ISSN 0362-1197, Human Physiology, 2017, Vol. 43, No. 6, pp. 729–740. © Pleiades Publishing, Inc., 2017.
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REVIEWS

Blood Serum 25-Hydroxyvitamin *D* in Various Populations of Russia, Ukraine, and Belarus: A Systematic Review with Elements of Meta-analysis

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Received March 6, 2017

Abstract—We analyzed published data on the serum level of 25-hydroxyvitamin *D* (25(*OH*)*D* in healthy subjects in Russia, Ukraine and Belarus (lat. 45°–65° N). The primary list included 158 publications. Reports with insufficient sample size and incomplete statistical descriptions were excluded from the analysis. The review covers 41 publications comprising 8569 individual assessments. The meta-analysis showed that the average levels of 25(*OH*)*D* were the highest among children under the age of 5 years, varied slightly between the age of 6 and 60 years, and decreased in older adults (60+). Gender differences become apparent at the postpuberty stage. The level of 25(*OH*)*D* was higher in men. No correlation between the level of 25(*OH*)*D* and latitude was found, but the relationship with the season and the duration of daylight was significant. No differences were revealed between ethnic and social groups.

Keywords: vitamin *D*, 25-hydroxyvitamin *D*, 25(*OH*)*D*, vitamin *D* status
DOI: 10.1134/S0362119717060044

The term vitamin *D* designates two steroid prohormones of different origins. Cholecalciferol *D*3 is synthesized in the skin exposed to ultraviolet irradiation, whereas the stores of ergocalciferol *D*2 are provided by phytosterol supplied with food. Chole- and ergocalciferol are converted in the liver to 25-hydroxyvitamin *D*: 25(*OH*)*D*. 25(*OH*)*D* circulating in the bloodstream serves as a transport form of the vitamin and its main reservoir in the body.

In vitamin *D* deficiency, the absorption of phosphorus and calcium in the intestine, as well as their reabsorption in the kidneys, is decreased. This causes a broad spectrum of consequences: metabolic disorders of bone tissue, abnormalities of carbohydrate and protein metabolism, decreased resistance to the causative agent of tuberculosis, as well as autoimmune, cardiovascular, and oncological diseases [1–6]. The establishment of these factors has become the most important cause of increased interest in the vitamin *D* status variables in different age and geographical population groups.

An important innovation was the development of radioimmune and immunoenzyme technologies for the measurement of the serum 25(*OH*)*D* level [7]. The appearance of the standard laboratory methods of analysis in the 2000s [8] allowed the scope of population studies to be substantially enlarged. The serum 25(*OH*)*D* level is thought to be the best biomarker of vitamin *D* status. In contrast to the qualitative estimates used earlier, the 25(*OH*)*D* concentration serves as a quantitative criterion. The rate of 25(*OH*)*D* production in the liver varies insignificantly and mainly depends on the arrival of substrates for synthesis in the body. In addition, 25(*OH*)*D* is physiologically stable: its half-life is two to three weeks [8]. This has opened up new possibilities for studying the epidemiology of the states connected with vitamin *D* metabolism.

Intensive studies of the vitamin *D* status of various populations have been conducted in many countries of the world over the past 20–25 years, but in Russia they have been carried out for the past decade.

At the same time, the problem of the prevalence of vitamin *D* deficiency has become a topical subject for Russia. Moreover, the character of the daily diet of most Russians is characterized by the traditionally low or seasonal consumption of ergocalciferol-containing products [9]. It is important to note that the entire territory of the Russian Federation is situated above 35° N, a conventional border to the north of which the level of insolation is insufficient for all-year autosynthesis of cholecalciferol *D*3 influenced by ultraviolet irradiation [10]. However, precisely this endogenous source of vitamin *D* is thought to be the main one: depending on the level of seasonal sun exposure, it meets 65–95% of the body requirements [11]. Thus, Russia should be considered to be a region of an increased risk of vitamin *D* deficiency.

The value of Russian data on vitamin *D* status for the international scientific community is determined by several causes: the climatic and ecological variability and northern location of the territory on the European scale; the markedness of seasonal daylight variations; the polyethnicity of the population and genetic polymorphism determined by it, and the variety of living and dietary conditions. Analysis of the influence of both individual factors and their complexes on the vitamin *D* status will allow the epidemiological situation to be cleared up not only in Russia, but also in the entire Eurasia.

No systematic review of the data on the 25(*OH*)*D* and vitamin *D* status of the population of Russia and the neighboring states has been attempted so far. In recent reviews claimed to be "worldwide" [12–14], the Russian population data are represented by the survey materials of only two (!) samples, and the information about the Ukraine and Belarus is completely absent.

The aim of this review was to analyze within the scope of the published array of data obtained during the study of the samples of apparently healthy population of Russia, Ukraine, and Belarus the variability in the serum 25(*OH*)*D* content depending on the age, gender, geographical position, and duration of daylight.

Note that we did not set the task to analyze the materials in the context of worldwide literature, nor did we consider the data on the vitamin *D* status of specific groups, such as the indigenous population of high-latitude regions.

METHODS

This work was performed in the genre of systematic review, a scientific research into a number of published homogeneous original studies with a view to their critically analyzing and assessing. This methodology allows us to generalize and interpret the data excluding random and systematic errors by using the standardized methods of selection, verification, and generalization of materials. The quantitative approach to the generalization of the published results of the studies ensures a component of a systematic review, namely, meta-analysis [15].

The publications for this review were selected using the following keywords (in the Russian and English variants): vitamin *D*, 25-hydroxyvitamin *D*, 25(*OH*)*D*, vitamin *D* status.

Systematic review of the Russian data is complicated by limited availability through network resources of complete texts of the articles published in national scientific editions. Part of the materials is contained in collections published in local press that are not readily available. The search for the sources in libraries and electron network resources using topical indices and keywords allowed us to obtain the primary list consisting of 158 publications. The studies from this list were included in this review considering the following criteria:

—A publication contains the results of examination of apparently healthy individuals (when patients were surveyed, only the traits of the control groups were considered).

—All the necessary statistical data (the means or the median of the trait, the variability values, the sample size) are published.

—The sample size is sufficient for analysis.

—The serum concentration of 25(*OH*)*D* has been determined using enzyme-linked immunosorbent assay (ELISA).

Following these criteria substantially narrowed the array of the materials analyzed. We had to exclude a considerable part of publications, because they contained the 25(*OH*)*D* content data only in the groups of individuals with various diseases or specific states.

Certain complications were caused by the necessity of excluding duplicate information. For example, a number of publications dealing with the analysis of allied topics (e.g., the description of vitamin *D* status in different pathologies) give the traits of the same control group satisfying the criteria of inclusion in the review and meta-analysis. Accordingly, this review contains references to only one of two or a series of such publications.

Often in the course of the current research projects, the data obtained at the previous stages of work are included in the samples of increasing size. With this in mind, we included in our analysis the latest publications by writing teams based on the largest samples.

The publications unsatisfactory from the point of view of statistical analysis, i.e., those based on the results of the survey of scanty (less than 10 individuals) samples, those providing only the trait means without the variation parameters, etc., were also excluded. As result, the volume of sources was sharply reduced: of 158 sources, only 41 were included in the analysis.

Note the following technical details.

The dimension of the 25(*OH*)*D* concentration was adjusted to nmol/L in all cases.

Since the distribution of the values of the trait in question is different from the normal law, it is correct to indicate the median and the centiles when describing the results. However, most publications provide the arithmetic means and the standard deviations. Taking this into account, we included both the mean and median values with the corresponding variation parameters in the summary tables.

The localization of the survey region for the samples included in the analysis was determined with an accuracy of one degree latitude, which meets the requirements of the present study.

The duration of daylight in the period of the study was determined by us using the http://www.timezone.ru/suncalc.php resource for the nearest geographical point in the middle period of the survey.

The diagnostic criteria of the vitamin *D* status used by different authors do not coincide. To facilitate the introduction of Russian data into scientific discourse, we adopted the dietary reference intakes of 25(*OH*)*D* according to the recommendations of the Institute of Medicine (United States) Committee [16]: vitamin deficiency, less than 30 nmol/L; insufficient content, 30–50 nmol/L; satisfactory vitamin *D* status, 50 nmol/L and higher. The review includes the works containing the above-mentioned diagnostic criteria of the vitamin *D* status or the data that allowed us to make the relevant recalculations.

RESULTS AND DISCUSSION

The analyzed array of secondary data [17–50] on the blood serum concentration of 25(*OH*)*D* in various age, sex, and territorial samples of the population of the Russian Federation, Belarus, and Ukraine formed on the basis of the results of the survey of 8569 individuals is represented in Tables 1 and 2.

Table 3 summarizes the materials of 22 publications [17, 18, 22, 23, 26, 27, 32, 34, 38–41, 43–46, 51–56] containing the data on the vitamin *D* status of various population groups meeting the uniform criteria.

Information analysis led us to the following results.

The Role of Ethnicity

The predominant majority of the publications included in the review are based on the data obtained in ethnically undifferentiated samples of the population of various regions of Belarus [29, 45], Ukraine [34, 50], and Russia. However, since the population of the Russian Federation includes representatives of various racial and ethnic groups, we considered the data on the possible anthropological specifics of the 25(*OH*)*D* content. The analysis of publications showed that such tasks were not set in the course of the studies in the republics of Bashkortostan [28, 43, 44], Karelia [23, 33], Tatarstan [19], and Chuvashia [47]: the relevant information is only territorially bound. That is why the data published in these studies provide only indirect information for researchers who are interested in the influence of the ethnicity-related factors, such as the type of nutrition, genetically determined metabolic features, etc., on the vitamin *D* status.

A small part of publications provide information about the samples with a clearly defined ethnic composition: Komi, Komi-Permyaks, and Udmurts [32, 46], as well as Yakuts [30]. According to the conclusions of the authors, all these groups do not differ in the level of 25(*OH*)*D* from the Russian population of the corresponding age cohorts and territories surveyed in the same seasons: the Urals region in the first three cases and Yakutia in the latter case.

The samples of two rural groups of Chuvashi women whose mean age was 33.2 [48] and 29.0 years [49] formed on the basis of ethnic identity differ from the mixed sample of the urban 18- to 27-year-old population of Chuvashia [47] in a very low 25(*OH*)*D* content. However, these differences may be determined by the influence of social factors, the specific features of the diet, etc. and are insufficient to reach a conclusion about the contribution of the ethnic (race) component to vitamin *D*-status formation.

Thus, we conclude that interethnic differences in the 25(*OH*)*D* content have not been revealed in the representatives of the extra-Arctic groups of population of the Russian Federation. Accordingly, we analyze the materials disregarding the factor of ethnic identity.

Age-Related Changes

In order to assess the general picture of the age-related dynamics of the 25(*OH*)*D* content, we used calculation of the weighted means of the trait. In order to weaken the influence of the seasonal factor, the samples surveyed in winter, namely, from the second half of November to the end of February, were excluded from the analysis. The materials cited in the publications [19, 22, 23, 25, 28, 31, 33, 35–47, 50] are grouped on the basis of the age cohorts. To completely adjust the age brackets did not seem to be possible; therefore, in child samples (up to the age of 16 years), the error with inclusion in one or another cohort was ±2 years; in the 17+ years samples, ±4 years. The analyzed array of data included 3429 primary observations. Note that since the distribution of the 25(*OH*)*D* values in the samples differs from the statistically normal one, the weighted means of the trait are inapplicable for assessing the significance of intergroup differences. The results are shown in Fig. 1.

In children, the 25(*OH*)*D* weighted means decrease from preteens to adolescents. Additional information about the age-related dynamics of the trait in younger children is provided by the materials of the studies conducted in different seasons, and for this reason only partially taken into account when the weighted means were calculated. These data show that the children aged 0–12 months are characterized by the highest 25(*OH*)*D* content, with this parameter being gradually decreased in the second year of life [17, 18, 22]. The 25-hydroxyvitamin *D* concentration in infants aged 6–12 months reaches the peak [17, 18].

Due to the discrepancy between the age brackets of the sample, the adult cohorts comprise comparatively wide age ranges. On the whole, Russian materials demonstrate a slight decrease in the 25(*OH*)*D* concentration in the cohorts from 13–16 to 46–59 years of

Table 1. 25(*OH*)*D* (nmol/L) in various age-related, gender, and territorial population groups of Russia, Belarus, and Ukraine (children 0–17 years of age)

Inspection site	*N* [1]	Age (years)[2]	Gender	Season/month	*N*	*M*	*SD*	*Me*	*m*	Reference
Stavropol	45	0–0.5	M + F	XI–III	44	61.65	33.10	59.9	5	17, 18
Stavropol	45	0.5–1	M + F	XI–III	31	83.37	52.78	65.64	9.5	17, 18
Stavropol	45	2	M + F	XI–III	29	47.17	21.49	44.93	4	17, 18
Stavropol	45	3	M + F	XI–III	27	43.18	10.91	43.43	2.1	17, 18
Kazan	56	0–1	M + F	–	52	43.01	48.96	–	6.79	19
RF	56	4–18	M + F	VI–VIII	140	57.25	18.25	–	–	20
RF	56	6–18	M + F	–	391	36.45	10.79	–	–	21
Arkhangelsk	65	0–3	M + F	Spring–autumn	153	79.55	–	69.14	–	22
Arkhangelsk	65	6–7	M + F	Spring–autumn	80	36.34	–	32.7	–	22
Arkhangelsk	65	13–15	M + F	Spring–autumn	184	45.77	–	43.43	–	22
St. Petersburg	60	7–17	M + F	With no view to	120	46.8	17.53	–	1.6	23
St. Petersburg	60	7–17	M + F	With no view to	54	–	–	42.56	–	24
Nizhny Novgorod	56	1.4–5	M + F	With no view to	15	100.5	44.3	–	–	25
RF	55	4–18	M + F	VI–VIII	140	57.25	18.25	–	–	26
Moscow	56	10–18	M	Year	161	40.68	20.56	–	1.6	27
Moscow	56	10–18	F	Year	199	42.88	19.33	–	1.4	27
Meleuz	53	8–9	M + F	IX	83	46.62	–	44.28	–	28
Zirgan village	54	8–9	M + F	IX	86	–	–	57.54	–	28
Minsk	54	5–17	M	Autumn–winter	40	–	–	23.96	–	29
Minsk	54	5–17	F	Autumn–winter	30	–	–	30.2	–	29
Yakutsk	62	9–15	M + F	II–III	80	35.04	19.68	–	2.2	30
Chita	52	6.9	M + F	IX–XII	21	57.3	12.6	–	–	31
Kortkeros, Komi Republic	61	13–16	M + F	XI	58	37.9	12.2	–	1.9	32
Izhma, Komi Republic	65	13–15	M + F	II	51	31.06	8.76	20.55	1.2	32
Orda, Perm krai	57	14–16	M + F	X	49	49.55	13	–	1.9	32
Petrozavodsk	62	11	M + F	III–IV	100	35		–	–	33
Ternopol	50	10–13	M	X–XII	34	34.7	11.4	–	–	34
Ternopol	50	14–16	M	X–XII	20	30.3	10	–	–	34
Ternopol	50	10–13	F	X–XII	46	31.1	11.1	–	–	34
Ternopol	50	14–16	F	X–XII	30	28.3	9.8	–	–	34
Perm	58	14–17	M + F	VIII–X	74	50.7	13.35	51	–	35
Perm	58	14–17	M + F	XI–I	13	38.2	18.2	33	–	35

[1] *N*, the latitude of inspection site; [2] the age range of those surveyed or the mean value for the sample (if there is no other); dash, no data.

age (Fig. 1). The same results were obtained in Ukraine in the course of a large-scale study (1575 individuals broken up into age cohorts at an interval of 10–15 years). The authors did not reveal a significant relationship between age and 25(*OH*)*D* ($r = -0.05$; $p = 0.05$) [50].

A noticeable decrease in the 25(*OH*)*D* content is observed only in the older cohort including individuals over 60 years (Fig. 1). The local study of the sample of representatives of this cohort confirmed negative correlation between 25(*OH*)*D* and the age ($r = -0.356$, $p = 0.001$) [43].

It may be concluded that children in the first years of life, especially those aged 6–12 months, are characterized by a high 25(*OH*)*D* content [17, 18, 22]. The serum vitamin *D* concentration then gradually decreases, and, beginning with the sixth year of life, the trait variations do not seem to correlate with age. Nevertheless, we have carried out further analysis separately for adults and children. From 18 to 60 years, the correlation between the 25(*OH*)*D* content in the body and age is weakly (insignificantly) negative. Several investigations revealed a statistically signifi-

Table 2. 25(*OH*)*D* (nmol/L) in various age-related, gender, and territorial population groups of Russia, Belarus, and Ukraine (adults)

Inspection site	*N* [1]	Age (years)[2]	Gender	Season/month	*N*	*M*	*SD*	*Me*	*m*	Reference
Arkhangelsk	65	18–22	M + F	Spring–autumn	88	51.51	–	48.92	–	22
Arkhangelsk	65	24–60	M + F	Spring–autumn	85	66.28	–	60.65	–	22
Petrozavodsk	61	22–60	M	With no view to	43	47.1	15.74	–	2.4	23
Petrozavodsk	61	22–60	F	With no view to	52	51.6	15.14	–	2.1	23
St. Petersburg	60	19–75	M	With no view to	1242	67.2	77.53	–	2.2	23
St. Petersburg	60	19–75	F	With no view to	207	53.9	11.51	–	0.8	23
Perm	58	18–59	M + F	VIII–X	28	50.8	24.6	44.5	–	35
Perm	58	18–59	M + F	XI–I	69	37.2	15.74	35	–	35
Perm	58	18–59	M + F	II	13	32.4	7.61	32.7	–	35
Perm	58	18–59	M + F	III	46	44.7	9.01	43.5	–	35
Novosibirsk	55	54.8	F	With no view to	15	50.92	14.08	–	–	36
Sverdlovsk oblast	59	23–38	M	III–IV	8	42.92	–	40.44	–	37
Sverdlovsk oblast	59	27–48	F	III–IV	24	42.69	–	40.19	–	37
Yekaterinburg	57	72.5	F	II–IV	53	27.2	9.2	–	–	38
Yekaterinburg	57	67.5	M	II–IV	44	29	11.1	–	–	38
St. Petersburg	60	21–52	M	XI–III	132	30.5	8.7	–	8.7	39
St. Petersburg	60	21–52	M	IV–VII	132	53.4	7.1	–	7.1	39
St. Petersburg	60	42–52	F	IX–V	320	52.9	22.7	–		40
St. Petersburg	60	25–70	M	With no view to	500	68.3	42.49	–	1.9	41
St. Petersburg	60	25–70	F	With no view to	500	51.9	42.49	–	1.9	41
Moscow	56	50+	F	XII–III	96	41.4	–		–	42
Moscow	56	50+	F	VIII–X	111	60.6	–	–	–	42
Moscow	56	50+	F	With no view to	207	45.5	–	–	–	42
Ufa	54	63.92	M	III	36	46.63	19.62	–	3.27	43
Ufa	54	67.10	F	III	68	41.81	14.02	–	1.7	43
Bashkiria, rural area	55	67.14	M	III	32	23.04	10.4	–	1.83	43
Bashkiria, rural area	55	65.83	F	III	52	20.27	9.4	–	1.31	43
Ufa	54	63.7	M	VIII	33	56.9	14.9	–	2.6	44
Ufa	54	70	F	VIII	64	54.7	20.8	–	2.6	44
Bashkiria, rural area	55	64.9	M	VIII	29	60.6	12.9	–	2.4	44
Bashkiria, rural area	55	68.3	F	VIII	49	59.1	30.1	–	4.3	44
Minsk	54	49–80	F	VIII–IX	50	23.64	13.73	–	–	45
Brest	52	49–80	F	VIII–IX	70	32.12	13.23	–	–	45
Mogilev	54	49–80	F	VIII–IX	28	63.72	27.33	–	–	45
Krasnokamsk	58	20–29	M + F	XI	34	39.71	16.5	–	2.83	46
Kudymkar	59	19–59	M + F	III	46	44.72	9	–	1.33	46
Izhevsk	57	21–58	M + F	XI	52	44.6	12.9	–	1.79	46
Syktyvkar	62	17–23	M + F	XI	52	47.65	12	–	1.66	46
Cheboksary	56	18–27	M + F	With no view to	70	56.4	17.6	–	2.1	47
Chuvashia, rural area	56	30–63	M	X–XII	186	24.46	16.97	–	–	48
Chuvashia, rural area	56	28–39	F	X–XII	68	25.21	9.48	–	–	48
Chuvashia, rural area	56	57–69	F	X–XII	98	20.47	10.23	–	–	48
Bashkiria, rural area	53	18–89	M	VI	91	–	–	25.5	–	49
Bashkiria, rural area	53	18–48	F	VI	49	–	–	23.3	–	49
Bashkiria, rural area	53	45–90	F	VI	50	–	–	20.6	–	49
Ukraine, entire territory	45–52	20–34	M + F	With no view to	117	33.95	–	–	–	50
Ukraine, entire territory	45–52	35–44	M + F	With no view to	140	25.8	–	–	–	50
Ukraine, entire territory	45–52	45–59	M + F	With no view to	521	31.71	–	–	–	50
Ukraine, entire territory	45–52	60–74	M + F	With no view to	670	31.26	–	–	–	50
Ukraine, entire territory	45–52	75+	M + F	With no view to	127	27.2	–	–	–	50

See Table 1 for designations.

Table 3. Vitamin *D* status in various population groups of Russia, Belarus, and Ukraine

Inspection site	Age (years)	Gender	Season	*N*	Vitamin *D* status in percent of the number of those surveyed*				Reference
					1	2	1 + 2	3	
Stavropol	0–0.5	M + F	XI–III	44	15.9	18.2	34.1	65.9	17, 18
Stavropol	0.5–1	M + F	XI–III	31	12.9	12.9	25.8	74.2	17, 18
Stavropol	2	M + F	XI–III	29	17.2	41.4	58.6	41.4	17, 18
Stavropol	3	M + F	XI–III	27	11.1	63	74.1	25.9	17, 18
Stavropol	0–3	M + F	–	52	–	–	38.5	61.5	51
Various RF regions	0–3	M + F	–	1230	–	–	41.7	58.3	52
Arkhangelsk	0–3	M + F	Spring–autumn	153	8	23	31	69	22
Arkhangelsk	6–7	M + F	Spring–autumn	80	22	49	71	29	22
Arkhangelsk	13–15	M + F	Spring–autumn	184	1	69	70	30	22
Arkhangelsk	18–22	M + F	Spring–autumn	88	1	50	51	49	22
Arkhangelsk	24–60	M + F	Spring-autumn	85	4	29	33	67	22
Moscow	10–18	M	Year	161	10.5	20.3	30.8	69.2	27
Moscow	10–18	F	Year	199	11.4	26.7	38.1	61.9	27
Moscow	4–18	M + F	VI–VIII	140	–	–	38.6	61.4	26
Perm krai, rural area	14–16	M + F	X	49	6	41	–	53	32
Komi, rural area	13–16	M + F	XI	43	14	72	–	14	32
Komi, rural area	13–15	M + F	II	51	35	63	–	2	32
Ternopol	10–13	M + F	X–XII	42	–	–	87	13	34
Ternopol	14–16	M + F	X–XII	76	–	–	95	5	34
Moscow	14–18	M	II–III	125	–	–	50.4	49.6	53
Moscow	14–18	F	XI–XII	158	–	–	82.1	17.9	53
Pyatigorsk	25–45	F	X–VI	70	8.6	91.4	–	–	54
Moscow	20–46	F	IX–III	34	–	–	53	47	55
Moscow	48	M + F	Year	414	–	–	41.3	58.7	56
Krasnokamsk	20–29	M + F	XI	46	21	56		23	46
St. Petersburg	42–52	F	IX–V	320	–	–	59	41	40
St. Petersburg	21–52	M	XI–III	132	–	–	76	24	39
St. Petersburg	21–52	M	IV–VII	132	–	–	35	65	39
St. Petersburg, Petrozavodsk	7–75	M + F	Year	1664	10.4	40.0		49.6	23
Yekaterinburg	70.2	M + F	II–IV	97	–	–	98	2	38
St. Petersburg	25–70	M	–	154	–	–	23.3	76.7	41
St. Petersburg	25–70	F	–	346	–	–	30.9	69.1	41
Syktyvkar	17–23	M + F	XI	52	2	60	–	38	46
Izhevsk	21–58	M + F	XI	52	10	54	–	36	46
Kudymkar	19–59	M + F	III	46	–	30	–	70	46
Ufa	66.1	M + F	III	104	–	–	70	30	43
Bashkiria, rural area	66.1	M + F	III	84	–	–	95	5	43
Ufa	67.9	M + F	VIII		–	–	1	99	44
Bashkiria, rural area	67.2	M + F	VIII		–	–	9	91	44
Belarus, entire territory	49–80	F	VIII–IX	148	–	–	75	25	45

* The diagnostic criteria according to the 25(*OH*)*D* dietary reference intake [16]: (1) deficiency < 30 nmol/L; (2) insufficient, 30–50 nmol/L; (3) sufficient, 50+ nmol/L.

cant vitamin *D* concentration decrease in 60+ individuals [43].

Gender Differences

No gender differences in the 25(*OH*)*D* content were revealed in the samples of children under 18 years [23, 26, 27, 33, 53]. Since the sample size in these studies varies between 40 and 199 individuals, it cannot be ruled out that the differences will not show up as a result of a small number of groups.

In 18- to 60-year-olds, the gender differences in comparatively small samples are not revealed either [23, 37]. However, in large samples including 200 to 1242 representatives of this age cohort, the vitamin *D* level in men is significantly ($p < 0.01$) higher than in women [23, 41].

In the individuals over 60 years, the gender differences are insignificant [38, 43, 44], despite the tendency for a higher 25(*OH*)*D* level to be retained in male versus female samples.

Thus, as judged by the available data, the relatively slight gender differences in the 25(*OH*)*D* content with a moderate excess of the parameter values in men arise in the postpuberty and are retained in later life.

Contribution of Latitude

The notion that the risk of *D*-vitamin deficiency increases with the northern localization of the group is commonplace in the epidemiology of vitamin *D*. We tested the validity of this opinion on the materials obtained on the territory of the Russian Federation having considered the variations in the 25(*OH*)*D* content depending on the latitude of the region. The meta-analysis includes the data on 18- to 60-year-old adults irrespective of the gender, ethnic identity, and the place of residence (urban/rural).

For 17 samples [35, 38, 39, 43, 46, 48] including 1081 individuals examined from November to March, the rank correlation between the mean 25(*OH*)*D* group values and the latitude of the region of the group localization is as follows: $Rsp = 0.41$ ($p = 0.11$; $n = 17$). In 13 samples studied from April to October (a total of 2879 individuals) [22, 23, 35, 41, 44, 46], $Rsp = 0.24$ ($p = 0.44$; $n = 13$).

Thus, according to the meta-analysis data, the correlation between the serum 25(*OH*)*D* content and the latitude of the region of the place of residence is very weak. The significance of correlation between the traits does not attain the 5% level either in winter or in the more favorable spring–summer–autumn period. It may be suggested that, in view of the modern lifestyle, natural factors influencing the vitamin *D* status of the body rather than geographical factors come to the fore.

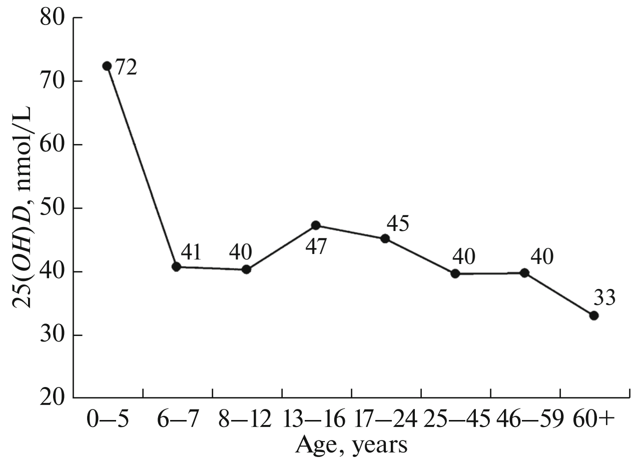

Fig. 1. Age-related dynamics of the 25(*OH*)*D* content as judged by the results of meta-analysis.

Seasonal Variation

The season is considered to be one of the factors determining the vitamin *D* content in the body.

Significant ($p < 0.05$) differences in the vitamin *D* status were found in infants from Stavropol city aged 1–36 months who were studied from November to March: the proportion of infants with vitamin *D* insufficiency and deficiency was significantly higher in January compared to November [18]. The study of 1230 children of the same age cohort in various regions of the Russian Federation showed that the maximal proportion of those surveyed with vitamin *D* deficiency of different severity was observed in October, December, and April; the minimal proportion, in July [52].

Seasonal variations in the 25(*OH*)*D* level were described in 10- to 17-year-old children from Moscow. Monthly variations in the vitamin content do not attain statistical significance, but seasonal differences are substantial ($p < 0.001$): in autumn (in October–November), the vitamin content is significantly higher than at the end of winter–the beginning of spring (February–March) [27].

The 25(*OH*)*D* content in 14- to 16-year-old adolescents and young adults from the Ural region in the autumn period (November) is also significantly ($p < 0.001$) higher than in the early spring (at the beginning of spring). In the latter, the proportion of those surveyed with vitamin *D* deficiency is considerably higher: 35% versus 14 and 6% in the two samples studied in November [32, 46].

Comparison of the data on the vitamin *D* status of several samples of children surveyed in the summer–autumn (from August to November) and winter (from November to February) seasons on the territory of the Russian Federation showed that in summer and in autumn, the proportion of those with a satisfactory vitamin *D* status varied between 31 and 48%, whereas in winter, it was considerably lower and did not exceed 24% [32, 33, 35, 53].

The presence of seasonal variations in the 25(*OH*)*D* level and changes in the vitamin *D* status are confirmed by most publications based on the materials of the study of large samples of the adult population.

The absence of significant differences in the 25(*OH*)*D* content between 40- to 52-year-old women from St. Petersburg surveyed in autumn (September–October), in winter (December–February), and in spring (March–May) should be considered an important exception [23, 40].

However, other investigations do not agree with these observations. For example, Toroptsova [57] reports that the vitamin *D* concentration in Moscow women aged 64 ± 8 years in January–April is significantly ($p = 0.02$) lower than in September–October. The 25(*OH*)*D* content is also significantly lower in November–March compared to April–June (30.5 and 53.4 nmol/L, respectively) in men from St. Petersburg aged 21–52 years [39]. The median 25(*OH*)*D* concentration values in adult dwellers of Perm city decrease in the period from the summer–autumn to the autumn–winter period and attain minimal values at the end of winter (February). Kruskal-Wallis rank analysis of variance confirms the significance of the seasonal factor ($p = 0.0081$); according to a posteriori paired comparison, the 25(*OH*)*D* content in the summer months is significantly ($p = 0.0076$) higher than in February [35]. The survey of a large sample of adult dwellers in Ukraine ($n = 1575$) also revealed seasonal differences in vitamin *D* content: the differences between the values of those studied in winter and in summer in the cohorts 21–34 and 60–74 years of age are significant ($p < 0.001$). In the summer period, the representatives of the 20- to 34-year-old group are characterized by the highest 25(*OH*)*D* content compared with the rest of the adult groups, but in winter the between-cohort differences are found to be leveled out [50]. Considerable seasonal differences in the 25(*OH*)*D* content were revealed in the population of Bashkortostan (the 60+ cohort). In those surveyed, the vitamin *D* level in August was higher than in March. Note that in rural dwellers, a stronger value increase was observed than in city dwellers [43, 44].

The Influence of the Duration of Daylight and Exposure to Sunlight

The survey season indirectly reflects the influence of the duration of daylight and sunlight on the level of 25(*OH*)*D*. Direct studies of the relationship between the vitamin *D* status and these natural factors are relatively few in the Russian Federation, and, at first sight, the results are ambiguous.

For example, no significant correlation between the absolute serum 25(*OH*)*D* values and the duration of daylight was revealed in the above-mentioned study of children from Stavropol aged 1–36 months, although seasonal differences in the vitamin *D* status are significant ($p < 0.05$) [18]. Nor do variations in the 25(*OH*)*D* content in 10- to 17-year-old children from Moscow surveyed during the months with a different number of sunny days attain the statistical significance [27].

On the other hand, the application of the method of rank correlation when studying the sample of Perm Krai inhabitants aged 14–59 years ($n = 245$; the sex- and age-related differences are nonsignificant) revealed a relationship between the duration of daylight and the 25(*OH*)*D* concentration ($Rsp = 0.396$; $p < 0.00001$) [35].

With this in mind, we conducted the meta-analysis of the group variables based on the materials of publications with indications of the date (period) of survey and comprising the groups with the ages varying between 14 and 60 years with a total number of primary observations of $n = 2360$ [23, 26, 32, 33, 35, 39, 53]. The duration of daylight in the survey period is calculated according to the unified method (see "Methods"). Spearman rank correlation between the average duration of daylight and the mean 25(*OH*)*D* concentration was assessed using the array of data including 21 samples. It was equal to $Rsp = 0.64$ ($p = 0.0017$; $n = 21$).

Thus, the meta-analysis confirms the suggestion that the duration of daylight influences the vitamin *D* content in adolescent and adult population of the Russian Federation.

Vitamin D Status of Urban and Rural Dwellers

The data on the 25(*OH*)*D* content in urban and rural dwellers of the Russian Federation are comparatively scarce [28, 32, 35, 38, 43, 44, 46–49, 58]. In addition, comparison can only be made in the samples close in terms of geographical regions and survey seasons. The materials of Evseeva et al. [58] were not considered earlier, because they did not fully comply with the requirements of the selection criteria; the information contained in these articles is sufficient to be included in the present review section.

As evidenced by the available data, children have a steady trend to a higher 25(*OH*)*D* content in rural groups in both the autumn–winter (November–January [28, 32, 35]) period and in spring [58] (Fig. 2).

It is more difficult to treat the survey materials of the adults (Fig. 3). The characteristics of the rural Chuvashi sample obtained in 1994 [48] have been excluded from this analysis, because the urban population of the region was surveyed almost 18 years later [47]. In this period, the level and quality of life and the dietary habits of the population of the Volga region have substantially changed [59], which could influence the 25(*OH*)*D* values. As a result, the rural Chuvashi sample is represented by the women with an

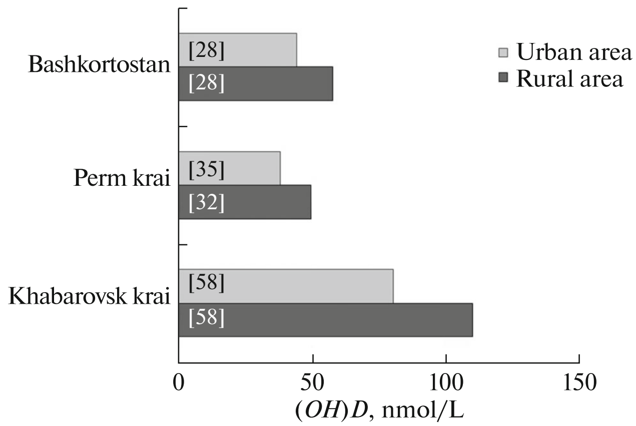

Fig. 2. 25(*OH*)*D* content in the urban and rural groups (children).

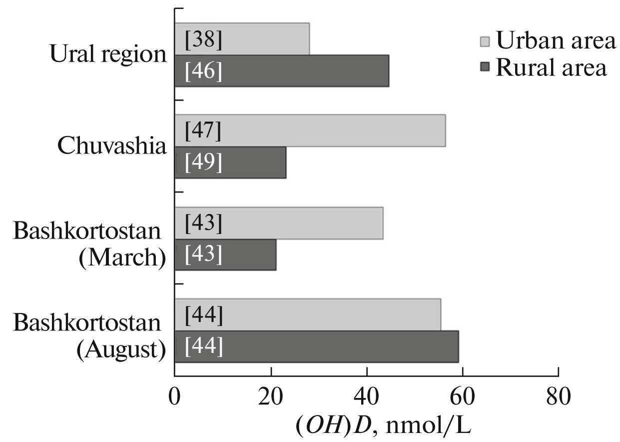

Fig. 3. 25(*OH*)*D* content in the urban and rural groups (adults).

average age of 29.0 years surveyed in 1999 [49], which is close to the age of the city dwellers: 20.0 years [47]. True, in this case, the period of time between two studies is 10–12 years. The comparison shows that the vitamin *D* content in the city dwellers is twice as high as the level of 25(*OH*)*D* in the rural sample.

On the contrary, the 25(*OH*)*D* content in rural dwellers is higher in the samples of the population of the Ural region [38, 46]. However, the surveyed urban dwellers are considerably older than the villagers (the mean age is 70.2 and 38.0 years, respectively), and, as shown earlier, the representatives of older age groups are characterized by a lower vitamin *D* content.

The possible influence of the age factor was counteracted in two pairs of samples from the territory of Bashkortostan: in all the cases, the individuals aged 60+ were surveyed [43, 44]. According to these studies, in the low insolation period (March), the vitamin *D* content in the city dwellers is significantly ($p = 0.05$) higher, whereas by the end of summer (August), the level of 25(*OH*)*D* in the rural dwellers increases more substantially than in the city dwellers: the differences between the samples become insignificant (the city dwellers even lag behind slightly in terms of the mean parameter values).

Thus, rural children surpass city dwellers in the vitamin *D* content, whereas in adults, the differences between the urban and rural samples are unstable. Note that, in the period of increased natural illumination (the level of sun exposure), the 25(*OH*)*D* content in adult rural dwellers increases more substantially than in city dwellers. It may be suggested that these differences in the vitamin *D* status are due to the country dwellers spending more time outdoors, i.e., they are connected with seasonal fluctuations in cholecalciferol *D*3 production. However, we did not find any relevant studies of the proportion of contribution of ergo- and cholecalciferol *D*3 to the vitamin *D* status of the representatives of various population groups of the temperate climatic zone of Russia.

CONCLUSIONS

This systematic review covers the data on the surveys of 8569 citizens of the temperate climatic zone of the Russian Federation, Ukraine, and Belarus (lat. 45°–65° N). The secondary information included in the review is contained in 41 publications.

The main results are as follows.

(1) The information about the vitamin *D* status of the representatives of various ethnic groups in the Russian Federation is scarce; researchers normally disregard the possible contribution of the ethnic and anthropologic factors to the specifics of vitamin metabolism.

No interethnic differences in the 25(*OH*)*D* content were found when we analyzed the works of Russian scientists published now.

(2) The age-related dynamics of the 25(*OH*)*D* content predominantly shows up in children. In the cohort 0–5-years of age, the weighted mean 25(*OH*)*D* values are equal to 72.3 nmol/L, gradually decreasing from 83 nmol/L at the age of 6–12 months to 43–45 nmol/L at the age of five years. In the cohorts 6–12 years of age, the correlation between the trait variations and age is weak. In adults whose ages vary between 18 and 60 years, the tendency for 25(*OH*)*D* to decrease is observed, but the relationship with age does not attain the 5% level of significance. The 60+ cohorts are characterized by a significant ($p = 0.001$) decline in the vitamin *D* concentration.

(3) The gender differences in the 25(*OH*)*D* content are formed in the postpuberty period. In the cohort 18–60 years of age, men are characterized by a higher vitamin *D* content compared to women ($p < 0.01$). The tendency to higher 25(*OH*)*D* in men is also retained in

the 60+ groups, but gender differences are statistically insignificant.

(4) The analysis did not reveal significant correlation between the serum 25(*OH*)*D* concentration and the latitude of the region where the group lives. It may be suggested (although the problem has not been considered in this case) that, under modern conditions, the geographical factor itself loses its significance, probably influenced by cultural and technological innovations (rational diet, the use of vitamin preparations and artificial sources of UV irradiation, etc.).

(5) Seasonal variations in the level of 25(*OH*)*D* are markedly pronounced in both child and adult samples. In summer and in autumn, the proportion of children with a sufficient vitamin *D* status (25(*OH*)*D* ≥ 50 nmol/L) varies within 31–48%; in winter, it does not exceed 24%.

The rank analysis of variance confirms the significance of the seasonal factor in the variation in 25(*OH*)*D* in adults ($p = 0.0081$). In the summer months, the vitamin *D* content is significantly higher than at the end of winter ($p = 0.0076$).

(6) Monthly variations in 25(*OH*)*D* are observed in a comparatively narrow range; monthly differences do not attain the statistical significance and reflect the vitamin status worse than seasonal variations. The increased vitamin *D* content values are formed at the end of a season with a high level of insolation (August–October); the lowest level of the vitamin is recorded at the end of winter/the beginning of spring (February–March).

(7) According to analysis of the primary data, the correlation between the duration of daylight and the 25(*OH*)*D* level in the cohort 14–59 years of age is $Rsp = 0.396$ ($p < 0.00001$; $n = 245$).

The meta-analysis confirms the suggestion that the duration of daylight influences the vitamin *D* content in the adolescent and adult population of the Russian Federation. The rank correlation between the mean group 25(*OH*)*D* concentration in 21 samples and the average duration of daylight is $Rsp = 0.64$ ($p = 0.0017$).

(8) The data on the possible contribution of social factors (including the urban and rural lifestyle) to the specifics of the 25(*OH*)*D* level in various population groups of Russia, Ukraine, and Belarus are insufficient.

Since the increase in the 25(*OH*)*D* content in the period of increased insolation is more significant in the rural population than in urban dwellers, it may be suggested that the differences between the urban and rural population predominantly emerge from the contribution of cholecalciferol *D*3 to the vitamin *D* balance. On the whole, children in rural areas surpass town dwellers in the level of vitamin *D*, whereas in adults, the differences between the urban and rural samples are unstable.

ACKNOWLEDGMENTS

We are grateful to I.N. Zakharova, R.Z. Nurlygayanov, E.L. Turova, and G. Livshits for giving attention to our work and help in solving a number of technical problems.

This study was supported by the Russian Foundation for Basic Research, project no. 15-04-02309.

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Translated by E. Babchenko