High Prevalence of Vitamin D Deficiency among Iranian Population: A Systematic Review and Meta-Analysis

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Received: 01 August 2016
Revised: 29 November 2016
Accepted: 18 December 2016

Abstract

Background: The prevention and correction of vitamin D deficiency requires a precise depiction of the current situation and identification of risk factors in each region. The present study attempted to determine these entities using a systematic review and meta-analysis in Iran.

Methods: Articles published online in Persian and English between 2000 and November 1, 2016, were reviewed. This was carried out using national databases such as SID, IranMedex, Magiran, and IranDoc and international databases such as PubMed, Google Scholar, and Scopus. The heterogeneity index among the studies was determined using the Cochran (Q) and F test. Based on the heterogeneity results, the random-effect model was applied to estimate the prevalence of vitamin D deficiency. In addition, meta-regression analysis was used to determine heterogeneity-suspected factors, and the Egger test was applied to identify publication bias.

Results: The meta-analysis of 48 studies identified 18531 individuals with vitamin D deficiency. According to the random-effect model, the prevalence of vitamin D deficiency among male, female, and pregnant women was estimated to be 45.64% (95% CI: 29.63 to 61.65), 61.90% (95% CI: 48.85 to 74.96), and 60.45% (95% CI: 23.73 to 97.16), respectively. The results of the meta-regression analysis indicated that the prevalence of vitamin D deficiency was significantly different in various geographical regions (β=4.4; P=0.023).

Conclusion: The results obtained showed a significant prevalence of vitamin D deficiency among the Iranian population, a condition to be addressed by appropriate planning.

Keywords ● Vitamin D deficiency ● Meta-analysis ● Iran

Introduction

Among the deficiencies of all micronutrients, vitamin D deficiency is currently considered a pandemic.1 According to the global estimations, more than 1 billion people are known to suffer from vitamin D deficiency, a matter of considerable importance in the 21st century.2 3

Vitamin D has a significant role in the health, survival, and fertility of humans.4 5 Several studies have emphasized its role in preventing diseases such as heart diseases, malignancies,
inflammatory bowel diseases, multiple sclerosis, rheumatoid arthritis, type 1 diabetes, immune disorders, and infectious diseases. Vitamin D leads to an increase in the absorption of phosphorus and calcium through intestines and their reduced excretion through kidneys, while improving ontogenesis. Hence, its deficiency is among the main factors in metabolic bone disorders, leading to skeletal abnormalities, short stature, and delayed growth in children and osteomalacia, osteoporosis, and pathologic fractures among adults.

The main source of vitamin D for humans is the exposure of the skin to sunlight and to a lower extent, the diet particularly vitamin D-containing dairy products. Theoretically speaking, although vitamin D deficiency is not expected in regions with intense sunlight, there are large numbers of reports indicating the high prevalence of vitamin D deficiency in countries with intense sunlight. This could be due to the various factors such as geographical locations, types of clothing, skin colors, and diets lacking in sufficient vitamin D.

Vitamin D status varies among different societies. Various studies have shown a high prevalence of vitamin D deficiency in countries with intense sunlight such as China, Turkey, India, Iran, and Saudi Arabia, with an estimated prevalence between 30% and 93% over the past 2 decades. According to another study, 40%–100% of European and American elderly males and females who live a normal life and are not cared for in elderly care centers suffer from vitamin D deficiency. Also, more than 50% of menopausal women who have undergone treatments for osteoporosis have insufficient amounts of 25-hydroxy vitamin D.

Numerous studies in Iran have indicated a high prevalence of vitamin D deficiency among various age groups, including students from Isfahan Province (at Lat: 32° 39 N), young women in Uremia Province (at Lat: 37° 32 N), and the general population in Tehran Province (at Lat: 36° 21 N). A study in Tehran during 2004 showed severe, moderate, and mild prevalence rates of vitamin D deficiency of 9.5%, 57.6%, and 14.2%, correspondingly. In a comprehensive study from several bone health centers in 2001, the rates of moderate to severe vitamin D deficiency in the urban population among the age groups of below 50, 50–60 years, and above 60 years were 7.2%, 45.47%, and 44.2% among males and 54.2%, 41.2%, and 37.5% among females.

Decrease in vitamin D is globally considered a major health problem. On the other hand, the prevention and correction of the current situation is feasible provided that proper decisions are arrived at, especially with respect to high-risk groups. This in turn requires a precise depiction of the current situation, identification of risk-factor determinants, and development of the data collection process from specific populations in each region.

With a view to providing a basis for future efforts aimed at addressing the consequences of vitamin D deficiency, we conducted the present study via a systematic review and meta-analysis to estimate the prevalence of vitamin D deficiency in the general population of Iran apropos age, sex, and regional subgroups.

**Methods**

**Literature search:** Articles published in national and international journals were searched using studies published online from 2000 to November 1, 2016. This was conducted by employing relevant keywords in national databases such as SID, IranMedex, Magiran, and IranDoc and international databases such as PubMed, Google Scholar, and Scopus. The search strategy for the articles was generally based on the keywords of vitamin D, 25-hydroxy vitamin D, deficiency, prevalence, vitamin D deficiency, 25(OH) D, frequency, Iran, and their Persian equivalents. The search was carried out independently by 2 of the researchers (November 1–15, 2015). Also, the references of the published studies were consulted to increase the sensitivity and selection of a higher number of investigations. The assessment of the research was made randomly by 1 of the researchers to ensure that none of the studies was omitted. Also, the hard copies were searched in order to access the articles which were not published online, and appropriate research centers and experts were consulted in regard to the unpublished investigations.

**Selection criteria and quality assessment:** The full text or the abstract of all researches, records, and reports from advanced searches were extracted. The unrelated and duplicated studies were omitted by screening the title, abstract, and full text of the articles, leading to the subsequent selection of the related articles. Also, according to the most published guidelines, vitamin D deficiency was defined as serum 25(OH) D below 20 ng/mL (<50 nmol/L). To prevent bias due to transverse and longitudinal publication, the researchers tried to screen, identify, and omit the duplicated studies. Having determined the related studies based on titles and contents, the researchers employed the checklist used in previous studies to evaluate the quality.
of the records. This checklist by checking the STROBE checklist content comprises questions on 12 items, covering various aspects of methodology such as those determining proper sample size, study type, sampling type, and research populations. Furthermore, the method of data collection, method of defining the variables, method of studying the samples, tools of data collection, statistical tests, and research objectives were considered to ascertain that the results obtained were compatible with the objectives. The meta-analysis required 1 point for each question in addition to any studies that achieved at least 8 points.

Data extraction: Data for each research were extracted based on the title, corresponding author, year of conducting the study, type of study, sampling method, sample size, language of the article, general prevalence of vitamin D deficiency, prevalence of vitamin D deficiency based on gender, prevalence of vitamin D deficiency based on specific groups (i.e., pregnant women, children [age≤18 y], and patients [diabetes type 2, metabolic syndrome, depression, and dialysis]), and geographical regions. (These categories were based on the number of the studies published in each region. If the number of the studies conducted in each region exceeded 1, they were separately categorized for meta-analysis by geographic regions; otherwise, the study was placed in another category.) The data extracted were entered in a Microsoft Excel spreadsheet.

Inclusion criteria: The aspects to be considered for the selection of materials included all Persian and English studies, which after the evaluation process and achieving the required score, reported the sample size, general prevalence of vitamin D deficiency, and prevalence of vitamin D deficiency based on gender. (Vitamin D deficiency was defined as 25(OH) D<20 ng/mL or <50 nmol/L).

Analysis: Stata software was used to analyze the data. The standard deviation (SD) of the general prevalence of vitamin D deficiency, prevalence of vitamin D deficiency based on gender, prevalence of vitamin D deficiency based on specific groups, and prevalence of vitamin D deficiency based on geographical regions in each study was calculated via the binomial distribution formula. Ultimately, the heterogeneity index among the studies was determined using the Cochran (Q) and I² test. Based on the heterogeneity results, the random-effect model was employed to estimate the general prevalence of vitamin D deficiency and the prevalence of vitamin D deficiency based on gender, in Iran. The point estimation of the general prevalence of vitamin D deficiency and the prevalence of vitamin D deficiency based on gender was calculated at a confidence interval (CI) of 95% in forest plots. Moreover, the Egger test was carried out to assess the publication bias and considering the significance level below 0.01 as a criterion for judgment. Also, meta-regression analysis was conducted to investigate the heterogeneity-related factors.

Results

Through an initial search, 2598 papers were found from national and international databases and after limiting the search strategy and omitting the duplicates, due to the overlap of the databases, 706 records were included in this study. Having screened the titles and abstracts, 539 reports were found to be nonrelevant. The full text of the remaining 167 articles was studied, of which 117 reports were unrelated. Furthermore, 3 articles found through studying the references were added to our search list. Subsequently, by evaluating the quality of the articles and considering the inclusion and exclusion criteria, we omitted 5 articles and subjected 48 articles to the meta-analysis process (figure 1).

The research type in all of the records included in the study was cross-sectional, and 33 of the 48 studies were selected randomly. The searched studies comprised 7 studies on pregnant women, 15 on children aged less than 18 years, 14 on patients (diagnosed with type 2 diabetes, metabolic syndrome, dialysis patients, etc.), and 12 on the general population above 18 years old with the exclusion of pregnant women, children, and patients (table 1).

The total number of the individuals in the 48 studies subjected to the meta-analysis was 18531, which varied from 53 individuals in Ataie-Jafari’s report to 1581 subjects in Rostami’s study. The average age of the studied individuals varied from 12.6 years in Talaeé’s study to 57.97 years in that of Hossein-Nezhad. The total vitamin D deficiency prevalence varied from 2.5% in Abbasián’s study to 96% in Karimi’s study (figure 2).

The vitamin D deficiency prevalence was reported in 18 of 5854 studied male individuals. The vitamin D deficiency prevalence varied from 11.3% in Rabbani’s study to 82.1% in Moradzadeh’s study. According to the meta-analysis (figure 3 and table 2), the pooled prevalence of vitamin D deficiency among male Iranians was estimated to be 45.64% (95% CI: 29.63 to 61.65).

The vitamin D deficiency prevalence was reported in 32 of 10868 Iranian women. The vitamin D deficiency prevalence varied from 2.1%
in Ardestani’s study to 100% in Ghanei’s report (table 1). According to the meta-analysis, the pooled prevalence of vitamin D deficiency among female Iranians was estimated to be 61.90% (95% CI: 48.85 to 74.96) (figure 4 and table 2).

The vitamin D deficiency prevalence was reported in 7 of 2615 studies concerning pregnant women. The vitamin D deficiency prevalence varied from 2.5% in Abbasian’s study to 85.3% in Akhlaghi’s study. Considering the presence of heterogeneity, based on the random-effect model, the pooled prevalence of vitamin D deficiency among Iranian pregnant women was estimated to be 60.45% (95% CI: 23.73 to 97.16) (figure 4 and table 2).

The vitamin D deficiency prevalence was not significantly different based on the mean age (β=-0.1; P=0.795), publication year (β=0.8; P=0.337), and population group (β=1.3; P=0.700); nonetheless, the geographical region was recognized as a source of heterogeneity (β=4.4; P=0.023) (figure 5).

Also, according to the Egger test, no bias was found in regard to publication assessment (β=-6.8; P=0.153).

**Discussion**

In the published records on the prevalence of vitamin D deficiency in Iran’s population, the prevalence rate varied from 2.5% to 98% in various studies and regions. The vitamin D deficiency prevalence was significantly different based on geographical regions, where a high rate of the vitamin D deficiency prevalence was observed in pregnant women.

Vis-à-vis various geographical regions, the prevalence of vitamin D deficiency was significantly different in our study, which was...
Table 1: Characteristics of the primary studies included in the present meta-analysis

| Id  | First author | Publication year | Target population     | Sample size | Prevalence of vitamin D deficiency |
|-----|--------------|------------------|-----------------------|-------------|-----------------------------------|
|     |              |                  |                       |             | Total Female Male Total Female Male |
| 1   | Shahla20     | 2005             | General population    | 162         | - 162 82.1 82.1 -                 |
| 2   | Salak21      | 2007             | Children              | 513         | 271 242 26 12.26 13.74            |
| 3   | Heidarpour22 | 2006             | Children              | 318         | 153 165 46.2 72.1 18.3             |
| 4   | Hatami23     | 2014             | Pregnant women        | 100         | - 100 76 76 -                      |
| 5   | Rostami24    | 2015             | Pregnant women        | 1581        | - 1581 84.4 84.4 -                 |
| 6   | Banakdaran25 | 2015             | General population    | 902         | 380 522 79.3 45.89 33.5            |
| 7   | Karimi26     | 2014             | Children              | 216         | - 216 96 96 -                      |
| 8   | Shakiba27    | 2008             | General population    | 82          | 41 41 91.5 -                        |
| 9   | Taal28       | 2011             | Children              | 420         | 200 220 84 99.1 66.5              |
| 10  | Asadi29      | 2015             | Pregnant women        | 186         | - 186 74.4 74.4 -                 |
| 11  | Rahimi30     | 2005             | General population    | 252         | - 252 64.2 64.2 -                 |
| 12  | Ghanei31     | 2014             | Children              | 124         | 59 65 81 100 61                   |
| 13  | Azizi32      | 2000             | General population    | 1172        | 490 682 79.63 91 60               |
| 14  | Akhlaghi33   | 2015             | Pregnant women        | 190         | - 190 85.3 85.3                   |
| 15  | Khalaji34    | 2013             | Children              | 1111        | 573 538 91.7 94.8 88.8            |
| 16  | Ghazi35      | 2001             | General population    | 172         | - - 54 -                         |
| 17  | Rabban36     | 2009             | Children              | 963         | 424 539 35 53.6 11.3             |
| 18  | Saki37       | 2015             | Children              | 477         | - 81.3 -                          |
| 19  | Salek38      | 2008             | Pregnant women        | 88          | - 88 26.1 26.1 -                 |
| 20  | Shakiba39    | 2009             | Children              | 167         | - 167 59.9 59.9 -                 |
| 21  | Asadi40      | 2009             | Children              | 250         | - 250 59.6 59.6 -                 |
| 22  | Zadeh41      | 2015             | Dialysis              | 135         | - - 63 -                         |
| 23  | Banakdaran42 | 2010             | Type 2 diabetes       | 119         | - - 26.1 -                       |
| 24  | Paknahad43   | 2015             | Metabolic syndrome    | 156         | - - 54.5 -                       |
| 25  | Kaykhae44    | 2011             | General population    | 993         | 431 562 85.2 89 80.3             |
| 26  | Savaj45      | 2012             | Kidney transplantation| 113         | - - 45 -                         |
| 27  | Hosseinpanah46| 2010           | General population    | 100         | - 100 36 36 -                     |
| 28  | Hosseinpanah46| 2010           | General population    | 100         | - 100 31 31 -                     |
| 29  | Atepe-Jafari47| 2012           | Type 1 diabetes       | 53          | - - 77 -                          |
| 30  | Javadian48   | 2016             | Knee osteoarthritis   | 92          | 20 72 69.5 75 50                 |
| 31  | Larijani49   | 2016             | Children              | 444         | 227 217 43.3 71.23 17.47         |
| 32  | Mirsaeg ghazi50| 2004           | General population    | 1172        | 490 682 52 69 35                 |
| 33  | Saki51       | 2016             | Type 1 diabetes       | 85          | 39 46 88.2 84.6 91.8            |
| 34  | Zolfaghari52 | 2016             | Degenerative diseases | 110         | 54 56 44.5 -                      |
| 35  | Hossein-Nezhad53| 2014          | Coronary artery       | 760         | 582 178 98 -                      |
| 36  | Heidari54    | 2012             | General population    | 696         | 120 576 70.1 70.8 67.5           |
| 37  | Shamsian55   | 2016             | General population    | 1110        | 262 848 68.8 -                    |
| 38  | Abbasi66     | 2016             | Pregnant women        | 284         | - 284 2.5 2.5 -                  |
| 39  | Chitsaz67    | 2013             | Parkinson’s disease   | 109         | 77 32 38.4 -                      |
| 40  | Heidari58    | 2016             | Type 2 diabetes       | 84          | 39 45 35.7 13.09 22.62           |
| 41  | Fallahi59    | 2016             | Children              | 62          | - - 56.5 -                        |
| 42  | Kelishad60   | 2016             | Children              | 1095        | 569 526 40 39.3 40.7            |
| 43  | Entezari-Maleki61| 2014          | Thromboembolism       | 60          | 32 28 60 57.1 61.1              |
| 44  | Asadi62      | 2016             | Pregnant women        | 186         | - - 74.4 -                       |
| 45  | Sobouti63    | 2016             | Pediatric burns       | 118         | 50 68 81.35 -                     |
| 46  | Ardestani64  | 2010             | Children              | 513         | 271 242 5 2.1 3.7               |
| 47  | Hejazi65     | 2015             | Asthma                | 120         | - - 73.3 -                       |
| 48  | Rafraf66     | 2013             | Children              | 216         | 216 - 96 96 -                     |
consistent with other studies. Also, it has been reported that individuals in northern America have a higher rate of vitamin D than those in Africa and Europe.17,32,67-72

The high prevalence of vitamin D deficiency in the Iranian population and the different prevalence rates in various regions of Iran may be due to various factors such as the amount
of skin pigments, low dietary vitamin D intakes, and genetic factors such as special vitamin D receptor polymorphisms. Vitamin D deficiency may also result from low calcium intakes, involved in the vitamin D catabolism.\textsuperscript{38,73}

The findings of this research showed a significant difference in the vitamin D deficiency prevalence between various age groups. This was in agreement with the results of systematic review analyses carried out in Asia and Africa in regard to age and region.\textsuperscript{74} The main reason for the higher vitamin D deficiency prevalence in ages above 18 years is the lesser exposure to sunlight due to various reasons such as increasing industrialization, spending more time at home, and the clothing that may result in reduced vitamin D synthesis.\textsuperscript{26} On the other hand, vitamin D deficiency among Iranian adults might be due to lower dietary vitamin D intakes. Unlike certain foods consumed by adolescents lacking sufficient amounts of vitamin D, foods such as fish oil, egg yolks, and certain types of fish and seafood are valuable sources of vitamin D. In general, according to present national reports, the vitamin D content is low in the Iranian diet.\textsuperscript{75-77}
Table 3: Prevalence of vitamin D deficiency by sub-group analysis

| Subgroup                        | Included studies | Sample size (n) | Pooled prevalence (%) | 95% confidence interval | Heterogeneity (I²-%) |
|---------------------------------|------------------|----------------|-----------------------|-------------------------|---------------------|
| Specific group                  |                  |                |                       |                         |                     |
| Pregnant women                  | 7                | 2615           | 60.45                 | 23.73-97.16             | 99.9                |
| Children*                       | 15               | 6889           | 60.10                 | 41.12-79.08             | 99.8                |
| Disease**                       | 14               | 2114           | 61.14                 | 45.98-76.30             | 98.8                |
| Total (age>18 y) (with the exclusion of pregnant women, children, and patients) | 12               | 6913           | 66.58                 | 58.85-74.30             | 98.2                |
| Male                            | 5                | 1911           | 55.21                 | 35.58-74.85             | 98.2                |
| Female                          | 9                | 3638           | 64.71                 | 52.74-76.69             | 98.9                |
| *Age≤18, **Group diseases included: diabetes type 2 (1 study), metabolic syndrome (1 study), depression (1 study), and dialysis (1 study) |

Figure 4: Prevalence of vitamin D deficiency among Iranian females by the random-effect model for each of the included studies. For the included studies, the estimate of prevalence and its 95% confidence interval were plotted with a box and a horizontal line.
Among the articles included in the present study, some studies showed no significant impact of age on the prevalence of vitamin D deficiency, which may be due to the limited age range studied, such as those focusing on a particular age, one age subgroup, or the age range of different subjects. On the other hand, no comprehensive research has been conducted to compare the level of vitamin D deficiency in children, adolescents, adults, and the elderly. Our findings, similar to the studies carried out in Asia, showed that females had a higher prevalence of vitamin D deficiency than males. This may be explained in terms of cultural aspects and social obligations in women such as women’s preference to wear...
particular clothing outdoors, which prevents darkening of their skins, and skin diseases due to direct exposure to sunlight. Studies have clearly demonstrated women’s clothing as an independent risk factor for vitamin D deficiency among women. Accordingly, the prevalence of vitamin D deficiency is higher in countries with intense sunlight such as Saudi Arabia, United Arab Emirates, Jordan, Turkey, and Lebanon, where women’s clothing covers most parts of the body and prevents the exposure of the skin to sunlight. The higher prevalence of vitamin D deficiency among pregnant women in the foregoing countries may be related to living in apartments and the other aforementioned factors. It seems that the thresholds of vitamin D and calcium intake for changing the serum level of these micronutrients are necessary for providing adequate levels, especially for mothers and infants, and the current determined needed amounts (i.e., 400 units for vitamin D and 800 mg per day for calcium) are far lower than the needed thresholds for significant serum changes.

In short, considering the vitamin D deficiency prevalence in both genders and also the considerable prevalence in females, despite sufficient amounts of sunlight in all seasons in Iran and other Asian countries and the adequate exposure to sunlight as indicated by some studies, there seems to be additional reasons to account for vitamin D deficiency. These may include the types of clothing, impacts of other factors such as lifestyle, dietary habits, skin pigmentation, air pollution, and inadequate vitamin D intakes, or even the disorders in the vitamin D metabolism in both genders. Another hypothesis for the prevalence of vitamin D deficiency in Asia, compared to other regions, is the increase in the vitamin D catabolism. Although this vitamin is widely available and cheap, various social and cultural factors such as modern lifestyle and the fear of harmful effects of sunlight on skin account for not benefitting from adequate amounts of vitamin D.

Considering all these, vitamin D deficiency is deemed a health problem and its significance grows by the increasing average age of populations and changing lifestyles. Given the process of industrialization in Iran and its young population, paying due attention to this important problem is of high priority. Hence, not only should the Iranian government make efforts to apply efficient interventions to reduce the prevalence of vitamin D deficiency, but also the country’s healthcare system should be controlled and managed through targeted and accurate planning. This can be achieved by improving the healthcare system, promoting comprehensive measures such as verbal communications, and updating the community’s awareness.

Last but not least are the limitations of this study, which are imposed by the writing styles of various authors, their inaccessibility, and having no response. Although all the 19 studies used in this research had gained the required score for entering the analysis, some fundamental properties such as the prevalence rate based on the main findings concerning subgroups have not been considered (table 1) or the prevalence rates have not been mentioned directly, which was calculated by the authors based on the data available from the studies. Also, it must be kept in mind that the best method of vitamin D assessment is the enzyme-linked immunosorbent assay (ELISA) and high performance liquid chromatography (HPLC). The high prevalence of vitamin D deficiency in our meta-analysis study may be due to different evaluation methods (17 studies using the ELISA method, 23 studies employing the method of radioimmunoassay [RIA], 6 studies utilizing the chemiluminescence method, and 2 studies drawing upon the HPLC method). Therefore, our findings should be interpreted with caution.

Although estimating the vitamin D deficiency prevalence based on cross-sectional studies is not error-free, the main advantage of this research is the accurate evaluation of the prevalence of vitamin D deficiency using a systematic review and meta-analysis, based on demographic groups in Iran.

**Acknowledgement**

This study was approved and financed by the Health Policy Research Center of Shiraz University of Medical Sciences, Iran, with number (95-01-62-13532).

**Conflict of Interest:** None declared.

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