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Vitamin D Deficiency in Orthopedic Patients in Different Latitudes—First Study Comparing German and Greek Populations

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Abstract: Vitamin D plays a pivotal role in calcium metabolism and bone mineralization. Sufficient vitamin D levels are important for the health and functionality of the musculoskeletal system. Hypovitaminosis D is a phenomenon affecting orthopedic patients worldwide. This study researched whether most orthopedic patients in two different cities of different countries had hypovitaminosis D, whether there was a correlation between sunshine hours and vitamin D serum levels, and whether hours of sunshine alone were enough to achieve vitamin D sufficiency among orthopedic patients regardless of their activities. The vitamin D serum levels of 500 orthopedic patients in Regensburg and 500 in Patras were assessed, in addition to their medical histories. The mean sunshine hours throughout the year were also calculated. Both the German and Greek groups showed hypovitaminosis D. Older patients were more affected. Although there were more hours of sunshine in Greece, Greek orthopedic patients also showed hypovitaminosis D. Hypovitaminosis D affects orthopedic patients independent of their latitude. Supplementation of vitamin D may be considered among orthopedic patients to achieve sufficient levels in serum. Sufficient vitamin D levels may be helpful for the treatment of orthopedic patients, reduce the negative effects of operations or postoperational settings.

Keywords: vitamin D; hypovitaminosis D; sunlight exposure; Greek–German population

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1. Introduction

Lack of vitamin D can cause bone demineralization, bone mass loss and secondary hyperparathyroidism, bone fractures, and osteoporosis [1]. The preventive role of vitamin D is not evidently proven for the case of fractures [2,3], but vitamin D plays a crucial role in the development and maintenance of a healthy skeleton throughout life [4]. Vitamin D regulates skeletal homeostasis [5] and the immune system [6]. Hypovitaminosis D increases the risk of respiratory and periprosthetic infections, whereas vitamin D supplementation may reduce the risk of influenza or an infection [7,8]. Although data is currently not sufficient, there are studies, including a randomized clinical pilot study, that suggest a prophylactic potential of vitamin D for COVID-19 patients [9]. Hypovitaminosis D can increase the risk of cardiovascular diseases, type 2 diabetes, and mental illness [10,11]. Multiple observational studies have demonstrated an association between a low level of serum of vitamin D and the presence and severity of several rheumatic diseases [12]. Vitamin D seems to be very important for general health and also for athletic performance [13]. While it is undisputed that severe vitamin D deficiency has adverse skeletal effects, including osteomalacia, high bone turnover and bone loss, and an increased risk of hip fractures in the elderly, skeletal effects of milder degrees of vitamin D deficiency have recently come under question. Milder degrees of vitamin D deficiency contribute to the development of osteoporosis, but supplementation with vitamin D alone does not appear to reduce fractures [14,15]. Skeletal benefits in the elderly will not likely be seen in those who are mildly vitamin D deficient and certainly not in those whose serum 25-hydroxyvitamin D is above the threshold value [16]. On the other hand, in severely vitamin D-deficient individuals, the beneficial effects of vitamin D in reducing fracture risk are more likely to be appreciated [14]. Both the production and metabolism of vitamin D change with aging. All age-related changes in vitamin D metabolism are magnified if there is concomitant vitamin D deficiency, because it limits the substrate supply for 25-OH-D and, ultimately, for 1,25-(OH)-2D [17].

Hypovitaminosis D has been referred to by some authors as a "pandemic" [18], and it mainly affects older people. Thus, it is essential to supplement vitamin D within vulnerable groups, especially the elderly with orthopedic problems, who cannot maintain a conscious and healthy lifestyle [19,20].

Low vitamin D levels have been described across race and age groups [21], including in postmenopausal US women in therapy with antiosteoporotics [22], the Chinese population, and Irish adolescents [23,24]. In a cohort of 14000 Germans, low levels (less than 20 ng/mL) of vitamin D were shown in 62%, 64%, 57%, and 58% of adolescent boys, adolescent girls, men, and women, respectively [25].

Vitamin D is produced intradermally after sunlight exposure [26]. Lower sunlight exposure in the UK reduces vitamin D levels in Bangladeshi migrants [27]. During the winter months, only small amounts of vitamin D are synthetized intradermally [28].

The aim of this study was to retrospectively gain facts about the prevalence of vitamin D deficiency, which may be helpful for the treatment of orthopedic patients, especially in the effort to reduce the negative effects of operations or in post-operational settings. Recent research has shed light on the importance of vitamin D in the setting of soft tissue healing and recovery, in addition to affecting post-operative outcomes after common orthopedic procedures [29]. The study was performed based on a collaboration of German and Greek researchers. Mean sunshine hours per month are significantly more in Greece and their impact on vitamin D level could be assessed.

2. Materials and Methods

In total, 500 patients in Greece and 500 patients in Germany, admitted to orthopedic surgery departments of 2 hospitals, were analyzed regarding their 25-OH-D serum levels between 1 January 2013 and 31 December 2013. The tested population was set to electively undergo an orthopedic operation.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the University of Patras (protocol code 4052 and date of 13 March 2017). In Regensburg and Patras, upon admission, all patients signed to grant consent that their personal, medical, and laboratory data may be retrospectively anonymously analyzed for further studies.

Blood was extracted on the day of admission for elective surgery, regardless of the kind of elective operation (no fasting serum). The mean age of the patients was 59 years old. Age was categorized into 4 groups (30 years and younger, 31–50 years old, 51–69 years old, and 70 years and older). The medical history information of the patients is listed in Table 1. Oral supplementation in the patients' history was estimated between 400 and 600 IU. Estimation of serum 25-OH-D was standardized; the clinic facilities utilized the 25-OH-D measure

(Laboratory Lindenlohe Bavaria for Germany and University Clinic Rio Patras for Greece). The method used to quantify serum 25-OH-D was a liquid chromatography–tandem mass spectrometry-based method, described by Meier et al. [1]. This is one of the most accurate methods [30]. Both laboratories, in Greece and Germany, used this method for serum 25-OH-D assessment (25-OH-D status was categorized according to the cutoff points used by Hollis [31] and Grant and Holick [32]). We defined a sufficient 25-OH-D serum status as greater than 30 ng/mL, as in Meier et al. [1]. Patients with 25-OH-D values lower than 30 ng/mL were defined as insufficient and patients with values under 20 ng/mL as deficient [1]. The age, sex, and medical history of each individual were documented (Table 1). The mean sunshine hours were calculated using information from the German weather service and the Greek weather service. The statistical analysis was performed with the statistical software IBM SPSS Statistics 28. Univariate analysis was performed in order to measure the central tendency (mean, median etc.), the range, the maximum and minimum values, and standard deviation of hypovitaminosis D related to osteoporosis. Multivariable regression analysis was performed in order to measure the degree to which hypovitaminosis D and various dependent variables (categorical variables) such as obesity, pulmonary diseases, etc., were linearly related to each other. Differences were considered significant with a *p*-value of <0.05. Mean sunshine hours per month were correlated with mean 25-OH-D levels with Pearson correlation coefficient.

Table 1. Characteristics of the tested patients. Sign.: statistical significance and *p*-value. Every *p*-value under <0.05 is considered to be significantly different and is highlighted in bold. 25-OH-D was measured in ng/mL. Obesity: (BMI > 30 kg/m^2).

	Both Groups	**Group Regensburg**		**Group Patras**	
			25-OH-D mean value (Sign.)		25-OH-D mean value (Sign.)
Patients (n)	1000	500	-	500	
Men (n)	433 (43.3%)	230 (46%)	17.70	204 (40.7%)	18.20
Women (n)	567 (56.7%)	270 (54%)	18.10	297 (59.3%)	18.40
Age (years)	59 (SD ±± 18.2)	60 (SD ±± 18.1)	-	59 (SD ±± 18.2)	
Osteoporosis	165 (16.5%)	57 (11.4%)	**23.50**	108 (21.6%)	**23.95**
Obesity (BMI)	248 (24.8%)	133 (26.7%)	16.00	115 (23%)	15.40
Thyroid disease	129 (12.9%)	64 (12.8%)	16	65 (13%)	17.60
Psychiatric diseases	171 (17.1%)	91 (18.2%)	16.9	80 (16%)	18.15
Infectious diseases	24 (2.4%)	13 (2.6%)	15.50	11 (2.2%)	16.40
Renal failure	92 (9.2%)	57 (11.4%)	17.80	35 (7%)	14.60
Pulmonary disease	85 (8.5%)	48 (9.6%)	18.50	37 (7.4%)	17.30
Cardiovascular disease	238 (23.8%)	133 (26.7%)	17.50	105 (21%)	17.30
Diabetes	146 (14.6%)	87 (17.4%)	16.50	59 (11.8%)	14.30
Hypertension	456 (45.6%)	253 (50.7%)	16.80	203 (40.5%)	17.10
Carcinoma	176 (17.6%)	96 (9.2%)	16.35	80 (16%)	17.20
Bone fracture	81 (8.1%)	46 (9.2%)	18.85	35 (7%)	18.50
Supplement VitD	132 (13.2%)	51 (10.2%)	**24.50**	81 (16.2%)	23.50
Spring	198 (19.8%)	92 (18.4%)	20.64	106 (21.2%)	20.39
Summer	206 (20.6%)	85 (17%)	21.89	121 (24.2%)	20.8
Autumn	353 (35.5%)	194 (38.8%)	20.62	159 (31.8%)	20.52
Winter	243 (24.3%)	129 (25.8%)	17.72	114 (20.8%)	19.17

3. Results

The values of 25-OH-D in the sera of 500 patients from Regensburg (REG) in Germany and 500 patients from Patras (PAT) in Greece were analyzed along with patient medical histories (Table 1). Overall, 83.1% of patients were 25-OH-D insufficient and 58.4% were 25-OH-D deficient. Of the 1000 25-OH-D serum levels measured in this study, only 15.8% were in the target range of 30 to 60 ng/mL, and 1.1% had 25-OH-D levels higher than 60 ng/mL. If divided into groups, 84.1% of the German patients were 25-OH-D insufficient and 60.4% were 25-OH-D deficient. Of the 500 25-OH-D serum levels measured in the German population, only 15% were in the target range, and 0.8% had 25-OH-D levels higher than 60 ng/mL. In Greece, 82% of patients were 25-OH-D insufficient and 56.4% were 25-OH-D deficient. Of the 500 25-OH-D serum levels measured in this study, only 16.6% were in the target range, and 1.4% of patients had 25-OH-D levels higher than 60 ng/mL.

The serum 25-OH-D levels for all German patients were normally distributed, with a mean of 20.08 ng/mL and minimum and maximum values of 2 ng/mL and 82.4 ng/mL, respectively. The serum 25-OH-D levels for all Greek patients were also normally distributed, with a mean of 21.2 ng/mL and minimum and maximum values of 2.2 ng/mL and 82.4 ng/mL, respectively.

Variations in 25-OH-D levels were seen among the different age groups of the patients. Within the German population, the median value of 25-OH-D level in the group of patients 30 years and younger (n = 43) was 18.60 ng/mL, in the 31–50 age group (n = 90) it was 19.20 ng/mL, in the 51–69 age group (n = 176) it was 18.00 ng/mL, and in the 70 years old and older age group (n= 190) it was 17.00 ng/mL. Within the Greek population, the median value of 25-OH-D level in the 30 years and younger group (n = 59) was 17.65 ng/mL, in the 31–50 age group (n = 43) it was 19.20 ng/mL, in the 51–69 age group (n = 116) it was 18.70 ng/mL, and in the 70 years old and older age group (n = 175) it was 17.30 ng/mL. The oldest groups of patients in both countries showed the lowest levels of 25-OH-D, followed by the youngest patients tested (Table 2).

Table 2. Differences of 25-OH-D serum level values divided into age groups and corresponding population (values in ng/mL); SD: standard deviation, I. Group Regensburg, II. Group Patras.

I					
Age Group	**Mean Value**	**SD**	**95% Confidence Interval**		**Median**
			Lower Limit	**Upper Limit**	
30 years and younger	19.40	±±8.26	16.89	21.91	18.60
31–50 years	21.05	±±10.58	18.83	23.27	19.20
51–69 years	19.55	±±9.84	18.09	21.02	18.00
70 years and older	20.28	±±11.75	18.60	21.96	17.00
II					
Age Group	**Mean Value**	**SD**	**95% Confidence Interval**		**Median**
			Lower Limit	**Upper Limit**	
30 years and younger	20.56	±±8.8	17.80	23.33	17.65
31–50 years	20.72	±±9.44	18.98	22.45	19.20
51–69 years	21.07	±±10.44	19.47	22.66	18.70
70 years and older	21.87	±±12.79	19.97	23.79	17.30

Variations in 25-OH-D levels across the seasons of the year were seen among the tested patients. Within the German population, the mean value of 25-OH-D level during the spring months (March, April, and May) was 17.60 ng/mL, in the summer months (June, July, and August) it was 21.40 ng/mL, in the autumn months (September, October, and November) it was 18.05 ng/mL, and during the winter months (December, January, and February) it was 16.40 ng/mL. Within the Greek population, the mean value of 25-OH-D level during the spring months was 18.25 ng/mL, during the summer months it was 22.30 ng/mL, during the autumn months it was 18.00 ng/mL, and during the winter months it was 16.65 ng/mL (Figure 1, Table 3).

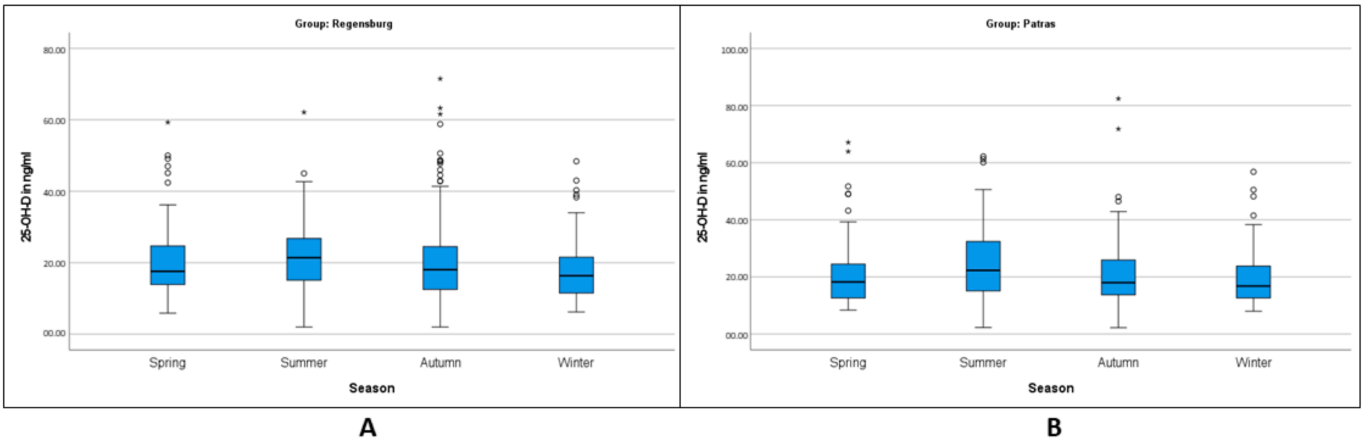


Figure 1. Seasonal distribution of 25-OH-D values among the patients. In the summer, the patients showed slightly higher values of vitamin D in serum of compared to the 25-OH-D values in serum in the winter months ((**A**): German patients, (**B**): Greek patients, ★ and ○: outliers).

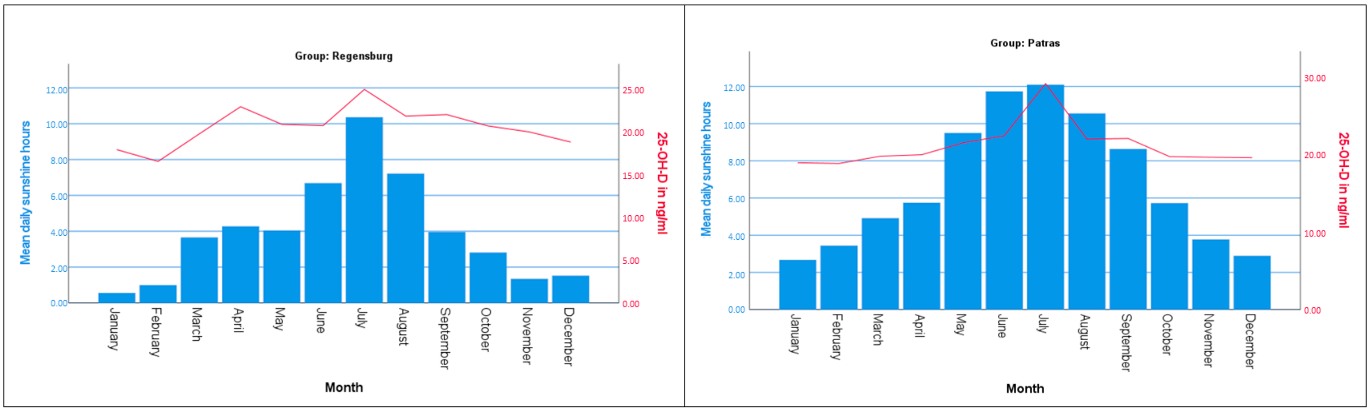
Table 3. 25-OH-D values analyzed by season (level in serum in ng/mL), SD: standard deviation, I. Group Regensburg, II. Group Patras.

		I			
Season	**Mean Value**	**SD**	**95% Confidence Interval** **Lower Limit**	**Upper Limit**	**Median**
Spring	20.65	±±10.38	18.50	22.80	17.60
Summer	21.89	±±10.42	19.63	24.14	21.40
Autumn	20.61	±±11.87	18.93	22.29	18.05
Winter	17.72	±±8.34	16.26	19.16	16.40
		II			
Season	**Mean Value**	**SD**	**95% Confidence Interval** **Lower Limit**	**Upper Limit**	**Median**
Spring	20.39	±±10.95	18.28	22.50	18.25
Summer	24.80	±±12.25	22.59	27.00	22.30
Autumn	20.52	±±10.49	18.89	22.17	18.00
Winter	19.19	±±9.40	17.44	20.94	16.65

The mean sunshine hours per month showed a strong correlation in Germany ($p < 0.05$, Pearson's correlation < 0.05) with mean 25-OH-D levels. Higher mean 25-OH-D serum levels were observed during the summer months with more sunshine hours. In Greece, a strong correlation was not shown, but in the summer months, the patients showed higher mean 25-OH-D serum levels (Figure 2).

Univariate analysis showed that the incidence of osteoporosis in Germany and in Greece ($p < 0.01$ and 0.015, respectively) was associated with hypovitaminosis D. This was also proven with multivariate linear regression analysis, which was performed to evaluate possible predictors for hypovitaminosis D. Variables were clinically relevant risk factors or predictors if the final p value was less than 0.05. As in the univariate analysis, osteoporosis was found to be significantly associated with low 25-OH-D levels ($p < 0.05$). An association with hypovitaminosis D was also nearly shown among the obese patients in Patras, Greece (pPAT = 0.057). Age (pREG = 0.622/pPAT = 0.199) and sex (pREG = 0.447/pPAT = 0.214), obesity in German patients (pREG = 0.395), thyroid abnormalities (pREG = 0.667/pPAT = 0.915), psychiatric diseases (pREG 0.743 = /pPAT = 0.783), infectious diseases (pREG = 0.219/pPAT = 1.00), renal failure (pREG = 0.336/pPAT = 0.725), pulmonary diseases (pREG = 0.778/pPAT = 0.470), cardiovascular diseases (pREG = 0.249/pPAT = 0.714), diabetes (pREG = 0.343/pPAT = 0.547), hypertonus (pREG = 0.182/pPAT = 0.864), carcinoma (pREG

= 0.702/pPAT = 0.782), and bone fracture (pREG = 0.445/pPAT = 0.793) were not associated with differences in 25-OH-D levels in our univariate analysis.



A B

Figure 2. Comparison of mean sunshine hours per month with 25-OH-D levels in ng/mL. In months with most mean sunshine hours, the values of 25-OH-D in serum of patients is the highest ((**A**): German patients; (**B**): Greek patients).

In both groups, only 20 patients (2%) with 25-OH-D levels above 50 ng/mL were evaluated. Of these, 13 (1.3%) had 25-OH-D-levels above 55 ng/mL.

4. Discussion

As shown in other studies, there is a wide prevalence of vitamin D deficiency among the world's population [33]; Hernigou et al. describe vitamin D deficiency as a common phenomenon [34]. In our study, a high percentage of the population in both Germany and Greece, without consideration of their medical history, showed hypovitaminosis D. More than 50% of the tested patients showed not only a 25-OH-D insufficiency but also a deficiency. The lowest values of 25-OH-D in serum were among the patients aged 70 years or more. As shown above, 25-OH-D values increased during the summer months, in which the most sunshine hours were measured. The correlation between sunshine hours and 25-OHD seems to be stronger in the Greek population. The strong correlation in the German population seems to be due to the low status in winter rather than the peak in summer. However, the patients still did not achieve scores of 25-OH-D above 30 ng/mL, which suggests that the expected typical daily exposure to sunlight may not be sufficient in order to achieve the minimum necessary value of 25-OH-D for the human organism. Low vitamin D levels are associated with stress fractures even in outdoor athletes [35]. With our study, we confirmed the results of the study of Maier at al.; our and their results showed widespread hypovitaminosis D in two cities of two different federal states of Germany. We also showed, for the first time, the extent of hypovitaminosis D within orthopedic patients in the city of Patras in Greece. Despite the statement of Maier et al. [1] that elderly patients are more likely to be indoors regardless of the time of year and, thus, a difficulty may occur for the correlation of vitamin D values with sunlight exposure, we showed in this study that more active and younger patients aged 30 years and under also suffer from hypovitaminosis D. Blood levels of 25-OH-D were examined in consecutive patients—regardless of the kind of elective operation—so that bias and influence of skeletal health was minimized. By having a wide range of orthopedic procedures performed, we avoided the influence of specific orthopedic diseases on skeletal health.

The desirable target range of serum vitamin D levels was set at 30–60 ng/mL, according to the Endocrine Society and the International Osteoporosis Foundation. In the literature there is a controversy over what vitamin D serum levels are considered optimal. Many national and international bodies consider a serum level of ≥20 ng/mL (≥50 nmol/L) to be adequate. These include the National Academy of Medicine (NAM), the D-A-CH nutrition societies of Germany, Austria, and Switzerland, the Scandinavian nutrition societies, the German Osteology governing body (DVO), and the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis. The Endocrine Society and the International Osteoporosis Foundation consider a level of 30 ng/mL to be adequate. In order for this study to be comparable with other studies performed by the same research group of Meier et al., the target range of vitamin D levels was set as previously described.

Even if a cut-off of 20 ng/mL was used as a basis for a vitamin D deficiency, the statistical results of this study would imply nothing more and nothing less than they do now.Both values result in slightly different assessments that do not change the overall statistical results. In both groups, more than 50% of orthopedic patients were vitamin D insufficient.

Although the Fact Sheet for Health Professionals on vitamin D issued by the US National Institutes of Health states that a 25-OH vitamin D level between 20 and 50 ng/mL is generally considered adequate for bone and overall health in healthy individuals, no adverse effects were documented within our orthopedic patients with high vitamin D levels (above 50 ng/mL). Nevertheless, the percentage of these patients was not statistically substantial (20 out of 1000 patients).

Vitamin D has protective and therapeutic effects [36], and it has been suggested that a possible positive effect for the correct functioning of the immune system can be observed for high levels of vitamin D. Vitamin D deficiency is associated with a higher rate of all-cause revision total shoulder arthroplasty [37] and other orthopedic indications for elective surgery [38]. Severe vitamin D deficiency has adverse skeletal effects including osteomalacia, high bone turnover and bone loss, and an increased risk of hip fractures in the elderly. Vitamin D supplementation alone is not enough to reduce fractures [14,15]. Skeletal benefits in the elderly will not likely be seen in those who are mildly vitamin D deficient, and certainly not in those whose serum 25(OH)D is above the threshold value [16].

Vitamin D insufficiency can lead to pathological abnormalities of the muscle and bone function. In our study, we showed that not only Caucasian orthopedic patients of central Europe with mostly dermal type 1 and 2, but also Caucasian orthopedic patients with mostly dermal type 2 and 3, such as in the Greek population, lacked high levels of vitamin D. A comparison with a cohort with darker skin-toned orthopedic patients was underrepresented in this study.

The extreme weather conditions in Germany dictate less sun exposure time than in Greece. Thus, there is an obvious difference in the way and time people go outdoors and expose themselves to the sun. In Greece, the milder weather conditions allow people to move and stay outside for more time than in Germany. Nevertheless, the vitamin D concentrations were not significantly higher. This could be due to the fact that Greeks have a different dermal type than Germans. Furthermore, outdoor activities in Germany are very well organized—better so than in Greece. Moreover, vitamin D substitution is recommended in Germany more often, and generously, because it is known that production of vitamin D in the skin in a latitude greater than 41° may be more difficult. More melanin pigment reduces the ultraviolet radiation available for vitamin D synthesis in the skin [39].

A limitation of the study is that the cohorts have a median age of 59 years and, therefore, most likely include community-dwelling individuals. Thus, these results may not be extrapolated to institutionalized and older individuals. Another limitation is that mean exposure time to the sun was not assessed for any patients; only mean sunshine hours were taken into consideration. Moreover, dermal type of the two populations was more or less assumed, but not assessed. This is in accordance with the majority of the literature regarding vitamin D and orthopedic patients. The fact that both populations are European populations suggests that in many cases cohort overlap will not allow a further statistical analysis concerning the dermal skin type. Further characterization of dermal type was not possible due to the retrospective character of the study, which does not allow re-evaluation and re-examination of tested populations. Although the study was not randomized, patients selected for this study were admitted into the hospital in the same year. Another strength of this study is that both laboratories used the same assays to assess vitamin D level.

In Germany, oral supplementation was highly correlated with vitamin D concentration. In Greece, people with oral vitamin D supplementation showed a higher mean vitamin D concentration in serum, but statistically, this result lacked a correlation. A possible explanation for this observation could be a lack of compliance on the side of Greek patients with taking their medication properly.

Additionally, Meier et al. described no significant correlation between vitamin D and obesity. In our study, this correlation was also not significant for the tested Greek and German patients.

5. Conclusions

Patients at risk should receive oral vitamin D supplementation. Individual vitamin D levels should be taken into consideration and medical supervision is obligatory. According to the results of this study, there should be no difference in the treatment of orthopedic patients undergoing an elective operation, in terms of vitamin D supplementation. A management plan for vitamin D deficiency has been proposed by Sizar et al. [40] and a possible vitamin D supplementation regarding maximum doses was introduced by Rizzoli [41]. We agree with the opinion of Charoenngam et al., who state that screening for vitamin D deficiency is recommended in individuals at risk, such as patients with diseases affecting vitamin D metabolism and absorption, osteoporosis, and older adults with a history of falls or nontraumatic fracture [12].

Author Contributions: A.M.: substantial contributions to research design or the acquisition, analysis, or interpretation of data; drafting, formatting and revising the paper; approval of the submitted and final versions. C.M. and P.D.: revising the paper critically, approval of the submitted and final versions. G.S.M. and S.Z.A.: approval of the submitted and final versions. K.K.: substantial contributions to research design or the acquisition, analysis, or interpretation of data; drafting the paper or revising it critically; approval of the submitted and final versions. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Not applicable, due to patients' anonymization.

Conflicts of Interest: The authors declare no conflict of interest.

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