

# Age-related differences in vitamin D status in Polish centenarians compared with 65-year-olds

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## KEY WORDS

1,25-dihydroxycholecalciferol, 25-hydroxycholecalciferol, centenarians, parathyroid hormone, vitamin D

## ABSTRACT

**INTRODUCTION** Vitamin D status is known to change with age. However, little is known about vitamin D status in centenarians.

**OBJECTIVES** The aim of the study was to assess vitamin D status and correlations among the levels of parathyroid hormone (PTH), 25-hydroxycholecalciferol (25(OH)D), 1,25-dihydroxycholecalciferol (1,25(OH)D), calcium, inorganic phosphorus, and alkaline phosphatase (ALP) activity in centenarians.

**PATIENTS AND METHODS** The study group included 97 participants: 81 women and 16 men (median [interquartile range (IQR)] age, 101.4 [100.5–102.16] years). Centenarians were visited at their homes where examinations were conducted and blood samples collected. The control group consisted of 57 elderly subjects: 35 women and 22 men (median [IQR] age, 65.9 [65.3–66.5] years). The concentrations of PTH, 25(OH)D, and 1,25(OH)D were measured in frozen plasma samples, and calcium, phosphorus, and ALP levels, in serum samples.

**RESULTS** The median calcium level was 8.88 mg/dl in centenarians versus 9.52 mg/dl in 65-year-old subjects ( $P < 0.01$ ); ALP, 223 IU versus 190 IU ( $P = 0.01$ ); phosphorus, 3.01 mg/dl versus 3.23 mg/dl ( $P = 0.13$ ); PTH, 45.59 pg/ml versus 29.27 pg/ml ( $P < 0.01$ ); 25(OH)D, 7.39 ng/ml versus 19.81 ng/ml ( $P < 0.01$ ); 1,25(OH)D, 57.5 pmol/l versus 78.6 pmol/l ( $P < 0.01$ ). Only centenarians demonstrated correlations among the measured laboratory parameters.

**CONCLUSIONS** Considering lower 25(OH)D, 1,25(OH)D, and calcium concentrations in the majority of centenarians, as well as the negative correlation between vitamin D active metabolites and PTH, vitamin D and calcium should be systematically supplemented in the oldest of the elderly.

**INTRODUCTION** The process of aging involves interdependent, complex involutions mechanisms at the cellular, organ, and systemic levels. It is still debated whether advanced age should be regarded as a continuation of the lifespan or a distinct stage of life. With advancing age, people appear to change their health status perception, and “geriatric giants” (a term coined by Bernard Isaacs in 1965 to encompass age-related impairments) contribute to more serious health consequences than in younger individuals.<sup>1–3</sup> The population of geriatric patients is significantly influenced by the elderly persons (aged 80 years and older). They represented 2% of the Polish population in 2000, and the fraction increased to 4.4% in 2019.<sup>4</sup> Furthermore, the Population Division of the United

Nations forecasted that the global number of centenarians could exceed 20 million in 2100.<sup>5</sup> The centenarian population exemplifies successful aging. Conversely, it also represents a group with advanced signs and symptoms of aging, often coexisting with an increased prevalence of disability and a wide range of deficiencies.<sup>6</sup> Vitamin D deficiency or insufficiency is one of the most commonly observed disorders.

Vitamin D status was widely studied in the last decade. Recent epidemiological research has shown that the concentration of 25-hydroxyvitamin D may have an impact on various diseases and mortality.<sup>7–9</sup>

The main cause of aging-associated vitamin D deficiency is low vitamin D production. The skin

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## WHAT'S NEW?

Centenarians are one of the fastest growing populations among the elderly. However, cases of extreme longevity are still underrepresented in the majority of studies. At the same time, this group represents a model of a successful aging process. Considering the uniqueness of this study group, it is impossible to provide observational, prospective data. Despite the small number of subjects, our study is representative for Polish centenarians, and its comparison with the younger group, performed at the beginning of the aging process in the elderly, let us find significant differences between these 2 aging periods. Our study also provides information on vitamin D status in extreme longevity, and such data regarding the Polish population have not been published yet. Likewise, the evaluation of calcium–phosphorus homeostasis and its correlations with the vitamin D concentration have not been studied in this population so far.

concentration of 7-dehydrocholesterol decreases with age.<sup>10</sup> Specifically, for each decade past the age of 40 years, there is approximately a 10% to 15% decrease in the 7-dehydrocholesterol level. Additionally, about a 35% decrease in intestinal calcium absorption is observed in those older than 70 years.<sup>11</sup> This decrease is even greater in women because of reduced fractional calcium absorption and estrogen changes after menopause with increased urinary calcium loss.<sup>12</sup> Other causes of aging-associated vitamin D deficiency are related to poor vitamin D and calcium supply as well as Poland's latitude (49° N to 54° N). The amount of sunlight sufficient for vitamin D production in the skin is available only between May and September. Apart from that, with advancing age, comorbidities should be considered, renal and liver insufficiency in particular.

Additionally, the impact of vitamin D deficiency on “geriatric giants” is influenced by muscle strength reduction, which may lead to an increased number of falls. Furthermore, the development of secondary hyperparathyroidism results in calcium imbalance and high bone turnover as well as accelerates age-related bone loss and leads to osteoporotic fractures.<sup>13</sup>

In all populations, regardless of age, vitamin D status is determined by measuring the total serum 25-hydroxycholecalciferol (25[OH]D) concentration. However, the recommended 25(OH)D concentration for the oldest of the elderly has been an issue of debate.

The relationship among vitamin D status, the musculoskeletal system condition, and physical performance could be the subject of a separate article. In this study, we focused on vitamin D status in individuals presenting extreme longevity. The primary aim of the study was to assess vitamin D status and evaluate correlations among parathyroid hormone (PTH), 25(OH)D, 1,25(OH)D, calcium, phosphorus, and alkaline phosphatase (ALP) levels in Polish centenarians. Another study objective was to compare the results obtained for centenarians and 65-year-old study subjects.

**PATIENTS AND METHODS** We used the Polish Centenarians (POLSTU) study, a multidisciplinary program of successful aging, in which 346 subjects over 100 years of age were visited. Biological material was collected from 285 of them. In 97 subjects, a sufficient amount of frozen plasma was taken to conduct vitamin D studies. The bioethics committee of the Central Clinical Hospital of the Ministry of the Interior and Administration in Warsaw (Poland) approved the study. The centenarians or their relatives provided written informed consent to participate in the study.

The study included 2 groups of individuals. The first group consisted of 97 centenarians in whom plasma samples were obtained and subsequently frozen. It included 81 women and 16 men aged 99.9 to 108 years, at a median age of 101.4 years. The other group was a control group of 57 subjects at the age of 65 years: 35 women and 22 men, at a median age of 65.9 years. The exclusion criteria were as follows: severe endocrinopathy or chronic digestive system diseases with malabsorption, advanced heart failure (New York Heart Association class IV), respiratory failure, and severe liver or kidney failure.

All centenarians were visited at their homes in cities, towns, and rural areas, where blood samples were collected. The 65-year-olds in the control group were examined and blood samples were obtained in outpatient clinics. The study subjects were examined throughout the year. The methods applied in this study included taking a medical history, performing detailed physical examination, and collecting a blood sample. The baseline characteristics of the study participants are presented in [TABLE 1](#). Laboratory tests included measuring serum levels of calcium, magnesium, inorganic phosphorus, and ALP activity. Thawed plasma was used to measure the levels of PTH (electrochemiluminescence assay with a range of 15–65 pg/ml), 25(OH)D (enzyme-linked immunosorbent assay [ELISA] with a range of 47.7–144 nmol/l or 19.08–57.6 ng/ml), and 1,25-dihydroxycholecalciferol (1,25[OH]D; ELISA with a range of 39–193 pmol/l). Plasma samples were assayed for total 25(OH)D and 1,25(OH)D concentrations using a commercially available ELISA kit (Immunodiagnostic Systems, Ltd., Boldon Colliery, United Kingdom).

**Statistical analysis** Laboratory parameter values were expressed as median and interquartile range. Centenarians and controls were compared using the nonparametric Mann–Whitney test. The association between laboratory parameters was assessed with the Pearson correlation coefficient. Study data were analyzed using the R 3.6.1 software (R Core Team, Vienna, Austria).

**RESULTS** The median concentrations of calcium and magnesium were significantly lower in centenarians compared with 65-year-olds, whereas the ALP activity was significantly higher (calcium, 8.88 mg/dl vs 9.52 mg/dl,  $P < 0.01$ ; magnesium,

**TABLE 1** Baseline characteristics of the study participants

Characteristic	Centenarians	65-year-olds
Male/female sex, n	81/16	35/22
Age, y, median (IQR)	101.4 (100.5–102.16)	65.9 (65.3–66.5)
Place of living, %	City	70.7
	Town	12.9
	Village	16.4
Body mass, kg, mean (SD)	51.2 (6)	70.3 (12)
Height, cm, mean (SD)	148 (7)	164 (16)
Creatinine, mg/dl, mean (SD) <sup>a</sup>	Men	0.95 (0.36)
	Women	1.34 (0.53)
Hemoglobin, g/l, mean (SD) <sup>b</sup>	119.7 (15.9)	137.7 (9.2)
Protein, g/dl, mean (SD) <sup>c</sup>	6.7 (0.7)	7.2 (0.3)
Glucose, mg/dl, mean (SD) <sup>d</sup>	89.7 (36.1)	97.6 (26.1)

**a** Reference range, 0.6–1.3 mg/dl

**b** Reference range, 120–160 g/l

**c** Reference range, 6–8 g/dl

**d** Reference range, 70–99 mg/dl

Abbreviations: IQR, interquartile range

**TABLE 2** Laboratory parameters in centenarians and 65-year-olds

Parameter	Centenarians (n = 97)	65-year-olds (n = 57)	P value <sup>a</sup>
Calcium <sup>b</sup> , mg/dl	8.88 (8.35–9.36)	9.52 (9.22–9.72)	<0.01
Inorganic phosphorus <sup>c</sup> , mg/dl	3.01 (2.8–3.38)	3.23 (2.89–3.43)	0.13
Magnesium <sup>d</sup> , mg/dl	1.96 (1.76–2.18)	2.08 (1.98–2.24)	<0.01
ALP <sup>e</sup> , IU	223 (184–267)	190 (151–239)	0.01
PTH <sup>f</sup> , pg/ml	45.59 (29.86–65.07)	29.27 (23.88–42.2)	<0.01
25(OH)D <sup>g</sup> , ng/ml, nmol/l	7.39 (5.47–12.36),	19.81 (15.41–24.45),	<0.01
	18.45 (13.7–30.8)	49.45 (38.47–61.05)	
1,25(OH)D <sup>h</sup> , pmol/l	57.5 (37.4–75.5)	78.6 (63–116.75)	<0.01

Data are presented as median (interquartile range).

**a** Mann–Whitney test

**b** Reference range, 8.08–10.04 mg/dl

**c** Reference range, 2.5–4.8 mg/dl

**d** Reference range, 1.8–2.9 mg/dl

**e** Reference range, 23–290 IU

**f** Reference range, 15–65 pg/ml

**g** Reference range, 19.08–57.6 ng/ml or 47.7–144 nmol/l

**h** Reference range, 39–193 pmol/l

Abbreviations: 1,25(OH)D, 1,25-dihydroxycholecalciferol; 25(OH)D, 25-hydroxycholecalciferol; ALP, alkaline phosphatase; PTH, parathyroid hormone

1.96 mg/dl vs 2.08 mg/dl,  $P < 0.01$ ; ALP, 223 IU vs 196 IU,  $P = 0.01$ ). Although the phosphorus concentration was lower in centenarians, the difference was nonsignificant (3.01 mg/dl vs 3.23 mg/dl;  $P = 0.13$ ). The PTH concentration was significantly higher in centenarians (45.59 pg/ml vs 29.27 pg/ml;  $P < 0.01$ ). However, in contrast, the concentrations of 25(OH)D and 1,25(OH)D

were significantly lower (25(OH)D, 7.39 ng/ml vs 19.81 ng/ml,  $P < 0.01$ ; 1,25(OH)D, 57.5 pmol/l vs 78.60 pmol/l,  $P < 0.01$ ). Detailed data are presented in **TABLE 2**.

It was found that, in the majority of centenarians (87%), the concentration of 25(OH)D was below the laboratory reference range (**FIGURE 1**). Although 13% of centenarians had 25(OH)D concentration within normal limits, in all of them it was distributed in the lower quarter of the reference range. In comparison, 48% of the 65-year-old study subjects had a 25(OH)D concentration below the laboratory reference range (**FIGURE 2**).

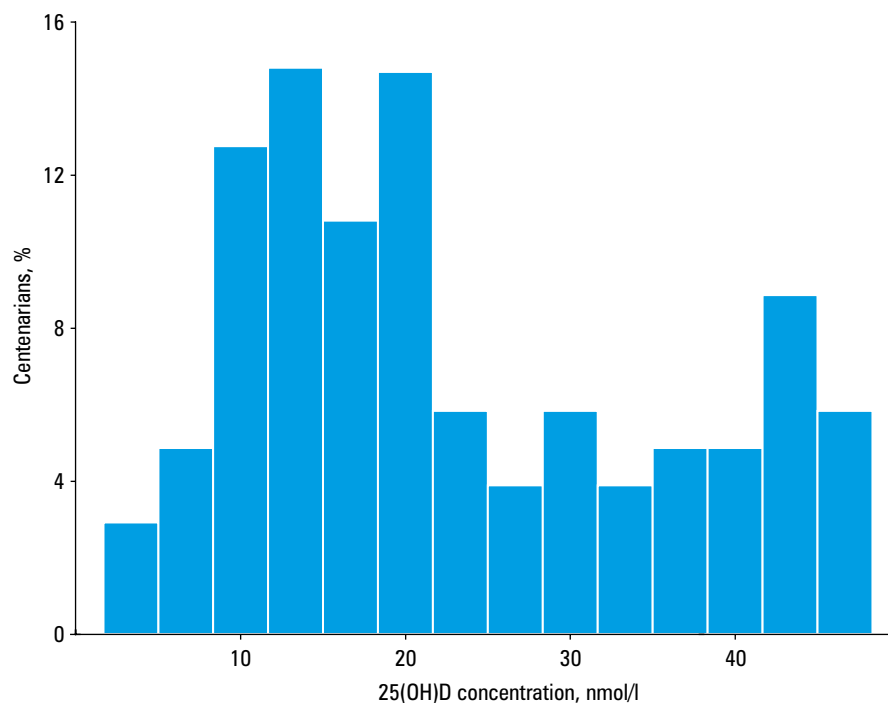
For 26.9% of centenarians, the 1,25(OH)D concentration was lower than 39 pmol/l, whereas 72% of them had a 1,25(OH)D concentration within normal range. In the majority of controls (98.1%), the 1,25(OH)D concentration was within normal limits. In nearly 40% of centenarians, the PTH concentration was very high: in 26.8% of them, it exceeded the laboratory reference range, and, in 12.4% of them, it was in the top quarter of the reference range. In the majority of the 65-year-old subjects (87.7%), the PTH concentration was within normal range, below the top quarter. No association regarding seasonal differences in vitamin D status was found in the study population ( $P = 0.71$ ) or relation between vitamin D status and location ( $P = 0.07$ ) or body mass ( $P = 0.49$ ), or body composition ( $P = 0.07$ ). The highest median value of vitamin D concentration (14.03 ng/ml) was observed in centenarians presenting inadequate adipose tissue. None of the centenarians was on any pure vitamin D supplement, but 73.2% of them (71 individuals) took a multivitamin product containing vitamin D (at a dose between 400 IU/d and 600 IU/d). In the control group, only 2 persons took a low dose of vitamin D (400 IU/d). No correlation was found between the ingested doses of vitamin D and vitamin D blood concentrations.

A correlation between calcium–phosphorus balance parameters was found only in centenarians. We observed associations among the following parameters: PTH, 25(OH)D, 1,25(OH)D, calcium, phosphorus, and ALP. Negative correlations were seen between 25(OH)D and PTH, 25(OH)D and ALP, PTH and calcium, and PTH and phosphorus. Positive correlations were noted between PTH and ALP, 25(OH)D and 1,25(OH)D, and 25(OH)D and calcium.

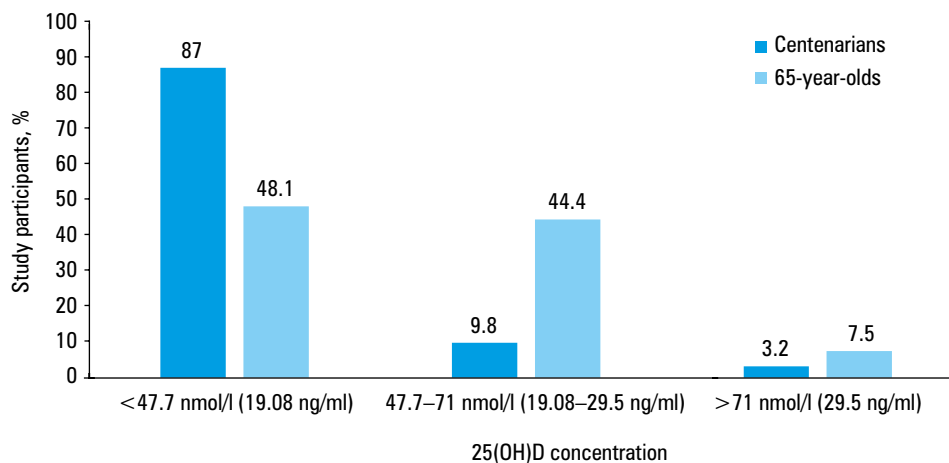
**DISCUSSION** Extreme longevity of the human population is advancing throughout the world. To our knowledge, this is the first study to focus on vitamin D status and its correlations with extremely old age in Poland. Admittedly, our study was limited by the number of frozen plasma samples available for laboratory measurements ( $n = 97$ ). However, as our study group demonstrated the distinctive characteristics of extreme aging, we assume that it is likely to be representative for the entire population of Polish centenarians. Undoubtedly, another limitation

**FIGURE 1**

Distribution of 25-hydroxycholecalciferol (25(OH)D) concentrations below 19.08 ng/ml (47.7 nmol/l) in centenarians

**FIGURE 2**

Distribution of 25-hydroxycholecalciferol (25(OH)D) concentrations in centenarians compared with 65-year-olds



of the study was the ELISA method, which was customarily used at the time of blood collection to evaluate vitamin D status. Recently, diagnostic laboratories focused on vitamin D assays controlled by Vitamin D External Quality Assessment Scheme (DEQAS)—the largest specialist scheme targeted at vitamin D metabolites, which was not fully implemented in Poland at the time when the Polish Centenarians study was conducted. However, ELISA is well established and still regarded as an accepted diagnostic tool. Nowadays, the available assays are controlled for their quality, just as they were in the past. Despite the abovementioned limitations, our study provided data established in a unique group of centenarians and highlighted the urgent need to improve vitamin D status among the oldest.

The levels of calcium, magnesium, 25(OH)D, and 1,25(OH)D were significantly lower in the centenarian group than in the control group of 65-year-olds. The phosphorus level did not

significantly differ between the 2 study groups, which supports the hypothesis that, at the beginning of the aging process as well as with advancing age, the PTH concentration is not influenced by phosphorus concentration. Although the centenarian group demonstrated a lower calcium level, the majority showed calcium concentration within normal range (generally in the lower quarter, compared with the results obtained in 65-year-old subjects). Lower calcium concentrations were associated with lower vitamin D status. This is probably due to long-term deficiency causing a decrease in 1,25(OH)D levels and reduction of intestinal absorption and renal reabsorption.<sup>14</sup> The significance of vitamin D deficiency within the context of calcium deficiency has been highlighted recently. In a systematic review of elderly nursing home residents, around 65% of men and 73% of women were at risk of inadequate calcium intake.<sup>15</sup> Our findings indicate that vitamin D deficiency is common in the oldest of the elderly, which suggests that long-term



influence of many factors (eg, poor diet, intestinal malabsorption, very low skin production) contributes to vitamin D deficiency.

Two large population studies on vitamin D status have been conducted in Poland, namely, the PolSenior study<sup>16</sup> with 3472 participants (aged between 65 and 99 years) and a study by Płudowski et al<sup>17</sup> with 5775 participants (mean [SD] age, 54 [15.9] years). In the PolSenior study, the mean (SD) serum 25-hydroxyvitamin D concentration was 20.5 (9.6) ng/ml. In study subjects over 85 years of age, severe vitamin D deficiency was found in 20.6% of women and 11.9% of men. Vitamin D insufficiency was observed in 73.1% of women and 74.8% of men. Severe deficiency in younger subjects in the PolSenior study (aged between 65 and 80 years) was found in 7.5% of women and 4.9% of men. Of note, only 48 participants in the PolSenior study were on vitamin D supplementation. Płudowski et al<sup>17</sup> reported a high prevalence of vitamin D deficiency in all studied subpopulations; in those at the beginning of the aging period (mean [SD], 18 [9.7] ng/ml in participants aged 50 to 60 years) compared with the oldest of the elderly (mean [SD], 19.2 [10.1] ng/ml in participants over 80 years of age). The authors pointed out a study limitation related to selection of their study population: recruiting subjects by advertisement may have attracted people more conscious of their health status and, consequently, may have resulted in a higher general vitamin D status than would have been found in a more representative sample. In some aspects, the aforementioned limitation may also apply to the PolSenior study sample, in which those who did not take part in the study had significantly poorer functional status and worse self-reported health status. Both studies included a large number of participants and a wide range of the elderly population members; however, data on the oldest of the elderly are limited. In our study, we found vitamin D status to be generally lower, particularly in the oldest study subjects. Of note, frozen plasma was used in the Polish Centenarians (POLSTU) study in 2005, and, at that time, significantly lower doses of vitamin D were recommended even for the oldest of the elderly. Nonetheless, some differences in the findings of these studies may result from various laboratory assays and recruitment methods used, thus limiting the comparison of conclusions regarding vitamin D status between the studies.

In our study, a negative correlation between 25(OH)D and PTH levels was observed in the centenarian group. Such a correlation was not found in the control group of 65-year-olds. These data suggest that, predominantly at very old age, secondary hyperparathyroidism is a common disorder. Interestingly, in accordance with this finding, Passeri et al<sup>18</sup> reported that nearly 64% of study subjects aged over 100 years presented with hyperparathyroidism. In contrast, in Chinese centenarians, Yao et al<sup>19</sup> showed that hyperparathyroidism was not a common finding (mean PTH

concentration, 48.8 pg/ml), and vitamin D deficiency was also relatively uncommon, observed only in 39.7% of the study participants. These diverging findings highlight the varying impact of race, latitude, and environmental factors on vitamin D concentration.

Seasonal correlations regarding 25(OH)D concentrations were not observed in our study population, which suggested that the season of the year does not influence 25-hydroxyvitamin D concentration in extreme longevity. Passeri et al<sup>20</sup> reported a higher prevalence of vitamin D deficiency in centenarians in Italy (44° N) than in Poland, with 99% of them exhibiting severe vitamin D deficiency. However, in the Newcastle 85+ study,<sup>21</sup> a decrease in 25(OH)D serum concentration (below 30 nmol/l) was observed throughout the year, but chiefly during winter and spring. It has also been reported that in the elderly, after regular ultraviolet exposure, skin vitamin D production remained high, and the median 25(OH)D concentration of over 50 nmol/l was achieved.<sup>22</sup> It is likely that lifestyle factors associated with physical performance and dressing habits as well as a long period of vitamin D deficiency contribute to vitamin D deficiency pathways in the oldest members of the elderly population.<sup>23,24</sup> Additionally, another study has shown that vitamin D supplementation appears to be the strongest predictor of 25(OH)D concentrations in very old adults.<sup>20</sup> Nonetheless, correlations between vitamin D intake and vitamin D status were not observed in our study, perhaps due to low doses of vitamin D having no clinical effect.

The optimal blood concentration of vitamin D can be defined by several criteria such as parathyroid hormone levels, greater calcium absorption, and higher bone mineral density.<sup>25</sup> It is likely that insufficient 25(OH)D plasma concentration was the main factor for a higher PTH serum concentration in our centenarian population. Significant, negative correlations between PTH and 25(OH)D levels imply that these factors contribute to the development of secondary hyperparathyroidism, which can accelerate osteoporotic bone loss.<sup>26</sup> No correlations among 25(OH)D, 1,25(OH)D, PTH, and calcium levels were found in 65-year-old study subjects, which indicated that these factors play a less significant role in younger elderly people than in the oldest of the elderly.

Although vitamin D deficiency has been linked to many diseases and its receptors have been detected in numerous organs, it remains unclear what level of vitamin D is optimal in patients with comorbidities and in the oldest of the elderly.<sup>27-29</sup> Łukaszuk et al<sup>30</sup> showed that a low vitamin D concentration, less than 20 ng/ml, was independently linked to the risk of dementia and functional decline in cognitive performance. In a study by Matheï et al,<sup>31</sup> no relation was found between vitamin D concentration and physical performance. However, in these 2 studies, the mean age of the study participants was 82.3 years and 84.7 years, respectively. Therefore, the data are

not representative for a population of extreme longevity characterized by the prevalence of “geriatric giants” such as frailty syndrome and advanced aging process. Seemingly, a single specific vitamin D level appears to be pointless owing to observed differences between sexes and age groups.<sup>32</sup> With the aging processes in the oldest of the elderly subpopulations, there is an increased number of diversifying factors, such as physical performance abilities and mental status. For this reason, the elderly should not be treated as a homogeneous population. According to the most recent “Vitamin D supplementation guidelines for general population and groups at risk of vitamin D deficiency in Poland,” vitamin D supplementation at a dose of 2000 IU/d to 4000 IU/d established based on body weight and dietary vitamin D intake is recommended throughout the year.<sup>33</sup>

Considering the increasing life expectancy in Poland and throughout the world, maintaining independence is of extreme importance for the oldest of the elderly. Presumably, factors that play a crucial role in the process of aging in younger groups do not have the same impact in older cohorts. Data on longevity in the elderly are still scarce, although a positive correlation between vitamin D status and grip strength in centenarians has been reported by Haslam et al.<sup>34</sup> As lower 25(OH)D and calcium concentrations in the majority of centenarians were observed in our study, sufficient, high-dose vitamin D and calcium supplementation should be systematically administered to the oldest of the elderly to avoid metabolic acceleration of secondary hyperparathyroidism. Further studies of the oldest of the elderly are needed to establish protocols for identifying signs and symptoms of vitamin D deficiency and the optimal vitamin D status in extreme longevity.

## ARTICLE INFORMATION

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**CONTRIBUTION STATEMENT** MKU contributed to the design and implementation of the study, analyzed the results, and wrote the manuscript. KB, MM, and KG contributed to the design and implementation of the study. EMS analyzed the results and was responsible for the final revision of the manuscript.

**CONFLICT OF INTEREST** None declared.

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