

The prevalence of headache may be related with the latitude: a possible role of Vitamin D insufficiency?

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Abstract According to recent observations, there is worldwide vitamin D insufficiency (VDI) in various populations. A number of observations suggest a link between low serum levels of vitamin D and higher incidence of chronic pain. A few case reports have shown a beneficial effect of vitamin D therapy in patients with headache disorders. Serum vitamin D level shows a strong correlation with the latitude. Here, we review the literature to delineate a relation of prevalence rate of headaches with the latitude. We noted a significant relation between the prevalence of both tension-type headache and migraine with the latitude. There was a tendency for headache prevalence to increase with increasing latitude. The relation was more obvious for the lifetime prevalence for both migraine and tension-type headache. One year prevalence for migraine was also higher at higher latitude. There were limited studies on the seasonal variation of headache disorders. However, available data indicate increased frequency of headache attacks in autumn–winter and least attacks in summer. This profile of headache matches with the seasonal variations of serum vitamin D levels. The presence of vitamin D receptor, 1α -hydroxylase and vitamin D-binding protein in the

hypothalamus further suggest a role of vitamin D deficiency in the generation of head pain.

Keywords Vitamin D · Headache · Migraine · Tension-type headache · Pain · Chronic daily headache · Vitamin D receptor

Introduction

The prevalence and incidence of headache differ widely between countries and there is an intriguing geographical pattern [1]. Several factors can be responsible for the differences of prevalence between countries, such as methodological differences in the studies, and cultural, environmental, metabolic and genetic factors, etc.

Vitamin D insufficiency (VDI) has emerged as a widespread global public health issue in the recent times. Rickets and osteomalacia are the most common manifestations of VDI. However, recent observations and hypotheses suggest that VDI may affect almost every system of the body [2]. A number of observations have suggested an association between low serum levels of vitamin D and higher incidence of chronic pain [3]. Anecdotal evidences suggest that vitamin D may be effective in a few headache disorders [4–6]. If the prevalence rate of a particular disease increases with increasing latitude, vitamin D deficiency is another possibility. The role of vitamin D in the pathogenesis of a few disorders was purported only when it was noticed that the prevalence of the disease has some relation with latitude.

We review the articles reporting a role of vitamin D in headache disorders. We also review the literature to delineate a relation of prevalence rate of headaches with the latitude.

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Review of literature

A number of recent observations, including small randomized controlled trials, suggest a link between low serum levels of vitamin D and higher incidence of chronic pain [3]. There is no consensus on the optimal levels of vitamin D. 25-Hydroxyvitamin D level (25(OH) D) of more than 30 ng/ml is usually considered as a sufficient vitamin D level. Vitamin D deficiency is considered when serum 25 (OH) D level is less than 20 ng/ml. Between 20 and 30 ng/ml of 25 (OH) D levels indicate a VDI state [2]. Observations of vitamin D levels with painful conditions have been made on musculoskeletal pain of limbs, trunk and joints. No such study has been done in patients with headache. There are just a few case reports or observations suggesting a role of vitamin D in headaches [4–6]. Recently, Turner et al. [7] studied the prevalence of vitamin D inadequacy (<20 ng/ml) among 267 patients with chronic pain, including headache (25 patients). The prevalence of VDI among these 267 patients was 26%. However, the details of vitamin D levels in headache patients were not provided. The first case report on a role of vitamin D (with calcium supplementation) was probably reported by Thys-Jacobs [5] in 1994. The author demonstrated the beneficial effect of vitamin D in two female patients with a history of menstrually related migraine and premenstrual syndrome. Both the patients had low serum vitamin D levels (case 1: less than 5 ng/ml; case 2: 17 ng/ml). Both patients received vitamin D (1,200–1,600 IU daily) and calcium (1,200–1,600 mg daily) supplementation. There was a significant reduction in migraine attacks in 2–3 months. Later on, the same author [6] showed dramatic reduction in the frequency and duration of migraine headaches in another two postmenopausal migraineurs with vitamin D and calcium supplementation. The serum 25 (OH) D levels in these two patients were 19.8 ng/ml (Case 1) and 15 ng/ml (Case 2). Wheeler [8] studied the serum vitamin D levels in chronic migraine patients; 14.8% of patients had levels of ≤ 20 ng/ml and another 25.9% of patients had levels between 20 and 30 ng/ml. Recently, Prakash and Shah [4] reported eight patients with vitamin D insufficiency having symptoms of both osteomalacia and chronic tension-type headache. All patients had vitamin D levels of ≤ 10 ng/ml. Both headache and osteomalacia responded to vitamin D and calcium supplementation in a few weeks' duration. Vitamin D insufficiency constitutes an unrecognized epidemic in many populations worldwide. Therefore, the causal association of any disease with vitamin D insufficiency or deficiency should be judged cautiously.

If vitamin D is important in the generation of head pain, the incidence of headache will be higher at higher latitudes. There is at least one report on the relation of headache

prevalence with latitude. Mitsikostas et al. [9] studied the prevalence of headache in Greece and noted a correlation of the frequency of daily headache with latitude. The prevalence and frequency of daily headache was higher in the northern regions (higher latitude) than in southern areas. We further searched the literature for a possible relation of headache prevalence with the latitude. Search methods included MEDLINE, review articles and reference lists of relevant manuscripts. The MEDLINE search was conducted using the keywords “headache”, “prevalence” and “epidemiology”. Studies were included if they were: (1) population based; (2) conducted in the general populations; (3) reporting lifetime or 1-year prevalence of total headaches, migrainous headaches and tension headaches; (4) studies using IHS classification or published after 1988; (5) studies conducted in a city or small county/provinces or small countries with a narrow latitudinal range (up to 5°). Articles were excluded if (1) the studies were not conducted on the general population (e.g., among students, clinic-based studies, in workplaces, only in a limited age group and only on one gender); (2) studies not describing the time frame for determination of prevalence rate; (3) national population survey done in a country with a wide latitudinal range (more than 5°, such as the USA, Canada, Brazil, Japan, France, Sweden, Germany, Denmark); (4) studies on rare types of headache disorders.

We looked for a relation of headache prevalence with latitude. The latitude of the city or country, described in the manuscript, was determined by “Google Earth”. The mean latitude of the country was used as a reference for seeking its relation with headache prevalence in small countries.

Although every effort was taken to include all the relevant data described in literature, it might be possible that some important data could have been missed. We faced a few problems in including the studies. There were many differences in methodology and reporting patterns among the studies. A few studies explored/reported the same population on two or more occasions. Time frame for determining the prevalence rate was not described in a few observations. Some articles described the prevalence rates in males and females separately, but failed to give a combined (male and female together) prevalence rate. On a few occasions, we calculated the combined prevalence rate. For calculating the total headache prevalence, we combined the total number of male and female patients (if number was given in the article) having headache and then expressed it in percentage (the usual method of determining headache prevalence). The headache types/subclassifications were not very clear in some studies (such as non-migrainous headaches, mixed headaches, etc.). We excluded such type of studies from the final review to minimize the confounding factors.

Both lifetime and 1-year prevalence for the total headaches did not show any significant relation with the latitude (and we did not include total headache prevalence in the table). However, we noted two studies with very low prevalence of total headache near equatorial areas. Both studies did not define the time frame for the headache prevalence. Gourie-Devi et al. [47] reported prevalence of various neurological disorders in Bangalore, India (12°N). Their survey recruited 102,557 subjects. Prevalence rate for headache was only 1.1%. Similarly, the prevalence of headache was relatively low (4%) in Hong Kong (22°N), in the screening of 7,356 persons [48]. These prevalence rates

are very low even if we consider these two as point prevalence.

We evaluated further to see the relation of latitude with the prevalence of tension headache, migraine and chronic daily headache. We noted a significant relation of lifetime prevalence of both tension-type headache and migraine with the latitude (Table 1) (Figs. 1, 2, 3). The lifetime prevalence for migraine was between 2.6 and 6.9 (six studies) for the people living in a city or country situated between 0 and 25° (N or S) of latitude. This rate was 12.5–26.5 (seven studies) in subjects living beyond 30° (N or S) of latitude. None of the studies on places above 30° of

Table 1 The prevalence of tension headache and migraine (arranged in ascending order of latitude)

City (country)	Author (year)	Population	Latitude	Lifetime prevalence		One year prevalence	
				Tension headache	Migraine	Tension headache	Migraine
Singapore (Nationwide)	Ho et al. (2003) [10]	2,096	1N	13	3		
San Pablo del Lago (Ecuador)	Cruz et al. (1995) [11]	2,723	1S	2.8	6.9		
Mbulu, Manyara, Tanzania (Africa)	Winkler et al. (2009) [12, 13]	7,412	3S			7.0	4.3
Gbêcon-Hounli, Abomey, Benin (Africa)	Houinato et al. (2010) [14]	1,113	7N		3.3		
Central Ethiopia	Tekle haimont et al. (1995) [15]	15,000	9N				3.0
Ibadan (Nigeria)	Osuntokun et al. (1992) [16]	18,954	8N		5.3		
Nachingwea (Tanzania) (Africa)	Dent et al. (2004) [17]	3,351	10S				5.0
Cuzco (Peru)	Jaillord et al. (1997) [18]	3,246	13S				5.3
Pureto Rico	Miranda et al. (2003) [19]	1,610	18N				13.5
Hongkong (Nationwide)	Cheung (2000) [20]	1,436	22N			26.9	4.7
Eastern province (Thugabah) (Saudi Arabia)	Al Rajeh et al. (1997) [21]	22,630	22N	9.5	5		
Ad Dakhliyah (Oman)	Delu et al. (2002) [22]	1,158	23N			11.2	10.1
Taipei (Taiwan)	Wang et al. (2000) [23]	3,377	25N				9.1
Qassim (Saudi Arabia)	Abduljabbar et al. (1996) [24]	5,891	25N	3.1	2.6		
Porto Alegre (Brazil)	Wiehe et al. (2002) [25]	1,174	30S		17.1		
Jordan (Nationwide)	Alzoubi et al. (2009) [26]	4,836	31N			36.1	7.7
Santiago Chile	Lavadose et al. (1997) [27, 28]	1,385	33S			26.9	7.3
Daisen (Japan)	Takeshima et al. (2003) [29]	4,795	35N			21.7	6.0
Korea (Nationwide)	Roh et al. (1998) [30]	2,500	37N			16.2	22.3
Baltimore, Atlanta, and Philadelphia (USA)	Bigal et al. (2006) [31]	30,215	39N				12.5
Maryland (USA)	Stewart et al. (1996) [32]	12,328	39N				16.6
Maryland (USA)	Schwartz et al. (1998) [33, 34]	13,345	39N			40.5	13.3
Philadelphia (USA)	Lipton et al. (2002) [35]	4,376	39N				11.6
Sivas (Turkey)	Kececi et al. (2002) [36]	947	39N		12.5		
Ederin (Turkey)	Celik et al. (2005) [37]	386	41N		20		
Tbilisi and Kakheti (Georgia)	Katsarava et al. (2009) [38]	1,145	41N			37.5	15.6
Bakar (Croatia)	Zivadinov et al. (2001), (2003) [39, 40]	3,794	45N	34.8	19		16.7
Doetinchem & Maastricht (Netherlands)	Launer et al. (1999) [41]	6,491	51N		23.2		16.3
Mainland (UK)	Steiner et al. (2003) [42]	4,007	52N				14.3
Copenhagen	Rasmussen et al. (1991) [43]	740	55N	78	16		
Akershus, Hedmark or Oppland (Norway)	Russell et al. [2008] [44]	2,177	63N		26.5		
Nord-Trøndelag (Norway)	Hagen et al. (2000) [45]	51,383	63N				12.0
Svalbard	Lilleng et al. (2009) [46]	1,029	77N				18.0

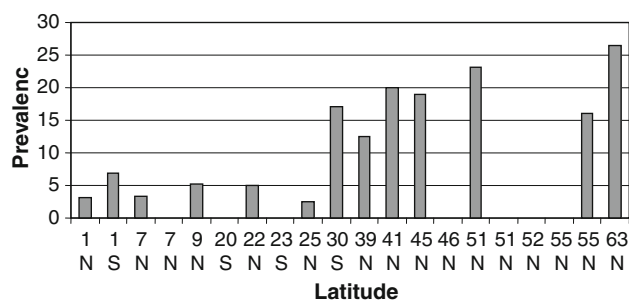


Fig. 1 Relation of lifetime prevalence of migraine with latitude

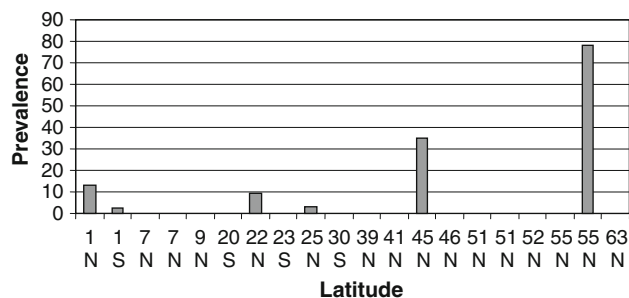


Fig. 2 Relation of lifetime prevalence of tension headache with latitude

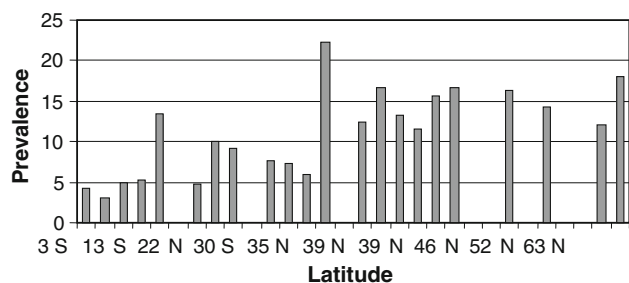


Fig. 3 Relation of 1-year prevalence of migraine with latitude

latitude had less than 12.5 lifetime prevalence rate for migraine. Conversely, the maximum lifetime prevalence rate for migraine at or below 25° of latitude was 6.9 (among six studies). This observation is important, as it clearly demonstrates a significant relation of lifetime prevalence of migraine with the latitude (Fig. 1). Although there were a limited number of population-based studies on tension headache, the relation of lifetime prevalence rate with the latitude was also obvious with tension headache. Four cities or provinces situated between 1 and 25° (N or S) had prevalence rates of 2.8–12.9. Conversely, two areas situated beyond 40°N had a prevalence rate of 34.8–78.0.

A total of about 50 publications relevant to 1-year prevalence were identified. Studies on populations of less than 1,000 were excluded for the observations. Finally, 22 studies were included for the observations (Table 1). The relation of 1-year prevalence rate with latitude was not as

strong as that observed with lifetime prevalence rate. However, there were some suggestions indicating that prevalence of headache would be higher at higher latitude. We noted 11 studies relevant to 1-year migraine prevalence in the cities or provinces situated between 0° and 35° (N or S). The prevalence rate was 3.0–13.5. Prevalence rate of more than 10 was noted only in two studies. The maximum 1-year prevalence rate was 13.5 below 35° latitude. There were 11 studies at latitudes higher than 35°. The prevalence ranged from 11.6 to 22.3%. None of the studies had prevalence rates less than 10. We found only nine population-based studies on tension-type headaches reporting a 1-year prevalence rate. Most of the studies were conducted on subjects residing between 22° and 41° of latitude. Six of these studies reported a 1-year prevalence rate of more than 25%. There is only one study outside this range (at 3°N) (Table 1). Because of the limited number of studies, we could not draw on any conclusion. However, a study done in Tanzania (3°S) [12] on 7,412 person demonstrated a very low 1-year prevalence rate (7%), and this may further support a possibility of low prevalence rate at the equatorial area (as noted above with lifetime prevalence rate for tension-type headache). We observed 16 studies on the 1-year prevalence of chronic daily headaches. However, because of the low prevalence rate, no conclusion or suggestions could be made.

We also tried to look at nationwide surveys of big countries that described the details of regional prevalence (especially, details of northern and southern areas). However, there were only a few studies with details of regional prevalence. Queiroz et al. [49] did an observational, cross-sectional population-based study for TTH in the 26 states of Brazil. They reported regionwise prevalence. Brazil is a very big country with a wide range of latitudes. Therefore, we should be very cautious in interpreting the data in relation to the latitudes. Nevertheless, the prevalence rate in southern Brazil (higher latitude) (14.1%) was more than two times that of northern Brazil (6.8%). However, this trend of prevalence was not corroborated in the same population for chronic daily headache. The prevalence of CDH was 6.0% in the south and 10.2% in the north [50].

Serum vitamin D levels vary with the season. It peaks in the months of May–September. The levels tend to be lower from November to March [51–53]. If vitamin D has any association with headache, the prevalence rate of headache should match with the usual seasonal variation of vitamin D levels. Sudden weather change is one of the most important factors for the attacks of headache (especially migraine). Bright sunlight exposure is another important factor for precipitating headache attacks [53, 54]. Therefore, it will be very difficult to comment on actual circ-annual or seasonal variations on headache prevalence.

Most of the studies on season and headache look for the effects of weather variables (such as temperature, rain, humidity, atmospheric changes, etc.) in precipitating headache attacks [53, 54]. Soriani et al. [54] studied the seasonal variation of migraine attacks in children and noted increased frequency of attacks in autumn–winter (especially November–January) with a minimum frequency in July. A circannual variation with a peak in January has also been reported for migraine in adults. [55]. Marrelli et al. [56] studied the seasonal and meteorological factors in primary headache disorders. The overall frequency of headaches was highest during winter and least in summer: 17.9% perceived more headaches in winter, 14.9% in spring, 11.5% in autumn and 10.6% in summer. Limited studies on this issue have prevented us from giving any comments with confidence. However, increased frequency of attacks in autumn–winter (October–January) and least attacks in summer indirectly suggest a role for VDI in the generation of recurrent headaches.

Discussion

The prevalence rates of a number of diseases increase with increasing latitude, i.e., prevalence rates tended to be very low near the equator and to increase as one moved toward the poles. Duration and intensity of sunlight shows a strong correlation with latitude (hence serum vitamin D level). The protective effect of vitamin D (or sunlight) in reducing the risk of cancer mortality rate was first suggested when Garland and Garland [57] noted that colon cancer mortality rates were highest in places where populations were exposed to the least amounts of natural light: major cities and rural areas in high latitudes. This ecological approach was used to find the first link between vitamin D insufficiency (minimal sun exposure) and increased risk for other carcinomas (breast and ovarian carcinoma) [58]. As the prevalence rate of headache is probably related with the latitude, a link between VDI and increased prevalence rate of headache disorders exist.

Low average income, illiteracy and poor health care facilities are considered as risk factors for various diseases. Also, the prevalence rate of headache has been demonstrated to be higher in the illiterate (or with low education level) population, population with low income and with poor healthcare facilities, etc. [59]. Average income, literacy and health-care facilities are poorer across the equator. Therefore, a high prevalence of headache should be suspected in these areas. However, we noted low prevalence in these areas. Therefore, we suspect the presence of some protective factors at the lower latitude areas. As higher serum vitamin D levels are found in the population living at a lower latitude, it may be one of the important factors for

the low prevalence. However, our observations (a positive relation of headache prevalence with latitude) should be judged very cautiously. At the present, it will be difficult to determine whether these observations are real or due to methodological differences in the studies. Genetic predisposition or racial differences are other factors to be considered in this discussion, although the prevalence of VDI also depends on genetic and racial factors [60]. The levels of vitamin D vary during the year. Therefore, the incidence or frequency of any disease causally related with VDI will vary with the timing of the studies. Although lifetime or 1-year prevalence of headache will not be affected much by the timing of the studies, we should be cautious in interpreting such data as recall bias may vary with timing: people tend to remember their more recent headaches. Besides latitude and season, many other factors affect the serum vitamin D levels. People who avoid sunlight, at any latitude, are at risk of vitamin D deficiency. Dark skin pigmentation, use of sunscreen, clothing, air pollution, cloud cover, etc., are other factors that affect the vitamin D status of a person or the population [2]. However, despite all these barriers, people may have normal serum vitamin D levels if they take adequate oral vitamin D, including the use of over-the-counter prescriptions. The analytical problems in relation to vitamin D assays are other points to be considered before deciding a causal association of any disease with vitamin D deficiency [61]. Therefore, our observations should be judged very cautiously, as the possibility of many confounding factors exist.

It is difficult to speculate on the exact role of vitamin D in the generation of head pain, as the pathogenesis of even bone and muscle pain in patients with VDI is still being determined. Recently, the presence of VDR and 1α -hydroxylase (1α -OHase), the enzyme responsible for the formation of the active vitamin, have been demonstrated in many areas of the central nervous system including the prefrontal cortex, hippocampus, cingulate gyrus, thalamus and hypothalamus [62]. Eyles et al. [62] studied the distribution of VDR and 1α -hydroxylase in the brain. The strongest immunohistochemical staining for both the receptor and enzyme was noted in the hypothalamus (and substantia nigra). Recently, Jirikowski et al. [63] studied immunostaining for vitamin D-binding protein (DBP) in rat hypothalamus. DBP was observed in widespread axonal projections throughout the lateral hypothalamus [63].

The exact functions of this VDR in the various sites of the brain are yet to be determined. However, the presence of VDR and 1α -hydroxylase in the areas (especially hypothalamus) implicated in the pathophysiology of various primary headache disorders suggests that VDI may have a role in the generation (or precipitation) of head pain.

In conclusion, increased incidence of headache prevalence at higher latitudes hints at a role of VDI in the

pathogenesis of headache disorders. Demonstration of vitamin D receptor, 1α -hydroxylase, and vitamin D-binding protein in the hypothalamus further supports a role of vitamin D deficiency in the generation of head pain. We hope our review will act as a catalyst for a controlled study to clarify the issue.

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Conflict of interest None.

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