

Vitamin D-insufficiency

An estimate of the situation in Germany

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Abbreviations: 25(OH)D, 25-OH-Vitamin D; ng, nanogram; ml, millilitre; nm, nanometer, UVB, ultraviolet radiation B; DBP, Vitamin D-Binding-Protein; approx, approximative; Min, minimum; Max, maximum; SD, standard deviation; MedDRA, Medical Dictionary for Regulatory Activities; PTH, parathyroid hormone; nmol, nanomol; l, liter; AP, alkaline phosphatase; GGT, gamma-glutamyl-transpeptidase; Crea, creatinine; vs., versus; SOC, System Organ Classes; GP, General Practitioners; CVD, cardio-vascular disease; V, coefficient of variation; DRI, Dietary Reference Intakes

Background: Vitamin D insufficiency is increasingly recognized as an important risk factor in the pathogenesis of falls and fractures and may increase the risk of other diseases. The aim of this study was to obtain information about the vitamin D supply from a representative cohort of the German population.

Methods: 264 General practitioners participated in the DeViD-Trial (D-vitamin in Deutschland) by taking blood samples from their consenting daily ambulant patients regardless of the actual reason for consultation. In these blood samples vitamin D [25(OH)D] and other related parameters were measured at a central laboratory. The patients filled in a simple questionnaire (i.e., age, sex, etc.). The trial was performed between February 26 and May 25, 2007.

Results: Laboratory and personal data were documented for 1343 individuals (615 men, 728 women). The age distribution ranged from 20 to 99 y, the mean age of the whole cohort was 57.6 y (men 58.2, women 57.2). The mean 25-OH-D-value for the whole cohort was 16.2 ng/ml (range: 6.0 to 66.8, median 14.1 ng/ml). Ten percent of the patients had 25(OH)D-values below 7 ng/ml, 65% below 20 ng/ml and 92% showed values below 30 ng/ml.

In the more recent literature, 25(OH)D values below 30 ng/ml are regarded as sub-optimal for bone, muscle and general health. Correspondingly it can be stated that in this representative population there is a high prevalence of moderate to severe vitamin D-insufficiency regardless of young or old age

Introduction

There is increasing evidence that vitamin D is not only necessary to regulate calcium and phosphorous metabolism but for maintaining human health in general. A robust relationship has long been established between vitamin D status and bone health.¹⁻³ Most impressive is healing of rickets or osteomalacia and its symptoms by a treatment with this vitamin.⁴⁻⁶ Also well-established is the improvement of neuromuscular coupling by repletion of vitamin D depots, resulting in a decrease of body sway and falls.⁷⁻¹² Neural development and functioning is depending on an adequate vitamin D supply already during fetal life and young adolescence resulting in a reduced occurrence of mental disturbances like schizophrenia.¹³⁻²² There is increasing evidence that some carcinoma types like colon, breast, prostate and skin cancer are less frequent with sufficient vitamin D supply.²³⁻⁴³ Also the occurrence and course of cardiovascular diseases, diseases of the immune system, especially multiple sclerosis, rheumatic arthritis, diabetes type I has been reported to

be related to vitamin D levels. Recent studies suggest that subjects with a 25(OH)D level lower than 30 ng/ml had not only an increased risk of myocardial infarction but an overall increased cardiovascular mortality.^{30,44,45} Two large prospective studies are planned to investigate these supposed pleiotropic actions of vitamin D.

Synthesis in the skin is the main source of vitamin D for most vertebrates including humans. In the skin 7-dehydrocholesterol (provitamin D₃), the immediate precursor in the cholesterol biosynthetic pathway, is produced in relatively large quantities. During exposure to sunlight, UV B (UVB) radiation (290–315 nm) penetrating the epidermis and dermis cleaves the B-ring of the precursor to form pre-cholecalciferol. Pre-cholecalciferol is unstable and rapidly undergoes rearrangement of its double bonds to form cholecalciferol. Thereafter, assisted by vitamin D binding protein (DBP), it enters into the dermal capillary bed. Cholecalciferol from the skin or ingested by diet undergoes two obligate hydroxylations, the first in the liver to 25-hydroxyvitamin D [25(OH)D]. 25(OH)D bound to its DBP enters the

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circulation and is transported to the kidney where the second hydroxylation takes place at the 1 α -position. 1,25(OH)₂D is the metabolite responsible for the specific vitamin D effects, the active D-hormone.

Since the production of vitamin D is sunlight dependent and the nutritional contribution in general is small, there is a high risk for vitamin D deficiency, especially during the winter months, when sunshine is not available. This is regularly the case in regions above 45° latitude.^{46,47} In these countries UVB irradiation is only available in very small amount or even totally missing in wintertime. But also during the rest of the year solar irradiation seems to be often insufficient. Different studies have shown that in European countries and in northern America vitamin D deficiency is widespread in the whole population including younger people.^{3,48,49}

Vitamin D supply of an individual is very well reflected by measuring 25(OH)D. Currently a level of at least 30 ng/ml 25(OH)D is considered as sufficient, values between 29 and 20 ng/ml as insufficiency, levels less than 20 ng/ml as deficiency and levels below 7 ng/ml as severe deficiency.^{3,49-56}

When we planned this study, only data on the vitamin D status of special cohorts were available, e.g., patients with osteoporosis, or with CVD. Since data were missing on the vitamin D status in the general German population our aim was to provide this important information. We planned to evaluate the vitamin D status at the end of wintertime in a population sample as representative as possible allowing an estimate for the whole population in our country. Furthermore we aimed to collect additional data on vitamin D related laboratory values as well as on personal conditions and individual factors influencing the vitamin D status.

Results

Composed data sets i.e., laboratory and questionnaire data could be evaluated from 1340 subjects. For some subjects blood analysis was not feasible for all items, so only 1328 samples were available for laboratory testing. Parathyroid hormone (PTH) which had to be sent in a special tube could be measured in 1285 samples. **Table 4** shows the results of the laboratory testing.

Subjects were recruited throughout Germany to avoid possible regional influences. Mean number of participating subjects per postal region was 134 (min. 71, max. 236, median 119, SD 48.2) with nearly equal sampling per region, except the region of the postal code 1 with 236 and 4 with only 71 subjects respectively.

Concerning gender distribution the recruitment resulted in 45.8% men and 54.3% women. Age categories showed the following percentages of subjects: decades 5–8 about 17% each, decades 3 and 4: 8% each, decade 9 and 10: 13%. The living situation was indicated by 91% of participants, from which 7 were institutionalized. No information was available concerning body weight, and educational level.

Vitamin D

To assess individual vitamin D status, blood 25(OH)D was measured. A blood level of at least 30 ng/ml was considered sufficient, 20–30 ng/ml as insufficient, less than 20 ng/ml as

deficient and less than 7 ng/ml as severe deficiency (nmol/l = 2.469 × ng/ml). The analysis kit had a lowest limit of quantification at 6.99 ng/ml, values below were assigned “< 7 ng/ml” by the laboratory. For calculation reasons we set this arbitrary with 6 ng/ml. Data from 1328 subjects could be evaluated. We found a total mean 25(OH)D level of 16.2 ng/ml (min 6.0, max 66.8, median 14.1, SD 8.8). This is clearly below the threshold of deficiency, with no significant difference between men and women. Only 8% of all subjects had values of 30 ng/ml or more, 75% had values in the range of deficiency therein 10% subjects with values lower than 7 ng/ml. In the range of deficiency 80% of subjects were older than 70 y and 69% of subjects younger than 50. Overall 92% of all subjects had a 25(OH)D deficiency. **Table 5** shows the number of subjects per vitamin D cluster and per decade.

Parathyroid hormone (PTH). In the 25(OH)D level groups of at least 30 ng/ml and 20–30 ng/ml we found 3% of subjects in each group with an increased (> 65 pg/ml) PTH level, within the subjects with 25(OH)D levels of 7–20 ng/ml 14% had an increased PTH level, and in the lowest 25(OH)D group (< 7 ng/ml) 24%. In all subjects with 25(OH)D levels below 20 ng/ml we found a hyperparathyroidism of 15%.

Alkaline phosphatase (AP). Alkaline phosphatase (AP) is an enzyme produced not only in bone tissue but also in liver, small gut and kidney. Elevated plasma activity may suggest bone disease (e.g., osteomalacia) if other parameters for liver and kidney are normal [i.e., gamma-glutamyl-transpeptidase (GGT) and creatinine (Crea)]. Using these criteria we identified a subgroup of 32 patients with possible osteomalacia having elevated AP and normal GGT and creatinine. In this subgroup subjects with a very low level of 25(OH)D (< 7 ng/ml) were observed in 13% compared with only 4% in subjects with 25(OH)D level $\geq 7 < 20$ and $\geq 20 < 30$ ng/ml respectively, and 2% in the group with ≥ 30 ng/ml.

Skin type. People with colored skin living in northern latitudes (> 45°) often suffer from vitamin D deficiency. To ensure that our data are not influenced by a relevant percentage of subjects with dark skin, information about the skin type was requested in the questionnaire. One thousand two hundred fifty-one subjects out of 1344 answered on this question and from 200 categorized as colored skin laboratory data were available. Mean 25(OH)D level was 18.2 ng/ml what was significantly higher vs. the whole study population ($p = 0.004$). In Germany the percentage of black people is very low, so we presume that these subjects were not really colored but people with an intensive outdoor life tanned by sun and weather, explaining the somewhat higher 25(OH)D level.

Falls. 105 (8%) out of 1340 subjects reported a fall within the past 12 mo before blood sampling. Mean 25(OH)D level of this subgroup was 14.4 ng/ml which was significantly ($p = 0.04$) lower than that of the total study population (16.2 ng/ml) but the comparison of the 25(OH)D levels by age decades did not show statistical differences. Furthermore the average age of these subjects was significantly ($p = 0.01$) higher with 62.0 (min 20.0, max 99.0, median 64, SD 19.7) vs. 57.6 (min 19.0, max 99.0, median 59.0, SD 18.0) years. Among the 105 fallers, 16 subjects (15%) had suffered a fracture.

Additional vitamin D supply. Vitamin D supplementation may be achieved either by direct intake, food supplements or by sunlight exposure in a region with sufficient UVB irradiation. During European wintertime this is only possible in regions at lower latitudes than 45°. In our study subjects were asked if they had visited a region < 45° latitude within the last 6 weeks before blood sampling. Forty-eight of 1340 subjects answered this question with “yes.” The mean age of this group did not differ significantly from the whole population but mean 25(OH)D level was significantly higher with 22.0 ng/ml vs. 16.2 ng/ml ($p < 0.0001$).

From 1309 subjects answering about vitamin D supplementation within the last 6 weeks before blood sampling 76 (5.8%) reported positive. The daily dose was reported only from 33 with a range from 200 IU (5 µg) to > 800 IU (20 µg). The mean age of this subgroup was significantly higher with 67.0 vs. 57.6 y ($p < 0.00001$). Mean 25(OH)D level of the supplement-user group was significantly higher with 21.5 vs 16.2 ng/ml ($p < 0.00001$) but PTH level did not differ ($p = 0.7$).

Diagnoses. Diagnoses were documented to characterize the general health status of the study population and to evaluate how many subjects suffered from a disease possibly related to vitamin D deficiency (e.g., osteoporosis or osteopenia). From the 1340 subjects 1133 (84.6%) reported at least the diagnosis of one persisting disease. Among these 8% reported to have osteoporosis or osteopenia.

The whole number of relevant diagnoses was 3823 from which 2424 (63%) concerned 3 System Organ classes (SOC) namely cardio-vascular system, musculoskeletal and connective tissue, metabolic system. Musculoskeletal and connective tissue disorders were mainly back pain and osteoarthritis related complaints.

The mean level of 25(OH)D of the 93 subjects with diagnosed osteoporosis/osteopenia was with 19.3 ng/ml, significantly ($p = 0.0005$) higher than the whole study population.

Discussion

There has always been and is still today an uncertainty about the “normal” blood level for vitamin D. One proposal was to accept the level at which PTH is maximally suppressed but corresponding studies found 25(OH)D values between 12 and 40 ng/ml though with an increased number around 30 ng/ml.^{57,58} Obviously no normal or optimal value for vitamin D could be found, but most of the beneficial effects of vitamin D can be seen when 25(OH)D is at about 30 ng/ml. Today 25(OH)D level below 30 ng/ml are considered as insufficiency, values lower than 20 ng/ml as deficiency and values below 7 ng/ml as severe deficiency.^{3,54} Recently somewhat different categories were proposed by an expert group of the US Institute of Medicine (IOM) developing dietary reference intakes (DRI) for calcium and vitamin D. The development of DRI does not search what level provides maximal benefit, but at what level the vast majority of the population can expect benefit. For this purpose they defined 25(OH)D < 12 ng/ml risk of deficiency, 12–20 ng/ml risk of inadequacy, 20–50 ng/ml adequate.⁵⁹

Our study was conducted to provide data to enable estimation of the vitamin D status of the German population at the end of wintertime. Selecting patients randomly from an official German population registry would have been very difficult. Therefore an alternative study design was sought, which would allow us to observe a cohort of subjects approximately representative for the whole population without selection by geographical region, health or care-status. Furthermore the aim was to recruit roughly equal numbers of subjects with regard to gender and age categories ranging from 20 to more than 80 y. Our concept was nationwide recruitment of general practitioners (GP) willing to contribute to the DeVid-Trial (D-vitamin in Deutschland) by taking blood samples from their daily ambulant patients regardless of the actual reason for consultation.

We suppose that a large cohort of routine patients seen in GP's daily practices is very close to a sample of the so-called normal population and therefore with only small limitation representative for the general population. GPs recruit from all groups of inhabitants over a wide range of age without any selection for certain diseases as it is in specialist centers. Most patients see their physician for minor complaints or even only for a health check-up. That means the vast majority are not acutely ill. There may be a somewhat higher proportion with chronic or severe disease. In our study any chronic disease was mentioned for 84.5% of the included subjects suffering mainly CVD, musculoskeletal disorders, and metabolic disturbances. Since subjects were recruited throughout Germany possible regional influences could be avoided.

Considering all these aspects we conclude that the data on 25(OH)D found in our study can be taken as representative for the adult population in Germany. This is supported by the data of the German National Health Interview and Examination Survey 1998 which found comparable data for the vitamin D status.⁶⁰ In that particular study vitamin D status was analyzed based on serum 25(OH)D measurements, its determinants and health correlates in a representative sample of 4030 German adults, 1763 men and 2267 women. The age range was 18–79 y of age. Vitamin D levels during wintertime lower than 20 ng/ml were found in 64% of the adult subjects.⁶⁰ This is very close to the 75% we found for the corresponding category of vitamin D inadequacy.

In further epidemiological studies on the vitamin D status performed in different European countries it was shown that 25(OH)D levels lower than 10 ng/ml can be found in up to 30% of the general population depending on the region. Among older persons this fraction may be as high as 75%. In general the lower levels are found more often in southern than in the northern countries especially in elderly, independent people.⁶¹ This can be explained by different cultural and dietary habits. In northern countries the consumption of fatty fish and cod liver oil as a vitamin D supplement is high whereas in southern countries direct sunlight exposure is avoided and relevant supplements are not widely taken.⁶² But this is only true when different countries are compared. In France with reasonably homogeneous cultural practices and diets but an important north to south gradient of sunshine exposure, vitamin D deficiency is more frequent in the

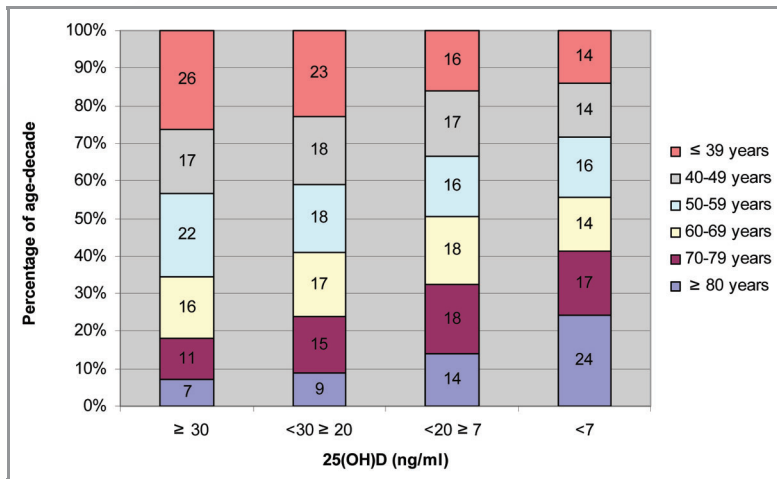


Figure 1. Repartition of the age decades in the vitamin D clusters.

northern than in the southern regions. In one particular trial the mean 25(OH)D in the north was 17 ng/ml versus 38 ng/ml in the south.⁴⁹ In countries with the same solar irradiation all over in the country, i.e. no north to south gradient of sunshine exposure, like The Netherlands or Switzerland, 25(OH)D levels lower than 20 ng/ml have been found in nearly 50% of the population. In these countries the percentage of people with vitamin D insufficiency is higher in the elderly and in institutionalized persons.^{63,64} Comparable data are available for Spain, Italy and Greece.⁶⁵⁻⁶⁹ All these data including our results prove that vitamin D insufficiency or even deficiency is widespread and important in nearly all European countries.

Mithal et al. published a review of the literature with data on the vitamin D status in six regions worldwide on the general population: Asia, Europe, Middle East and Africa, Latin America, North America, and Oceania. In all these regions hypovitaminosis-D is also widespread with level lower than 30 ng/ml in most regions and lower than 10 ng/ml especially in South Asia and Middle East. Risk factors for hypovitaminosis D were identified as older age, female sex, lower latitude, winter season, darker skin pigmentation, degree of sunlight exposure determined by clothing and cultural practices, dietary habits and national policies of vitamin D fortification.⁷⁰

Conclusion

Our epidemiological investigation demonstrates that vitamin D deficiency is extremely common in Germany at least at the end of wintertime reflecting a poor supply during summertime. It is not only a problem of the elderly but widespread in the whole population (Fig. 1). Also in the group of the so called active middle-aged people between 40 and 60 y vitamin D deficiency is very common. We found 25(OH)D levels lower than 20 ng/ml in 32% of subjects of this age group. This may be due to the fact that today's life takes place mainly indoors. Indoor lifestyle, nearly complete covering of the body with clothes as well as abundant use of UV-blocking creams when outdoors prevents the formation of vitamin D in the skin.⁷¹⁻⁷⁴ This virtual screening of sunlight from our modern lives could be a fatal mistake increasing the risk for a number of important diseases like CVD, different types of malignancy, type-I Diabetes. Although the subjects in our study were selected being under medical supervision or treatment, 92% of them had at least a vitamin D insufficiency. This shows that the awareness among physicians of our country about the necessity of sufficient vitamin supply is very poor. Since vitamin D is able to regulate much more than calcium and phosphate homeostasis and heal rickets or osteomalacia, educational work seems to be mandatory. Future prospective studies should investigate whether it is possible to reduce morbidity or mortality in a given population by increasing vitamin D supply and thereby reduce the high economic burden for national health systems.

Patients and Methods

A population based study throughout a whole country is very complicated and expensive. Therefore we decided to involve GPs since their patients can be considered as approximately representative for the whole population. In total 264 GP practices were contacted by the sponsor's sales forces (Rottapharm Madaus GmbH), and recruited participants randomly throughout Germany. They received study sampling kits consisting of study information including questionnaires, blood sampling material and transportation material ready to be sent.

Table 1. Laboratory parameters and methods of analysis

Parameter	Method	Manufacturer	Analysis device	Stability at ambient temperature
Vitamin D	ECLIA*	Diasorin	Liaison	3 d
Calcium	Photometric	Roche Diagnostics	Modular	7 d
Alk. Phosphatase	IFCC, liquid 37°C	Roche Diagnostics	Modular	7 d
GGT	Enzymatic	Roche Diagnostics	Modular	7 d
Creatinine	Jaffé	Roche Diagnostics	Modular	7 d
Phosphate	UV-colortest	Roche Diagnostics	Modular	3 d
Parathyroid hormone	ECLIA*	Roche Diagnostics	Modular	2 d

*Electro Chemo Lumineszens Immuno Assay

Table 2. Number of subjects per life-decade

Decade	< 20-39	40-49	50-59	60-69	70-79	80-~
No. of subjects (N:1310)	231	220	223	230	227	179
m (N: 597) (%)	103 (45%)	89 (41%)	103 (46%)	115 (50%)	108 (48%)	79 (44%)
w (N: 713) (%)	128 (55%)	131 (59%)	120 (54%)	115 (50%)	119 (52%)	100 (56%)

Table 3. Number of subjects per region (postal code)

Postal code	Subjects (N)	25-OH-VitD	Age
0	159	N	159
		Mean	59.34
		Min.	21.00
		Max.	97.00
		Median	63.00
		SD	18.06
1	236	N	236
		Mean	57.84
		Min.	20.00
		Max.	99.00
		Median	59.00
		SD	17.42
2	114	N	113
		Mean	57.12
		Min.	20.00
		Max.	93.00
		Median	57.00
		SD	17.83
3	134	N	133
		Mean	58.30
		Min.	20.00
		Max.	96.00
		Median	62.00
		SD	17.81
4	71	N	71
		Mean	55.77
		Min.	21.00
		Max.	93.00
		Median	55.00
		SD	17.52
5	188	N	188
		Mean	56.39
		Min.	20.00
		Max.	93.00
		Median	57.00
		SD	18.43

A central laboratory analyzed 25(OH)D, parathyroid hormone, calcium, alkaline phosphatase, creatinine, gamma-GT, phosphate. Subjects had to fill in a simple questionnaire giving their age, sex, living situation, previous falls or fractures within the last 12 mo, skin type, vitamin D-supplementation or stay in a lower-latitude country during the last 6 weeks before blood sampling, acute or chronic diseases, medications of the last 6 weeks. To ensure well balanced age groups and sex distribution, each center had to recruit one patient to each of the following predefined sex/age categories: male/female and age categories 20-39, 40-49, 50-59, 60-69, 70-79, and ≥ 80 y.

The trial was performed between February 26 and May 25, 2007. Forty-eight percent of the blood samples were collected between February 26, 2007 and March 24, 2007.

Blood sampling was geographically distributed throughout Germany. The allocation to the different regions, identified by postal code, and the respective number of subjects per region is shown in Table 3.

During routine blood sampling from otherwise unselected patients regardless of the actual reason for consultation they were asked to give blood (approximately 10 ml) for the study. After sampling, blood was processed according to the instructions of the central laboratory (Spranger Laboratories, Lindberghstr. 9-13, 85051 Ingolstadt, Germany) and sent to the laboratory the same

Table 3. Number of subjects per region (postal code) (cont.)

Postal code	Subjects (N)	25-OH-VitD	Age
6	106	N	106
		Mean	54.61
		Min.	20.00
		Max.	86.00
		Median	54.50
		SD	17.43
7	103	N	103
		Mean	56.81
		Min.	19.00
		Max.	86.00
		Median	58.00
		SD	18.96
8	107	N	106
		Mean	59.85
		Min.	20.00
		Max.	89.00
		Median	64.00
		SD	18.18
9	125	N	113
		Mean	59.10
		Min.	22.00
		Max.	87.00
		Median	62.00
		SD	18.19

Table 4. Clinical chemistry

Reference Unit	VitD ng/ml	Ca (2.11–2.63) mmol/l	AP (< 104) U/l	GGT (< 42) U/l	Crea (< 0.96) mg/dl	PO4 (0.87–1.45) mmol/l	PTH (15–65) pg/ml
N	1328	1328	1328	1328	1328	1328	1285
Mean	16.23	2.39	71.73	42.71	0.92	1.49	44.53
Min.	6.00	1.79	20.00	5.00	0.47	0.61	10.18
Max.	66.80	3.96	1738.00	4806.00	4.26	9.82	201.60
Median	14.10	2.38	67.00	25.00	0.88	1.28	40.10
SD	8.82	0.11	51.11	141.00	0.265	0.855	21.31
V	0.54	0.05	0.71	3.30	0.29	0.58	0.48

day. **Table 1** shows the laboratory methods used. The laboratory was certified by an external quality assessment scheme for the relevant testing including 25(OH)D.

Finally out of the 264 participating physicians' practices 176 sent back filled in questionnaires and laboratory data. Laboratory data were available for a total of 1409 subjects and questionnaires

from 1352 subjects of whom 616 were male, 730 female, and 7 subjects without gender information.. After compiling laboratory data and filled in questionnaires complete data sets could be evaluated from 1340 subjects. This final population consisted of 613 men and 727 women, mean age 57.6 y (Min. 19.0, Max. 99.0, SD 18.00, Median 59.0). **Table 2** shows mean age and

Table 5.

25(OH)D (ng/ml)	No of subjects				No. / Decade			
	N	%	m		W		N: 99	
			N	%	N	%	< = 39	26 26%
> = 30	102	8	39	39	63	61	40–49	17 17%
							50–59	22 22%
							60–69	16 16%
							70–79	11 11%
							> = 80	7 7%
							N: 225	
< 30 > = 20	230	17	97	42	133	58	< = 39	52 23%
							40–49	41 18%
							50–59	40 18%
							60–69	38 17%
							70–79	34 15%
							> = 80	20 9%
N: 841								
< 20 > = 7	857	65	424	32	433	33	< = 39	133 16%
							40–49	141 17%
							50–59	138 16%
							60–69	155 18%
							70–79	155 18%
							> = 80	119 14%
N: 132								
< 7	139	10	47	34	92	66	< = 39	19 14%
							40–49	19 14%
							50–59	21 16%
							60–69	19 14%
							70–79	23 17%
							> = 80	31 24%

Table 6.

25(OH)D (ng/ml)	ITEM (normal) unit	PTH (15–65) pg/ml	AP (< 104) U/l	Creatinine (< 0,96) mg/dl	Phosphate (0,87–1,45) mmol/l	GGT (< 42) U/l
> = 30	N	99	61	102	102	102
	Mean	36,08	61,82	0,90	1,68	28,09
	Min.	15,90	33,00	0,53	0,71	8,00
	Max.	134,90	104,00	1,81	7,65	141,00
	Median	32,00	62,00	0,89	1,29	20,00
	SD	15,75	14,18	0,22	1,22	22,20
< 30 > = 20	N	221	135	230	230	230
	Mean	38,14	63,56	0,91	1,47	32,39
	Min.	12,70	32,00	0,52	0,61	6,00
	Max.	140,20	143,00	2,62	6,95	288,00
	Median	36,46	60,00	0,87	1,31	22,00
	SD	15,30	19,28	0,25	0,75	34,71
< 20 > = 7	N	815	439	857	857	857
	Mean	45,29	67,05	0,93	1,45	41,40
	Min.	10,18	20,00	0,47	0,63	5,00
	Max.	186,40	130,00	4,26	9,82	739,00
	Median	41,20	65,00	0,88	1,27	26,00
	SD	20,28	18,53	0,28	0,79	54,46
< 7	N	135	76	139	139	139
	Mean	56,94	79,11	0,88	1,58	78,58
	Min.	16,70	22,00	0,48	0,67	8,00
	Max.	201,60	148,00	1,91	8,80	4806,00
	Median	47,87	80,00	0,84	1,33	26,00
	SD	31,32	25,45	0,24	1,03	410,84

number of subjects and their distribution per decades. Out of 1290 subjects giving information whether they were institutionalized or not, 7 were institutionalized (1 man, 6 women).

Statistics.. The statistic evaluation was descriptive and explorative. All available data were included in the calculations. The mean, standard deviation, minimum, maximum, and median were calculated for each item. Missing data was left blank. Cohorts with the same characteristics (e.g., age group, sex, fall) were created and tested vs. the whole study population. Student's testing was performed for measuring differences statistically

significant. A p-value of $p < 0.05$ was considered statistically significant based on two-sided tests. No adjustment for multiple testing was applied.

For calculation reasons the listed diagnoses in the questionnaire were coded according to MedDRA 10.1.

Disclosure of Potential Conflicts of Interest

The associated Ethic Committees in each region were consulted and approved the study before starting. Each subject gave informed consent before entering the study.

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