hypercalcaemia and bone density

Conclusions: The research volumes help to clarify the changes in the trends of use of supplements and the development of their complications, according to the different geographical areas, socio-economic status and online literacy

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The growing interest in vitamin D is positively related to that of its kidney complications and is negatively related to that of bone benefit: an analysis based on Google Trends.

Short title: Worldwide public interest in vitamin D.

Marco Zaffanello, Franco Antoniazzi, Giorgio Piacentini

Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, University of Verona, Verona, Italy.

E-mail: marco.zaffanello@univr.it; franco.antoniazzi@univr.it; giorgio.piacentini@univr.it.

Corresponding Author

Marco Zaffanello, MD.
Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, Pediatric Division, University of Verona,
Verona, Italy
Electronic address: marco.zaffanello@univr.it

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Abstract

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Conclusions. The research volumes help to clarify the changes in the trends of use of supplements and the development of their complications, according to the different geographical areas, socio-economic status and online literacy.

Key words: Vitamin D; hypercalcemia; kidney stone; renal failure; bone density.

1.1 Introduction

Vitamin D is a fat-soluble vitamin which promotes the absorption of calcium, regulates bone growth and plays a crucial role in immune function. Vitamin D is fat-soluble, existing in two leading forms: vitamin D2 (ergocalciferol or calciferol) and vitamin D3 (cholecalciferol). In the liver vitamin D2 is transformed into 25-hydroxyvitamin D2 and vitamin D3 into 25-hydroxyvitamin D3. These two compounds are collectively known as calcifediol. (1) Notably, vitamin D3 is more effective than vitamin D2 in increasing the circulating values of calcifediol and hence appears to a more important player than D2 in improving vitamin D status. Vitamin D3 has been the most used form of vitamin D in practice and clinical trials. (2)

Vitamin D plays an integral role in calcium absorption and calcium homeostasis. Additional benefits of vitamin D concern muscle strength, cardiovascular health, whilst this hormone is also essential to prevent osteoporosis. Nevertheless, convincing evidence has also been published that an excessive intake of vitamin D may lead to toxic effects, and this holds especially true considering the growing public acknowledgment of its health benefits. (3) Recent cases of acute intoxication due to errors in manufacturing, formulation, or prescription have been described, mostly characterized by severe hypercalcemia, hypercalciuria, or nephrocalcinosis.(4-6) Prolonged vitamin D toxicity can also trigger reversible hypercalcemia and partially reversible renal impairment. (7) In addition, the effects of vitamin D on fractures, falls and bone mineral density remain uncertain. In unselected, community-dwelling populations without known osteoporosis or vitamin D deficiency, the currently available evidence does not support an unquestionable role of vitamin D in lowering the risk of fractures after vitamin D supplementation. (8)

Google Trends is a freely available Internet tool, which analyzes the popularity of some search queries in Google Search throughout many geographical locations and languages. (9) Recent evidence suggests that this tool may be useful for addressing epidemiological trends of diseases and

therapies.(10) Therefore, this study was aimed at exploring the trends of worldwide interest on vitamin D, hypercalcemia, kidney adverse effect (stone and failure) and bone density, using Google Trends.

1.2 Material and Methods

An electronic search was carried in Google Trends, using the keywords “vitamin D3” OR “cholecalciferol” AND “vitamin D2” OR “ergocalciferol” or “calciferol”, AND “hypercalcemia” OR “acute renal failure” OR “kidney stones” OR “bone density”, limiting the searches under the “health” criterion.

Language restriction was applied (English), and the searches were carried out from the first date available in Google Trends (i.e., January 1st, 2004) to the present time (i.e., October 1st, 2018). As for the Google Trends algorithm, results were then combined and scaled according to the peak of popularity (i.e., a value of 100 indicates top popularity of a given search term) recorded throughout the search period. Scores were then tabulated in Microsoft ® Excel Software. The statistical analysis was carried out with SPSS 22.0 statistics software for Windows. The Kolmogorov-Smirnov test was carried out to explore the normality of distribution. Descriptive statistics of the score of interests, as mean and standard deviation (SD), were calculated. Spearman correlation analysis was performed for exploring the correlation between vitamin D3 (cholecalciferol) or vitamin D2 (ergocalciferol or calciferol) and “hypercalcemia” or “renal failure” or “kidney stones” or “bone density” scores of interests, and for assessing mutually increased or decreased total interest throughout the search period.

The study was conducted in accordance with the Declaration of Helsinki and under the terms of relevant local legislation.

1.3 Results

Descriptive statistics (mean and SD) of Google Trends score is shown in Table 1. The score of popularity was found to be higher for cholecalciferol (vitamin D3) than for ergocalciferol and calciferol (vitamin D2). The score of popularity was also higher for kidney stones than for hypercalcemia, kidney failure and bone density throughout the search period. The Kolmogorov-Smirnov test showed that all these variables, except kidney stone, were normally distributed. The time distribution of popularity of cholecalciferol, ergocalciferol and calciferol is shown in Figure 1. The score seemingly increased faster for cholecalciferol (vitamin D3) than for ergocalciferol and calciferol (vitamin D2). The time distribution of Google searches for hypercalcemia, kidney failure, kidney stones and bone density is shown in Figure 2. The popularity appeared to grow faster for kidney stones, a lower increase of popularity was noted for kidney failure, whilst the popularity of Google searches seemed to be decreasing for both hypercalcemia and bone density.

Table 2 shows the Spearman's correlation between vitamin D and hypercalcemia or kidney or bone density popularity. A positive correlation can be observed between cholecalciferol (vitamin D3) and kidney failure, and between cholecalciferol (vitamin D3) and kidney stones. A negative correlation was instead noted between vitamin D and hypercalcemia or bone density. A positive correlation was found between ergocalciferol (or calciferol (vitamin D2)) and kidney failure or kidney stones, whilst the correlation was found to be negative between ergocalciferol (or calciferol (vitamin D2)) and hypercalcemia or bone density. The correlation between cholecalciferol and hypercalcemia (panel A) or kidney failure (panel B) or kidney stones (panel C) or bone density (panel D) is shown in Figure 3. The correlation between ergocalciferol and hypercalcemia (panel A) or kidney failure (panel B) or kidney stones (panel C) or bone density (panel D), is shown in Figure 4. Notably, a positive correlation was between vitamin D3 or vitamin D2 and kidney stones or kidney failure.

The worldwide score of popularity for cholecalciferol and ergocalciferol throughout the search

period is shown in Figure 5 (panel A). Higher scores of popularity for ergocalciferol (Vitamin D2) were found in searches from Mexico (100%), Peru (100%), Argentine (100%), Chile (100%), Brazil (58%) and Spain (57%). When the popularity score of vitamin D3 and kidney stone were compared (Figure 5, panel B), quite different trends were noticed in Italy (25% vs 75%), Switzerland (57% vs 43%), South Africa (4% vs 96%), Canada (7% vs 93%) and USA (7% vs 93%). Likewise, different trends of popularity could also be observed comparing searches for vitamin D3 and bone density in Italy (34% vs 66%), Switzerland (100% vs 0%), South Africa (8% vs 92%), Canada (15% vs 85%) and USA (21% vs 79%).

1.4 Discussion

The evidence emerged from our analysis suggests that the worldwide interest in vitamin D3 (cholecalciferol), vitamin D2 (ergocalciferol or calciferol), kidney stones and kidney failure is progressively growing over time. Although vitamin D and kidney stones or kidney failure are seldom associated in the scientific literature, an opposite trend was noted using Google Trends, and we cannot exclude this association was only due to the chance of incidentally coincident searches. On the other hand, vitamin D was found to be negatively correlated with hypercalcemia and bone density.

A controversial association between vitamin D and kidney stones is currently reported in the scientific literature, whilst the estimated lifetime risk of nephrolithiasis is continuously increasing. (11) A previous study concluded that it may be appropriate to monitor urinary calcium excretion in vitamin D-supplemented stone formers.(12) Urinary calcium excretion has been shown to increase in response to vitamin D supplements in some predisposed individuals.(11) Hypercalciuria is one of the

main risk factors of kidney stone formation. (11) High serum levels of vitamin D may play an important role in the pathogenesis of urolithiasis in infants with hypercalcemia.(13) Another study reported that vitamin D is associated with an increased incidence of kidney stones formation.(8)

Other studies reported that vitamin D and supplemental calcium were not associated with the risk of renal stones,(14) although an increased risk in people assuming high doses cannot be excluded.(15) Stone formers with hypercalciuria were found to have higher 25(OH)D values compared to stone formers with urine calcium within normal ranges. (16) More recently, a systematic review and meta-analysis concluded that long-term vitamin D supplementation was associated with an increased risk of hypercalcemia and hypercalciuria, whilst no increased risk of kidney stones was noted. (17) In addition, the association between kidney failure and hypercalcemia was only described in some case reports of subjects with vitamin D intoxication. (6, 18, 19)

Another interesting result emerged from our analysis is the negative association between bone density and either vitamin D3 or vitamin D2. In line with this finding, recent evidence suggests that vitamin D supplementation does not prevent fractures or falls, nor it has clinically meaningful effects on bone mineral density, since no difference could be observed between the effects of higher and lower doses of vitamin D. A review by Chakhtoura et al. showed that the prevalence of hypovitaminosis D, defined as a level of 25 (OH) D less than 20 ng / ml, ranged between 12-96% in children and adolescents in the Middle East and North Africa. Among these, they have not identified fracture studies. (20) No support to using vitamin D supplements is hence available for maintaining or improving musculoskeletal health.(21)

Another finding of our analysis is the different distribution of popularity of the searches in different countries. Most searches for vitamin D2 were carried out in Mexico, Peru, Argentine, Chile, Brazil and Spain, whilst vitamin D3 searches appeared more frequent in Italy, Switzerland, South Africa, Canada and USA. When the score of the popularity of vitamin D3 and kidney stone was compared, Italy, Switzerland, South Africa, Canada and the USA displayed different trends. Similarly, when the

score of the popularity of vitamin D3 and bone density was compared, again Italy, Switzerland, South Africa, Canada and the USA displayed different trends. Taken together, these results would suggest that vitamin D3 and its possible related conditions exhibited a very modest overlapping popularity of searches, irrespective of the increasing interest in vitamin D.

Google Trends is a free web tool, which is aimed to analyze the number of specific Google searches and then generates geographical and temporal information about a specific search term.(22) Recent evidence suggested that Google Trends may be also useful in healthcare, since it provides valuable insights on population behaviours (23) and their associations with health, disease and related treatments, thus reflecting the public interest on a certain topic.(10, 24)

1.5 Conclusions

The results of our analysis suggest that the worldwide popularity of vitamin D3 seems higher than that of vitamin D2 and also shows different geographical preferences. The growing interest in vitamin D parallels that of kidney stones and kidney failure, while decreasing popularity has been noted for hypercalcaemia and bone density. The research volumes help to clarify the changes in the trends of use of supplements and the development of their complications, according to the different geographical areas, socio-economic status and online literacy.

Table 1

Descriptive statistics of Google Trends score of interest in cholecalciferol, ergocalciferol and calciferol, and hypercalcemia, kidney failure and kidney stones during the period of interest (from 2004 to date).

Google trends score	Mean	Standard deviation	Minimum	Maximum
Step 1				

Cholecalciferol	42.94	21.838	8	100
Ergocalciferol	24.11	7.198	3	39
Calciferol	11.86	3.088	1	22
Step 2				
Hypercalcemia	7.68	1.002	6	11
Kidney failure	30.74	4.111	23	43
Kidney stones	69.65	6.770	52	100
Bone density	13.24	3.670	8	26

Table 2

Spearman correlation analysis between vitamin D types and hypercalcemia, renal conditions (stones and failure) and bone density scores.

Google trends score	**Hypercalcemia r (p)**	**Bone density r (p)**	**Kidney failure r (p)**	**Kidney stones r (p)**
Cholecalciferol	-0.283 (p<0.001)	-0.664 (p<0.001)	0.671 (p<0.001)	0.564 (p<0.001)
Ergocalciferol	-0.215 (p<0.004)	-0.553 (p<001	0.253 (p=0.001)	0.225 (p=0.003)
Calciferol	-0.005 (p=0.945)	-0.001 (0.992)	0.270 P<0.001	0.262 (p<0.001)

Figure 1

Scores of Vitamin D popular interest of cholecalciferol (vitamin D3, blue spots), ergocalciferol (vitamin D2, orange spots) and calciferol (vitamin D2, grey spots) from the year 2004 to date.

Figure 1

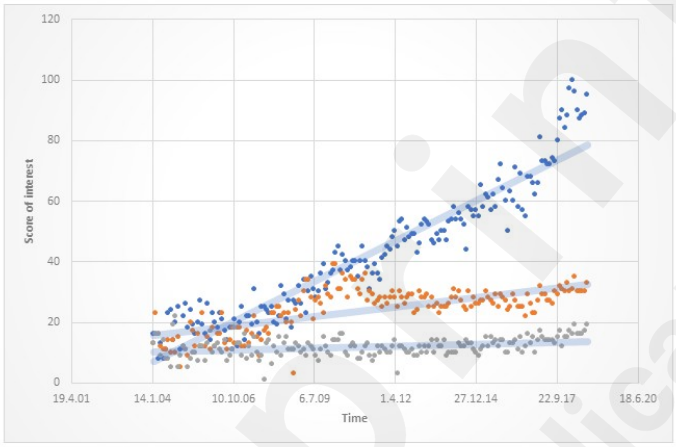


Figure 2

Scores of kidney stones (green spots), kidney failure (light blue spots), bone density (blue spots), hypercalcemia (yellow spots) from the year 2004 to date.

Figure 2

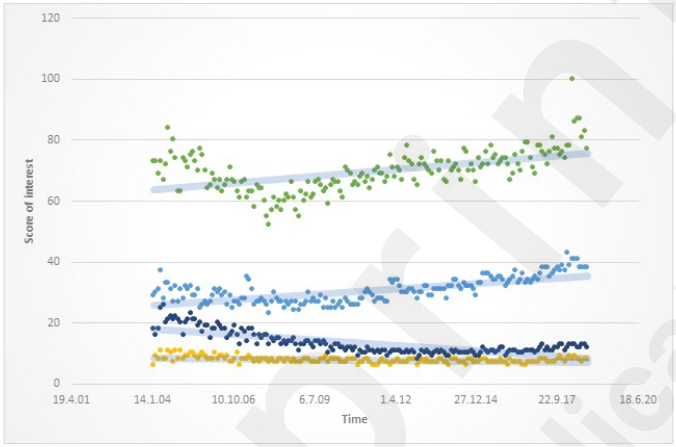


Figure 3

Correlation between cholecalciferol (vitamin D3) score and hypercalcemia (panel A), kidney failure (panel B, kidney stones (panel C) and bone density (panel D) scores.

Figure 3

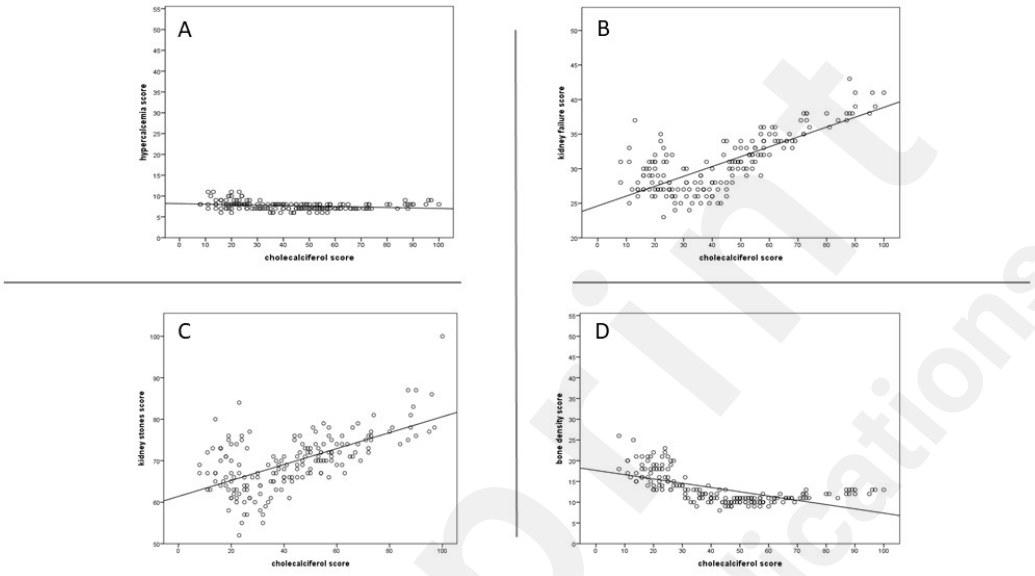


Figure 4

Correlation between ergocalciferol (vitamin D2) score and hypercalcemia (panel A), kidney failure (panel B), kidney stones (panel C) and bone density (panel D) scores.

Figure 4

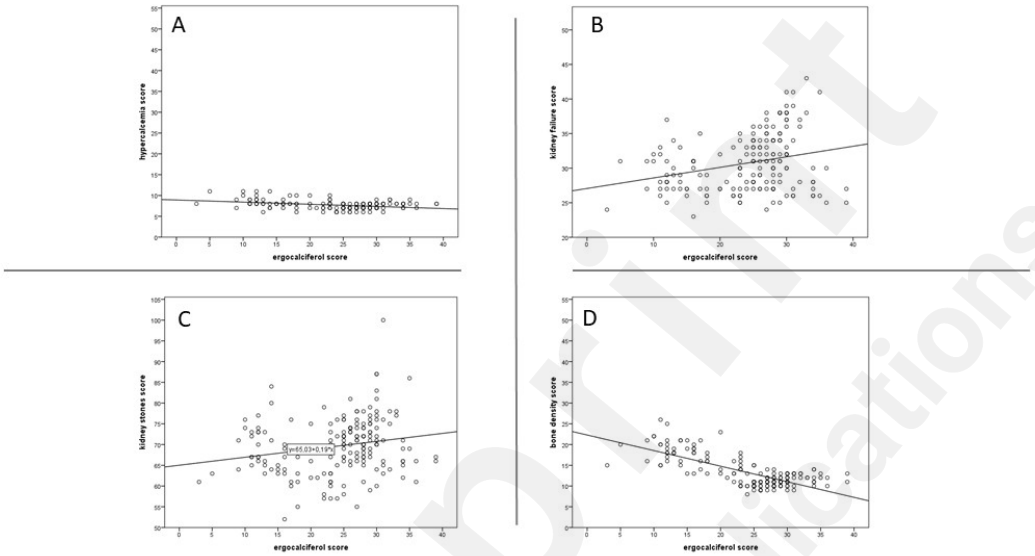
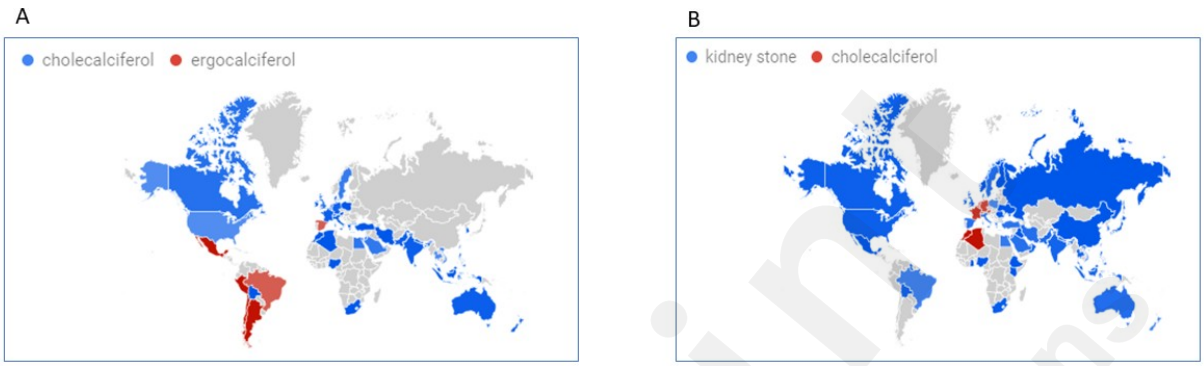


Figure 5

Score of interest in cholecalciferol and ergocalciferol around the world from the year 2004 to date.

Figure 5



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