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Correction of Low Vitamin D Improves Fatigue: Effect of Correction of Low Vitamin D in Fatigue Study (EViDiF Study)

Satyajeet Roy, Anthony Sherman, Mary Joan Monari-Sparks, Olga Schweiker, and Krystal Hunter[1]

Department of Medicine, Cooper University Hospital, Cooper Medical School of Rowan University, Camden, New Jersey, USA
[1]*Cooper Research Institute, Cooper University Hospital, Cooper Medical School of Rowan University, Camden, New Jersey, USA*
Address for correspondence: Dr. Satyajeet Roy, Department of Medicine, Cooper University Hospital, 1103 North Kings Highway, Suite 203, Cherry Hill, NJ 08034, USA. E-mail: roy-satyajeet@cooperhealth.edu

Abstract

Background:

Fatigue is a common presenting complaint of patients in the primary care offices. Low levels of vitamin D have been associated with fatigue in cancer patients. Normalization of vitamin D level improves their fatigue. Whether low vitamin D plays a role in fatigue in medically stable patients is not known.

Aims:

This prospective non-randomized therapeutic study observed the prevalence of low vitamin D in fatigue and the effect of normalization of vitamin D on fatigue.

Material and Methods:

One hundred and seventy four adult patients, who presented in our primary care office with fatigue and stable chronic medical conditions,completed fatigue assessment questionnaires. Patients with low vitamin D levels received ergocalciferol therapy for 5 weeks. Scores of pre- and post-treatment fatigue assessment questionnaires were compared.

Results:

Prevalence of low vitamin D was 77.2% in patients who presented with fatigue. After normalization of vitamin D levels fatigue symptom scores improved significantly ($P < 0.001$) in all five subscale categories of fatigue assessment questionnaires.

Conclusion:

The prevalence of low vitamin D is high in patients who present with fatigue and stable chronic medical conditions, if any. Normalization of vitamin D levels with ergocalciferol therapy significantly improves the severity of their fatigue symptoms.

Keywords: Ergocalciferol therapy, Fatigue in primary care, Hypovitaminosis D, Low vitamin D

Introduction

Fatigue is a common complaint of 33% patients presenting in the ambulatory primary care offices in the USA.[1] The prevalence of fatigue in the USA workforce has been estimated as 37.9% in a 2-week period.[2] Although fatigue is defined as a state of inability to maintain or sustain a force, nevertheless it is interchangeably used by the patients to describe a state of tiredness or "low energy."[3] It has significant negative impact on social life, family life, and work performance.[4] Excluding advanced systemic illness (e.g., malignancy), major organ dysfunction (e.g., stroke, congestive heart failure, chronic obstructive airway disorder, end stage liver disease, severe anemia, myxedema, end stage renal disease, advanced rheumatologic disease, etc.), or acute illness (e.g., infection, psychiatric illness); most patients with fatigue have no obvious cause. A detailed diagnostic work up of fatigue can find a specific cause in only 5%.[5]

Studies have shown an association of low vitamin D levels and fatigue in cancer patients and in patients with myasthenia gravis; and improvement in fatigue symptom scores after normalization of vitamin D levels.[6,7,8] There are many reports which indicate high prevalence of low vitamin D in the general population.[9,10] Low vitamin D leads to bone abnormalities (e.g., osteomalacia, osteopenia, and osteoporosis) and worsens muscle strength.[11] In otherwise healthy individuals, fatigue can be a manifestation of low vitamin D levels and its impact on reduced maximum functioning of skeletal muscles via vitamin D receptors.[12] Whether correction of low vitamin D alleviates fatigue in such individuals is not known. We designed this study to observe the effect of correction of low Vitamin D in patients with fatigue and stable comorbid medical condition(s), if any.

Materials and Methods

Study selection

This study was a prospective non-randomized therapeutic study that observed the effect of correction of low vitamin D in fatigue scores of the patients who presented with fatigue, stable comorbid medical condition(s) if any, and low serum 25-hydroxyvitamin D (25-OHD) levels. Patient enrolment started in May 2012 and the follow-up completed in November 2013. The study was reviewed and approved by the Institutional Review Board of the Cooper Health System, Camden, New Jersey, USA.

Adult patients between the ages of 18 and 75 who presented in our internal medicine office with fatigue as their chief complaint volunteered to enroll in the study. We excluded patients over age 75 due to several factors that are known to contribute fatigue in this age group such as, decline in the functional ability, physical health, sensorycapacity, cognitive and mental health, and socio-environmental limitations.[13] Furthermore, studies have shown a strong association between age greater than 75 and functional decline,[13] and fatigue.[11,14]

The inclusion criteria were fatigue present for greater than 4 weeks and stable chronic medical condition(s), if any. The exclusion criteria were normal level of serum 25-OHD, active or advanced cancer, advanced neurological condition (e.g., cerebrovascular disease, degenerative neurological disease, multiple sclerosis, etc.), advanced cardiac condition with poor performance state (e.g., NYHA II-IV congestive heart failure, left ventricular ejection fraction of less than 40%), advanced pulmonary disorder (e.g., chronic obstructive or restrictive airway disease requiring ambulatory oxygen therapy), chronic kidney disease (e.g., end stage renal disease requiting hemodialysis), end stage liver disease (e.g., cirrhosis), hematological disorders leading to severe anemia (hemoglobin less than 9.0 g/dl), uncontrolled endocrine disorder (e.g., uncontrolled hypothyroidism or hyperthyroidism, diabetes mellitus with glycosylated hemoglobin greater than 9%, etc.), advanced or uncontrolled rheumatologic disorder (e.g., rheumatoid arthritis, systemic lupus erythematosus, osteoarthritis, etc.), chronic fatigue syndrome, fibromyalgia, advanced multisystem disorder (e.g., sarcoidosis), pregnancy, nursing mother, inability to adhere with the instructions of the intervention (e.g., developmental disorder, mentally challenged, severe dementia, non-compliance, etc.), contraindication to

vitamin D therapy (e.g., hypercalcemia), and established sleep disorder.

Data collection

After obtaining informed consent the study physicians asked patients to complete a fatigue scale assessment questionnaire (Multidimensional Fatigue Symptom Inventory- Short Form, MFSI-SF).[15] Patients' serum 25-OHD levels were tested. All patients with low serum 25-OHD levels (less than 30 ng/ml) received oral vitamin D (Ergocalciferol 50,000 USP international unit; manufactured by Sigmapharm Laboratories, LLC, Bensalem, Pennsylvania) three times per week for 5 weeks, if not contraindicated. This therapeutic regimen has been extensively reported as safe and effective treatment.[16] Any adverse events due to ergocalciferol therapy were documented. After completion of ergocalciferol therapy all patients were asked to complete the MFSI-SF and their serum 25-OHD were retested to ensure normalization.

We collected the following data for each patient: age, gender, race, associated stable medical condition(s), use of over the counter supplemental vitamin D if any, pulse rate, blood pressure, MFSI-SF Score before treatment, serum 25-OHD level (ng/ml) before treatment, MFSI-SF Score after treatment, serum 25-OHD level (ng/ml) after treatment, and adverse effect(s) of ergocalciferol therapy.

Data synthesis and analysis

We entered the patient data in Microsoft Excel 2007 spreadsheet, and analyzed using Statistical Package for the Social Sciences (SPSS) (version 15.01). A total of 116 patients were planned for sequential sampling who presented with fatigue and low serum 25-OHD levels in order to achieve the largest sample that would provide 80% power to the study hypotheses. We used Wilcoxon paired test (nonparametric analog of the paired t test) to calculate the median difference on pre and post treatment serum 25-OHD levels assuming the distribution of difference of scores is not normal. Al-Sunduqchi (1990) showed that sample size and power calculations for the Wilcoxon test can be made using the standard t test results with a simple adjustment to the sample size. A sample size of 116 achieved 84% power to detect a 50% relative increase in serum 25-OHD levels over an average baseline of 10 ng/ml (+5 ng/ml) with a standard deviation of 10 ng/ml using a two-sided Wilcoxon test with $P \leq 0.05$ defining statistical significance and assuming that the actual distribution of post-pre differences is uniformly distributed over subjects. It should be noted that once the data was collected, we found that it was normally distributed and so for analysis, the paired t test was used to compare the mean of vitamin D levels and fatigue scores pre and post-intervention except for the comparison between pre and post-intervention physical score and total score.

Univariate analysis was done on the data. Paired t test was used to compare the mean pre- and post-intervention vitamin D levels, and fatigue scores except the physical scale. Wilcoxon Ranked Sum Test was used to compare the median pre- and post-intervention physical scale scores and total scores. Independent T Test was used to compare continuous variables between the normal and abnormal (low) vitamin D group. Pearson Chi Square and Fisher Exact tests were used to compare categorical variables between the normal and abnormal (low) vitamin D group.

Correlations were used to assess the relationship between pre-intervention vitamin D levels with the pre-intervention fatigue scores, and the relationship between post-intervention vitamin D levels with the post-intervention fatigue scores. Multivariable logistic regression was applied to assess the relationship between having a normal post-intervention serum 25-OHD level and change on total MFSI-SF adjusting for the association for the effects of demographics and stable medical condition(s) that were significant at the $P \leq 0.2$ level. The variables that were placed in the model were race, depression, and use of over-the-counter supplemental vitamin D.

Results

A total of 174 patients with fatigue completed MFSI-SF fatigue assessment questionnaires. Of Them, 171 (98.3%) patients underwent serum 25-OHD level tests while 3 (1.7%) did not. Thirty-nine (22.8%) patients were excluded due to normal levels of serum 25-OHD, and the rest 132 (77.2%) patients received vitamin D therapy [Figure 1]. The prevalence of low vitamin D was 77.2% in all 171 patients, despite the fact that 51.5% patients with low vitamin D levels were regularly taking over-the-counter vitamin D-3 between 1000 and 2000 international units [Table 1].

Baseline characteristics

All patients with fatigue were between the ages of 18 and 75. Majority of the patients were in the age range of 36 and 65 [Figure 2], female (72.4%), and non-Hispanic Caucasians (59.6%) [Table 1]. Demographics of 171 patients showed a higher prevalence of low vitamin D in the African-American patients (88.6%) and in the other race category (Asian and Hispanic patients) (85.3%), compared to 70.6% in the non-Hispanic Caucasian patients. There was no significant difference between the number of patients taking over-the-counter vitamin D-3 in low vitamin D group (51.5%) and normal vitamin D group (64.1%) ($P = 0.166$). Other factors, such as associated stable comorbid conditions, pulse and blood pressure between low vitamin D group and normal vitamin D group were comparable, except for the history of depression. Patients with history of depression were twice likely to have a normal vitamin D level than a low vitamin D level [Table 1]. After completion of vitamin D therapy 16 (12.1%) patients did not go for serum 25-OHD test; Hence, they were excluded from the study [Figure 1].

Fatigue assessment score

The MFSI-SF[15] is a 30-item form that provides scores in the empirically derived 5 subscale categories. The assessment of fatigue is based on scores on the items that are rated on a 5-point scale indicating patients' agreement to the truthfulness of each statement asking about their experience during the previous week (0 = not at all, to 4 = extremely). The MFSI-SF has excellent psychometric properties, hence it is an effective substitute for a more time consuming 83-item self-report measure (Multidimensional Fatigue Symptom Inventory).[15] The questions are randomly arranged to assess five different subscales, which include general scale, physical scale, emotional scale, mental scale, and vigor scale. Each scale has six questions, hence a possible maximum score for each subscale is 24. A high level of fatigue is indicated by high scores in general, physical, emotional, and mental scales, and low score in vigor scale. The total score is calculated by subtracting the score of vigor scale from the sum of the scores of all other scales. A high total score indicates high level of fatigue.

There was no statistically significant difference in the mean MFSI-SF scores in the general scale, emotional scale, mental scale and vigor scale; and the median MFSI-SF scores in the physical scale and total score between all 171 patients and 116 patients with low vitamin D levels at initial encounter [Table 2]. There was no significant correlation between the baseline vitamin D levels and baseline MFSI-SF scores in 171 patients; and post vitamin D therapy normalized vitamin D levels and MFSI-SF scores in 116 patients. Pearson correlation was used to calculate all except for the vitamin D levels and MFSI-SF total scores, for which Spearman Rho correlation was used.

After 5 weeks of vitamin D therapy in 116 patients, 111 (95.7%) patients achieved normal levels of serum 25-OHD and 5 (4.3%) patients required a second course of vitamin D therapy to achieve normal levels of serum 25-OHD. After ergocalciferol therapy mean serum 25-OHD level of all 116 patients normalized and significantly improved from a mean pre-treatment level of 19.71 (SD, 5.98) ng/mL to a mean post-treatment level of 52.29 (SD, 21.73) ng/mL ($P < 0.001$) [Table 2]. All patients tolerated ergocalciferol therapy well and no one experienced an adverse event.

Symptom scores after normalization of vitamin D levels

Mean MFSI-SF scores in the general scale, emotional scale, mental scale, and vigor scale; and the median MFSI-SF scores in the physical scale and total score improved significantly ($P < 0.001$) after normalization of vitamin D levels [Table 2]. The multivariate analysis showed that history of depression was the only significant factor that impacted the post-intervention vitamin D level. Patients who had a history of depression had 12 times greater odds of having a normal vitamin D level than those who did not have a history of depression (95% CI, 1.7 to 88 times).

The reasons of discontinuation and consequent exclusion from the study were non-willingness for continued participation in 3 (1.7%) patients, inability to go for serum 25-OHD test due to loss of medical insurance coverage in 7 (6.0%) patients, and protocol violation due to a significant delay in getting serum 25-OHD test in 5 (3.8%) patients.

Discussion

This prospective study of low vitamin D and fatigue demonstrated two major observations: First, a very high prevalence of low vitamin D (serum 25-OHD) in patients who complained of fatigue. Second, a significant reduction in the severity of fatigue (fatigue symptom scores) after normalization of vitamin D levels. Our strict exclusion criteria supported the observation that improvement in fatigue symptoms were primarily due to normalization of low vitamin D levels and not secondary to amelioration of the chronic medical condition(s) in patients who had one or more associated stable comorbid condition(s).

Fatigue has been associated with many adverse health outcomes. Patients who suffer from fatigue have higher mortality, morbidity, and disability especially after middle age.[17] Vitamin D is essential in calcium homeostasis. It facilitates the absorption of calcium from the intestine, reabsorption of calcium from the kidneys, and release of calcium from the skeleton.[10] A low vitamin D level reduces serum total and ionized calcium which results into increase in parathormone level, decrease in bone density, increase in bone turnover, decrease in urinary calcium excretion, increase in urinary phosphate excretion, and decrease in serum phosphate level, ultimately resulting into skeletal demineralization and muscle weakness.[18]

Fatigue is the end result of the underlying muscle fatigue, which is more commonly encountered than muscle weakness.[18] Low vitamin D is also associated with inappropriate activation of the renin-angiotensin system, which fails to inhibit abnormal cell proliferation.[19,20]

Additionally, vitamin D influences our innate immune system by enhancing the production of Human cathelicidin antimicrobial peptide, and modulates the adaptive immune system by controlling cytokine responses and T helper cell balance.[21] The overall impact of these mechanisms results into further lowering of vitamin D levels, which have been associated with fatigue in patients with cancer[6], and myasthenia gravis.[8] Low vitamin D levels are also associated with cardiovascular diseases[22,23,24,25,26], hypertension[27], congestive heart failure[28], cancer[29], diabetes mellitus[30], neuromuscular disorders[31], pneumonia[21], upper respiratory tract infections[21], chronic obstructive pulmonary disease[32], and all-cause mortality.[33] A meta-analysis of 18 randomized clinical trials concluded that vitamin D supplementation was associated with lower all-cause mortality.[33]

A survey of over 18,000 subjects in the United States' general population showed 6.7% current and 24.4% lifetime prevalence of fatigue.[34] Although fatigue is twice as common in women as in men, it is not strongly associated with age or occupation.[35] More recent analysis of 74 million adults in the United States aged 51 and above showed 31.2% prevalence of fatigue, being more in women (33.3%) than men (28.6%) and more in minorities (47.5%) than in Caucasians (27.5%).[17] In our study we found that fatigue was more common in non-Hispanic Caucasians (59.6%), and it affected about three-quarter (72.4%) of women than men.

In the USA, 41% of men and 53% of women have low vitamin D levels.[36] We observed a higher prevalence of low vitamin D (77.2%) in our patients who presented with fatigue, despite the fact that more than half of the patients were taking over-the-counter vitamin D-3 regularly. Low vitamin D may be caused by less exposure to sunlight, application of sunscreen, elevated melanin in skin, or fully covered skin.[18] A higher prevalence of low vitamin D in the African American patients (88.6%) in our study can be explained by the racial differences in vitamin D metabolism. The African American population has an increased activity of 25-hydroxyvitamin D-1-α-hydroxylase (CYP27B1), either driven by increased parathormone activity or by racial differences in CYP27B1 affinity for substrate, which results into lower serum 25-OHD levels.[37,38] Racial difference in variable vitamin D receptor affinity for vitamin D metabolites may explain similar variation in the prevalence of low vitamin D across other races with the observation of at least one vitamin D receptor polymorphism (FokI) which is known to differ by race and ethnicity.[39,40,41]

A critical review of methods and instruments that have been developed to measure fatigue found good psychometric properties in only 3 comprehensive instruments: Fatigue Symptom Inventory (FSI), Multidimensional Assessment of Fatigue (MAF), and MFSI-SF.[42] MFSI-SF is a valid, reliable and least time consuming instrument in the outpatient setting.[43,44,45,46] Functional neuroimaging offers a more objective assessment of fatigue by measuring fatigue during brain scan and correlating it with cerebral activation.[47] Its implementation as a valid paradigm is yet to be determined.

A comparison of our study results with other relevant studies showed similar observations in different settings. Correction of low vitamin D in breast cancer patients with fatigue showed improvement in fatigue and other musculoskeletal symptoms.[6,48] Similarly, improvement in fatigue scores were observed in patients with myasthenia gravis after vitamin D replacement.[8] Our findings provide a consistent body of evidence that normalization of low vitamin D levels in patients with fatigue and stable chronic medical conditions, if any, significantly improves their fatigue symptom scores. Among various therapeutic regimens of oral ergocalciferol the 50,000 international unit 3 times weekly for 5 weeks regimen has shown the highest efficacy (82%), without adverse events, or toxicity.[16,49]

Our study has some limitations. A double-blind randomized controlled trial with ergocalciferol and placebo interventions could have provided a comparative analysis, nevertheless correction of low serum 25-OHD was mandatory in all patients based on the current guidelines.

Conclusion

Normalization of low vitamin D level with ergocalciferol therapy significantly improves the severity of fatigue symptoms in adult patients who present in the primary care office with fatigue and stable chronic medical conditions, if any. With fatigue being a major presenting complaint in the primary care offices, serum 25-OHD level should be tested and low serum 25-OHD levels should be corrected with an effective ergocalciferol therapy regimen in order to improve their symptoms.

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Footnotes

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Conflict of Interest: None declared.

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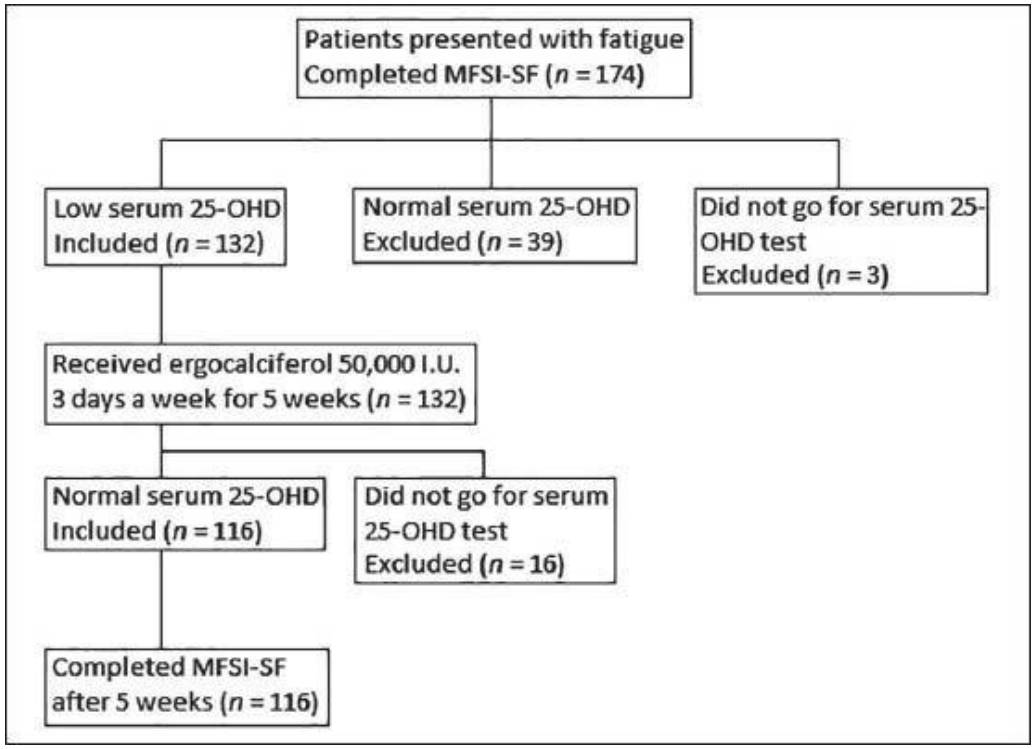
Figures and Tables

Figure 1



Study flow diagram

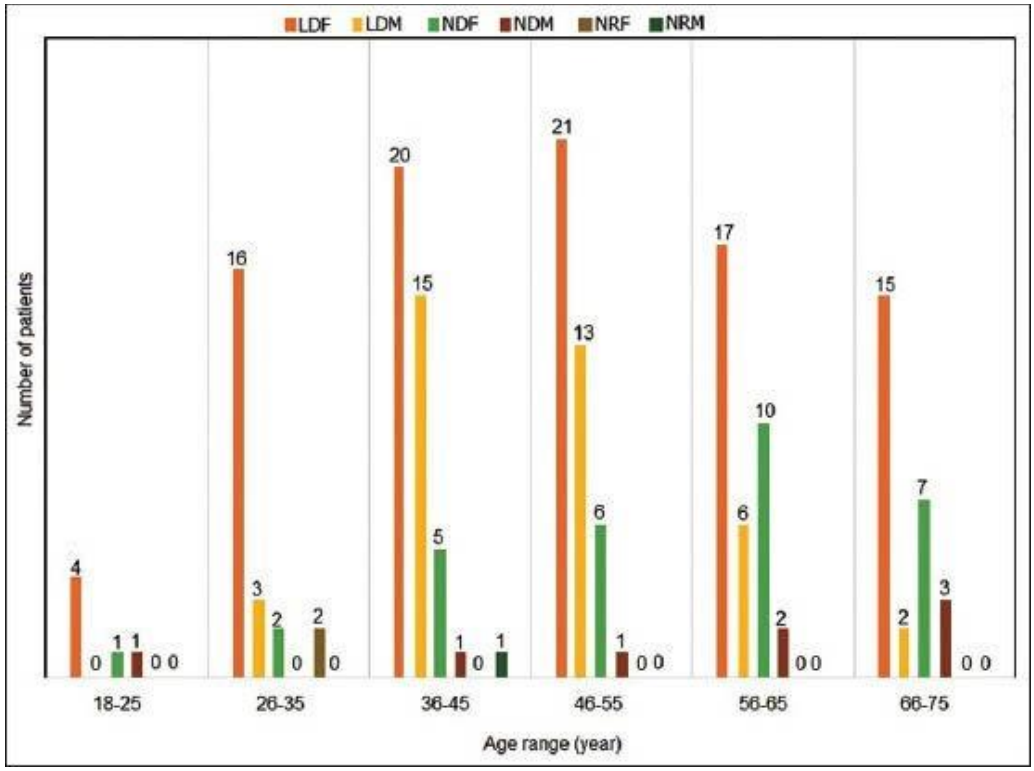
Table 1

Variable	All patients (*n* = 171)	Patients with normal vitamin D (*n* = 39)	Patients with low vitamin D (*n* = 132)
Gender			
Male, *n* (%)	47 (27.5)	8 (20.5)	39 (29.5)
Female, *n* (%)	124 (72.5)	31 (79.5)	93 (70.5)
Race			
Non-Hispanic Caucasian, *n* (%)	102 (59.6)	30 (76.9)	72 (54.5)
African-American, *n* (%)	35 (20.5)	4 (10.3)	31 (23.5)
Other, *n* (%)	34 (19.9)	5 (12.8)	29 (22.0)
Comorbid medical diagnoses			
Diabetes mellitus, *n* (%)	22 (12.9)	4 (10.3)	18 (13.6)
Hypertension, *n* (%)	61 (35.7)	12 (30.8)	49 (37.1)
Hypothyroidism, *n* (%)	26 (15.2)	6 (15.4)	20 (15.2)
Depression, *n* (%)	26 (15.2)	9 (23.1)	17 (12.9)
Congestive heart failure, *n* (%)	1 (0.6)	0 (0.0)	1 (0.8)
COPD, *n* (%)	2 (1.2)	1 (2.6)	1 (0.8)
Anemia (Hb> 9 g/dL), *n* (%)	2 (1.2)	0 (0.0)	2 (1.5)
Stable arthritic disorder, *n* (%)	13 (7.6)	3 (7.7)	10 (7.6)
Vitals			
Pulse rate (per minute), mean (SD)		78.59 (11.95)	74.81 (11.19)
Systolic BP (mmHg), mean (SD)		120.77 (14.56)	120.72 (12.89)
Diastolic BP (mmHg), mean (SD)		75.13 (11.89)	76.74 (9.08)
On OTC vitamin D, *n* (%)	93 (54.4)	25 (64.1)	68 (51.5)

COPD = Chronic obstructive pulmonary disease, Hb = Hemoglobin, BP = Blood pressure, OTC = Over-the-counter

Baseline characteristics

Figure 2



Frequency of fatigue through age ranges, gender, and vitamin D levels

(LDF = Low serum 25-OHD female, LDM = Low serum 25-OHD male, NDF = Normal serum 25-OHD female, NDM = Normal serum 25-OHD male, NRF = Did not go for serum 25-OHD test female, NRM = Did not go for serum 25-OHD test male)

Table 2

Variable	(A) All patients (n = 171)	(B) Patients with low vitamin D before vitamin D therapy (n = 116)	(C) Patients with low vitamin D after vitamin D therapy (n = 116)	(B vs. C) *P*-value
General scale, mean (SD)	16.26 (5.66)	16.10 (5.76)	8.91 (6.44)	<0.001
Physical scale, median (IQR)	8 (4 to 14)	8 (4 to 13.75)	3 (1 to 8)	<0.001*
Emotional scale, mean (SD)	8.98 (6.06)	9.14 (6.27)	5.42 (5.39)	<0.001
Mental scale, mean (SD)	8.13 (6.12)	7.89 (5.94)	5.61 (4.60)	<0.001
Vigor scale, mean (SD)	8.24 (4.27)	7.98 (4.44)	10.62 (4.79)	<0.001
Total score, median (IQR)	33 (15 to 51.5)	31.50 (14 to 53.75)	11 (-2 to 28)	<0.001*
Serum 25-OHD (ng/mL), mean (SD)		19.72 (5.98)	52.29 (21.73)	<0.001

*Wilcoxon ranked sum test used, all others paired T test used

Fatigue scores: Multidimensional fatigue symptom inventory-short form