COMPARING VITAMIN D STATUS IN CENTRAL ASIA AND NORTHERN EUROPE

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Abstract

Over the past two decades, the understanding of the roles of vitamin D has expanded to include many nonskeletal effects such as reduced risk of acute respiratory tract infections, autoimmune diseases, cancer, cardiovascular disease, diabetes mellitus, neurological diseases, and adverse pregnancy and birth outcomes. The role of vitamin D for optimal health is well known in Western developed countries but less so in Central Asian countries. This narrative review compares the status of vitamin D between Central Asian countries and Northern European countries. The analysis also summarizes the evidence for the beneficial effects of vitamin D and recommendations for Central Asian countries.

Keywords: Vitamin D, Central Asia, Europe, Hypothesis

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INTRODUCTION

In the past two decades, the understanding of the roles of vitamin D has expanded beyond the classical role of regulating calcium-phosphorus homeostasis and controlling bone metabolism. Evidence continues to mount that vitamin D has many other functions. It reduces risk of musculoskeletal disorders (muscle weakness, falls, fractures), infectious diseases, autoimmune

diseases, cardiovascular disease, type 1 and type 2 diabetes mellitus, several cancers, neurocognitive dysfunction and mental illness, as well as infertility and adverse pregnancy and birth outcomes [1,2]. The benefits of vitamin D are generally appreciated in Europe and the United States but relatively unappreciated in Central Asia (CA). This paper strives to determine the health outcomes in CA that would benefit from increasing vitamin D status,

present the evidence regarding vitamin D for those outcomes, and recommend action for future research. Data on vitamin D status and health outcomes for three northern European (NE) countries are included for comparison.

In this work, health outcomes considered are largely related to mortality rates. Mortality rate data were obtained from the World Health Organization.

To gain an understanding of the interest in vitamin D in CA and NE countries, pubmed.gov and Scopus for CA were searched, using the terms “vitamin D” and “25-hydroxyvitamin D” and the name of each country. To find evidence that better vitamin D status improves various health outcomes, both

pubmed.gov and scholar.google.com were searched, using “vitamin D” and “25-hydroxyvitamin D” and the name of the health outcome.

DATA FOR COUNTRIES IN CENTRAL ASIA AND NORTHERN EUROPE

Table 1 gives the latitude and longitude of the capital cities of each country, along with the population, life expectancy and healthy life expectancy at birth, infant mortality rate, and chronic disease mortality rate for people aged 30–70 years [3]. Life expectancy and healthy life expectancy at birth is about 10 years shorter in CA than in NE, infant mortality rates are much higher, and chronic disease mortality rates are about three times those in NE.

Table 1. Country data, 2017 [3]

Country	Capital	Latitude (°N), Longitude (°E)	Population (millions)	LE Birth (yrs)	HLE Birth (yrs)	Neonatal Mortality Rate per 1000	Chronic disease Mortality rate, 2015, 30–70 yrs (%)
Afghanistan	Kabul	34.56, 69.21	34.7	62.7	53.0	40.0	29.8
Kazakhstan	Nur-Sultan	51.16, 71.47	18.0	71.1	63.4	5.9	26.8
Kyrgyzstan	Bishkek	42.87, 74.57	6.0	71.4	63.5	11.8	24.9
Mongolia	Ulaanbaatar	47.89, 106.91	3.0	69.8	61.9	9.7	30.2
Tajikistan	Dushanbe	38.36, 68.79	8.7	70.8	63.5	19.9	25.3
Turkmenistan	Ashgabat	37.96, 58.33	5.7?	68.2	61.4	22.3	29.5
Uzbekistan	Tashkent	41.30, 69.24	29.9	69.4	62.4	20.4	31.0
Finland	Helsinki	60.17, 24.94	5.5	81.4	71.7	1.2	10.2
Norway	Oslo	59.91, 10.75	5.3	82.5	73.0	1.5	9.2
Sweden	Stockholm	59.33, 10.07	9.8	82.4	72.4	1.6	9.1

HLE: healthy life expectancy; LE: life expectancy

Table 2 gives age-adjusted mortality rates for males and females for the chronic diseases with the highest mortality rates for CA and NE countries [4].

Although cancer mortality rates are similar between CA and NE, diabetes mellitus mortality rates are much higher in several CA countries.

Cardiovascular disease rates, including both ischemic heart disease (IHD) and stroke, are about five times higher. Chronic obstructive pulmonary disease rates are about twice as high; cirrhosis of

the liver rates are more than 10 times higher than in Norway and Sweden; and kidney disease rates are about six times higher.

Table 2. Mortality rate data by country for various causes, 2015 [4]

Country	Quality of Data	Cancer	Diabetes	Neurological	CVD	IHD	Stroke	COPD	Cirrhosis	Kidney Disease
Afghanistan	P	119.5	60.4	39.0	459.6	287.0	137.9	40.8	17.9	43.3
Kazakhstan	Y	151.2	8.4	27.8	481.4	311.3	125.2	37.7	49.9	11.2
Kyrgyzstan	G	100.3	9.6	8.0	528.2	365.2	133.1	35.5	42.8	12.3
Mongolia	T	209.6*	4.6	25.1	449.0	249.2	168.1	13.2	57.4	15.3
Tajikistan	T	86.5	17.7	28.1	465.2	292.1	143.7	37.3	25.2	9.6
Turkmenistan	T	110.4	18.3	27.3	560.6	385.1	137.5	11.4	52.9	24.1
Uzbekistan	G	59.9	27.0	9.0	502.0	334.1	86.5	9.1	29.3	23.3
Finland	G	99.7	4.1	60.0	128.6	71.8	28.1	9.4	12.3	2.6
Norway	G	114.1	5.7	34.6	93.3	48.5	21.3	22.7	2.7	3.7
Sweden	G	106.8	8.3	35.4	113.1	61.3	22.4	15.2	4.4	3.6

Age-standardized rate per 100,000 population by cause and WHO member state (2015) (1812-GHE2016_Death-rates-country)

*Liver cancer rate, 92.5; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; IHD, ischemic heart disease; quality of data: G, high; P, death registration data unavailable; T, severe quality issues; Y, moderate.

One reason that 25(OH)D concentrations are higher in NE than in CA is that more fatty ocean fish is consumed in NE [5]. Another reason is that summer temperatures in CA are so hot that people probably do not spend much time in the sun.

Serum 25-hydroxyvitamin D [25(OH)D] concentrations are much lower in CA than in NE. As

Table 3 shows [6-19], mean serum 25(OH)D concentrations range from 4 to 23 ng/ml in CA and from 19 to 32 ng/ml in NE. (To convert ng/ml to nmol/L, divide by 2.5.) Few papers were found regarding serum 25(OH)D concentrations in CA, offering further evidence that little concern has been given to vitamin D in that region.

Table 3. Representative serum 25(OH)D concentrations for various countries

Country	25(OH)D (ng/ml)	Population	Date	Age (yrs)	Reference
Afghanistan	M, 7 (3–11); F, 4 (3–13)	Socioeconomically deprived children	Jan. 2005	0.5-1	[6]
Afghanistan	M, 5 (2–17); F, 5 (2–25)	Socioeconomically deprived children	Jan. 2005	1–4	[6]
Afghanistan	10.5	82 Immigrants in Norway	2010		[7]
Kazakhstan	24 (16–34)	HIV patients			[8]
	18±10	126 Children	2009–10	0.5-3	[9]
Kyrgyzstan	21±7	110 Healthy children, autumn		13–18	[10]
Mongolia	8±4	420 Mothers of schoolchildren	March–April 2009	35±5	[11]
Mongolia	Win, 8 (5–11); sum, 23 (15–33)	Healthy men, women	2011–2013	20–58	[12]
Mongolia	Win, 11±4; sum, 19±7	390 Pregnant women, win, sum	2011–2013	16–40+	[13]
Tajikistan	No data				
Turkmenistan	No data				
Uzbekistan	79% <12	474 Infants	Feb.–May 2004	5–61 wks	[14]
Finland	23	2822 Men and women		45–74	[15]
Norway	19±7	6112	2006–08	20+	[16]
Norway	26±7	4465	2012–14	40–69	[17]
Sweden	T1, 26±10; T3, 30±14	1810 Pregnant women	2013–14		[18]
Sweden	32±10	44 Patients with back pain, 44 controls, general population	2012	55±15	[19]

25(OH)D, 25-hydroxyvitamin D; F, female; HIV, human immunodeficiency virus; M, male; sum, summer; T1, first trimester; T3, third trimester; win, winter

I now turn to evidence that vitamin D has significant benefits in reducing risk of adverse health outcomes.

Cancer

Geographical ecological studies report inverse relationships between solar ultraviolet-B (UVB) doses and incidence/mortality rates for about 20 cancers [20]. In Nordic countries, outdoor occupation with UVB exposure is significantly inversely correlated with incidence of 14 cancers [21]. Observational studies show inverse correlations between serum 25(OH)D concentrations and colorectal cancer [22]. Pooled studies involving women, many of whom were taking high doses of vitamin D, indicate inverse correlations between serum 25(OH)D concentration

and both all-cancer incidence [23] and breast cancer incidence [24]. Recently the results of a large randomized controlled trial (RCT), VITamin D and Omega-3 Trial (VITAL), were released regarding supplementation with 2000 IU/d of vitamin D₃ and all-cancer incidence. Although the results for the entire 25,000 participants were not significant, they were for some subgroups. For participants with body mass index <25 kg/m² of body surface area, the hazard ratio (HR) was 0.76 (95% Confidence Interval [CI], 0.76 to 0.90); for blacks, HR = 0.77 (95% CI, 0.59 to 1.01); and when results during the first year were omitted, the HR for all-cancer death was 0.79 (95% CI, 0.63 to 0.99). A recent letter to the editor made the case for accepting secondary analyses such as these [5].

Diabetes mellitus type 2

Observational studies show that higher serum 25(OH)D concentration is associated with reduced risk of developing type 2 diabetes mellitus (T2DM). A meta-analysis reported a relative risk of 0.66 (95% CI, 0.61 to 0.73) for T2DM with respect to high versus low 25(OH)D concentration [25]. A recent RCT in which participants were given 4000 IU/d of vitamin D₃ in the treatment arm reported that several subgroups had significant (or nearly so) reductions in progression to T2DM: body mass index <30, HR = 0.71 (95% CI, 0.53 to 0.95); non-Hispanics, HR = 0.86 (95% CI, 0.72 to 1.02); males, HR = 0.82 (95% CI, 0.66 to 1.01); people >60.9 yrs, HR = 0.80 (95% CI, 0.64 to 1.01); people at or above 37° N latitude, 0.85 (95% CI, 0.70 to 1.03); and people with no calcium supplements intake, HR = 0.81 (0.66 to 0.98) [26]. A recent commentary in *Nature* argued that $p = 0.05$ is an arbitrary cutoff between significant and not significant [27]. Thus, the 95% CI values slightly larger than 1.00 should be considered to demonstrate significance even though the p -value is slightly larger than 0.05.

Ischemic heart disease

Good observational evidence indicates that serum 25(OH)D concentration is inversely correlated with IHD incidence, but no evidence has come from vitamin D supplementation studies. A 2012 meta-analysis reported that the relative risk of IHD doubled when baseline 25(OH)D concentration decreased from 20 to 6 ng/ml [28]. The most recent vitamin D RCT, the VITAL study, showed no significant benefit for IHD with 2000 IU/d of vitamin D₃ supplementation [29]. However, the mean baseline 25(OH)D concentration for participants who provided data was near 31 ng/ml, with few having 25(OH)D concentration below 15 ng/ml. In addition, participants in the control arm were permitted to take up to 600 IU/d (800 IU/d if older than 70 yrs) of vitamin D₃.

Stroke

In a meta-analysis of 19 studies, a significantly increased risk of stroke for low 25(OH)D concentration was evident. The risk ratio for stroke incidence for low versus high 25(OH)D from 16 prospective studies was 1.32 (95% CI, 1.19 to 1.46), whereas that from three case-control studies was 6.6 (95% CI, 1.2 to 37.0) [30]. The total risk ratio was

1.60 (95% CI, 1.33 to 1.92). However, vitamin D supplementation has not been shown to reduce risk of stroke [31]. But stroke often occurs for people with very low 25(OH)D concentration, and such people are generally not included in vitamin D RCTs. In addition, hypertension is an important risk factor for stroke [32], and an open-label study reported that participants with hypertension who took 4000 IU/d of vitamin D reduced systolic and diastolic blood pressure by 10–15 mmHg, to below the threshold for hypertension [33].

Chronic obstructive pulmonary disease

A meta-analysis reported that vitamin D supplementation can substantially reduce the rate of moderate/severe chronic obstructive pulmonary disease exacerbations for people with baseline 25(OH)D concentration <10 ng/ml (adjusted incidence rate ratio = 0.55 [95% CI, 0.36 to 0.84]) but not for those with higher baseline concentrations [34].

Cirrhosis of the liver

“Vitamin D deficiency in cirrhosis relates to liver dysfunction rather than aetiology, with lower levels of vitamin D in alcoholic cirrhosis than in primary biliary cirrhosis” [35]. However, vitamin D supplementation improves the probability of achieving a sustained immune response after antiviral treatment for people with 25(OH)D concentration <20 ng/ml [36]. A review of vitamin D’s antimicrobial properties appears in a review by Youssef and colleagues [37].

Chronic kidney disease

A meta-analysis of 16 studies involving 17,053 chronic kidney disease (CKD) patients with 7517 incident deaths indicated that a 10-ng/ml increment in 25(OH)D was associated with a 21% reduction in overall mortality (RR = 0.79 [95% CI, 0.70 to 0.87]) for people with baseline 25(OH)D concentration below about 35 ng/ml [38]. Another meta-analysis showed that the reduction in all-cause mortality rate was higher for CKD patients not receiving dialysis (four studies; risk ratio = 0.53 [95% CI, 0.32 to 0.87]) than those receiving dialysis (16 studies) (risk ratio = 0.66 [95% CI, 0.57 to 0.75]) [39]. However, that paper also reported that vitamin D RCTs have not shown a significant benefit in reducing all-cause or

cardiovascular disease mortality rates for CKD patients.

Acute respiratory tract infections

Acute respiratory tract infections (ARIs) are most common in winter, when UVB doses—and thus vitamin D status—are low [40]. A meta-analysis of vitamin D RCTs for ARIs showed that supplementing with vitamin D reduced the risk of ARIs, with greatest impact on people with 25(OH)D concentrations <10 ng/ml (Adjusted Odds Ratio = 0.30 [95% CI, 0.17 to 0.53]) [41].

Pregnancy

Vitamin D status during pregnancy and lactation is an important consideration. The developing fetus relies on genes to guide somatic development. The hormonal metabolite of vitamin D, 1,25(OH)₂D, affects the expression of many genes through vitamin D receptors coupled to chromosomes [42]. One important effect of vitamin D during pregnancy is to reduce the risk of preterm delivery. In an open-label study in South Carolina, women had their 25(OH)D concentration measured near the 12th week of pregnancy and were then given bottles of 5000-IU vitamin D and counseled on how to achieve concentrations of >40 ng/ml [43]. Those women who achieved >40 ng/ml had 61% reduced risk of preterm delivery in comparison with those with 25(OH)D <20 ng/ml (relative risk = 0.41 [95% CI, 0.24 to 0.72]). Higher vitamin D status has also been associated with reduced risk of preeclampsia [44] and gestational diabetes [45] as well as reduced risk of offspring with rickets [46].

All-cause mortality rate

On the basis of the understanding of 25(OH)D concentration–health outcome relations, it was estimated in 2011 that if continental population mean 25(OH)D concentrations were raised from 22 to 44 ng/ml, mortality rates would decrease by 8% (for countries with low life expectancies) to 17% (for countries with high life expectancies). That decrease translates to about 2 years of increased life expectancy [47]. A meta-analysis of 32

observational studies reported that all-cause mortality rates were reduced by about 30±20% when 25(OH)D was increased from 20 to 40 ng/ml [48].

CONCLUSION

Several steps can be taken to improve the vitamin D status in CA. One is to consider fortifying commonly consumed foods such as dairy, flour, and oil foodstuffs [49]. The goal of food fortification should be to have most people achieve a 25(OH)D concentration of at least 20 ng/ml. The second step would be to consider making vitamin D supplements more readily available and to publicize the need for vitamin D, especially for various subgroups of the population. The goal should be to have supplement takers achieve concentrations of at least 30 ng/ml, if not 40 ng/ml [50]. The third step would be to conduct observational studies and clinical trials regarding the health benefits of vitamin D in CA, which may differ from what has been found in other countries.

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CONFLICTS OF INTEREST

None

DISCLAIMER

No part of the manuscript has been submitted simultaneously or published elsewhere.

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Орталық Азия мен Солтүстік Еуропада Д дәруменінің рөлін салыстыру

Түйіндеме

Соңғы екі онжылдықта Д дәруменінің рөлін түсіну кеңейіп, қазіргі кезде жедел респираторлық инфекциялар, аутоиммунды аурулар, қатерлі ісік, жүрек-қантaмыр аурулары, қант диабеті, неврологиялық аурулар, жүктілік пен босанудың қолайсыздығының қаупін азайту сияқты көптеген әсерлерді қамтиды. Қоғамдық денсаулықтың оңтайлы деңгейін қамтамасыз етудегі Д дәруменінің рөлі Батыстың дамыған елдерінде жақсы белгілі, бірақ ол Орталық Азия елдерінде аз белгілі. Бұл әдебиетке шолу барысында Орта Азия мен Солтүстік Еуропадағы Д дәруменіне байланысты ақпараттың қанықтылығы салыстырылады. Талдау сонымен қатар Д дәруменінің оң әсері туралы мәліметтер мен Орталық Азия елдері үшін ұсыныстарды қамтиды.

Түйін сөздер: Д дәрумені, Орталық Азия, Еуропа, Гипотеза

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Сравнительный анализ статуса витамина D в странах Центральной Азии и Северной Европы

Резюме

В течение двух последних десятилетий было расширено понимание роли витамина D для организма человека. Помимо эффектов, оказываемых на скелет, были выявлены такие эффекты как снижение риска развития острых инфекционных заболеваний дыхательных

путей, аутоиммунных заболеваний, рака, сердечно-сосудистых заболеваний, сахарного диабета, неврологических заболеваний, а также снижение риска неблагоприятных исходов беременности и родов. Сегодня в развитых странах Запада хорошо изучена роль витамина D как элемента для обеспечения оптимального уровня общественного здоровья, однако в странах Центральной Азии витамин D изучен не так хорошо. В данном литературном обзоре сравнивается статус витамина D в странах Центральной Азии и Северной Европы. Анализ также содержит данные о положительных эффектах витамина D и рекомендации для стран Центральной Азии.

Ключевые слова: Витамин D, Центральная Азия, Европа, Гипотеза

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