Vitamin D deficiency is frequent and selenium deficiency is rare in newly diagnosed breast cancer patients

Cosima Zemlin
Laura Altmayer
Caroline Stuhlert
Julia Theresa Schleicher
Carolin Wörmann
Marina Lang
Laura-Sophie Scherer
Ida Clara Thul
Lisanne Sophie Spenner
Jana Alisa Simon
Alina Wind
Elisabeth Kaiser
Regine Stutz
Sybelle Goedicke-Fritz
Gudrun Wagenpfeil
Michael Zemlin
Erich-Franz Solomayer
Carolin Müller (carolin.mueller@uks.eu)
Universitatsklinikum des Saarlandes und Medizinische Fakultat der Universitat des Saarlandes
https://orcid.org/0000-0003-3488-5073

Research Article

Keywords: Vitamin D, Selenium, breast cancer, nutrition

Posted Date: July 18th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1730411/v1

Abstract

Purpose:

In recent years, controversial discussions increased whether vitamin D and selenium have an influence on cancer. In the present study, we examined serum vitamin D and selenium levels in breast cancer patients and potential influencing factors.

Methods:

110 non-metastatic breast cancer patients were included in the prospective observational “BEGYN” study at Saarland University Medical Center between September 2019 and January 2021. Clinicopathological characteristics were documented. At the baseline visit prior to therapy initiation serum vitamin D and selenium levels were measured and patients received a questionnaire on sun exposure, nutrition, and supplement use.

Results:

Median vitamin D value was 24 µg/l, and median selenium level was 81 µg/l. Vitamin D levels were higher among the 17 patients that reported the use of vitamin D substitution (43 µg/l versus 22 µg/l; $p<0.001$). In the univariate analysis, vitamin D levels were higher in summer compared to spring ($p=0.004$), autumn ($p=0.028$) and winter ($p<0.001$). Patients with triple negative carcinomas had a higher vitamin D level (+8,9 µg/l compared to other sub entities, $p=0.035$). The consumption of cream, gouda, and butter was associated with slightly lower vitamin D levels (regression coefficient: -0.36; $p=0.004$). Vitamin D and selenium levels are comparable to the healthy German population.

Conclusion:

Almost 2/3 of all breast cancer patients suffer from vitamin D deficiency at diagnosis, whereas selenium levels were in normal range in 96.2 % of the patients. Vitamin D should be measured routinely, to prevent side effects of vitamin D deficiency.

Introduction

There has been controversial discussion about the intake of nutritional supplements, immune stabilizing micronutrients or vitamins in recent years, especially in cancer patients [1]. Patients’ vitamin levels are not determined in clinical routine. Thus, many patients unknowingly suffer from vitamin deficiency. In an analysis of vitamin D status in 2,267 German women, 57.8 % had a severe, moderate or mild vitamin D deficiency [2]. Early treatment of vitamin D deficiency is important to prevent long-term complications such as bone loss. In addition, vitamin D deficiency is associated with cardiovascular diseases, metabolic syndrome, impaired cognitive function and depression, respectively [3, 4]. Importantly, Jennaro et al. found that under paclitaxel chemotherapy patients with pre-existing vitamin D deficiency have a higher risk of polyneuropathy and other side effects [5]. Selenium is another important micronutrient. Selenium

deficiency can lead to hair loss and fatigue, but might also cause myocardial dysfunction [6] or influence autoimmune thyroid diseases [7, 8]. Selenium plays an important role as antioxidant in several enzymes [1]. In Germany, healthy people have mean selenium levels of 84 µg/l [1], whereas some studies observed lower selenium serum concentrations in cancer patients [1, 9].

Many patients believe that the intake of micronutrients or vitamins could improve their health status and the intake of nutritional supplements by oncological patients has continued to increase in recent years [1]. Depending on the study population, 30-90% of oncological patients take supplements or presumably immunoprotective micronutrients [1, 10], usually without the knowledge of their physician [1]. The SWOG 0221 trial for example, examined supplement use in 1,467 breast cancer patients before diagnosis and during treatment [11]. 595 patients (48.1 %) took multivitamins before breast cancer diagnosis [11]. Nevertheless, effectiveness or influence on oncologic disease and therapy is discussed very controversial [1]. In addition, most patients take supplements without knowing whether they have a vitamin D or selenium deficiency or not, thus risking under- or overdosing.

In the present study, we analyzed serum vitamin D and selenium levels and potential modulators (e.g., supplementation, nutrition, sun exposure and tumor biology) in patients with newly diagnosed breast cancer.

Patients And Methods

Data collection:

Data collection was performed during the BEGYN study [12]. This prospective observational study included 110 non-metastatic breast cancer patients between September 2019 and January 2021 at Saarland University Medical Center. At the baseline visit (before start of therapy), serum vitamin D and selenium levels were measured, supplementation of vitamins and trace elements were documented, and patients received a questionnaire about sun exposure and nutrition (see appendix). Clinicopathological characteristics (e.g., age, tumor biology, Karnofsky performance status scale) were documented.

Statistics:

Statistical analyses were performed using SPSS 28.0 (IBM, Armonk, USA). Qualitative parameters (e.g., tumor stage) are presented as frequencies. Quantitative parameters are given as mean with standard deviation or as median and range. The Kolmogorow-Smirnow-Test was used to test for normal distribution. Univariate linear regression was performed to analyze possible modulators of vitamin D and selenium levels. All variables that reached significance in the univariate analysis were then examined in a multivariable linear regression analysis.

Results

110 non-metastatic breast cancer patients participated in the BEGYN study during September 2019 and January 2021 [12]. Patients' age was 54 (± 12) years. 5 patients (4.5 %) suffered from bilateral breast cancer. The patients were in good general condition: 102 patients (92.7 %) indicated a Karnofsky performance status scale of 90 or 100 % and thus had no or minimal limitations due to the malignant disease. 8 patients (7.3 %) had a Karnofsky performance status scale of 80 % (they could engage in normal activity with effort). Median BMI was 26 (range 19-39). 42 patients (38,2 %) were previous smokers or are currently smoking, with 17 (± 16) pack years. Moderate alcohol consumption was reported by 101 patients (91,6 %). Tumor biology, tumor entity and tumor stage are given in table 1-3. Ki67 index was 29 (± 21). 94 patients (85.5 %) had their first malignant disease, whereas 16 patients (14.5 %) suffered of recurrent cancer or a second carcinoma. In all patients, median vitamin D value was 24 µg/l (range 5 – 65 µg/l) (reference for standard values: 30-100 µg/l) [3]. 17 patients (15.6 %) took vitamin D supplements at baseline visit. Median vitamin D levels were higher among the 17 patients that reported the use of vitamin D substitution (43 µg/l versus 22 µg/l; $p<0.001$). Serum vitamin D was below / within / above the recommended values in 64.8 % / 35.2 % / 0 % of patients. Figure 1 shows the distribution of vitamin D levels at baseline visit. The month of laboratory analysis of vitamin D is presented in figure 2. 91 of the 110 (83 %) patients filled the questionnaire on sun exposure and nutrition during the study. 90 of the 91 answering patients (98.8%) knew that UV radiation is needed to produce vitamin D. For this reason, 41 patients (45.1 %) stated that they spent more time in the sun. Nevertheless, 90 patients (98.8 %) were informed that sun exposure can lead to genetic damage and the development of skin cancer. 52 patients (57.1%) stated that they spent less time in the sun for this reason. 49 patients (53.8 %) classified themselves as skin type I/II (light skin color, red or blond hair, blue or green eyes). 42 patients (46.2 %) reported skin type III (medium skin color, dark hair, brown eyes). Daily sun exposure, use of sun protection and avoidance of "sunny hours" are shown in table 4-6. In addition, patients were asked about their eating habits. Table 7 shows the monthly consumption of certain foods that are rich in vitamin D.

Median selenium level of all patients was 81 µg/l (range 44 – 123 µg/l) (reference for standard values: 50-120 µg/l) [13]. 5 patients (4.6 %) indicated substitution of selenium at baseline visit. Their median selenium level was 107 µg/l (range 88 – 123 µg/l), compared to median selenium level of 80 µg/l (range 44 – 117 µg/l) in patients without substitution ($p<0.001$). Serum selenium was below / within / above the recommended values in 1.9 % / 96.2 % / 1.9 % of patients. Selenium values are shown in figure 3.

Linear regression was performed to identify possible influencing factors in vitamin D and selenium levels. Vitamin D substitution led to a significantly higher vitamin D level (regression coefficient 5.5, $p<0.001$). So, patients with vitamin D substitution (*n=17*) at baseline visit were excluded from further analysis. Patients' age, BMI, tumor stage (cT, cN), alcohol, smoking and prior cancer history showed no significant influence on vitamin D levels. Furthermore, there was no correlation between vitamin D and selenium levels ($p=0.546$). Concerning tumor biology, patients with triple-negative carcinomas had a higher vitamin D level in univariate and multivariable regression analysis (+8,9 µg/l, $p=0.035$). In contrast, no significant influence on vitamin D levels could be demonstrated for Luminal A, Luminal B and Her2 positive tumors. To determine seasonal effects on vitamin D levels, data was split into spring (March, April, May), summer (June, July, August), autumn (September, October, November) and winter (December, January, February).

Compared to values measured in summer, median vitamin D levels were lower in spring and autumn (-11.4 µg/l and -6.2 µg/l), respectively. This difference was statistically significant in univariate regression analysis (p=0.004, spring / p=0.028, autumn). In winter, vitamin D levels were in average 13.6 µg/l lower than in summer (p<0.001). However, the seasonal differences of vitamin D levels did not reach statistical significance in the multivariable analysis. Patients with darker skin (skin type III) had slightly lower vitamin D levels compared to patients with lighter skin (type I) (24 µg/l versus 25 µg/l, p=0.645, not significant). Patients who stated that they stayed longer in the sun had higher vitamin D levels (regression coefficient: spring 1.4; summer 0.4, autumn 0.6, winter 1.1). However, none of the analyzes were statistically significant (p-values: spring 0.16; summer 0.69, autumn 0.54, winter 0.25). Of all food types, only cream / gouda / butter showed a significant influence on vitamin D levels in univariate and multivariable regression analysis (p=0.004). Patients who consumed more of these foods had a slightly lower vitamin D level (regression coefficient: -0.36).

Patients who substituted selenium at baseline visit had a higher selenium level compared to patients without substitution (regression coefficient 5.7; p=0.002). So, patients with selenium substitution (*n=5*) were excluded for further statistics. Patients' age, BMI, tumor biology, tumor stage (cT, cN), smoking and prior cancer history showed no significant influence on selenium levels. Patients reporting moderate alcohol consumption had a 11.0 µg/l higher selenium level (p=0.045 in univariate analysis, not significant in multivariable regression analysis). Data was split into spring, summer, autumn and winter with median selenium levels of 78 µg/l / 86 µg/l / 77 µg/l / 88 µg/l, to determine seasonal influences. In patients whose selenium level was determined in autumn, a statistically significant difference could be demonstrated compared to a determination in summer (p=0.008). Selenium level was on average 10.8 µg/l lower in autumn compared to summer.

Discussion

It is known that vitamin D deficiency is associated with long-term mortality especially in hospitalized, malnourished patients [14]. Furthermore, some studies suggest that higher vitamin D levels might reduce the risk of developing breast cancer [15–18]. Animal studies have also shown that vitamin D deficiency might play a role in primary tumor growth and development of metastases in breast cancer cells [19]. Similarly, there is an ongoing discussion on the potential role of selenium deficiency in tumor genesis and outcome [9].

In the present study we show that almost two thirds of newly diagnosed German breast cancer patients suffer from vitamin D deficiency. The median vitamin D serum concentration was below the recommended minimum value (median vitamin D level of 24 µg/l; vitamin D reference for standard values: 30–100 µg/l) [3]. As expected, patients who consumed supplements had higher vitamin D levels in average. However, despite supplementation, seven out of 17 patients had still mild vitamin D deficiency. None of the patients was above recommended reference values. This supports that vitamin D intoxication and subsequent hypercalcemia and hyperphosphatemia are extremely rare [3]. Vitamin D deficiency was slightly higher in the present study (64.8%) compared to the healthy, cancer free German

population, where almost 60% suffer from vitamin D deficiency [2]. A definite connection between breast cancer development and vitamin D levels has not yet been proven [20] and the slightly higher proportion of vitamin D deficiency in the present study seems negligible. Nevertheless, breast cancer patients might be particularly susceptible to suffer complications of vitamin D deficiency such as bone fractures due to additional risk factors caused by the disease itself and by cancer therapy. For example, disease associated immobilization, chemotherapy, endocrine therapy, radiotherapy, and metastases may further increase bone loss and the risk of fractures. Thus, in breast cancer patients, special attention should be paid to achieve and maintain vitamin D levels within the reference range regardless of the potential influence of vitamin D on the cancer cells [20].

We observed higher vitamin D levels in summer than in other seasons. Furthermore, patients who stated that they stayed longer in the sun had higher vitamin D levels. Even if this did not reach statistical significance due to the limited patient number, our observations are in agreement with previous population based publications that describe seasonal variations of vitamin D levels due to varying sun light exposure [21–23]. Sufficient vitamin D values at the end of summer do not prevent vitamin D deficiency in winter [23]. This illustrates the need of vitamin D monitoring and supplementation in clinical routine- especially in highly vulnerable cancer patients [1].

Although exposure to sunlight is the main factor influencing vitamin D levels in human [21], there are some natural sources like fish (e.g. mackerel, salmon or tuna) and fortified foods (e.g. milk, yogurt, butter, margarine, cheese) that contain high amounts of vitamin D [3]. For this reason, patients in the present study were asked about their eating habits. It remains unclear why in our study, increased consumption of cream / gouda and butter was associated with a minimal decrease in serum vitamin D values. However, this effect was negligible, as it was associated only with a reduction of -0.36 µg/l vitamin D in a total range of 30–100 µg/l. Possibly, these patients increased their consumption of foods rich in vitamin D to counteract a known or presumed vitamin D deficiency. This suggests that in our cohort the diet had only little effect on vitamin D levels compared to sunlight exposure and intake of supplemental vitamin D.

Previous publications link particularly aggressive and triple negative carcinomas with reduced vitamin D levels [18, 24]. In a systematic review with 13,135 breast cancer patients, low vitamin D levels were also associated with triple negative breast cancer [25]. This contrasts with the present study, where triple negative patients had higher vitamin D serum levels compared to other tumor subtypes (Luminal A / Luminal B / Her2 positive). As patients with vitamin D supplementation were excluded from analysis, a possible explanation for higher vitamin D levels in triple negative patients might be coincidentally increased sun exposure. Further studies with larger sample sizes are needed to investigate this connection.

There is an ongoing controversial discussion on the potential influence of selenium concentration on cancer development and the course of the disease as well as therapy side effects (e.g., toxicity of chemo- and radiotherapy) [1, 9]. For example, Szwiec et al. described an influence of selenium levels on 10-year survival of breast cancer patients [26]. Lopez-Saez et al. examined selenium serum concentrations of

patients suffering from breast cancer and healthy women [9]. They found a statistically significant difference (81.1 µg/l in breast cancer patients and 98.5 µg/l in women with non-tumoral disease; $p < 0.001$) [9]. Considering the reference range for selenium level of 50–120 µg/l [13], the clinical relevance of this difference is questionable. In a recent systematic review, beneficial effects of selenium supplements on carcinogenesis could not be proven [27]. Furthermore, a prospective cohort study from Sweden also could not prove an influence of increased selenium intake and serum levels on the risk for breast cancer [28]. In the healthy German population median selenium levels range between 70 and 80 µg/l [13]. In the present study, the median selenium level of breast cancer patients was 81 µg/l with 96.2% of patients being within the recommended reference range. Five patients took selenium supplements - none of them had a deficiency, but one patient was slightly above the recommended reference range (> 120 µg/l). Thus, our study does not support the hypothesis that the risk for breast cancer would be associated with lower serum selenium levels.

Surprisingly, we observed lower selenium levels in autumn compared to determination of selenium levels in summer in the current study. As seafood, organic meats, cereals and grains are typical food sources of selenium [8], the seasonal difference of selenium levels might be due to coincidentally changes of nutritional selenium intake. Furthermore, in harmony with previous studies, we found a positive correlation between selenium levels and alcohol consumption [29, 30]. In the third National Examination Survey of 7,517 American women, those who drank alcohol had significantly higher selenium levels compared to non-drinkers [30].

Limitations of the study are the limited number of patients and the fact that nutritional habits and sun exposure were retrospectively reported by the patients themselves. Nevertheless, these results give important insights into the serum vitamin D and selenium levels of newly diagnosed breast cancer patients which has been rarely studied.

Conclusion

In the present study, we found that vitamin D deficiency is a major problem in newly diagnosed breast cancer patients, whereas the selenium levels were in the normal range in almost every patient. Efforts should be made to include vitamin D determination in clinical routine and to substitute vitamin D deficient patients to prevent side effects and long-term consequences of a vitamin D deficiency in the vulnerable cohort of breast cancer patients. Further studies are needed to explore effects of vitamin D deficiency in breast cancer patients and during oncological treatment.

Declarations

Funding:

This work was supported by *miteinander gegen Krebs e.V. (to C.Z.)*, by a grant from the federal state of Saarland (to C.M. and C.Z.) and by intramural funds of the Saarland University Medical Center.

Conflicts of interest:

All authors declare no conflict of interest.

Ethics approval:

The study is carried out at the Department for Gynecology, Saarland University Medical Center and has been approved by the ethics committee of the Medical Association of Saarland (study # 229/18). Written consent is obtained from the patient in accordance with the Declaration of Helsinki. This study is registered at German Clinical Trials Register (DRKS) (DRKS00024829). Patient recruitment took place between September 2019 and January 2021 and data collection continued until March 2022.

Acknowledgements

The authors would like to thank Dr. Maria Cacacciola-Ketter, Cross against Cancer – *miteinander gegen Krebs e.V.,* Bernd Neuhardt (Laufschule Saarpfalz, Runners Gym Zweibrücken)

AUTHOR CONTRIBUTION

C.Z. wrote the study conception and design. C.Z implemented the study in the clinic, recruited the patients and supervised the study. E.-F.S. and M.Z. gave advice for the study design, supervised the study. Material preparation and data collection were performed by L.A., C.S., J.T.S., C.W., M.L., L.-S.S., I.C.T., L.S., J.A.S., A.W., E.K., R.S., S.G.-F.. The data analysis was performed by C.M., C.Z. and G.W.. The first draft of the manuscript was written by C.M. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Cosima Zemlin: study conception and design, implentation of the study in the clinic, recruitment of the patients, and supervison of the study, data analysis, manuscript editing

Laura Altmayer, Caroline Stuhlert, Julia Theresa Schleicher, Carolin Wörmann, Marina Lang, Laura-Sophie Scherer, Ida Clara Thul, Lisanne Spenner, Jana Alisa Simon, Alina Wind, Elisabeth Kaiser, Regine Stutz, Sybelle Goedicke-Fritz: material preparation, data collection, manuscript editing

Gudrun Wagenpfeil: data analysis, manuscript editing

Michael Zemlin: study design, manuscript editing

Erich-Franz Solomayer: study design, manuscript editing

Carolin Müller: data analysis, manuscript writing

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Tables

Table 1: Tumor biology

Tumor biology	Frequency (n)	Percentage (%)
Luminal A (ER ±, PR±, Ki67 ≤ 15)	32	29.1
Luminal B (ER ±, PR±, Ki67 ≥ 15)	40	36.4
Her2neu positive	27	24.5
Triple negative	11	10.0
Total	110	100

“ER” = estrogen receptor, “PR” = progesterone receptor

Table 2: Tumor entity

Tumor entity	Frequency (n)	Percentage (%)
NST	91	82.7
Invasive lobular	12	10.9
Inflammatory	2	1.8
Mucinous	1	0.9
Tubular	2	1.8
Metaplastic	1	0.9
Mixed (NST, tubular)	1	0.9
Total	110	100

“NST” = No special type

Table 3: Tumor stage

cT	Frequency (n)	Percentage (%)
cT0*	2	1.8
cT1	72	65.5
cT2	31	28.2
cT3	1	0.9
cT4	4	3.6
cN	**Frequency (n)**	**Percentage (%)**
cN0	91	82.7
cN+	19	17.3
M	**Frequency (n)**	**Percentage (%)**
M0	110	100
Grading	**Frequency (n)**	**Percentage (%)**
G1	8	7.3
G2	59	53.6
G3	43	39.1
Total	110	100

* 2 patients had a recurrent tumor in the lymph nodes without tumor manifestation in the breast, thus cT0.

Table 4: Daily sun exposure

Spring	Frequency (n)	Percentage (%)
< 10 minutes	25	27.5
10-20 minutes	26	28.6
15-25 minutes	12	13.2
25-50 minutes	19	20.9
> 50 minutes	9	9.9
Summer	**Frequency (n)**	**Percentage (%)**
< 5 minutes	16	17.6
5-10 minutes	17	18.7
10-15 minutes	15	16.5
15-30 minutes	17	18.7
> 30 minutes	26	28.6
Autumn	**Frequency (n)**	**Percentage (%)**
< 10 minutes	21	23.1
10-20 minutes	22	24.2
15-25 minutes	12	13.2
25-50 minutes	25	27.5
> 50 minutes	11	12.1
Winter	**Frequency (n)**	**Percentage (%)**
< 10 minutes	35	38.5
10-20 minutes	17	18.7
15-25 minutes	15	16.5
25-50 minutes	16	17.6
> 50 minutes	8	8.8

Table 5: Use of sun protection

Spring	Frequency (n)	Percentage (%)
Never	50	54.9
1-3 days / week	21	23.1
3-6 days / week	6	6.6
Every day	14	15.4
Summer	**Frequency (n)**	**Percentage (%)**
Never	6	6.6
1-3 days / week	32	35.2
3-6 days / week	22	24.2
Every day	31	34.1
Autumn	**Frequency (n)**	**Percentage (%)**
Never	49	53.8
1-3 days / week	25	27.5
3-6 days / week	8	8.8
Every day	9	9.9
Winter	**Frequency (n)**	**Percentage (%)**
Never	69	75.8
1-3 days / week	11	12.1
3-6 days / week	4	4.4
Every day	7	7.7

Table 6: Avoidance of going outdoors during “sunny hours” (from 12:00 p.m. to 4:00 p.m.)

Spring	Frequency (n)	Percentage (%)
Never	52	57.1
1-3 days / week	11	12.1
3-6 days / week	6	6.6
Every day	22	24.2
Summer	**Frequency (n)**	**Percentage (%)**
Never	15	16.5
1-3 days / week	23	25.3
3-6 days / week	19	20.9
Every day	34	37.4
Autumn	**Frequency (n)**	**Percentage (%)**
Never	52	57.1
1-3 days / week	15	16.5
3-6 days / week	4	4.4
Every day	20	22.0
Winter	**Frequency (n)**	**Percentage (%)**
Never	62	68.1
1-3 days / week	7	7.7
3-6 days / week	6	6.6
Every day	16	17.6

Table 7: Monthly uptake of food rich in vitamin D

Type of food	Meals per month (mean ± standard deviation)
herring / trout / salmon	3.4 (± 2.6)
mackerel / tuna	2.0 (± 2.1)
eggs / margarine	13.3 (± 7.6)
cream / gouda / butter	16.7 (± 10.4)
whole milk / quark / yoghurt	18.4 (± 9.5)
chanterelle / mushrooms / porcini mushrooms	4.2 (± 4.3)
beef or calf liver	0.4 (± 0.9)
cod liver oil	0
wine / champagne	3.9 (± 5.9)

Appendix

The Appendix is not available with this version

Figures

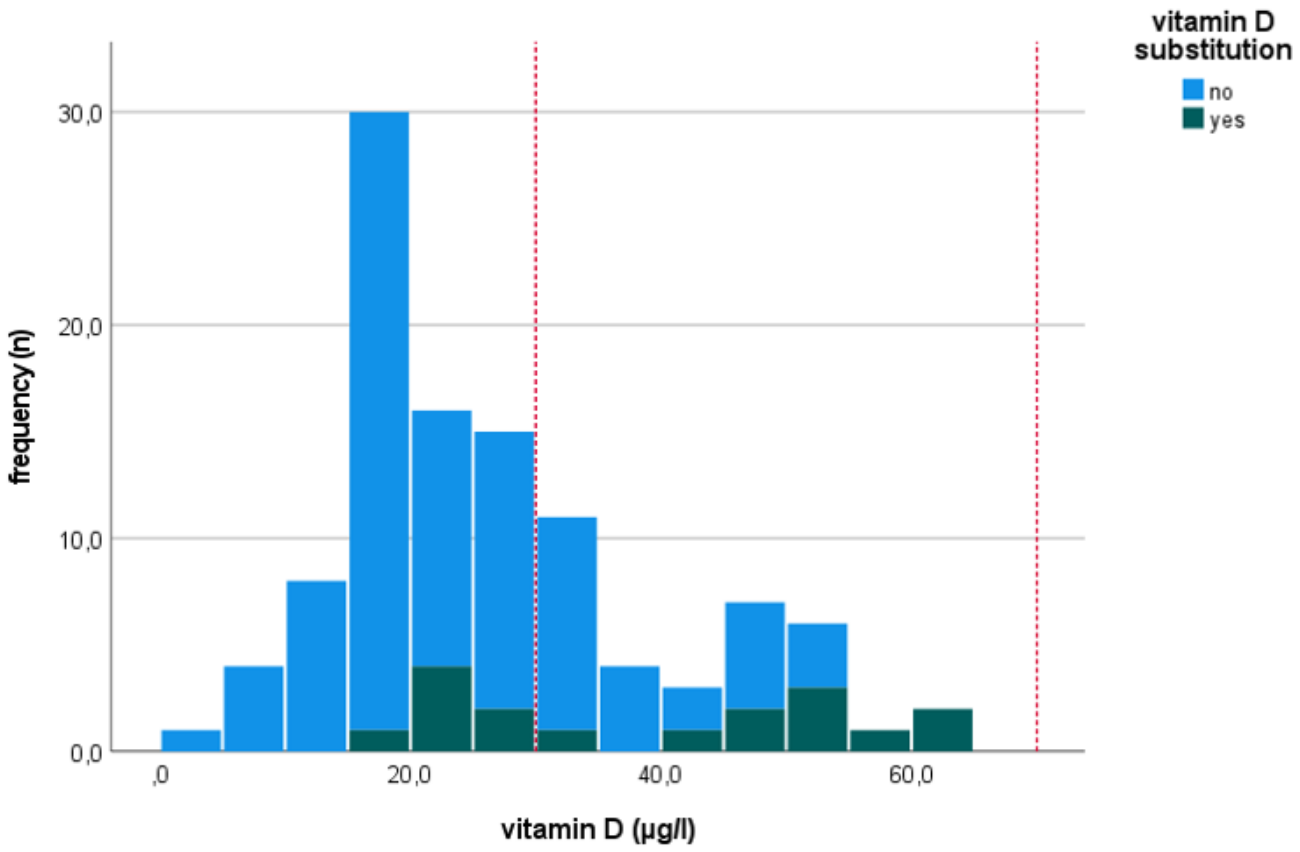

Figure 1

Serum vitamin D values (µg/l) at baseline visit in patients with and without vitamin D substitution.

Reference for standard values: 30-100 µg/l (see area in dashed red lines).

(n) = absolute frequencies

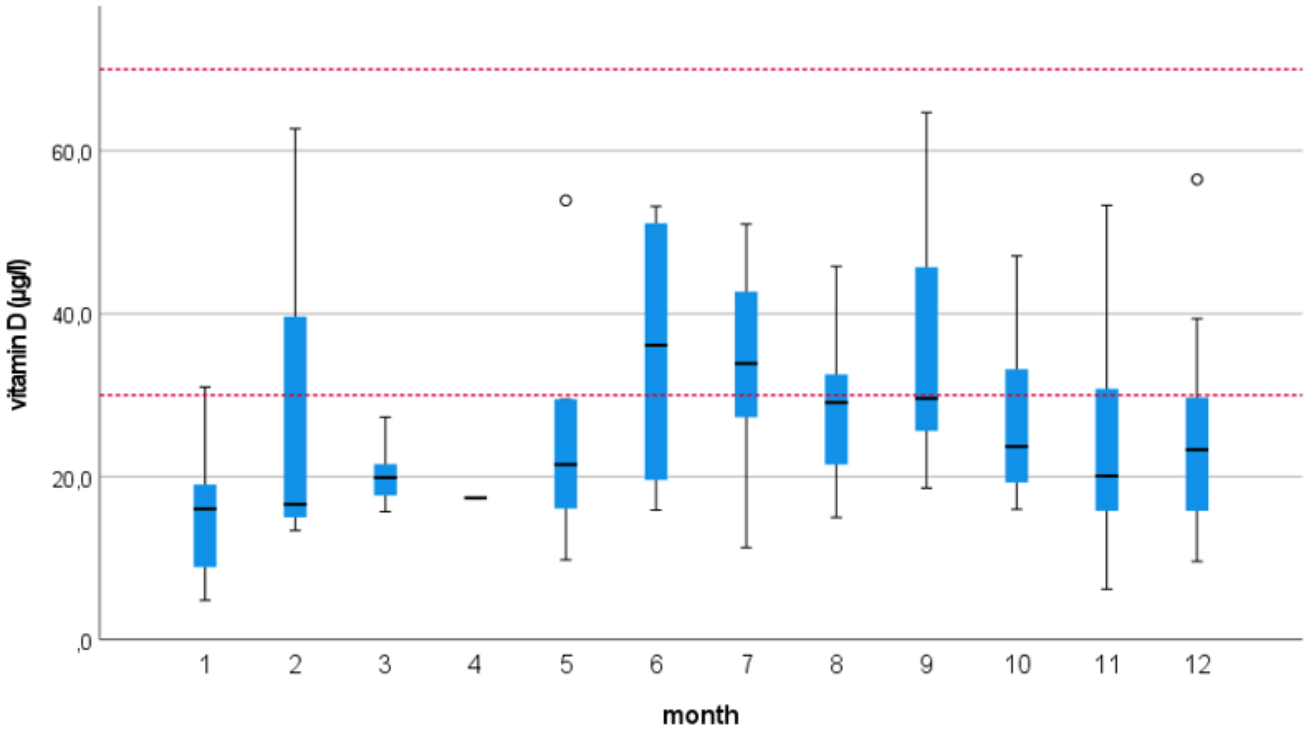

Figure 2

Month of vitamin D determination and vitamin D levels. Median vitamin D levels in spring (March, April, May) 20 µg/l, summer (June, July, August) 31 µg/l, autumn (September, October, November) 25 µg/l and winter (December, January, February) 17 µg/l.

Reference for standard vitamin D values: 30-100 µg/l (see area in dashed red lines)

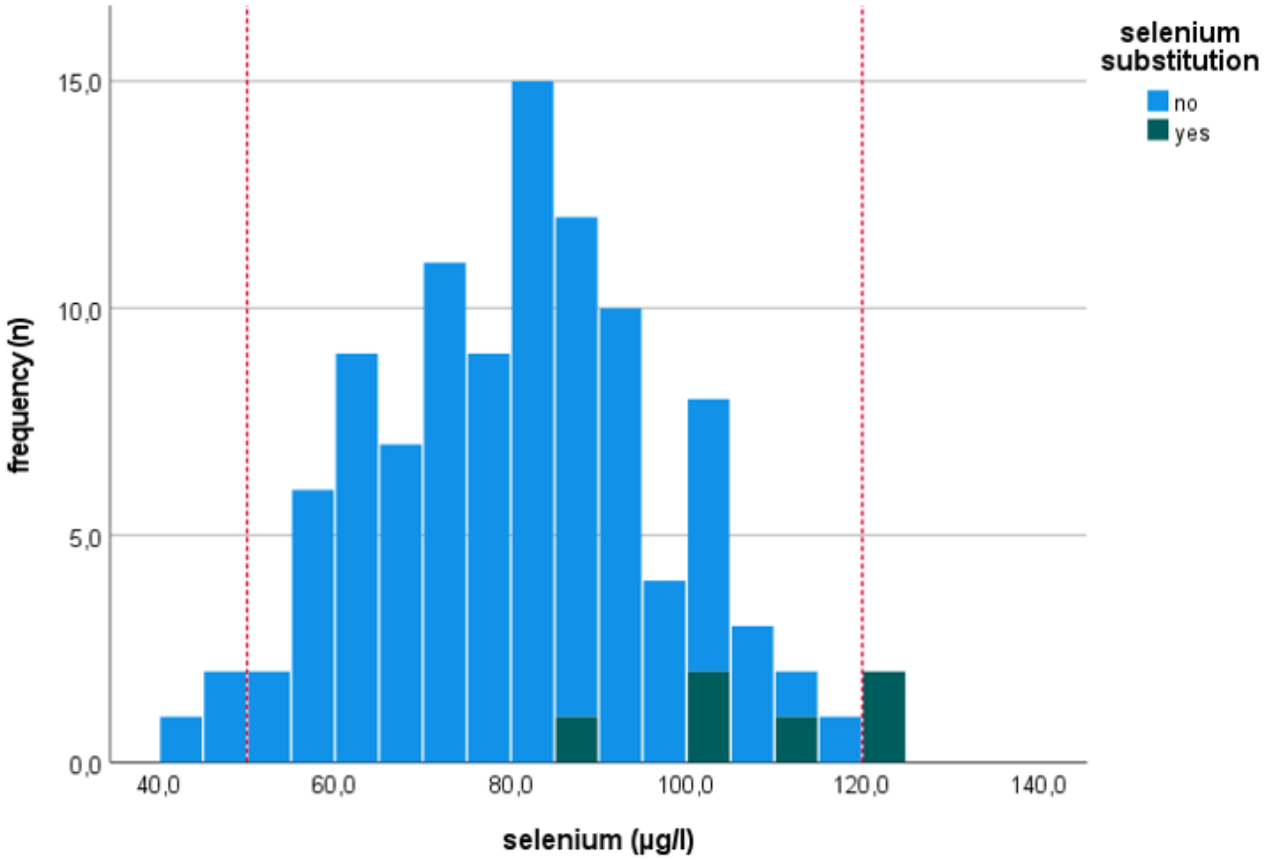

Figure 3

Serum values at baseline visit in patients with and without selenium substitution.

Reference for standard values: 50-120 µg/l (see area in dashed red lines).

(n) = absolute frequencies