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Review Article

Efficacy of Food Fortification with Vitamin D in Iranian Adults: A Systematic Review and Meta-Analysis

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ABSTRACT

There are a number of reports showing high prevalence of hypovitaminosis D across Iran. The objective of this study was to evaluate whether food fortification with vitamin D has the potential to increase serum 25(OH)D concentrations in Iranian people. MEDLINE, PubMed, EMBASE, and The Cochrane Central Register of Controlled Trials were searched for randomized controlled clinical trials involvingIranian participants to assess the effect of fortified food either with vitamin D2 or D3 (with or without calcium) versus control on serum 25(OH)D concentrations. Four studies used dairy products as a food source and bread was used in one experiment. The daily dose of vitamin D3, 1000 and 2000 IU, and the duration of administration ranged from 8 to 12 weeks. The moderate heterogeneity was detected across the included studies (P<0.00001; I^2=55%).Using a random effects analysis (n=193), the efficacy effect was 34.6nmol/L (95% CI: 28.6, 40.8). The present meta-analysis showed that food fortification with vitamin D could be an effective tool to prevent and control hypovitaminosis D and Iranian population will most probably benefit from the vitamin D fortification as a national policy.

Keywords: Fortification, Vitamin D, Iran

Introduction

Hypovitaminosis D has been shown to be very common in the population around the world and this problem is a public health issue affecting all sex, age and economic subgroups. On the other hand, A burgeoning body of research has suggested the link between vitamin D status and risks of many chronic diseases including autoimmune disorders, cardiovascular diseases, cancers and diabetes (1).

Circulating concentrations of 25-hydroxycalciferol (25(OH)D) is the best indicator of vitamin D status reflecting combined contributions of both the diet and sunlight exposure (2).The majority of circulating 25(OH)D comes from the cutaneous synthesis under the action of sunlight (80–90%) (3). However, for the reason that so many environmental, cultural, and physiologic factors including latitude of living place, season, gender and obesity can influence cutaneous synthesis of vitamin D, reliance on intake is indispensable (4).

There are a number of reports showing high prevalence of hypovitaminosis D across Iran. The National Food and Nutrition Surveillance (NFNS) assessed vitamin D status in a population sample of persons from 5 to 65 years including latitudes from 29◦ to higher than 37º, reported that hypovitaminosis D is very common in Iranian population and more than 90% of population had undesirable vitamin D status (serum25(OH)D <50nmol/l) (5-6).

Natural sources of vitamin D in Iranian diet are rare. The Iranian population is, therefore, largely dependent on subcutaneous synthesis of vitamin D. However, NFNS showed that even sunlight in summertime cannot guarantee optimal vitamin D status (7).To address the issue of vitamin D deficiency in the general population in Iran, the Ministry of Health started evaluating different aspects of mass fortification of staple foods as an appropriate public health strategy. Indeed in many countries fortified foods, including milk, bread, yogurt, cheese,

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margarine and orange juice constitute the major dietary sources of vitamin D (8).The objective of this study was to evaluate whether food fortification with vitamin D has the potential to increase serum 25(OH)D concentrations in Iranian people.

Materials and Methods

Search strategy: The research team searched multiple databases, including MEDLINE, PubMed, EMBASE, and The Cochrane Central Register of Controlled Trials. The team restricted the studies to those published in English/Persian and involving human participants. The team only included studies that assessed the effect of fortified food either with vitamin D2 or D3 (with or without calcium) versus control on serum 25(OH)D concentrations and in Iranian participants. The search utilized the keywords "vitamin D," "cholecalciferol", "fortified", "fortification", "25(OH)D", "25-hydroxycholecalciferol". The data extracted from each study were name of first author, year of publication, used vehicle, dose of fortificant and mean of 25(OH)D in baseline and endpoint of intervention in control and intervention groups. The exposure and outcome were intake of vitamin D via fortified food and circulating 25(OH)D, respectively.

Risk of Bias Assessment: The quality and bias risk of the included studies were evaluated by two authors independently, with disagreements were resolved by consensus. (27) and the Jadad scoring scale (28) were used to assess the methodological quality of the included RCTs. The bias risk assessment tool recommended by the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0 (9) and oxford quality scoring system (Jadad scale) (10) were utilized in order to assess the risk of bias of each study.

Statistical analysis: All analyses were conducted using Review Manager Version 4.3 (Revman; The Cochrane Collaboration, Oxford, UK). The absolute change values for control and intervention groups were used to estimate overall efficacy effects that were defined as the mean difference. In addition to forest plots, the I^2 statistic of inconsistency was used to assess statistical heterogeneity. An I^2 of 25, 50, and 75% were defined as low, moderate, and high heterogeneity, respectively(11).

For standardization of results of different assay methods, harmonization methods were used (12).

Results

The searches in June 2018 yielded 13 papers. Eight of them were excluded after initial screening of the titles and abstracts and removal of duplicates (Fig. 1). A total of 5 clinical trials (13-17) involving 59 to 101 participants (Table 1). All studies were conducted in adult populations. Four studies were conducted in participants with type 2 diabetes (13-15, 18) and 1 in women only (17). Four studies used dairy products (13, 15, 17-18) as a food source and bread was used in one experiment (14). The daily dose of vitamin D3, 1000 and 2000 IU, and the duration of administration ranged from 8 to 12 weeks. Three studies used HPLC (high pressure liquid chromatography) to measure serum 25(OH)D(13-14, 18) and two studies used ELISA (enzyme linked immunosorbent assay) (15, 17). All studies scored ≥3 on the Jadad scale. Moreover, we judged all studies at low risk of bias using Cochrane tools. Foods, doses, and serum 25(OH)D concentrations are presented in Table1.

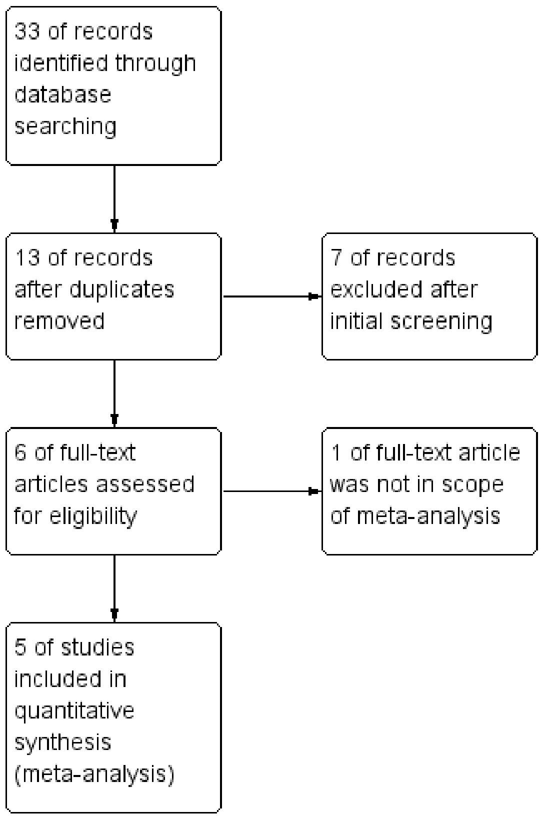

Figure 1. Study flow chart

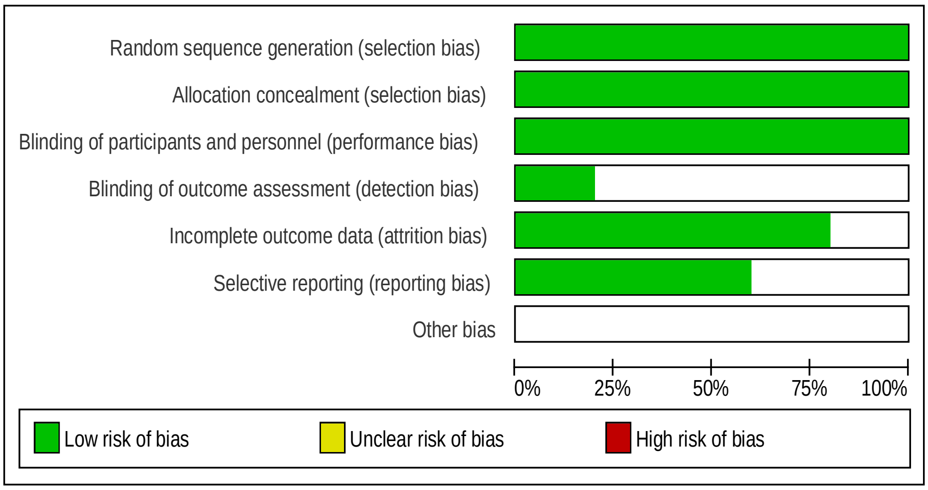

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Table1. Characteristics, foods, doses and serum 25(OH)D concentrations of studies

			control			Intervention						
	Age (yr)	Food carrier	Endpoint 25(OH)D (nmol/L)	Baseline 25(OH)D (nmol/L)	n	Endpoint 25(OH)D (nmol/L)	Baseline 25(OH)D (nmol/L)	Added vitamin D (IU)	n	Duration	Method	Location
Nikooyeh, et al, 2011, (13)	30-60	Yogurt drink	37.2±44	41.6±44.5	30	77.7±28.6	44.4±28.7	1000	30	12 wk	HPLC	Tehran
Nikooyeh, et al, 2016, (14)	20-60	Bread	25.4±21.8	34.7±30.5	30	72.9±23.1	33.9±21.9	1000	30	8 wk	HPLC	Tehran
Salehi, et al, 2018 (15)	31-74	milk	50.0±42.5	40.0±30.0	50	77.5±47.5	42.5±27.5	1000	51	9 wk	ELISA	Shiraz
Shab-bidar, et al, 2011, (18)	20-60	Yogurt drink	33.4±22.8	38.0±22.8	50	72.0±23.5	38.5±20.2	1000	50	12 wk	HPLC	Tehran
Jafari, et al, 2015 (17)	>50	Yogurt	56.1±2.8	62.7±4.2	29	86.8±4.8	62.2±4.5	2000	30	12 wk	ELISA	Isfahan

The outcome variable of interest was circulating 25(OH)D as the best marker of vitamin D status. The moderate heterogeneity was detected across the included studies ($P < 0.00001$; $I^2 = 55\%$). Using a random effects analysis (n = 193) (Fig. 3), the efficacy effect was 34.6nmol/L (95% CI: 28.6, 40.8).

Four studies out of five used daily dose of 25 µg/d, heterogeneity was 44% in those studies. (13-15, 18). The overall efficacy effect was 37.1 nmol/L (95% CI, 28.6-45.7), relating to a 1.4 nmol/L increase in 25(OH)D for each 1 µg/d ingested. We were not able to further subgroup analysis, due to the small number of studies.

Though circulating 25(OH)D is the commonly accepted biomarker for vitamin D status, there is no agreement among different methods(19-20). To address this issue, we used the equations to harmonize the results obtained from different assay systems (12). By using these equations, the efficacy effect was 36.8 nmol/L (95% CI: 32.3, 41.2). There was a low level of heterogeneity across the 5 studies ($P < 0.00001$; $I^2 = 13\%$) (Figure 4.)

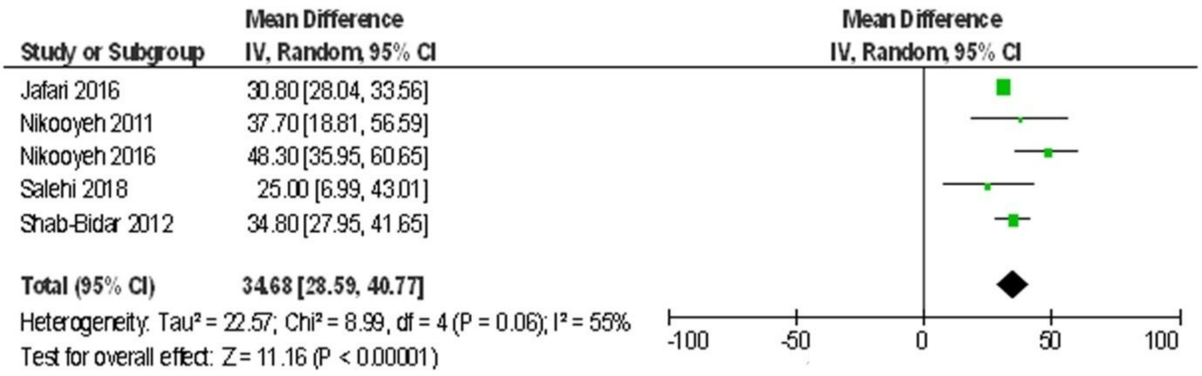

Figure 3. Weighed mean differences in serum 25(OH)D concentrations (nmol/L)

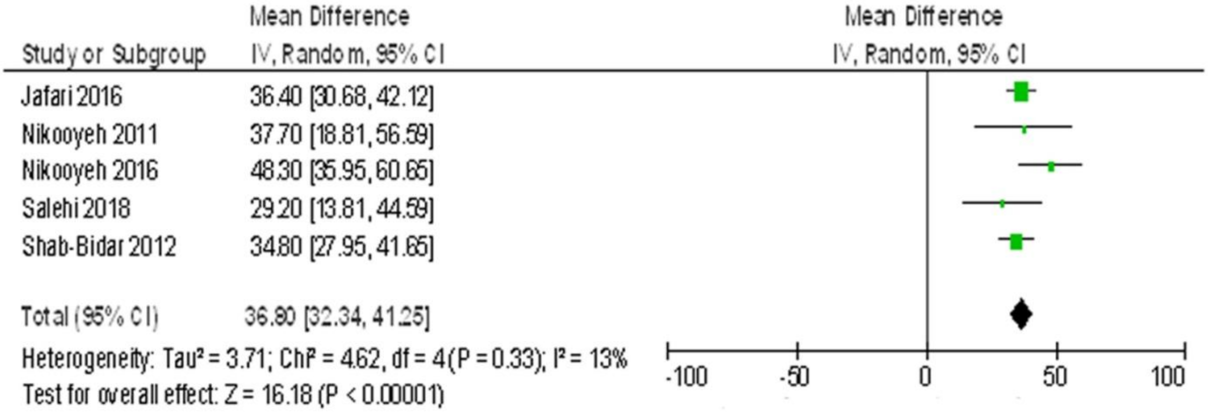

Figure 4. Weighed mean differences in serum 25(OH)D concentrations (nmol/L) after harmonization of results

Discussion

The results of present meta-analysis demonstrate that vitamin D fortification substantially improved the vitamin D status. All studies were successful at improving vitamin D status and none of them reported clinical or laboratory evidence of toxicity.

There have been several reports detailing the prevalence for vitamin D deficiency across Iran. Recently, National Food and Nutrition Surveillance reported that above 90% of Iranian population had hypovitaminosis D in winter (5, 21).There are a few strategies available to improve vitamin D status in population. Food-based strategies are of considerable importance in protecting against vitamin D deficiency, in particular when sun exposure is low or limited due to environmental, cultural and/or individual characteristics. As the natural dietary sources of vitamin D are limited, the high occurrence of undesirable vitamin D status among Iranian population is not surprising(22).Vitamin D supplements can increase serum 25(OH)D concentrations across population subgroups undoubtedly(23). However, this strategy cannot be used for a long time and for the majority of the population(24).

Vitamin D fortification of foods either mandatory or voluntary has been suggested as a strategy to improve 25(OH)D levels significantly in the population(25). Many countries have added vitamin D to foods such as milk products, bread, and orange juice as a main strategy to combat hypovitaminosis D. In Finland, vitamin D has been added to liquid milk products (0.5 µg/dL), as well as margarines and butter (10 µg/100 g) from 2003. Reports showed that national vitamin D fortification substantially improved the vitamin D status (26). In Canada, the foods that require fortification with vitamin D are milk products (400 IU/ 250mL) and margarine (530 IU/100g)(27). However, studies suggested that current fortification programs in Canada are not successful in preventing undesirable status of vitamin D, particularly among at risk populations during winter time (28-29). In fortification programs

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milk products, bread, orange juice, vegetable oils and margarine have been used as a fortification vehicle for vitamin D (26-27, 30). Some evidence showed that milk can be an effective vehicle for fortification(30). However, several national and sporadic reports have shown that milk is not adequately consumed in Iran(31). Alternatively, staple foods such as bread and oil could be used to improve vitamin D status of the general population. The Optimal Fortification with vitamin D (OPTIFORD) European project examined the possibility of fortification as a strategy for improving vitamin D status and revealed that the high potential of bread as a safe and practical vehicle for fortification(32).

In those studies, that used dose of 25 µg/day, the efficacy effect was 37.1 nmol/L (95% CI, 28.6-45.7), on average, 1.4 nmol/L increase in serum 25(OH)D concentrations for each 1 µg/d ingested. Previous studies also reported that 1 µg of ingested vitamin D can increase 25OHD concentration by 1

to 1.2 nmol/L(33).

Noteworthy, disagreement among different systems of 25(OH)D assay is another challenge(34). Large discrepancies among the results obtained from different assay methods make national comparisons of the prevalence of suboptimal status of vitamin D extremely difficult (12).Consequently, suggested harmonization methods were used for comparison of assay results(12).This resulted in increment of overall efficacy effect and a decrement in heterogeneity across the studies.

The risk of bias in all trials was low and the statistical heterogeneity was low to medium based on the I^2 statistic of inconsistency. In addition, there was no difference in the dose of used vitamin D, and the intervention duration in most studies.

However, there were some limitations in this meta-analysis. Due to limited studies, we were not able to subgroup analysis for example for dose of vitamin D and type of vehicles. Also we could not exclude other possible unmeasured confounders in this meta-analysis.

Conclusion

It is essential to combat vitamin D deficiency via appropriate strategies in Iran. Present meta-analysis showed that food fortification with vitamin D could be an effective tool to prevent and control hypovitaminosis D and Iranian population will most probably benefit from the vitamin D fortification as a national policy. Vitamin D food fortification policies in Iran are regulated by Ministry of Health. At this time, there is no program for mandatory vitamin D fortification of foods in Iran. Overall, if policy-makers decide to support national programs of fortification with vitamin D, bread, milk and dairy products could be appropriate vehicles.

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