Pain Physician 2013; 16:165-176 • ISSN 1533-3159

Prospective Evaluation

Prevalence of Vitamin D Deficiency in Patients with Lumbar Spinal Stenosis and its Relationship with Pain

Tae-Hwan Kim, MD[1], Byung Ho Lee, MD[2], Hwan-Mo Lee, MD[2], Seung-Hwan Lee, MD[2], Jin-Oh Park, MD[2], Hak-Sun Kim, MD[2], Seok Woo Kim, MD[1], and Seong-Hwan Moon, MD[2]

From: [1]Spine Center, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Korea; [2]Department of Orthopedic Surgery, Yonsei University College of Medicine, Seoul, Korea.

Address Correspondence:
Seong-Hwan Moon, MD
Department of Orthopedic Surgery, Yonsei University College of Medicine
120-752, CPO box 8044
50 Yonsei-Ro
Seodaemun-gu
Seoul, Korea
E-mail: shmoon@yuhs.ac; arthurkimo823@gmail.com

Disclaimer: There was no external funding in the preparation of this manuscript. Conflict of interest: None.

Manuscript received: 11-28-12
Accepted for publication: 12-13-12

Free full manuscript: www.painphysicianjournal.com

Background: Patients with lumbar spinal stenosis (LSS) are at a great risk of a fall and fracture, which vitamin D protects against. Vitamin D deficiency is expected to be highly prevalent in LSS patient, and pain is thought to have a profound effect on vitamin D status by limiting activity and sunlight exposure.

Objective: To identify the prevalence of vitamin D deficiency (serum 25-hydroxyvitamin D [25-OHD] < 20ng/mL) and its relationship with pain.

Study Design: Nonblinded, cross-sectional clinical study.

Setting: University-based outpatient clinic of the Department of Orthopedic Surgery, Yonsei University College of Medicine, Korea.

Methods: Consecutive patients who visited the orthopedic outpatient clinic for chronic low back pain and leg pain and were diagnosed as LSS between May 2012 and October 2012 were included. Pain was categorized into 4 groups based on location and severity: 1) mild to moderate back or leg pain; 2) severe back pain; 3) severe leg pain; and 4) severe back and leg pain. Covariates for vitamin D deficiency included age, sex, body mass index, level of education, medical history, season, region of residence, sunlight exposure score and functional disability. 25-OHD level was measured by radioimmunoassay, and bone metabolic status including bone mineral density and bone turnover markers was also measured. Multivariable logistic regression modeling was used to adjust all risk estimates for covariates.

Results: The study had 350 patients enrolled. Mean serum 25-OHD level was 15.9 ± 7.1 ng/mL (range, 2.5 ~ 36.6). of the 350 patients, 260 patients out of 350 (74.3%) were vitamin D deficient. Univariate logistic regression analysis showed a significantly higher prevalence of vitamin D deficiency in the following patients: 1) medical comorbidity; 2) urban residence rather than rural; 3) lower score for sunlight exposure; and 4) severe leg pain, or severe back and leg pain rather than mild to moderate pain. Pain category was significantly associated with lower sunlight exposure; however, the association between pain category and vitamin D deficiency remained significant even after adjustment for the sunlight exposure. Furthermore, severe back pain, and severe back and leg pain were also associated with higher incidence of osteoporosis and higher level of bone resorption marker (serum CTx).

Limitations: The limitation of our study is that due to its cross-sectional design, causal relationships between pain and vitamin D deficiency could not be established.

Conclusion: Vitamin D deficiency was highly prevalent in LSS patients (74.3%), and severe pain was associated with higher prevalence of vitamin D deficiency and osteoporosis which could be potential risk factors or a fall and fracture. As evidenced by the present study, assessment of serum 25-OHD and bone mineral density are recommended in LSS patients with severe pain, and active treatment combining vitamin D, calcium, or bisphosphonate should be considered according to the status of the bone metabolism.

Key words: Vitamin D, lumbar spinal stenosis, pain, bone mineral density

Pain Physician 2013; 16:165-176

Vitamin D performs an important physiological role in maintaining extracellular calcium ion levels, which is the prerequisite for the diverse signaling pathways related to musculoskeletal function (1,2). Vitamin D supplementation has not only a protective effect on fractures by its critical role in bone mineralization (3), but also on falls through improved muscle function (4-6). Moreover, vitamin D receptors are expressed in many other tissues beyond the musculoskeletal system, and it also plays protective physiologic roles against several chronic diseases such as cancer, osteoarthritis, diabetes, and cardiovascular conditions (7-10). Furthermore a meta-analysis showed vitamin D supplementation reduced all causes of mortality (11), and it is different from vitamin E, A, or beta-carotene which showed an increase in the mortality rate (12).

Lumbar spinal stenosis (LSS) is a common degenerative disease in the elderly, caused by impingement of the spinal canal by degenerative spurs and hypertrophy of ligaments. Patients with symptomatic LSS have an impaired walking ability (13), high turnover bone metabolism (14), and co-morbidities such as diabetes and hypertension (15), which, in part, are thought to be related to vitamin D deficiency. As a result, vitamin D deficiency is expected to be highly prevalent in LSS patients (16). This is clinically important because a vitamin D deficiency can have a deleterious impact on falls by aggravating a functional disturbance of the lower extremity eventually causing a fracture. However, there has been no study regarding the etiology of vitamin D deficiency in LSS patients.

Vitamin D is acquired mainly through the sunlight exposure (80 – 90%) and additionally through nutritional intake (10 – 20%) (17). Based on this, there have been numerous studies demonstrating the potential determinants of vitamin D deficiency in the general population (18). Age, seasons, living areas, and occupations were identified as risk factors (19). However, such risk factors seem to have only a small role as the determinant of the vitamin D level in patients with specific diseases that are directly associated with vitamin D metabolism, such as chronic renal failure, Crohn's disease, and chronic liver disease. Instead, vitamin D status was more influenced by the severity of the disease (20-22). It can be hypothesized that the degree of pain experienced by LSS patients is closely related to their vitamin D status; in other words, severe pain might hinder daily activities and consequently sunlight exposure. This assumption is in line with previous reports demonstrating the strong relationship between disease severity and vitamin D deficiency in Parkinson disease (23). A recent study also demonstrated that vitamin D was significantly correlated with functional improvement at one year postoperatively in the patients with LSS (16).

Knowledge about vitamin D levels in LSS patients might provide important clinical information, since it draws attention to the poor vitamin D levels in LSS patients and provides possible strategies to improve those levels. Therefore, the objectives of present study were to determine the prevalence of vitamin D deficiency in LSS patients and its determinants including the degree of pain.

Methods

Study Subject

A single-center cross-sectional study was performed. The study was designed according to STROBE (Strengthening the Reporting of Observational studies in Epidemiology) guidelines. Consecutive patients who visited the orthopedic outpatient clinic for chronic low back pain and leg pain and were diagnosed as LSS between May 2012 and October 2012 were included. The diagnosis of LSS was previously established with radiculopathy and neurogenic claudication with low back pain confirmed by neural canal stenosis at the relevant level based on magnetic resonance imaging (MRI). Stenotic lesion was defined as a midsagittal diameter of less than 12 mm on MRI (24). Patients were excluded if they met any of the following criteria:

1. Premenopausal women;
2. Identifiable motor weakness on both lower extremities;
3. Neurodegenerative disorders that can have an effect on walking;
4. History of fracture within one year;
5. Evidence of metabolic bone disease (hypo- or hyperparathyroidism and chronic renal disease, in particular);
6. Known rheumatoid arthritis or symptomatic osteoarthritis of the hip, knee, and ankle (Kellgren Lawrence grade III or more on x-ray);
7. Any history or sign of medical comorbidity affecting vitamin D metabolism (gastric surgery, chronic liver disease, renal failure, intestinal malabsorption, systemic infection, and neoplasm in particular);
8. Use of medications that can influence bone metabolism (anti-osteoporotic drug, corticosteroid,

hormone replacement, anticonvulsant, and products containing vitamin D, in particular); and
9. History of psychiatric disorder including depression.

The following assessments were conducted by a trained clinical research coordinator, who followed detailed testing protocols. The institutional review board of our institute approved the study protocol (No. 4-2012-0207), and informed consent was obtained from the patients.

Assessment of Pain

The assessment of pain in older adults is complex because they present with pain of varying severity, duration, and location (25). This is also true with LSS patients who present with chronic pain of varying severity in the wide region from the back to the lower extremities. For this study, assessment was done for pain occurring quite often or almost every day during the past month. Pain was then categorized by location and severity according to the previous study (26,27).

Pain location was recorded using a validated McGill Pain Map (28,29) showing the front and back of a human figure, and divided as back pain and/or leg pain. Pain severity was measured as the average pain in the past month based on a numeric rating scale (NRS), which has been validated for use in older populations with varying cognitive status, ranging from 0 to 10 (with 10 representing the worst pain) (30). Pain severity was described with location-specific ratings (for back and/or leg), and divided into categorized subgroups: mild, moderate, and severe. According to the previous study, an NRS score of 1 to 4 was used for mild pain, 5 – 6 for moderate, and 7 – 10 for severe pain (31-33). Ultimately pain was categorized into 4 groups based on location and severity:

1. Mild to moderate back or leg pain (also expressed as mild to moderate pain),
2. Severe back pain and mild to moderate leg pain (also expressed as severe back pain),
3. Severe leg pain and mild to moderate to back pain (also expressed as severe leg pain), and
4. Back and leg pain, severe in both sites (also expressed as severe back and leg pain).

Measurement of 25-Hydroxyvitamin D (25-OHD)

After an overnight fasting, a blood sample was taken between 8:30 and 9:30 AM to correct for circadian variation. Then, serum 25-OHD was measured in all 350 patients by radioimmunoassay (Diasorin, Inc., Stillwater, Minnesota, USA). The intra-assay coefficient of variation (CV) was less than 12.5% and the inter-assay CV was less than 11.0% (34) . According to the level of 25-OHD, vitamin D deficiency was defined as a 25-OHD level of less than 20 ng/ml (50 nmol/L), vitamin D insufficiency as 21 to 29 ng/ml, and a normal level as above 30 ng/ml (75 nmol/L) (35-38).

Assessment of Bone Metabolism

The following assessments were done to understand the bone metabolic status of LSS patients. Bone mineral density (BMD) of the total lumbar, total hip, and femoral neck was measured by dual-energy x-ray absorptiometry (QDR-4500A, Hologic, Waltham, MA, USA). Patients with a T score below -2.5 in at least one of the 3 sites were diagnosed with osteoporosis. After an overnight fasting, the following blood samples were taken between 8:30 and 9:30 AM to correct for circadian variation. Serum measurements included alkaline phosphatase (ALP) and osteocalcin as bone formation markers, and C-terminal telopeptide of type I collagen (CTx) as a bone resorption marker. ALP was measured using an enzymatic method (Hitachi 7600, Hitachi Co., Tokyo, Japan), and the coefficient variation (CV) was 2.88%. Osteocalcin and CTx were measured by electrochemiluminescence immunoassay using an automated instrument (Cobas 6000, Roche Diagnostics, Mannheim, Germany). The CV values for CTx were 2.97% and 1.51% at plasma levels of 0.32 and 2.77 mg/L, respectively. The CV values for osteocalcin were 0.97% and 1.06% at plasma levels of 25.3 and 84.1 mg/L, respectively.

Covariates

Sociodemographic data

Sociodemographic characteristics assessed in the interview included age, sex, and years of education. Height and weight for body mass index (BMI) were measured, and categorized as < 23, 23 to < 25, and ≥ 25 kg/m2, which are the cut-off points for normal (including underweight), overweight, and obesity for Asian populations.

Medical history

A medical history was obtained from every patient with use of a standardized questionnaire.

Region of Residence and Functional Disability by Oswestry Disability Index Scores

The region of residence was asked and dichotomized as urban and rural according to the previous study (19). Functional disability was measured by the validated Korean version of the Oswestry disability index (ODI) (version 2.0) (39) with scores ranging from 0 to 100), which is widely used for patients with LSS.

Season and Sunlight Exposure

Dates for the measurement of serum 25-OHD were recorded and categorized as spring (March to May), summer (June to August), fall (September to November), and winter (February and December). Sunlight exposure was based on a previous study (40) as a 5-point scale; a score of one was assigned to patients who avoided sunlight exposure and a score of 5 to patients who were exposed to sunlight on average for more than 30 minutes per day.

Statistical Analysis

Independent variables including pain and covariates were categorized as shown (Table 1). To explore the graded association with other variables, functional disability and bone markers were divided into 3 categories based on the 33th and 66th percentiles. Univariate logistic regression analysis was performed to identify odds ratios and their P-values for each independent variable for vitamin D deficiency (Table 1). To find the association between pain and the other covariates, data were presented according to the pain (Table 2), then, Chi-square analysis for categorical variables and analysis of the variance test for quantitative variables were done. Multivariate logistic regression models were used to investigate the association between pain category and vitamin D deficiency (Table 2). The pain category of mild to moderate pain served as a reference group. Variables significantly associated with vitamin D deficiency in the univariate analysis ($P < 0.10$) were then entered in a multivariate analysis using a logistic regression model. To identify the association between pain category and bone metabolism (osteoporosis, CTx, osteocalcin, and ALP), multivariate binary or ordinal logistic regression analysis was carried out with adjustment for age, sex, and BMI. All statistical analyses were performed using the SPSS 17.0.0 statistics package (SPSS, Inc., Chicago, IL). A value of $P < 0.05$ was accepted as significant.

Results

Patients Characteristics and Prevalence of Vitamin D Deficiency

A total of 350 patients were included in the study. Mean age of the study population was 66.1 years (range, 50 to 79). Included were 268 (76.6%) women and 82 (23.4%) men. All patients in this study were of the same ethnicity. Mean serum 25-OHD level was 15.9 ± 7.1 ng/ml (range, 2.5 ~ 36.6). Of the included patients, 74.3% (260 of 350) were vitamin D deficient, 22.9% (80 of 350) were vitamin D insufficient, and only 2.9% (10 of 350) were normal (Table 3).

Variables Associated with Vitamin D Deficiency

Univariate logistic regression analysis showed an increased prevalence of vitamin D deficiency according to medical history, region of residence, sunlight exposure score, and pain (Table 1). In detail, the prevalence of vitamin D deficiency was significantly higher in patients with

1. Medical comorbidity;
2. Urban residence;
3. Lower score for sunlight exposure; and
4. Severe leg pain or severe back and leg pain ($P < 0.05$).

The prevalence of vitamin D deficiency was not affected by age, sex, BMI, level of education, season when the blood sample was drawn, and functional disability (ODI score).

Relationship Between Pain and Other Variables Including Bone Metabolism

Pain was significantly associated with sunlight exposure scores ($P = 0.010$). The other covariates, including functional disability ($P = 0.169$), were not associated with pain (Table 2). Severe back pain and severe back and leg pain were also associated with a higher incidence of osteoporosis and higher level of bone resorption marker (serum CTx) after adjustment for age, sex, and BMI (Fig. 1a, 1b).

Prevalence of Vitamin D Deficiency According to Pain Category

After multivariate adjustment, the more severe pain category continued to be independently associat-

Table 1. *Variables associated with vitamin D deficiency.*

Variables	Category	No. of all patients	No. with vitamin D deficiency	Prevalence of vitamin D deficiency	Odds ratio	*P* value
Age (years)	50–59	72	56	77.8%	1.472 (0.764, 2.836)	0.473
	60–69	152	107	70.4%	reference	
	70–79	126	94	74.6%	1.235 (0.726, 2.101)	
Sex	Women	268	198	73.9%	1.103 (0.634, 1.918)	0.729
	Men	82	59	72.0%	reference	
Body mass index (kg/m2)	<23	114	90	78.9%	1.820 (0.986, 3.359)	0.160
	23 to <25	101	68	67.3%	reference	
	≥25	135	99	73.3%	1.335 (0.759, 2.346)	
Level of education	<High school	238	180	75.6%	1.693 (0.789, 3.631)	0.327
	High school graduate	78	55	70.5%	1.304 (0.555, 3.068)	
	>High school	34	22	64.7%	reference	
Medical history	No	109	68	62.4%	2.191 (1.337, 3.593)	0.002
	Yes	241	189	78.4%		
Season	Spring	96	77	80.2%	1.902 (0.940, 3.851)	0.273
	Summer	93	65	69.9%	1.090 (0.561, 2.118)	
	Autumn	72	49	68.1%	reference	
	Winter	89	66	74.2%	1.347 (0.678, 2.675)	
Region	Urban	244	190	77.9%	2.048 (1.246, 3.367)	0.005
	Rural	106	67	63.2%	reference	
Sunlight exposure	1–5 points				0.725 (0.596, 0.881)	0.001
Pain	mild to moderate pain	101	56	55.4%	reference	< 0.001
	severe back pain	61	45	73.8%	2.260 (1.131, 4.517)	
	severe leg pain	89	72	80.9%	3.403 (1.762, 6.573)	
	severe back and leg pain	99	84	84.8%	4.500 (2.291, 8.839)	
Functional disability (ODI scores)	first tertile (17.8–44.0)	113	79	69.9%	reference	0.362
	second tertile (44.4–58.0)	111	80	72.1%	1.134 (0.643, 1.999)	
	third tertile (60.0–98.0)	126	98	77.8%	1.477 (0.820. 2.663)	

ed with an increased prevalence of vitamin D deficiency (Fig. 2). After adjustment for medical history, region of residence, and sunlight exposure score, the association between pain and vitamin D deficiency remained significant, although severe back pain did not show a significantly increased odds ratio for vitamin D deficiency compared with mild to moderate pain ($P = 0.068$).

Discussion

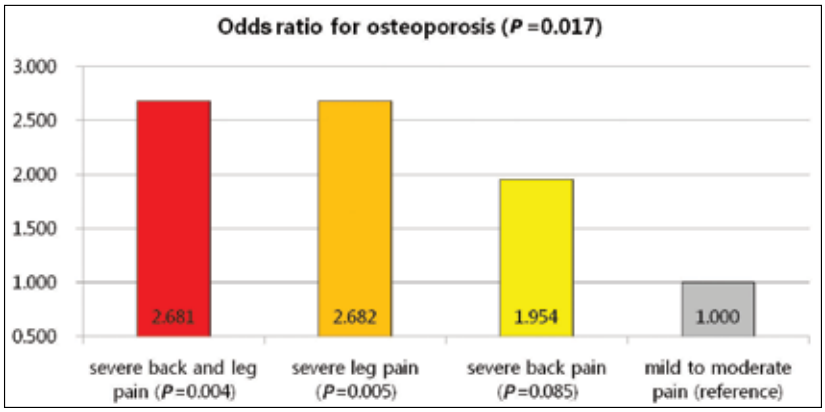
There have been consistent reports on the association between low vitamin D level and poor functional performance (41,42). Vitamin D supplementation increased muscle strength and balance (6,43), and a meta-analysis of 5 randomized clinical trials (with a

Table 2. *Relationship between pain and other covariate*

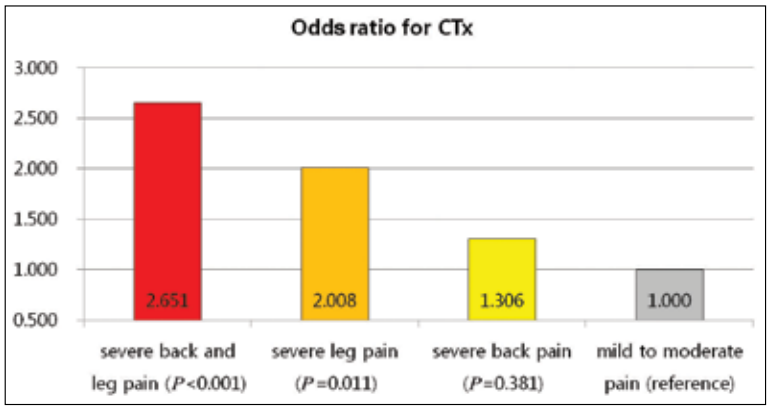
Variables	Category	mild to moderate pain	severe back pain	severe leg pain	severe back and leg pain	*P* value
No. of patients		101	61	89	99	
Age (years)	50–59	24 (23.8%)	11 (18.0%)	19 (21.3%)	18 (18.2%)	0.840
	60–69	46 (45.5%)	28 (45.9%)	35 (39.3%)	43 (43.4%)	
	70–79	31 (30.7%)	22 (36.1%)	35 (39.3%)	38 (38.4%)	
Sex	Women	75 (74.3%)	47 (77.0%)	68 (76.4%)	78 (78.8%)	0.901
	Men	26 (25.7%)	14 (23.0%)	21 (23.6%)	21 (21.2%)	
Body mass index (kg/m2)	< 23	30 (29.7%)	25 (41.0%)	25 (28.1%)	34 (34.3%)	0.289
	23 to < 25	36 (35.6%)	17 (27.9%)	22 (24.7%)	28 (28.3%)	
	≥ 25	35 (34.7%)	19 (31.1%)	42 (47.2%)	37 (37.4%)	
Level of education	<High school	65 (64.4%)	41 (67.2%)	67 (75.3%)	65 (65.7%)	0.601
	High school graduate	24 (23.8%)	16 (26.2%)	14 (15.7%)	24 (24.2%)	
	> High school	12 (11.9%)	4 (6.6%)	8 (9.0%)	10 (10.1%)	
Medical history	No	37 (36.6%)	18 (29.5%)	31 (34.8%)	23 (23.2%)	0.176
	Yes	64 (63.4%)	43 (70.5%)	58 (65.2%)	76 (76.8%)	
Season	Spring	23 (22.8%)	19 (31.1%)	25 (28.1%)	29 (29.3%)	0.137
	Summer	21 (20.8%)	20 (32.8%0	25 (28.1%)	27 (27.3%)	
	Autumn	31 (30.7%)	5 (8.2%)	18 (20.2%)	18 (18.2%)	
	Winter	26 (25.7%)	17 (27.9%)	21 (23.6%)	25 (25.3%)	
Region	Urban	70 (69.3%)	44 (72.1%)	56 (62.9%)	74 (74.7%)	0.346
	Rural	31 (30.7%)	17 (27.9%)	33 (37.1%)	25 (25.3%)	
Sunlight exposure	1–5 points	3.5 ± 1.3	2.9 ± 1.4	3.2 ± 1.2	3.0 ± 1.2	0.010
Functional disability (ODI scores)	first tertile (17.8–44.0)	42 (41.6%)	21 (34.4%)	23 (25.8%)	31 (31.3%)	0.169
	second tertile (44.4–58.0)	36 (35.6%)	18 (29.5%)	32 (36.0%)	31 (31.3%)	
	third tertile (60.0–98.0)	23 (22.8%)	22 (36.1%)	34 (38.2%)	37 (37.4%)	

Table 3. *Patients characteristics and prevalence of vitamin D deficiency*

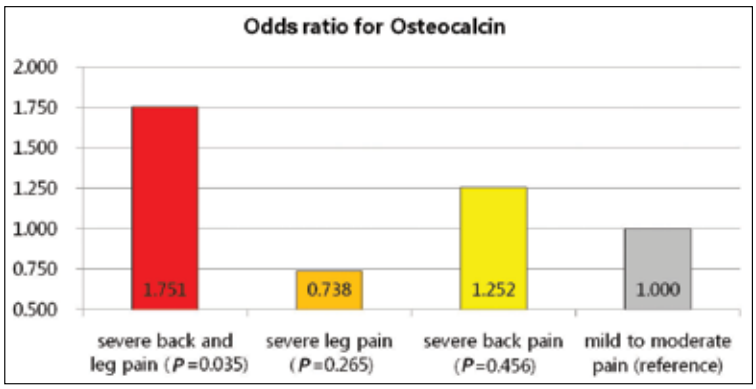
	Category	No. of patients	25–OHD level	No. of patients with vitamin D deficiency (%)	No. of patients with vitamin D insufficiency (%)	No. of patients with normal vitamin D
All patients		350	15.9 (7.1)	260 (74.3%)	80 (22.9%)	10 (2.9%)
Age	50–59	72	16.0 (7.1)	57 (79.2%)	11 (15.3%)	4 (5.5%)
	60–69	152	15.9 (6.7)	109 (71.7%)	41 (27.0%)	2 (1.3%)
	70–79	126	15.8 (7.6)	94 (74.6%)	28 (22.2%)	4 (3.2%)
Sex	Women	268	16.0 (6.6)	200 (74.6%)	60 (22.4%)	8 (3.0%)
	Men	82	15.9 (7.2)	60 (73.2%)	20 (24.4%)	2 (2.4%)
BMI	< 23	114	15.5 (7.0)	90 (79.0%)	21 (18.4%)	3 (2.6%)
	23 to < 25	101	17.2 (6.9)	71 (70.3%)	26 (25.7%)	4 (4.0%)
	≥ 25	135	15.3 (7.2)	99 (73.3%)	33 (24.4%)	3 (2.2%)



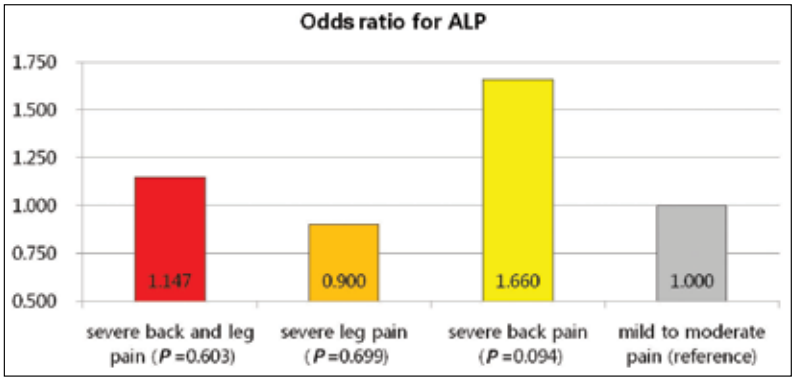
A



B



C



D

Fig. 1. *Relationship between pain category and bone metabolism. a) result of multivariate binary logistic regression analysis, adjusted for age, gender, and BMI. b), c), and d) result of multivariate ordinal logistic regression analysis, adjusted for age, gender, and BMI.*

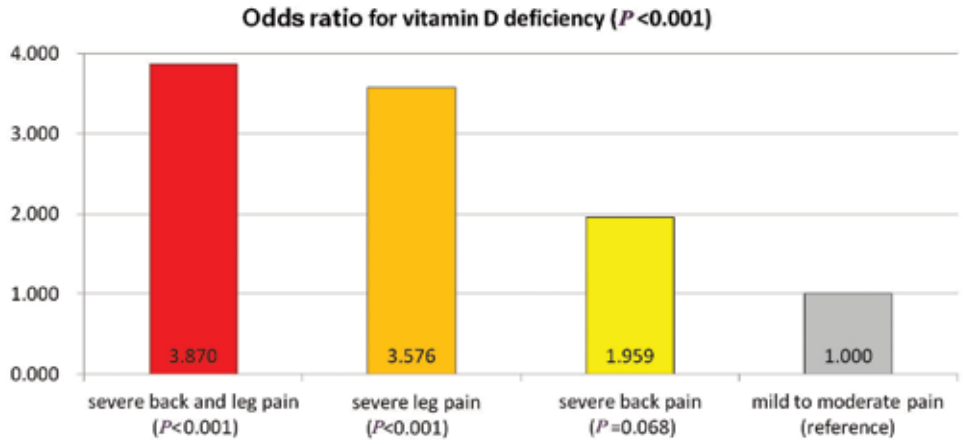


Fig. 2. *Prevalence of vitamin D deficiency according to pain category.*

total of 1,237 subjects) revealed that increased vitamin D intake reduced the risk of a fall by 22% among older individuals with stable health (44). Although the exact mechanisms of such protective effects are not well understood, increased protein synthesis in muscle through vitamin D receptor activation or myopathy of vitamin D deficiency are suggested (4,45). Vitamin D deficiency in LSS patients might render additional hazardous effects on lower extremity function, since patients already have impaired lower extremity function and increased risk of a fall by neurologic claudication and radiculopathy. Hence it is safe to say that patients with LSS might be in a vicious cycle of walking impairment and vitamin D deficiency, and vice versa.

As expected, our study showed a high prevalence of vitamin D deficiency (74.3%) in 350 LSS patients. A normal range of 25-OHD was noted in only 2.9% (10 of 350) of patients. The mean serum 25-OHD level was 15.9 ± 7.1 ng/mL (range 2.5 ~ 36.6) (Table 3). This is a significantly lower value than the domestic norm data such as the fourth Korea National Health and Nutrition Examination Surveys (KNHANES IV), which was the largest nationwide epidemiologic study of vitamin D status in Korea and assessed serum 25-OHD by the same analytical technique. According to the result of KNHANES IV, serum 25-OHD levels (mean ± standard deviation) were as follows: 22.9 ± 7.6 and 19.9 ± 7.5 each for 50- to 59-year old men and women; 23.8 ± 7.5 and 20.0 ± 7.9 each for 60- to 69-year old men and women; and 23.0 ± 8.3 and 19.0 ± 8.0 each for 70- to 79-year old men and women (19). Such low vitamin D status has another important meaning in that it is associated with low bone mineral density (46). In this case, the International Osteoporosis Foundation (47) and the Endocrine Society (48) suggested a threshold of 30 ng/mL for the reduction of falls and fractures, which LSS patients are expected to have a higher chance of, and there is a greater gap compared with our results.

The combination of pain and poor vitamin D levels of LSS patients was highlighted for the first time by the findings from the current analysis. Vitamin D deficiency was more common among patients with severe pain (severe leg pain and severe back and leg pain) compared to patients with mild to moderate pain. Furthermore, the 2 pain subgroups were associated with a higher incidence of osteoporosis (Fig. 1a) and higher bone resorption marker (CTx). Univariate logistic regression included medical history, region of residence, and sunlight exposure scores as other significant variables for vitamin D deficiency; however, demographic data including age, gender, and BMI were not associated with vitamin D deficiency in LSS patients. There was also no association between disability by ODI scores and vitamin D deficiency. Pain location, severity, and disability are closely related as key dimensions for pain assessment recommended by the American Geriatrics Society (49), and the ODI score is a widely used and validated measurement tool for disability in LSS patients (39). However, ODI scores seem not to reflect outdoor activity related to sunlight exposure in LSS patients (16,50).

Because serum 25-OHD concentration is strongly associated with sunlight exposure (17), the relationship between disease severity and serum 25-OHD level is

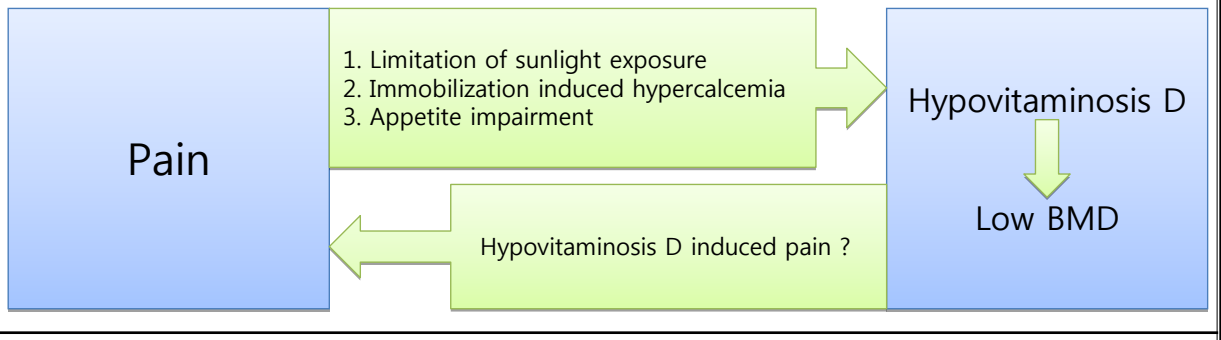


Fig. 3. *Diagram for the relationship between pain and hypovitaminosis D.*

also present in several diseases associated with patients' mobility, such as Parkinson disease (23) and peripheral arterial disease (51). In this sense, the first hypothesis for the relationship between pain and vitamin D in LSS patients (Fig. 3) is that pain, typically presented by neurologic claudication and lower leg radiculopathy in LSS patients, is also directly associated with patients' mobility, and can cause hypovitaminosis D by limiting sunlight exposure. However, in this study LSS patients demonstrated a strong association between pain and vitamin D deficiency even after adjustment for sunlight exposure, implying pain itself has a more profound effect on vitamin D status than sunlight exposure. Moreover, sunlight exposure scores failed to show significant differences within 3 severe pain categories (severe leg pain, severe back pain, and severe back and leg pain) despite their evident differences from the odds ratios for vitamin D deficiency.

The second hypothesis is an immobilization-induced hypercalemia. Hypercalcemia is closely related with immobilization (52,53) and can decrease 1,25-hydroxyvitamin D by inhibiting 1-α hydroxylase or inhibiting PTH secretion. This tendency was demonstrated in patients with Parkinson disease (23), and 25-OHD level was also significantly decreased in patients with a more advanced stage. To confirm this relationship, more precise evaluation of the bone metabolic status including serum PTH, 1,25-hydroxyvitamin D, and serum calcium is needed.

The next hypothesis is about hypovitaminosis D induced pain. There is evidence for an association between low vitamin D status and pain in the general population (54-57). The pain included chronic back pain, diffuse musculoskeletal pain or chronic widespread pain, and polymyalgia; and vitamin D was suggested as the cause of such nonspecific pain. Although low back and leg pain has definitive causes in LSS patients, the contribution of vitamin D on pain cannot be completely ignored. Therefore, it can be said that an already lower vitamin D level in patients with LSS results in increased pain perception from neurologic claudication.

The final hypothesis is that pain might be also associated with vitamin D intake. A cross-sectional study showed a strong association between chronic nonmalignant pain and decreased appetite, and appetite impairment was significantly associated with higher pain intensity scores, even adjusted for potential confounders including pain medication (58). Therefore, vitamin D intake is also expected to be low in LSS patients with severe pain. Moreover, the association between serum 25-OHD and vitamin D intake may be stronger when the influence of solar radiation is weaker, especially in areas of the world with limited UVB exposure including Korea (59-61).

Limitations

The main limitation of our study is that due to its cross-sectional design, causal relationships between pain and vitamin D deficiency could not be established. Second, sun exposure was measured indirectly by asking the duration of sunlight exposure. For estimates of self-reported individual sunlight exposure, no validated sunlight questionnaires are widely used. Moreover, regardless of the details in the questionnaire, measurement of sunlight exposure through questionnaire shows a low correlation with serum 25-OHD (62). Direct, validated, and reliable tools to quantify serum 25-OHD from sunlight might have provided more convincing evidence. Third, an investigation of

vitamin D intake was not performed. However, the known inaccuracy is always present in assessing vitamin D from existing nutrient databases (59). Moreover, there are no domestic instruments that can investigate the vitamin D intake and also no data that can be used to find the contents contained in Korean foods (60). Therefore, it was impossible to assess vitamin D intake in our study. Fourth, we did not investigate the general activity level, which can also influence vitamin D deficiency. However, in LSS patients, physical activity is expected to be closely related to disability (63) which was investigated as ODI scores in our study, and we judged that adding such a variable may weaken the power of regression analysis.

Conclusion

Vitamin D deficiency (serum 25-OHD < 20ng/ml) was highly prevalent in LSS patients (74.3%). Severe pain was associated with a higher prevalence of vitamin D deficiency and osteoporosis, which could be a potential risk factor for falls and fractures. Therefore, as evidenced by the present study, assessment of serum 25-OHD and bone mineral density are recommended in LSS patients with severe pain, and active treatment combining vitamin D, calcium, or bisphosphonate should be considered according to the status of the bone metabolism. In addition, pain in LSS patients should be targeted for aggressive treatment not only for the patients' activity of daily living but also for preventing possible bone loss.

References

1. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. *Endocr Rev* 2001; 22:477-501.
2. Bischoff HA, Stahelin HB, Urscheler N, Ehrsam R, Vonthein R, Perrig-Chiello P, Tyndall A, Theiler R. Muscle strength in the elderly: its relation to vitamin D metabolites. *Arch Phys Med Rehabil* 1999; 80:54-58.
3. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med* 1997; 337:670-676.
4. Sorensen OH, Lund B, Saltin B, Andersen RB, Hjorth L, Melsen F, Mosekilde L. Myopathy in bone loss of ageing: improvement by treatment with 1 alpha-hydroxycholecalciferol and calcium. *Clin Sci (Lond)* 1979; 56:157-161.
5. Pfeifer M, Begerow B, Minne HW, Abrams C, Nachtigall D, Hansen C. Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. *J Bone Miner Res* 2000; 15:1113-1118.
6. Pfeifer M, Begerow B, Minne HW, Suppan K, Fahrleitner-Pammer A, Dobnig H. Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. *Osteoporos Int* 2009; 20:315-322.
7. Hayes CE, Nashold FE, Spach KM, Pedersen LB. The immunological functions of the vitamin D endocrine system. *Cell Mol Biol (Noisy-le-grand)* 2003; 49:277-300.
8. Grant WB. An estimate of premature cancer mortality in the U.S. due to inadequate doses of solar ultraviolet-B radiation. *Cancer* 2002; 94:1867-1875.
9. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007; 357:266-281.
10. Hayes CE, Cantorna MT, DeLuca HF. Vitamin D and multiple sclerosis. *Proc Soc Exp Biol Med* 1997; 216:21-27.
11. Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2007; 167:1730-1737.
12. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. *Cochrane Database Syst Rev* 2012; 3:CD007176.
13. Winter C, Brandes M, Müller C, Schubert T, Ringling M, Hillmann A, Rosenbaum D, Schulte T. Walking ability during daily life in patients with osteoarthritis of the knee or the hip and lumbar spinal stenosis: a cross sectional study. *BMC Musculoskelet Disord* 2010; 11:233.
14. Lee BH, Moon SH, Kim HJ, Lee HM, Kim TH. Osteoporotic profiles in elderly patients with symptomatic lumbar spinal canal stenosis. *Indian J Orthop* 2012; 46:279-284.
15. Lotan R, Oron A, Anekstein Y, Shalmon E, Mirovsky Y. Lumbar stenosis and systemic diseases: is there any relevance? *J Spinal Disord Tech* 2008; 21:247-251.
16. Kim TH, Yoon JY, Lee BH, Jung HS, Park MS, Park JO, Moon ES, Kim HS, Lee HM, Moon SH. Changes in Vitamin D Status After Surgery in Female Patients With Lumbar Spinal Stenosis and its Clinical Significance. *Spine (Phila Pa 1976)* 2012.
17. Holick M. Evolution, biologic functions, and recommended dietary allowances for vitamin D. *Vitamin D: Physiology, Molecular Biology and Clinical Applications* 1999:1-16.
18. Mithal A, Wahl D, Bonjour JP, Burckhardt P, Dawson-Hughes B, Eisman J, El-Hajj Fuleihan G, Josse R, Lips P, Morales-Torres J. Global vitamin D status and determinants of hypovitaminosis D. *Osteoporosis Int* 2009; 20:1807-1820.
19. Choi HS, Oh HJ, Choi H, Choi WH, Kim JG, Kim KM, Kim KJ, Rhee Y, Lim SK. Vitamin D insufficiency in Korea--a greater threat to younger generation: the Korea National Health and Nutrition Examination Survey (KNHANES) 2008. *J Clin Endocrinol Metab* 2011; 96:643-651.
20. Gilman J, Shanahan F, Cashman K. Determinants of vitamin D status in adult Crohn's disease patients, with particular emphasis on supplemental vitamin D use. *Eur J Clin Nutr* 2006; 60:889-896.
21. Ishimura E, Nishizawa Y, Inaba M, Matsumoto N, Emoto M, Kawagishi T, SHOJI S, OKUNO S, Kim M, Miki T. Serum levels of 1, 25-dihydroxyvitamin D, 24, 25-dihydroxyvitamin D, and 25-hy-

droxyvitamin D in nondialyzed patients with chronic renal failure. *Kidney Int* 1999; 55:1019-1027.

22. Arteh J, Narra S, Nair S. Prevalence of vitamin D deficiency in chronic liver disease. *Dig Dis Sci* 2010; 55:2624-2628.
23. Sato Y, Kikuyama M, Oizumi K. High prevalence of vitamin D deficiency and reduced bone mass in Parkinson's disease. *Neurology* 1997; 49:1273-1278.
24. Verbiest H. The significance and principles of computerized axial tomography in idiopathic developmental stenosis of the bony lumbar vertebral canal. *Spine (Phila Pa 1976)* 1979; 4:369-378.
25. Leveille SG, Guralnik JM, Ferrucci L, Hirsch R, Simonsick E, Hochberg MC. Foot pain and disability in older women. *Am J Epidemiol* 1998; 148:657-665.
26. Leveille SG, Bean J, Bandeen-Roche K, Jones R, Hochberg M, Guralnik JM. Musculoskeletal pain and risk for falls in older disabled women living in the community. *J Am Geriatr Soc* 2002; 50:671-678.
27. Hicks GE, Shardell M, Miller R, Bandinelli S, Guralnik J, Cherubini A, Lauretani F, Ferrucci L. Associations between vitamin D status and pain in older adults: the Invecchiare in Chianti study. *J Am Geriatr Soc* 2008; 56:785-791.
28. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. *Pain* 1975; 1:277-299.
29. Escalante A, Lichtenstein MJ, Lawrence VA, Roberson M, Hazuda HP. Where does it hurt? Stability of recordings of pain location using the McGill Pain Map. *J Rheumatol* 1996; 23:1788-1793.
30. Taylor LJ, Harris J, Epps CD, Herr K. Psychometric evaluation of selected pain intensity scales for use with cognitively impaired and cognitively intact older adults. *Rehabil Nurs* 2005; 30:55-61.
31. Serlin RC, Mendoza TR, Nakamura Y, Edwards KR, Cleeland CS. When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. *Pain* 1995; 61:277-284.
32. Hanley MA, Masedo A, Jensen MP, Cardenas D, Turner JA. Pain interference in persons with spinal cord injury: classification of mild, moderate, and severe pain. *J Pain* 2006; 7:129-133.
33. Zelman DC, Hoffman DL, Seifeldin R, Dukes EM. Development of a metric for a day of manageable pain control: derivation of pain severity cut-points for low back pain and osteoarthritis. *Pain* 2003; 106:35-42.
34. Wagner D, Hanwell HE, Vieth R. An evaluation of automated methods for measurement of serum 25-hydroxyvitamin D. *Clin Biochem* 2009; 42:1549-1556.
35. Rosen CJ. Clinical practice. Vitamin D insufficiency. *N Engl J Med* 2011; 364:248-254.
36. Lee JH, O'Keefe JH, Bell D, Hensrud DD, Holick MF. Vitamin D deficiency an important, common, and easily treatable cardiovascular risk factor? *J Am Coll Cardiol* 2008; 52:1949-1956.
37. Holick MF, Siris ES, Binkley N, Beard MK, Khan A, Katzer JT, Petruschke RA, Chen E, de Papp AE. Prevalence of Vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. *J Clin Endocrinol Metab* 2005; 90:3215-3224.
38. Ginde A, Liu MC, Camargo CA. Demographic differences and trends of vitamin D insufficiency in the US population, 1988-2004. *Arch Intern Med* 2009; 169:626-632.
39. Kim D, Lee S, Lee H, Chang S, Chung S, Kim H. Validation of the Korean version of the oswestry disability index. *Spine (Phila Pa. 1976)* 2005; 30:E123-E127.
40. Isaia G, Giorgino R, Rini GB, Bevilacqua M, Maugeri D, Adami S. Prevalence of hypovitaminosis D in elderly women in Italy: clinical consequences and risk factors. *Osteoporos Int* 2003; 14:577-582.
41. Annweiler C, Schott AM, Berrut G, Fantino B, Beauchet O. Vitamin D-related changes in physical performance: a systematic review. *J Nutr Health Aging* 2009; 13:893-898.
42. Bischoff-Ferrari H, Dawson-Hughes B, Staehelin H, Orav J, Stuck A, Theiler R, Wong J, Egli A, Kiel D, Henschkowski J. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. *BMJ* 2009; 339.
43. Bischoff HA, Stahelin HB, Dick W, Akos R, Knecht M, Salis C, Nebiker M, Theiler R, Pfeifer M, Begerow B, Lew RA, Conzelmann M. Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial. *J Bone Miner Res* 2003; 18:343-351.
44. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, Staehelin HB, Bazemore MG, Zee RY, Wong JB. Effect of Vitamin D on falls: a meta-analysis. *JAMA* 2004; 291:1999-2006.
45. Schott GD, Wills MR. Muscle weakness in osteomalacia. *Lancet* 1976; 1:626-629.
46. Mezquita Raya P, Muoz-Torres M, Luna JD, Luna V, Lopez Rodriguez F, Torres Vela E, Escobar-Jimnez F. Relation between vitamin D insufficiency, bone density, and bone metabolism in healthy postmenopausal women. *J Bone Miner Res* 2001; 16:1408-1415.
47. Dawson-Hughes B, Mithal A, Bonjour JP, Boonen S, Burckhardt P, Fuleihan GE, Josse RG, Lips P, Morales-Torres J, Yoshimura N. IOF position statement: vitamin D recommendations for older adults. *Osteoporos Int* 2010; 21:1151-1154.
48. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2011; 96:1911-1930.
49. The management of persistent pain in older persons. *J Am Geriatr Soc* 2002; 50:S205-224.
50. Kim HJ, Chun HJ, Han CD, Moon SH, Kang KT, Kim HS, Park JO, Moon ES, Kim BR, Sohn JS, Shin SY, Jang JW, Lee KI, Lee HM. The risk assessment of a fall in patients with lumbar spinal stenosis. *Spine (Phila Pa 1976)* 2011; 36:E588-592.
51. Fahrleitner-Pammer A, Obernosterer A, Pilger E, Dobnig H, Dimai HP, Leb G, Kudlacek S, Obermayer-Pietsch BM. Hypovitaminosis D, impaired bone turnover and low bone mass are common in patients with peripheral arterial disease. *Osteoporos Int* 2005; 16:319-324.
52. Lawrence G, Loeffler R, Martin L, Connor T. Immobilization Hypercalcemia SOME NEW ASPECTS OF DIAGNOSIS AND TREATMENT. *J Bone Joint Surg Am* 1973; 55:87-94.
53. Stewart AF, Adler M, Byers CM, Segre GV, Broadus AE. Calcium homeostasis in immobilization: an example of resorptive hypercalciuria. *N Engl J Med* 1982; 306:1136-1140.
54. Lotfi A, Abdel-Nasser AM, Hamdy A, Omran AA, El-Rehany MA. Hypovitaminosis D in female patients with chronic low back pain. *Clin Rheumatol* 2007; 26:1895-1901.
55. Plotnikoff GA, Quigley JM. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. *Mayo Clin Proc* 2003; 78:1463-1470.
56. Al Faraj S, Al Mutairi K. Vitamin D deficiency and chronic low back pain in Saudi Arabia. *Spine (Phila Pa 1976)* 2003; 28:177-179.
57. Straube S, Andrew Moore R, Derry S,

McQuay HJ. Vitamin D and chronic pain. *Pain* 2009; 141:10-13.

58. Bosley BN, Weiner DK, Rudy TE, Granieri E. Is chronic nonmalignant pain associated with decreased appetite in older adults? Preliminary evidence. *J Am Geriatr Soc* 2004; 52:247-251.
59. Millen AE, Bodnar LM. Vitamin D assessment in population-based studies: a review of the issues. *Am J Clin Nutr* 2008; 87:1102S-1105S.
60. Kim JH, Moon SJ. Time spent outdoors and seasonal variation in serum concentrations of 25-hydroxyvitamin D in Korean women. *Int J Food Sci Nutr* 2000; 51:439-451.
61. Sullivan SS, Rosen CJ, Halteman WA, Chen TC, Holick MF. Adolescent girls in Maine are at risk for vitamin D insufficiency. *J Am Diet Assoc* 2005; 105:971-974.
62. McCarty CA. Sunlight exposure assessment: can we accurately assess vitamin D exposure from sunlight questionnaires? *Am J Clin Nutr* 2008; 87:1097S-1101S.
63. Verbunt JA, Sieben JM, Seelen HA, Vlaeyen JW, Bousema EJ, van der Heijden GJ, Knottnerus JA. Decline in physical activity, disability and pain-related fear in sub-acute low back pain. *Eur J Pain* 2005; 9:417-425.