Effects of different doses of Vitamin D replacement in Middle Eastern and North African population: a systematic review and meta-analysis

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Review question

1A-Determine the mean 25-hydroxyvitamin D (25(OH)D) level reached with low (<= 800IU), moderate (800-2000 IU) or high (>2000IU) daily dose of vitamin D in subjects in Middle East and North Africa (MENA) countries, by age and reproductive status.
1B-Estimate the mean serum 25(OH) D level reached by 97.5% of individuals in above treatment groups and the proportion of subjects who reach a mean 25(OH) D level above 20 ng/ml in above treatment groups.
1C-Investigate the applicability of the Institute of Medicine recommended daily allowance to subjects in MENA countries.
2-Other outcomes assessed, comparing any two treatment arms, be it between vitamin D groups themselves, or vitamin D groups and placebo, and in each age category and reproductive status, are fracture rates, mortality, hypercalcemia-hypercalciuria, metabolic parameters (diabetes and lipids), bone mineral density, kidney stones and muscle strength.

Searches

Search was done in MEDLINE (1946 to present), EMBASE, PubMed and the Cochrane Library without time or language limitation.
Search was also done also in Popline, Index Medicus and Global Health and in trials registries: on ClinicalTrial.gov. and in the WHO international Clinical Trials Registry (ICTRP)

Search strategy

http://www.crd.york.ac.uk/PROSPEROFILES/10488_STRATEGY_20140630.pdf

Types of study to be included

Inclusion criteria- Randomized controlled trials that examined the response to different doses of vitamin D supplementation (with or without a placebo arm) whatever their endpoint of interest, but should have reported 25(OH)D level at baseline and at the end of the study.- English and Non-English articles will be included.- Published and unpublished data will be included; We will try to get access to unpublished data of studies identified on trials registry through contact of authors. - No publication date restrictionExclusion criteria:- Prospective interventional studies that are not randomized- Studies that did not report pre or post intervention 25(OH)D level. In such a case, first we will try to contact the authors to get information about 25(OH)D level; If such information would not be available or we would not get any reply, the study will be excluded.

Condition or domain being studied

Hypovitaminosis D is a worldwide problem (Hilger 2014). Low 25-hydroxyvitamin D levels, defined as below 20ng/ml, are prevalent in developing countries, especially in the Middle East, South Asia and Sub Saharan Africa (Mithal 2009). In the Middle East and North Africa (MENA) region, in addition to advancing age and female gender, specific risk factors in adults including multiparity, clothing style, season, socio-economic status and urban living have been associated with vitamin D deficiency (Arabi 2010; Bassil 2013). Prolonged breast feeding without adequate supplementation is a major predictor of hypovitaminosis D in infants (Bassil 2013).
Vitamin D receptors are widespread in different tissue, explaining the different physiologic effects of vitamin D beyond the skeleton. Observational studies have associated hypovitaminosis D with increased risk of infections, cancer, auto-immune and cardio-vascular diseases (Bouillon 2013). Meta-analysis of randomized controlled trials have shown that vitamin D supplementation improves multiple skeletal and non-skeletal

outcomes, including, in adults, a protective effect of vitamin D against falls (Bischoff-Ferrari 2009) and fractures (Bischoff-Ferrari 2012) and maybe decreased overall mortality (Bjelakovic 2014), and, in children, improvement in BMD (Winzenberg 2011).
The latest Institute of Medicine (IOM) and Endocrine Society (ES) guidelines on vitamin D replacement in the general population, in 2010, were based on a systematic review of literature and defined the dietary requirements of vitamin D based on mineral and skeletal outcomes (Ross 2011; Holick 2011). They did not target specifically MENA countries where 25(OH)D levels are lower compared to Western population (Mithal 2009). Furthermore, the ES guidelines have collected a wealth of randomized controlled trials conducted in each age category but suggested to use higher doses to reach their target of 25(OH)D level of at least 30 ng/ml (Holick 2011); doses that have been infrequently used in randomized controlled trials. IOM and ES differ in their recommendations in terms of target populations and desirable levels as well as other criteria used.
A previous systematic review by Autier et al. in 2012, assessed the influence of vitamin D supplementation on 25(OH)D level. However, this review targeted Caucasian population and only individuals above age 50 years; In addition, the authors did not systematically assess the scientific quality of the different trials that were included. Similarly, Cashman et al. conducted a systematic review and meta-regression analysis of randomized controlled trials of vitamin D intake in 2011 to help define dietary intake recommendations in Europe. This review was limited to trials conducted in winter (minimal sun exposure), at latitudes higher than 40°S or 40°N and using vitamin D doses of 2000IU or less per day and published before September 2007. Finally, a more recent review that included all randomised controlled trials that used high doses of vitamin D revealed that these were exclusively conducted in Caucasian subjects in western societies (Bouillon 2013). On the other hand, recent meta-analysis failed to show a significant protective effect of vitamin D supplementation on multiple skeletal (adult BMD, hip fractures) (Bolland 2014; Reid 2014) and non-skeletal clinical outcomes (cancer, cardiovascular and overall mortality) (Bolland 2014; Elamin 2011). However, these studies have multiple limitations; First, the change in 25(OH)D levels have not been consistently documented in the trials, and if so, the mean 25(OH)D level achieved was between 50 and 70 nmol/l, implying that 50% of the study population reached levels that were below the above cut-offs. Conversely, a participant level meta-analysis revealed that vitamin D intake 800-2000 IU/day decreased the risk of both hip and vertebral fractures (Bischoff-Ferrari 2012). Second, some of the trials included in these meta-analyses used infrequent dosing (every 3, 6 or 12 months) with high dose of vitamin D supplementation, regimens that might not maintain steady 25(OH)D levels for the study duration. Interestingly, the study by Sanders et al. revealed an increase in hip fracture risk using a high dose of 500,000IU once (Sanders 2010).

Participants/population

Inclusion criteria:
- Participants from Middle and North Africa including the following countries: Algeria, Egypt, Libya, Morocco, Tunisia, Afghanistan, Bahrain, Iran, Iraq, Palestine/Israel, Syria, Lebanon, Kuwait, Yemen, Oman, Qatar, Saudi Arabia, Turkey, Jordan, United Arab Emirates.
- Apparently healthy, community dwelling individuals.
- Healthy individuals given vitamin D as a preventive measure of certain diseases or individuals with mild diseases that have no reason to have altered vitamin D metabolism.
- Both sexes
- All age groups
- Pregnant or lactating women

Exclusion criteria:
- Rickets in children and osteomalacia in adults characterized by low 25(OH)D, below 15 ng/ml with evidence laboratory and radiologic abnormalities, as these individuals require higher doses of vitamin D supplementation (higher than the doses recommended for the general population).
- Institutionalized and hospitalized individuals; this would only apply to elderly, and their needs are different. Public health guidelines should target general population not this unique subgroup.
- Individuals with chronic illnesses (chronic kidney disease(GFR at or below 30 ml/min), liver disease, heart failure (NYHA class 3 or more)
- Individuals with conditions or on drug therapy that might affect vitamin D metabolism and vitamin D binding protein /metabolism (anticonvulsants, steroids, anti fungal, malabsorption, bypass surgery)

Intervention(s), exposure(s)

Inclusion criteria:

Vitamin D (D2 or D3) supplementation of any dose, given orally, daily, weekly or monthly, with or without Calcium supplementation
Exclusion criteria:
- Studies that used active vitamin D supplementation as this type of supplementation is not recommended for the general population.
- Studies that used vitamin D supplementation given intra muscularly as the intra muscular preparations have a more delayed peak in 25(OH)D level that can occur at 120 days.
- Studies that gave vitamin D supplementation for less than 3 months since 25(OH)D has a half-life of 2 weeks and at least 10 weeks are needed to reach a steady state.
- Studies that gave vitamin D supplementation spaced more than 1 month, given that 25(OH)D levels cannot be maintained with infrequent dosing (at intervals more than 1 month).
- Studies that used vitamin D supplementation as fortified food as the amount of vitamin cannot be defined accurately .

Comparator(s)/control
Vitamin D (as described above) or placebo or no supplements

Context

Main outcome(s)
25(OH)D level reached with low (800IU), moderate (800-2000 IU) or high (>2000IU) daily dose of vitamin D in subjects in MENA countries, by age and reproductive status.

Timing and effect measures

Our primary outcome measure is the mean difference in 25(OH)D level reached between any two treatment arms, be it between vitamin D groups themselves, or vitamin D groups and placebo, in each age category and reproductive status, at the end of the intervention.

Additional outcome(s)
- Serum calcium, PTH, fasting blood glucose, HbA1c, LDL, HDL, triglyceride levels.
- Urinary calcium level.
- Bone mineral density.
- Muscle strength and other muscle parameters.
- Fracture rate.
- Kidney stones rate.
- Incidence of fall and imbalance episodes.
- Mortality.
- Other adverse events.

Timing and effect measures

We will calculate the relative risk (RR) and 95% confidence interval (CI) of fracture, kidney stones, hypercalcemia/hypercalciuria, falls and imbalance episodes and other adverse events between any two treatment arms, vitamin D or placebo, at the end of the intervention. We will calculate the mean difference of serum calcium, PTH, fasting blood glucose, HbA1c, LDL, HDL, triglycerides, and the mean difference of muscle strength and BMD, between treatment groups. For mortality, hazard ratio (HR) and 95% CI will be calculated.

Data extraction (selection and coding)
References retrieved in the search strategies mentioned above will be reviewed in duplicate by independent reviewers. One reviewer (MC) will screen all references. Two other reviewers (SG and KS) will partake references screening and each one of them will screen half of the references. After exclusion of duplicates (duplicates retrieved from different databases (using endnote library) and duplicate reporting using manual check, screening of abstracts will be done based on the study design (RCT), the population (Middle Eastern and North African) and intervention (vitamin D). We will retrieve the full text of citations included by at least one reviewer. Full texts of retrieved articles will be screened in duplicate and independent manner. Disagreements will be resolved by discussion with an expert author (GEHF).
Data extraction will be done on the following variables:
1. Characteristics of study participants, per each treatment arm:

-Country of origin
-Age
-Sex
-Ethnicity
-Presence or absence of comorbities.
-Presence or absence of medications
-Mean BMI
-Mean 25(OH)Dlevel at baseline
2. Characteristics of intervention:
-Type of vitamin D supplemented (D2 or D3)
-vitamin D vehicle
-Dose
-Frequency
-Duration
-Compliance
-Presence or absence of concomitant Calcium administration
-Comparator used
Placebo
Vitamin D:Type, Dose, frequency, vehicle, presence or absence of concomitant Calcium.
3. Characteristics of outcome measure, per each treatment arm:
- Proportion of individuals who reach 25(OH)D at or above 20 ng/ml and mean 25(OH)D level at the end of the study
Vitamin D assay used (RIA, ELISA, LCMS, HPLC, etc..)
Laboratory quality assurance:DEQAS…
- Muscle strength and other muscle parameters.
- Serum calcium, PTH and urinary calcium levels.
- Metabolic parameters (Fasting blood glucose, HbA1c, LDL, HDL, triglycerides)
- Incidence of fracture
- Incidence of hypercalcemia
- Incidence of kidney stones
- Incidence of fall and imbalance episodes.
- Mortality
- Other adverse events

Risk of bias (quality) assessment

The risk of bias will be assessed using the Cochrane Tool for assessment of risk of bias (Cochrane Book 2011). This tool consists of seven domains: adequacy of randomization, concealment of allocation, blinding of participants and personnel, blinding of outcome assessor, extent of loss to follow-up (incomplete outcome data), selective outcome reporting and other sources of bias.
For each domain, judgment will be done qualitatively, based on answering a specific question. An answer “yes” indicates a low risk of bias. An answer “No” indicates a high risk of bias. “Unclear” judgement is made when the risk of bias in unknown.
A calibration exercise will be done among reviewers to ensure adequate assessment by different reviewers.

Strategy for data synthesis

A meta-analysis will be done when at least two studies are available for each comparison, in each age category. A meta-regression will be performed if at least 10 studies will be retrieved for each age group.
The primary analysis will done using a random effects model. To test the robustness of our results, a sensitivity analysis, using a fixed effect model, will also be used.
Assessment of heterogeneity:
Statistical heterogeneity between studies will assessed using Chi square with significance at p-value = 0.1.
The quantitative assessment of heterogeneity was done using I-squared.

Analysis of subgroups or subsets

In case of heterogeneity in results, subgroup analysis will be done, based on covariates that we expect to affect the response to vitamin D supplementation and 25(OH)D level, as follows:
- Vitamin D assays, well known to affect 25(OH)D level.
- Type of vitamin D, D2 vs D3, since D2 may raise 25(OH)D to a lesser extent compared to D3.

- Presence or absence of concomitant calcium supplementation, as side effects secondary to calcium might reduce compliance, as well as a direct effect on 25(OH)D level, reflecting decreased 25(OH)D metabolism.
- Gender, universal confounder
- Obesity as BMI might is one of the predictors of circulating 25(OH)D level.

Sensitivity analysis will be performed in order to assess the effect of relevant factors on the effect measure, if applicable, as follows:
- restricting the analysis to published trials only.
- restricting the analysis to MENA individuals living in MENA countries exclusively
- restricting the analysis to studies with baseline 25(OH)D below 50 nmol/l

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None known

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Review_Ongoing

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11 August 2014

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Revision note for this version
Minor Changes:The vitamin D assays were added for studies in Appendix 1

Details of any existing review of the same topic by the same authors
None

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	No	Yes
Piloting of the study selection process	No	Yes
Formal screening of search results against eligibility criteria	No	Yes
Data extraction	Yes	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Revision note
Minor Changes:The vitamin D assays were added for studies in Appendix 1

Versions
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