

Efficacy of Hypovitaminosis D Correction in Children of the Older Age Group Residing in Moscow

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Abstract: School-aged children and their health conditions, in particular, deficient conditions are not less note worthy than in younger children, while the recognition of present low vitamin D provision in children of all age groups has not still resulted in implementation of mass prophylaxis of hypovitaminosis D. There are several factors on which blood concentration of 25 (OH) D—calcidiol—depends. However, it is evident that among numerous factors we should orient on several most significant and develop correction scheme for the deficient condition in every region. Aim: to assess vitamin D levels in adolescents residing in Moscow, to correct their calcidiol status based on a baseline blood concentration of the transport metabolite. Materials and methods: 769 adolescents aged 11-18 years were examined and their blood concentration of 25 (OH) D was determined. Then, 218 patients were randomized to 2 groups: the treatment group received food supplement "Minisun® Vitamin D₃" in tablets, the control group received placebo. Cholecalciferol dosage was prescribed depending on the baseline calcidiol level in patients. The study continued for 6 months, after that blood was re-withdrawn for calcidiol level. Results: low calcidiol provision was observed among school children: median 25 (OH) D was 16.3 [11.4-20.8] ng/mL, only 5.2% of patients had normal blood concentration of calcidiol. There-examination showed significant differences in vitamin D status in the treatment and control group, in the meantime, during cholecalciferol supplementation, median 25 (OH) D in patients of the treatment group was increased from 16.2 [12.25-19.3] ng/mL to 24.2 [21.05-26.4] ng/mL ($p < 0.001$). Conclusions: the larger part of child population—70.6% has 25 (OH) D concentration < 20 ng/mL, cholecalciferol doses used in the study allow eliminating calcidiol deficiency and overcome the boundary of 20 ng/mL, but for normalization of vitamin D status in blood of adolescents residing in Moscow higher dosages shall be used which is to be confirmed by further studies.

Key words: School-aged children, adolescents, vitamin D provision, vitamin D insufficiency, vitamin D deficiency, correction of a low vitamin D status.

1. Rationale

During the last decades, most investigators and physicians of practical healthcare have assured that it is necessary to normalize vitamin D status, and more precisely, its transport metabolite-calcidiol-25 (OH) D, in children of the older age group [1-4]. The reverse correlation between a child's age and his/her calcidiol provision has been numerously proven [5-7].

Among 790 school children aged 7-14 years of the Central and North-Western regions of Russia, only 10% of children had normal blood concentration of calcidiol (> 30 ng/mL) [8]. Among 120 children aged 7-17 years residing in Saint-Petersburg, 25 (OH) D levels exceeded 30 ng/mL only in 8 persons (6.7%) [9].

According to foreign investigators, the mean calcidiol level in children aged 14-18 years ($n = 110$) in Great Britain does not exceed 20 ng/mL [10, 11], and in adolescents residing in the South-East of China,

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it amounts to 18.9 ng/mL [7]. The study carried out in Turkey not only showed the negative correlation between vitamin D level and age of children, but also rather regular seasonal variations of calcidiol provision. In the end of winter and beginning of spring, deficiency prevalence is significantly high, the analogous data are obtained in Spain [12, 13].

Despite the fact that the problem of low vitamin D provision in population of various countries of the world is known [14-16], up to the present time, recommendations on dosing of cholecalciferol products have been rather cautious and several experts assume them as the ineffective prophylactic measure for hypovitaminosis D [17-19].

Since 2010, many scientific societies have established acceptable daily doses of cholecalciferol to achieve and maintain necessary 25 (OH) D concentrations in the range 40-60 ng/mL, hereby children below 18 years in various countries of the world are recommended to take 400 to 1,000 IU [18].

Persons with diagnosed vitamin D deficiency need higher doses of vitamin D than those doses that are generally recommended for population (Table 1) [17, 20-23].

In Russia, treatment schemes for correction of hypovitaminosis D are also developed and analyzed in the context of safety and efficacy. Multicenter study RODNICHOK-2 showed high efficacy and safety of cholecalciferol product administration during 1 month in younger children depending on baseline 25 (OH) D levels [10].

In 2013, recommendations of experts from the Central Europe were published [22] in which the emphasises made that dosing should be considered in each specific region based on age, body weight, ethnical group (skin type) and latitude of residence place.

The aim of the present study was to assess vitamin D provision and analyze the results of hypovitaminosis D correction in Moscow children and adolescents.

Table 1 Clinical recommendations on correction of vitamin D insufficiency in various groups of population.

Document	Group of patients	Recommendation of insufficiency correction
Clinical Recommendations of the US Endocrine Society 2011 [17]	Infants and children below 1 year	2,000 IU/day or 50,000 IU once a week during 6 weeks to achieve 25 (OH) D level above 30 ng/mL, with subsequent switch to maintenance dose 400-1,000 IU/day
	Children and adolescents 1 year to 18 years	At least 2,000 IU/day or 50,000 IU once a week during 6 weeks to achieve 25 (OH) D level above 30 ng/mL, with subsequent switch to maintenance dose 600-1,000 IU/day
	Adults	50,000 IU once a week during 8 weeks or 6,000 IU/day to achieve 25 (OH) D level above 30 ng/mL, with subsequent switch to maintenance dose 1,500-2,000 IU/day
Practical Recommendations on Prevention and Management of Vitamin D Deficiency in the Central Europe, 2013 [22]	Infants	1,000 IU/day (25 µg/day) during 1-3 months
	Children 1 to 12 months	1,000-3,000 IU/day (25-75 µg/day), depending on body weight
	Children and adolescents 1 to 18 years	3,000-5,000 IU/day (75-125 µg/day), depending on body weight
	Adults and elderly	7,000-10,000 IU/day (175-250 µg/day), depending on the weight, or 50,000 IU a week (1,250 µg/week)
Global Consensus on Prevention and Management of Nutritional Rickets, 2016 [21]	Infants and children up to 3 months	2,000 IU/day, course lasting for up to 90 days, with subsequent transfer to maintenance dose 400 IU/day
	Children 3 to 12 months	2,000 IU/day course lasting for up to 90 days, with subsequent transfer to maintenance dose 600 IU/day
	Children 1 year to 12 years	3,000-6,000 IU/day for up to 90 days with subsequent transfer to maintenance dose 600 IU/day
	Children above 12 years	6,000 IU/day for up to 90 days with subsequent transfer to maintenance dose 600 IU/day

2. Materials and Methods

The prospective blind randomized placebo-controlled study was carried out.

2.1 Inclusion Criteria

- age 11-18 years;
- children not taking Ca products and active metabolites of vitamin D at the examination moment;
- children without organic pathology and genetic syndromes;
- Moscow residents.

2.2 Study Conditions and Determination of 25 (OH) D Content

The 769 children took part in the study: 214 (27.8%) boys and 555 (72.2%) girls. The children represented the following age groups: 11 years—75 (9.8%), 12 years—61 (7.9%), 13 years—118 (15.3%), 14 years—148 (19.2%), 15 years—120 (15.6%), 16 years—139 (18.0%), 17 years—92 (12.1%), 18 years—16 (2.1%) persons.

Study participants were the school children of the Moscow secondary general education institutions, as well as Moscow Cadet Corps “Boarding school of the Ministry of Defense of the Russian Federation”. Only children from the Boarding school participated in the second study phase (n = 218). In this educational institution, adolescents get not only balanced food diet, but also follow rational day regime, sufficient level of their physical activity is provided as well.

After obtaining the informed consent from parents and patient enrollment to the study, their venous blood was withdrawn in morning hours (8.00-12.00 h) to determine the major transport metabolite of vitamin D—25 (OH) D—in blood serum with the method of

CLIA (chemiluminescent assay) using analyzer LIAISON®.

Severe vitamin D deficiency was diagnosed at 25 (OH) D level < 10 ng/mL, deficiency—at calcidiol level 10-19 ng/mL, insufficiency at 20-29 ng/mL, calcidiol concentration > 30 ng/mL was considered as normal vitamin D provision [17, 24, 25].

On the second stage, patients were randomized to the treatment and control groups. Children of the treatment group received food supplement “Minisun® Vitamin D₃” (vitamin D₃ 10 µg, sorbitol E 420, xylitol E 967, magnesium stearate E 470) in tablets (1 capsule contains vitamin D₃ 10 µg) during 6 months and during the period of the most pronounced insufficiency (December-May), hereby a daily product dose was determined depending on baseline 25 (OH) D status. The children of the control group received placebo during 3 months (March-May), the number of placebo tablets they took was calculated in the same way as in children of the treatment group (Table 2).

On the second stage of the study, 218 girls were enrolled to the study. Among them, 192 participants performed the protocol and completed the study. Prior the study and based on the results of 6-month administration of food supplement “Minisun® Vitamin D₃” in the treatment group and 3-month placebo administration in the control group, 25 (OH) D level was measured in each adolescent, and the analysis of dynamics of vitamin D status was made on its basis.

2.3 Ethical Expertise

The study was approved by the Research Ethics Committee at FSBEI HPT RMAPGE of MoH RF (protocol № 10 dated 13.10.2015).

Table 2 Daily cholecalciferol dosage in children of the treatment group and placebo dose in children of the control group.

Baseline 25 (OH) D level	Control group placebo dose	Treatment group Minisun® dose IU/day
< 10 ng/mL	5 tab.	2,000 IU (5 tab.)
10-19 ng/mL	4 tab.	1,600 IU (4 tab.)
ng/mL	3 tab.	1,200 IU (3 tab.)
≥ 30 ng/mL	2 tab.	8,00 IU (2 tab.)

The statistical analysis of study results was made with software package Microsoft Excel 2007 and IBMSPSS v20.0. To identify a type of data distribution, Shapiro-Wilks test was used. For parametric qualitative data, mean arithmetic (M) and error of the mean arithmetic (m) was determined. For non-parametric quantitative data, median (Me) and quartiles [25Q-75Q] were determined.

In case of normal distribution to assess inter group differences, student’s t-test was used in the analysis of quantitative parametric data. In case of distribution that was different from normal in groups with quantitative non-parametric data, Mann-Whithney U-test was used. To identify statistical significance of differences between quantitative data, Pearson’s test was used (χ^2) to adjust for small samples and Fisher’s exact test (if one of the values was less than 4, and total number of values less than 30). To assess the relationship between the values, Pearson’s (r) and Kendall’s pair correlation coefficients were used. The differences were considered significant at $p \leq 0.05$ [26].

3. Study Results and Discussion

The analysis of vitamin D provision of Moscow adolescents shows the significant prevalence of a low

vitamin D status. The structure of vitamin D status is demonstrated in Fig. 1.

The larger part of examined participants (70.6%) has vitamin D deficiency, hereby calcidiol level does not exceed 10 ng/mL in each fifth child. Unfortunately, only every twentieth adolescent has 25 (OH) D value corresponding to the normal level of vitamin D.

The 25 (OH) D level and structure of vitamin D provision in children of various ages are presented in Table 3.

The comprehensive analysis shows that Russian children have steadily low vitamin D levels throughout the adolescence, hereby the number of children with deficiency (level below 20 ng/mL) varies in the range 62.5% in 15 years to 81.3% in 18 years. The number of children with normal levels (over 30 ng/mL) is only 5.2% in the whole group and does not exceed 4% in adolescents aged 13, 16 and 17 years.

Fig. 2 presents the distribution histogram of calcidiol level in examined adolescents depending on the year season.

The analysis of changes in calcidiol and structure of vitamin D levels throughout the year demonstrates rather evident regular patterns related to impossibility

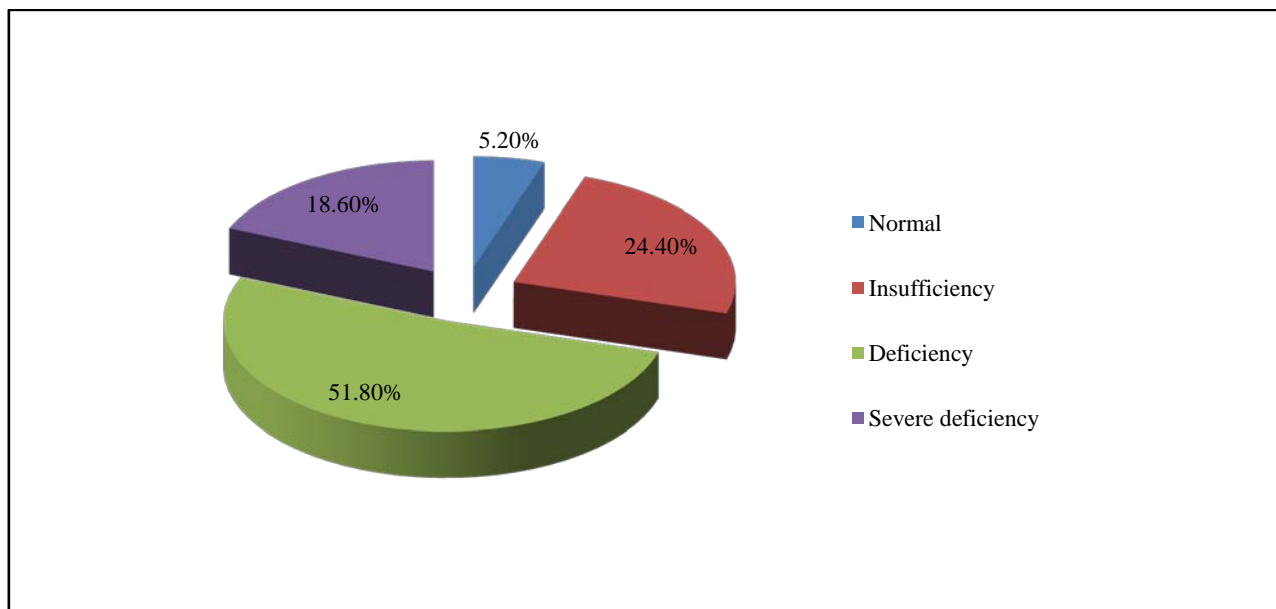
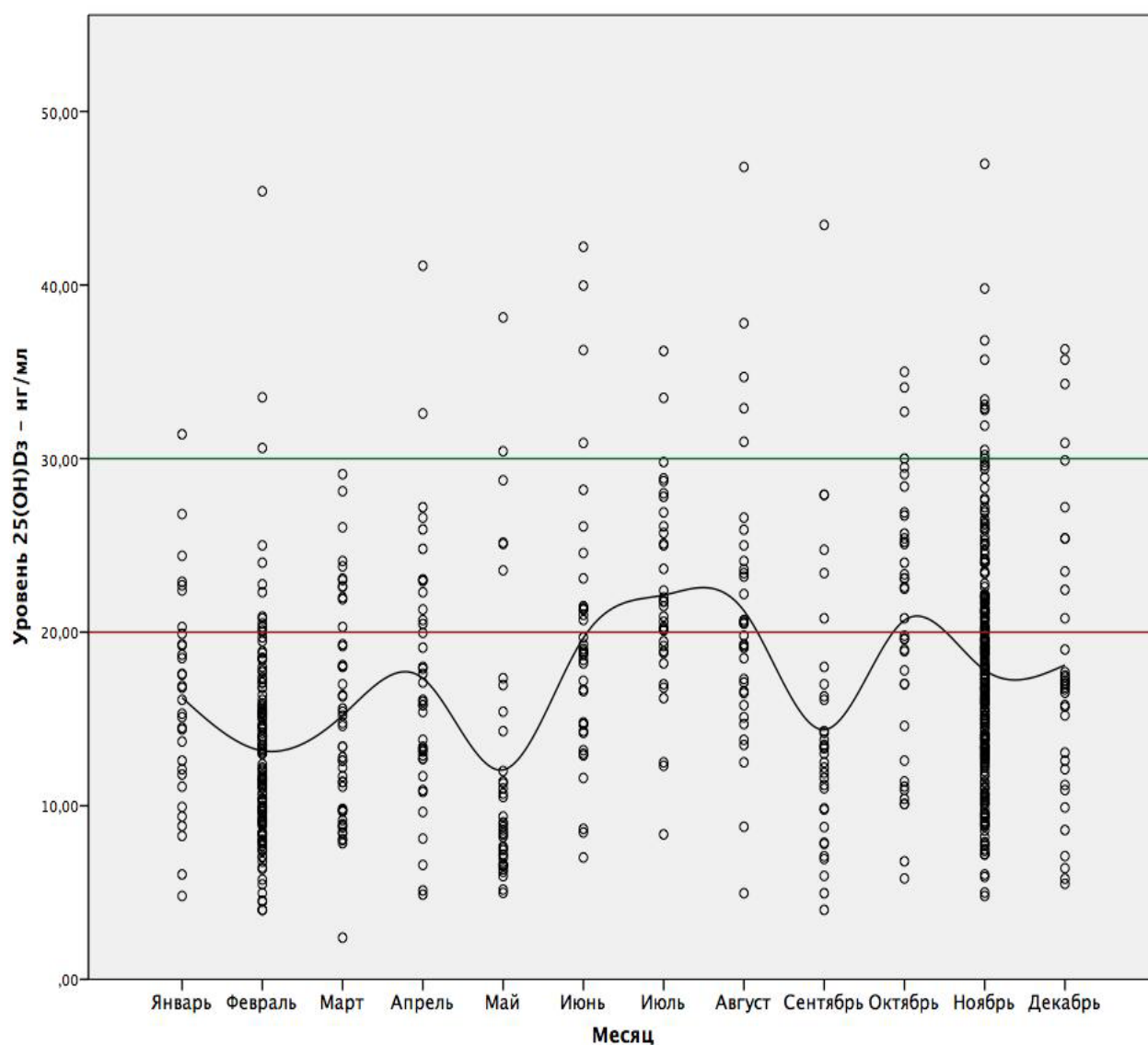


Fig. 1 Structure of 25 (OH) D levels in adolescents (n = 769).

Table 3 Calcidiol level in adolescents depending on the age.

Age	Number of children	25 (OH) D level, Me [25Q-75Q], ng/mL	Vitamin D levels, n (%)			
			less than 10 ng/mL	10 to 19 ng/mL	20 to 29 ng/mL	more than 30 ng/mL
11 years	75	14.3 [11.2-20.6]	15 (20.0%)	38 (50.7%)	16 (21.3%)	6 (8.0%)
12 years	61	14.0 [11.1-19.2]	12 (19.7%)	35 (57.4%)	11 (18.0%)	3 (4.9%)
13 years	118	15.7 [9.3-19.5]	32 (27.1%)	58 (49.2%)	24 (20.3%)	4 (3.4%)
14 years	148	17.6 [13.4-22.0]	18 (12.2%)	78 (52.7%)	45 (30.4%)	7 (4.7%)
15 years	120	16.9 [11.6-22.7]	21 (17.5%)	54 (45.0%)	34 (28.3%)	11 (9.2%)
16 years	139	15.9 [11.3-20.1]	27 (19.4%)	75 (54.0%)	33 (23.7%)	4 (2.9%)
17 years	92	16.9 [12.5-20.9]	15 (16.3%)	50 (54.4%)	24 (26.1%)	3 (3.2%)
18 years	16	16.9 [12.5-17.6]	3 (18.8%)	10 (62.5%)	1 (6.2%)	2 (12.5%)
Total	769	16.3 [11.4-20.8]	143 (18.6%)	398 (51.8%)	188 (24.4%)	40 (5.2%)



25 (OH) D 3-level—ng/mL

January, February, March, April, May, June, July, August, September, October, November, December
Month

Fig. 2 Calcidiol level in adolescents depending on a year season.

to maintain a normal calcidiol level in the territory of Russia through insolation. Only during three months (July, August and October), median 25 (OH) D is significantly higher than the level of 20 ng/mL, and the number of children with severe deficiency does not exceed 10%. The most unfavorable situation is observed in May—8.78 [7.08-11.35] ng/mL, hereby severe vitamin D deficiency was detected in more than half of the adolescents (level less than 10 ng/mL).

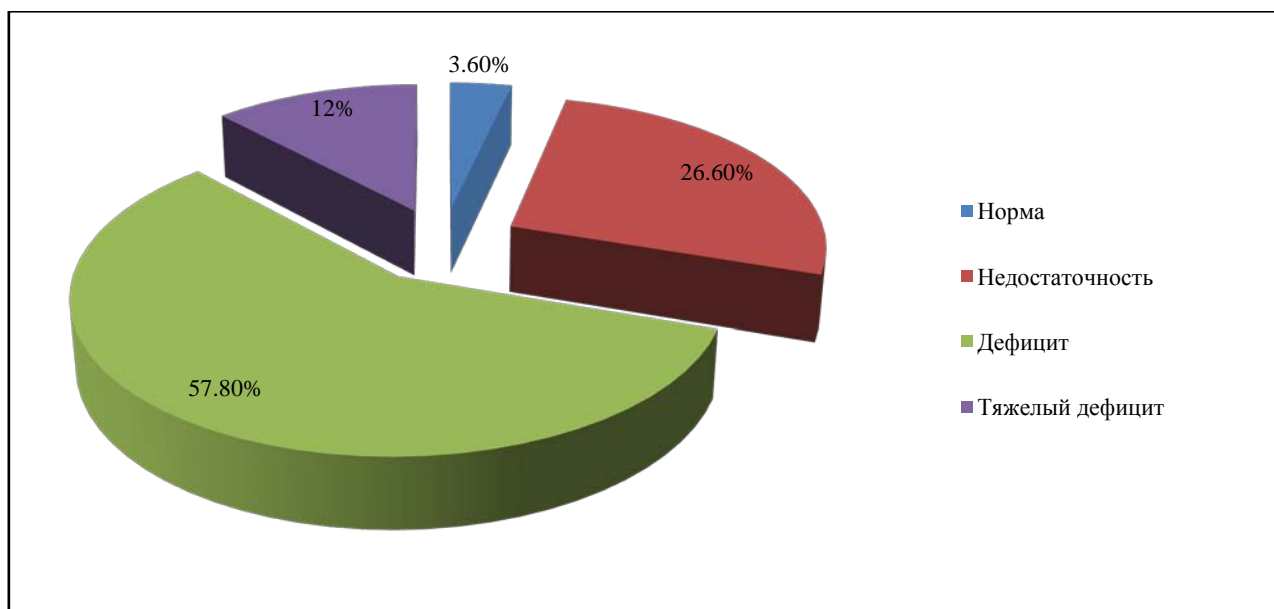
It is typical that without diet supplementation with cholecalciferol products vitamin D levels in a significant part of children and adolescents even in summer months may just insignificantly vary in the range from 10 to 30 ng/mL, and general prevalence of severe deficiency is 5.7% in summer. During the rest of the year, the status of vitamin D deteriorated significantly in adolescents residing in Moscow. The number of children with calcidiol level over 30 ng/mL since May to September is only 4.3%. Compared to autumn, in spring months the evident trend to the decrease of calcidiol level was observed due to the depletion of vitamin D reserves. These reserves may not be formed in the conditions of the central part of Russia during winter-spring period without targeted

prophylactic administration of cholecalciferol products.

On the second study stage, the baseline of vitamin D provision was assessed in 218 girls aged 11-18 years (mean age 14.4 ± 1.5 years) (Fig. 3) and the dynamics of calcidiol level was analyzed during calcidiol supplementation. In the treatment group ($n = 111$), baseline 25 (OH) D level—16.8 [13.2-20.4], in the control group ($n = 107$)—17.3 [13.4-21.3] ($p > 0.05$). Both groups of adolescents were comparable by age and BMI ($p > 0.05$).

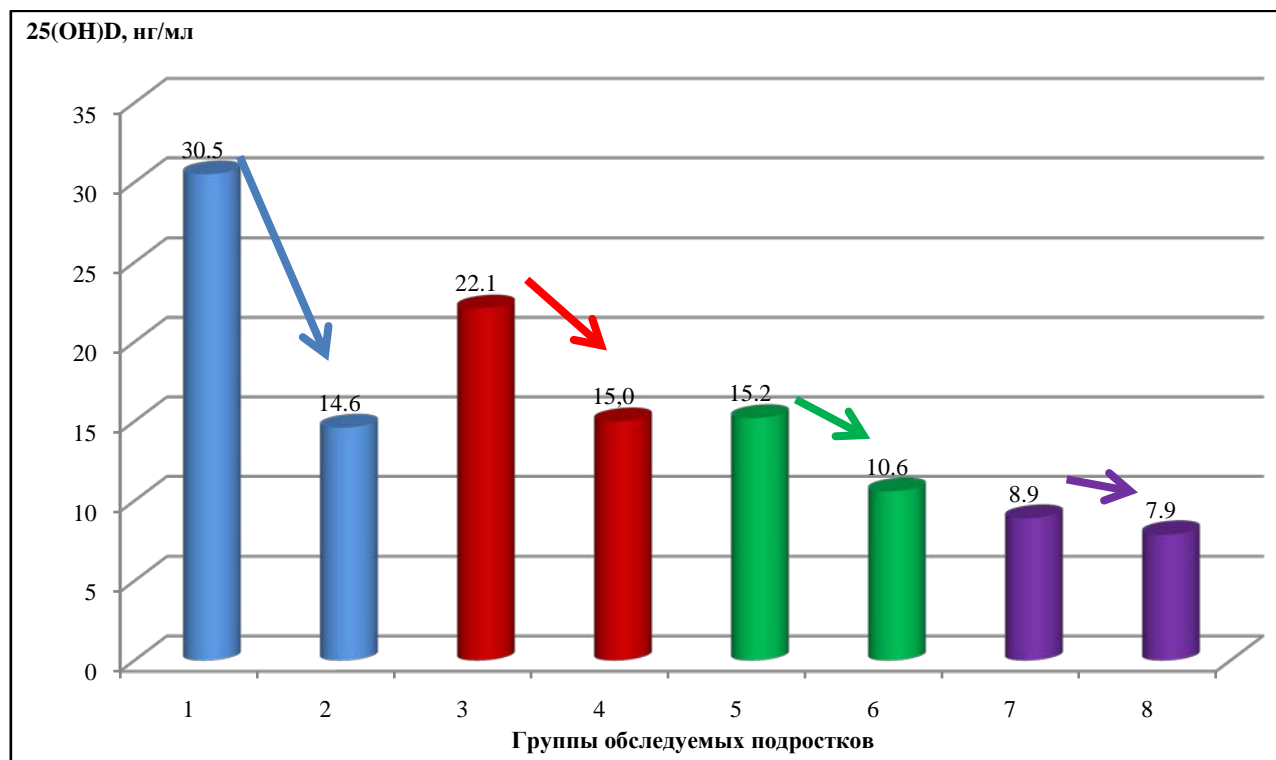
Calcidiol level based on placebo administration within three spring months in the control group, decreased significantly among the study completers ($n = 94$)—from 17.3 [13.4-21.3] to 11.4 [9.2-15.0] ng/mL ($p < 0.05$).

The children of the control group having normal 25 (OH) D level at the beginning of the study, as well as children in which vitamin D insufficiency and deficiency was diagnosed, after three-month course of placebo administration, had vitamin D deficiency, i.e. metabolite level varied in the range of 10-19 ng/mL. During placebo administration, no changes occurred in the group of children with baseline severe deficiency (Fig. 4).



Normal values; Insufficiency; Deficiency; Severe deficiency.

Fig. 3 Structure of 25 (OH) D provision of adolescent girls attending the Boarding school of MD of RF, ($n = 218$).



25 (OH) D, ng/mL; Groups of examined adolescents.

Fig. 4 Dynamics of calcidiol provision in adolescents during placebo administration: 1—group with normal baseline 25 (OH) D status, 2—after treatment, 3—group within sufficiency, 4—after treatment, 5—group with deficiency, 6—after treatment, 7—group with severe deficiency, 8—after treatment.

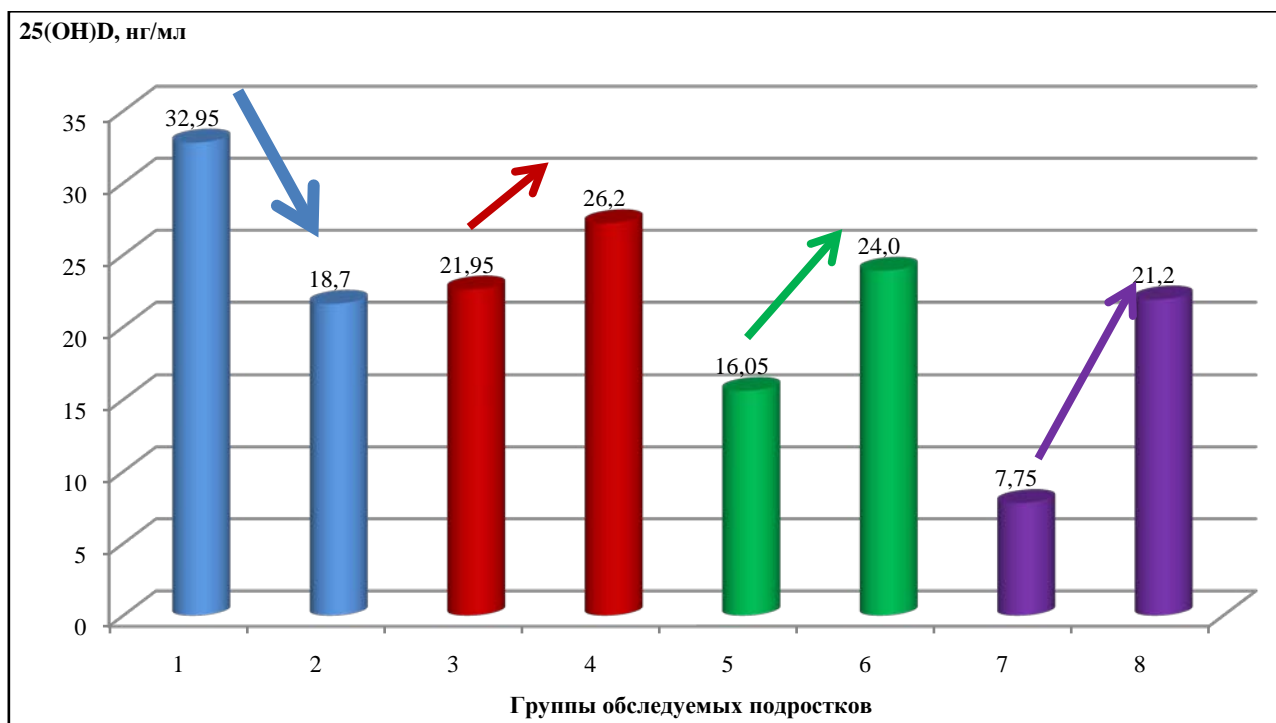
The girls of the control group had the decrease of the mean calcidiol level due to the facts “reserves” in a human body depleted during the winter period. The lowest levels are reported in the end of spring when repeated blood sampling occurred in study participants. One of the studies carried out by the investigators demonstrated the trend to seasonal variability of 25 (OH) D status in Moscow adolescents—the lowest provision was observed in May, the highest—in July, and since December to April, the mean blood level of calcidiol in children and adolescents residing in Moscow was gradually decreasing [27].

In the treatment group ($n = 98$) taking food supplement “Minisun[®] Vitamin D₃” during 6 months, median 25 (OH) D was increased in 1.49 times and amounted to 24.2 [21.05-26.4] ng/mL ($p < 0.001$).

With initially different vitamin D statuses, most school girls completing the study had the level of 25 (OH) D > 20 ng/mL (Fig. 5), however only 10 (10.2%) of persons had anormal metabolite level

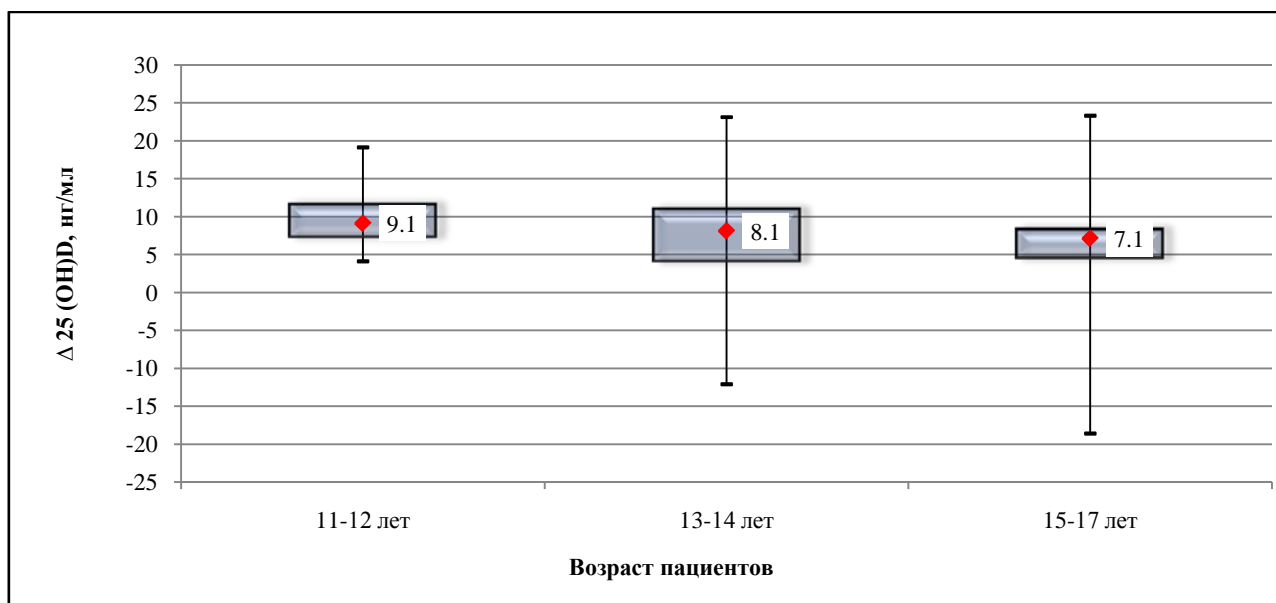
above 30 ng/mL.

The analysis of the data presented in Fig. 5 allows making several important conclusions. On the one hand, the administration of cholecalciferol products in doses 1,200-2,000 IU/day within half of the year to all children with vitamin D deficiency and insufficiency is accompanied with the gain of median 25 (OH) D. However, neither in the case of baseline severe deficiency nor in the case of starting values in the interval 10 to 30 ng/mL allows achieving calcidiol level 30 ng/mL based on the course results corresponding to normal provision. The correlation analysis showed the presence of the significant relationship between a dose and gain of 25 (OH) D level based on the correction course ($r = 0.56$, $p < 0.001$). On the other hand, the daily intake of cholecalciferol 800 IU/day in children of the older age group during the winter-spring period is not an effective prophylactic dose to maintain a normal level of vitamin D.



25 (OH) D, ng/mL; Groups of examined adolescents.

Fig. 5 Dynamics of Vitamin D provision in adolescents during the treatment: 1—group with normal baseline 25 (OH) D status, 2—after treatment, 3—group with insufficiency, 4—after treatment, 5—group with deficiency, 6—after treatment, 7— group with severe deficiency, 8—after treatment.



25 (OH) D, ng/mL; 11-12 years; 13-14 years; 15-17 years.

Age of patients.

Fig. 6 Gain of 25 (OH) D during cholecalciferol correction in children of various age.

Fig. 6 presents data on the gain of calcidiol level in adolescents of various ages during six-month

correction course with food supplement “Minisun® Vitamin D₃”.

The analysis of response to cholecalciferol therapy depending on the age showed that the median of 25 (OH) D gain higher in children aged 11-12 years in comparison with the children of older age categories ($p < 0.05$). The fact may be explained that the doses used by the investigators are more applicable for children of repubertalage, however the hypothesis shall be further investigated.

During the review of articles and meta-analyses, the group of authors chaired by O. A. Gromova offered the formula in accordance to which “averaged” effective dose of vitamin D for children aged 0-1 mon. is 740 IU/day. With every year, the effective prophylactic dose sufficient for achievement of 25 (OH) D > 20 ng/mL on average, is increased on 93 IU/day: $740 + (\text{Age [years]} \times 93 \text{ [IU/day]})$ [28]. If we follow the formula, cholecalciferol dose in children aged 11 years should be 1,763 IU/day, 12 years—1,856 IU/day, 13 years—1,949 IU/day, 14 years—2,042 IU/day, 15 years—2,135 IU/day, 16 years—2,228 IU/day, 17 years—2,321 IU/day, respectively, to achieve target calcidiol concentration 40-60 ng/mL, dose of vitamin D, dose of cholecalciferol should be higher.

Probably, the prescription of prophylactic and, in particular, treatment dosage of cholecalciferol in children and adolescents may be based not only on the age and baseline status of vitamin D, but also on BMI. Despite the fact that the present study has not revealed correlation relationship between BMI and 25 (OH) D level ($r = 0.02$), rather conclusive results are available confirming the presence of the relationship [29-31].

In our opinion, the study results are rather comparable with the data obtained by the authors from Beirut (Lebanon), although the city is located slightly more southerly than Moscow (33°n.l.). In the group of adolescents receiving 2,000 IU of cholecalciferol for 12 months, 96% of children had calcidiol level not below 20 ng/mL, and BMI and baseline calcidiol status are considered by the authors as the most informative factors influencing the selection of

vitamin D dosage [30]. Indeed, the expression of vitamin D receptor gene—VDR [32] as well as blood concentration of other vitamins affects blood concentration of calcidiol. However, consideration of such factors in the development of mass recommendations is impracticable due to the complexity of such kind of tests introduction to routine practice.

4. Conclusions

The laboratory examination of 769 children aged 11 to 18 years residing in Moscow showed low vitamin D levels in this population category that was observed throughout the entire calendar year. The possibilities of endogenous cholecalciferol synthesis through natural insolation in adolescents residing in Moscow are rather limited and do not allow achieving normal vitamin D levels in any year season.

The proposed correction scheme demonstrated relatively satisfactory results throughout the winter-spring season in adolescents with baseline low 25 (OH) D values. However, dose 800 IU/day used as prophylactic in children with normal 25 (OH) D provisions should be reviewed as it does not allow maintaining calcidiol concentration above 30 ng/mL in adolescents for a long time.

It is evident the development and large-scale implementation of targeted actions aimed to prophylaxis and correction of vitamin D deficiency in Russian adolescents are required. Taking into account the geographic location of Russia, the strategy of year-round prophylactic use of cholecalciferol products should be considered.

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