Effects of Vitamin D on Migraine: A Meta-analysis

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BACKGROUND

- Vitamin D is involved in endogenous transmission and modulation of pain in migraine (1,2)

OBJECTIVES

- To evaluate
  - The difference in mean serum 25-OH vitamin D level between migraineurs and non-migraineurs
  - The association between hypovitaminosis D (≤20 ng/ml) and migraine
  - The effects of oral vitamin D supplementation on migraine-frequency, duration, and severity as compared to placebo

METHODS

- **Study design:** Systematic review and meta-analysis
- **Databases searched:** MEDLINE/PubMed, IndMED, ClinicalTrials.gov, WHO ICTRP, and Cochrane Library (in the English language) until 20th May 2019
- **Search terms:** "vitamin D", "cholecalciferol", "25-OH vitamin D", "25-hydroxy vitamin D", "headache", and "migraine"
- **Studies included:** Observational studies and RCTs
- **Risk of bias assessment:** Newcastle-Ottawa Scale (observational studies), and Cochrane risk of bias tool (RCTs)
- **Meta-analysis:** WMD and OR (random-effects model) in MetaXL version 5.3 (© EpiGear International Pvt. Ltd.)
- **Heterogeneity:** x^2 test on n-1 degrees of freedom
- **Quality of generated evidence:** GRADE

RESULTS

- 71 studies were screened; and 8 observational studies and 2 RCTs were included
- 6 among the 8 observational studies were of 'good qualities' and both the RCTs had low risks of bias

Table 1. Characteristics of the included studies

Author, year (country)	Age (years)	n	Population	Co-medications	Serum 25-OH vitamin D estimation technique	Serum 25-OH vitamin D level (ng/ml) for labeling as deficient	Normal range of serum 25-OH vitamin D (ng/mL)
Donmez, et al., 2018 (Turkey) (3)*	5–16	68 (cases), 69 (control)	Patients with headache, and healthy control	NSAIDs, calcium, vitamin D, and steroids not allowed	High-performance liquid chromatography	20	≥ 30
Rapisarda, et al., 2018a (Italy) (4)#	Cases: 41.4 ± 13.5 Controls: 47.6 ± 13.6	100 (cases), 38 (control)	Chronic migraine patients, and healthy controls	Vitamin D not allowed	-	20	≥ 30
Rapisarda, et al., 2018b (Italy) (4)#	Cases: 39.8 ± 11.9 Controls: 47.6 ± 13.6	34 (cases), 38 (control)	Episodic migraine patients, and healthy controls	Vitamin D not allowed	-	20	≥ 30
Togha,et al., 2018a (Iran) (5)#	18–60	34 (cases), 70 (control)	Chronic migraine patients, and age and sex-matched healthy controls	Abortive drugs, NSAIDs, analgesics (codeine), triptans, beta-blockers, tricyclic antidepressants, topiramate, and sodium valproate were allowed	Enzyme-linked immunosorbent assay	20	30–100
Togha,et al., 2018b (Iran) (5)#	18–60	36 (cases), 38 (control)	Episodic migraine patients, and age and sex-matched healthy controls	Abortive drugs, NSAIDs, analgesics (codeine), triptans, beta-blockers, tricyclic antidepressants, topiramate, and sodium valproate were allowed	Enzyme-linked immunosorbent assay	20	30–100
Zandifar, et al., 2014 (Iran) (6)#	15–65	105 (cases), 110 (control)	Newly diagnosed migraine patients, and age, sex, socioeconomic status, education, and sun exposure-matched controls	Vitamin D, drugs with effect on 25-OH vitamin D, and migraine prophylactic drugs not allowed	Chemiluminescent immunoassay	< 10	> 20
Celikbilek, et al., 2014 (Turkey) (7)#	18–50	52 (cases), 49 (control)	Newly diagnosed migraine patients and age, and sex-matched controls of Caucasian origin without having a headache of any kind	Vitamin D supplements, anticonvulsants, rifampicin, and antiretroviral drugs not allowed	Enzyme-linked immunosorbent assay	25	30–100
Hanci, et al., 2019 (Turkey) (8)*	5–7	165 (cases), 98 (control)	Patients with episodic, acute, and chronic migraine with and without aura, and nutrition, sunlight exposure time, and climate-matched controls	Prophylactic medication for migraine not allowed	-	15	> 20
Kjærgaard, et al., 2012a (Norway) (9)#	30–87	248 (cases), 6121 (control)	Non-smokers from the sixth survey of the Tromsø Study	-	Chemiluminescent immunoassay	22	11.2–42.8
Kjærgaard, et al., 2012b (Norway) (9)#	30–87	74 (cases), 1432 (control)	Smokers from the sixth survey of the Tromsø Study	-	Chemiluminescent immunoassay	28.4	11.2–42.8
Sohn, et al., 2018 (Korea) (10)*	Cases: 35.1 ± 8.2 Controls: 35.4 ± 9.1	36 (cases), 36 (control)	Migraine patients and age, gender, and season-matched controls	Vitamin D supplement or drugs that influence vitamin D metabolism (e.g., antiepileptics, rifampin, antiretrovirals, etc.) not allowed	Chemiluminescent immunoassay	20	30–50
Author, year (country)	**Age (years)**	**n**	**Serum 25-OH vitamin D (ng/mL) at baseline (mean ± SD)**	**Co-medications**	**Comparator**	**Dose of oral vitamin D**	**Treatment duration (weeks)**
Gazerani, et al., 2019 (Denmark) (11)^	18–65	21 (vitamin D arm), 24 (comparator arm)	Treatment group: 34.8 ± 12.8 Comparator group: 31.6 ± 12.4	Digoxin, thiazides, and vitamin D > 400 IU/day not allowed	Placebo	4000 IU/day	24
Mottaghi, et al., 2015 (Iran) (12)^	10–61	33 (vitamin D arm), 32 (comparator arm)	Treatment group: 16 ± 5.4 Comparator group: 20.2 ± 2.5	Magnesium, calcium, vitamin D, B_{12}, B_9, B_6, steroids, and oral contraceptive not allowed	Placebo	50000 IU/week	10

*Retrospective observational studies, #Prospective observational studies, ^Randomized controlled trials

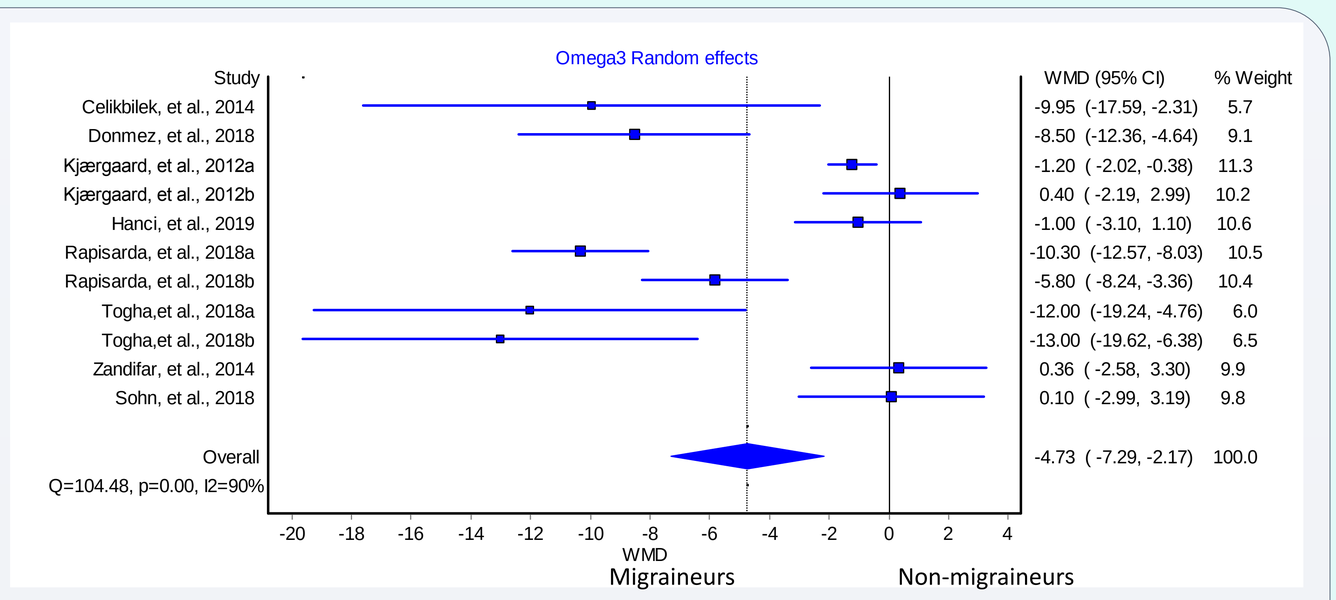

Fig. 1. Mean difference in serum 25-OH vitamin D level between the migraineurs and the non-migraineurs

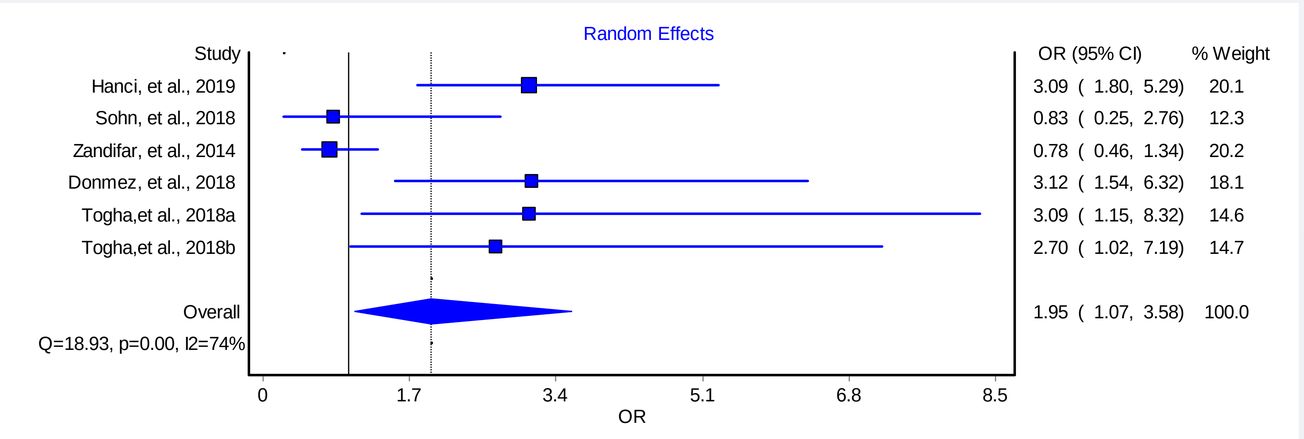

Fig. 2. Association of hypovitaminosis D with migraine

- Adult and pediatric population individually: lower level of serum 25-OH vitamin D in the migraineurs [mean difference, **– 4.89 ng/mL (95% CI: – 7.95, – 1.83) (i^2 :91%, p<0.001)** and – 4.57 ng/mL (95% CI: – 11.91, 2.77) (i^2 :83%, p<0.001), respectively] than in the non-migraineurs

Table 2. Effects of oral vitamin D supplementation on migraine

Parameters	Weighted mean difference vs. placebo	I^2- value (p-value)
Migraine-frequency (/month)	– 2.20 (95% CI: – 3.04, – 1.36)	0% (0.48)
Migraine-duration (h/month)	– 16.00 h (95% CI: – 42.77, 10.76)	48% (0.16)
Migraine-severity (score)	– 0.37 (95% CI: – 1.33, 0.59)	69% (0.07)

CONCLUSIONS

- Serum 25-OH vitamin D was significantly lower in the migraineurs than in the non-migraineurs (low-GRADE evidence)
- Hypovitaminosis D was significantly associated with migraine (low-GRADE evidence)
- Oral vitamin D supplementation reduced migraine-frequency, but not its duration and severity vs. placebo (moderate-GRADE evidence)

LIMITATIONS

- Confounders not adjusted for the association studies
- RCTs: few in number, dose and duration of therapy varied
- Presence of high heterogeneities

PROTOCOL

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- **Conflict of interest:** Nil

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