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Is Vitamin D Deficiency a Risk Factor for the Development of Statin-Induced Myalgia in Patients Receiving Statins?

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Abstract

Objective: In recent years, discussions regarding the possibility of vitamin D deficiency playing a role in statin myopathy development have started. The purpose of this study is to determine whether or not there is a significant difference with respect to vitamin D levels and objective muscle strength measures in males with or without statin-induced myalgia.
Material and Methods: This study includes 17 male patients with statin-induced myalgia and 23 male patients without statin-induced myalgia; the latter being matched with the former. 25-OH vitamin D levels of all patients were recorded. Body fat rates of the patients were studied with bio-impedance analysis. Visual analog scale and McGill–Melzack pain questionnaire were applied to the patients with myalgia. Grip strength and isometric and isokinetic measurements on the biceps and quadriceps muscles of all patients were performed.
Results: Mean vitamin D levels were above the sufficiency level in both of the groups, and there was no significant difference between them. When the measurements with the hand dynamometer and the isometric and isokinetic muscular strength analyses for both groups were compared, there was no statistically significant difference between them.
Conclusion: In this study, it is demonstrated that vitamin D deficiency may not be a risk factor for the development of statin-induced myalgia; furthermore, there is no statistical difference between the objective muscle strength measures of male patients with or without statin-induced myalgia.
Keywords: Vitamin D, statin induced myalgia, isokinetic measurement

Introduction

Vitamin D is a hydrophobic vitamin (or hormone as it is popularly called in recent years), which is mostly synthesized in human skin by way of ultraviolet sunlight (the reason for it being called hormone) or assimilated in the body in negligible amounts by ingestion of egg yolk, some kinds of fish, and mushroom. It is then 25 hydroxylated in the liver and 1α-hydroxylated in the kidney to produce its biologically active form. In association with parathormone, vitamin D provides Ca homeostasis via its major target organs, i.e., small intestine, bone, and kidney (1). Nowadays, vitamin D deficiency is a worldwide health problem, and it is estimated that 30%–50% of the world's population is vitamin D deficient (2). It is mostly because of the industrialization of the communities resulting in an indoor life and partly

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because of the publicity regarding the malignancy-inducing effect of sunlight (3). The sufficiency level for vitamin D is 30 ng/mL, values between 20 and 30 ng/mL are called insufficiency and below 20 ng/mL are called deficiency (4).

In recent years, it has been proven that >30 different tissues, including skeletal muscle tissue express vitamin D receptors (VDR) (5). In the skeletal muscle cell, vitamin D is effective in muscle contraction and relaxation as well as in muscle cell proliferation and differentiation by VDR. Therefore, in vitamin D deficiency not only bone mineral density but also the other systems, including muscle function, are affected and an entity called osteomalacic myopathy takes place. It is characterized by diffuse muscle pain, proximal muscle weakness, difficulty in rising from a chair, and climbing up stairs (6).

It is claimed that vitamin D deficiency can play a role in statin myopathy development in the recent literature (1,7-11). Statins are used in the treatment of cardiovascular diseases with an increasing frequency over the years, and this is expected to continue (12). The most important side effect is myopathy, and it is estimated that 1.5 million people are affected worldwide every year (13-16). The mechanism of statin-derived myopathy is unknown (15), and it seems that it is worth investigating whether vitamin D deficiency is responsible or plays a role in statin-derived myopathy. The purpose of this study is to determine whether or not there is a significant difference in the means of vitamin D levels and objective muscle strength tests in statin-treated males with or without myalgia.

Material and Methods

Patients

This is a cross-sectional study. Forty male patients aged <65 years and being treated with statins for at least 1 month were enrolled in this study. Seventeen male patients who were clinically diagnosed with statin-induced myalgia were matched with 23 male patients who were treated with statins but without myalgia.

The participants were included in the study at the Physical Medicine and Rehabilitation Department of Hacettepe University Faculty of Medicine between June and August 2011. The hospital's ethical committee approval and signed informed consent of all participants were obtained.

Females were excluded from the study because of the marked effect of cultural and religious diversities of the Turkish population on the clothing style and ultimately on the vitamin D status. The other exclusion criteria were as follows: exogenous vitamin D reinforcement, factors affecting endogenous vitamin D metabolism (such as malabsorption syndromes, chronic liver/renal disease, and antiepileptic/glucocorticoid/rifampin use), factors affecting statin metabolism (such as BMI <20 m/cm^2, hypothyroidism, alcoholism, known muscle disease, and fibrate drugs/gemfibrozil/macrolide antibiotics/verapamil/diltiazem/azole/antifungals/amiadorone/cyclosporine/HIV protease inhibitors use), other clinical conditions that cause musculoskeletal pain (such as fibromyalgia syndrome, myofascial pain syndrome, tendinitis, bursitis, strain/sprain-type injuries, osteoarthritis, and radiculopathies), and last of all marked myositis and rhabdomyolysis.

Assignment

Twenty-three male patients without statin-induced myalgia and 17 male patients with statin-induced myalgia, the latter being matched with the former, were assigned to group 1 and 2, respectively. In group 2, the diagnosis of statin-induced myalgia was clinically made. Statin-induced myalgia was defined as generalized muscle pain that was more prominent at the proximal sites of the extremities and that exaggerated with exercise. It must become obvious minimally 1 week after initiating statin therapy and can be accompanied by fatigue, nocturnal cramps, and tendon pain (14-17).

Intervention

The clinical characteristics [age, occupation, height, weight, and BMI (kg/m^2)] and besides chronic diseases, drug use, dose and duration of statin therapy, and the status of exogenous vitamin D replacement were recorded for all patients. In group 2, the duration of myalgia was noted. Body fat rates of patients were measured with bio-impedance analysis. Visual analog scale (VAS) and McGill–Melzack pain questionnaire were applied to the patients with myalgia. Grip strength of all patients were measured using the Jamar hydraulic hand dynamometer (Sammons Preston, IL, USA), and isometric and isokinetic measurements of the biceps and quadriceps muscles were performed using the Biodex System 3 device (Biodex Medical Systems, New York, USA). Finally, blood samples of patients were collected for 25-OH vitamin D level analysis (Shimadzu, Kyoto, Japan). The physical examination and other evaluations of all patients were determined by the same physician

Measurements Used in the Study

VAS is a commonly used simple scale to measure pain intensity. It is a 10-cm long horizontal line. The beginning point means no pain, and the final point means the worst pain one can ever feel. The patient was instructed to mark a point on this line that fits his/her pain intensity. The point marked by the patient (measured in centimeters by a ruler) gives the result of the measurement (between 0 and 10) (18,19).

McGill–Melzack pain questionnaire is also a questionnaire that allows clinicians to measure pain. Turkish validation of the questionnaire was accomplished by Kuğuluoğlu and Eti Aslan (20) in 2003. It is comprised of four parts. In part I, the patient is instructed to mark the painful parts of his/her body on a diagram showing the front and rear parts of the human body. Part II comprises 20 sets of words, each set including 2–6 words regarding pain feelings. Every word in the 20 sets was read to the patients, and the patients were required to choose the most appropriate word that describes their pain. Finally, the pain rating index (PRI), which is the sum of the rank values of the chosen words in each set, is calculated. Part III is regarding the time of pain and factors that increase and decrease pain. Part IV is for assessing pain intensity. In this part, the patient was asked to rate his/her pain between 1 and 5 (1=mild, 2=discomforting, 3=distressing, 4=horrible, and 5=excruciating) for three different time intervals: at that moment, the time when the pain is maximal, and the time when the pain is minimal. Eventually,

three different parameters were obtained: present pain intensity (PPI) for the pain at that moment, most severe pain (MSP) for the time when the pain is maximal, and slightest pain (SP) for the time when the pain is minimal (21).

Measurement of Body Fat Rates

Body fat rates (BFR) of the participants were estimated using the Biodynamics Model 310 Body Composition Analyzer (Biodynamics Corporation, Seattle, USA). This is a medical impedance meter used in the supine position with four gel-type electrodes, two of them are current and two of them are voltage electrodes. One of the two current electrodes was placed between the first and second metatarsophalangeal joints on the dorsum of the right foot and the other was placed between the second and third metacarpophalangeal joints on the dorsum of the right hand. One of the two voltage electrodes was placed between the medial and lateral malleolus of the right foot and the other voltage electrode was placed between the right radius and ulnar styloid process (22).

Measurement of Grip Strength

The grip strengths were measured using the Jamar hydraulic hand dynamometer (Sammons Preston, IL, USA) on the dominant hand using the American Society of Hand Therapists (ASHT) protocol. The patient is seated, shoulders are adducted and neutrally rotated, elbow is flexed at 90°, forearm is in the neutral position, and wrist is between 0° and 30° dorsiflexion. The mean of the three measurements was used (23).

Isokinetic/Isometric Measurements

Isokinetic and isometric measurements were performed by the Biodex System 3 dynamometer (Biodex Medical Systems; New York, USA) on the dominant extremity for the knee extensor and elbow flexor muscles. Subjects were seated in an upright position with back support on the chair of the dynamometer. Chest, pelvis, and thigh straps were used to restrict the motion of the other parts of the body. During test, the hip joint was at 90° flexion. For knee extensor strength measurements, the axis of rotation of the dynamometer lever arm was visually aligned with the anatomical axis of the knee joint. Then, isokinetic measurements of the knee extensors were performed; patients performed five maximal knee extension repetitions at 60°/s and 10 maximal knee extension repetitions at 180°/s. Peak torque (PT) and peak torque/body weight (PT/BW) were recorded for both of the angular velocities; in addition to these, total work (TW) was recorded at 180°/s. Subsequently, for the isometric measurements of the knee extensor group, patients performed three isometric contractions at 60° for 5 s with 5-s intervals between the contractions and PT, and PT/BW were recorded. For elbow flexor strength measurements, the forearm is situated in a supinated position with the axis of rotation of the dynamometer lever arm visually aligned with the anatomical axis of the elbow joint. Then, isokinetic measurements of the elbow flexors were performed; patients performed five maximal elbow flexion repetitions at 60°/s and 10 maximal elbow flexion repetitions at 120°/s. PT and PT/BW were recorded for both of the angular velocities; in addition to these, TW was recorded at 120°/s. For the isometric measurements of the elbow flexor group, patients performed three isometric contractions at 45° for 5 s with 5-s intervals between the contractions and PT, and PT/BW were recorded (24-26).

Statistical Analysis

Descriptive statistics and regression analysis were performed with SPSS 20.0 package (SPSS Inc.; Chicago, IL, USA). All normally distributed data were expressed as mean±SD, and categorical variables were expressed as percentages. In independent samples, t-test was applied to compare the continuous variables between the groups, whereas Mann–Whitney U test was applied to compare the non-normally distributed variables. Pearson's correlation coefficient was used to evaluate the correlation between the normally distributed variables and Spearman's correlation coefficient for non-normally distributed variables. Correlation analysis was used to assess the strength of association between the pain scale results and vitamin D levels. Logistic regression analysis was used to assess the factors affecting pain severity. For all statistical tests, a p value of <0.05 was considered statistically significant.

Results

There were 40 patients enrolled in the study; 17 (42.5%) with statin-induced myalgia and 23 (57.5%) without myalgia. The clinical characteristics of patients are summarized in Table 1. No statistical differences were observed regarding age, BMI, BFR, or statin dose, type, and exposure time ($p>0.05$).

Mean 25-OH vitamin D levels of the groups with statin-induced myalgia and without myalgia were 34.8 (±11.09 ng/mL) and 31.9 (±10.98 ng/mL), respectively, and there was no statistically significant difference between them ($p=0.407$). The vitamin D levels were homogeneously distributed in both of the groups. The relation of myalgia and 25-OH vitamin D levels were evaluated by logistic regression analyses, and it was determined that the risk of myalgia in the patients with low vitamin D status is 2.71 times the risk of myalgia in the patients with normal vitamin D status (95% CI, 0.69–10.5); however, this was not statistically significant ($p=0.15$).

In the group with statin-induced myalgia, the mean values of pain scales were as follows: VAS: 4.035±2.08, PRI: 16.59±12.29, PPI: 1.41±0.507, SP: 1.18±0.529, and MSP: 2.71±1.26. The re-

Table 1. Clinical characteristics of patients

	With myalgia Mean±SD (n=17)	Without myalgia Mean±SD (n=23)	p
Age	49.1±7.9	50.6±9.0	0.589
BMI (kg/m^2)	29.5±3.5	29.4±3.5	0.897
BFR (%)	26.3±5.4	26.2±6.1	0.975
Statin dose (mg)	19.1±16.7	17.0±7.7	0.639
Statin exposure time (month)	32.9±28.4	40.4±39.4	0.606

BMI: Body mass index; BFR: body fat rate; SD: standard deviation

Table 2. The results of grip strength and isometric and isokinetic measurements

	Group without myalgia (n=17)		Group with myalgia myalgia (n=23)		
	Mean±SD	(min–max)	Mean±SD	(min–max)	p
Hand dynamometer (kg)	43.04±6.24	(32.0–54.0)	41.11±8.47	(25.0–56.0)	0.45
QIM60PT (N-m)	149.0±35.6	(80.0–205.7)	159.8±39.1	(86.2–226.7)	0.42
QIM60PT/BW (%)	161.5±31.9	(93.6–209.5)	178.7±43.6	(113–243.4)	0.19
BIM45PT (N-m)	105.1±19	(75.1–145.8)	101.5±26.3	(62.8–159.1)	0.48
BIM45PT/BW (%)	117.2±29.6	(77.1–183.6)	114.2±25.7	(68.1–178.5)	0.79
QIK60PT(N-m)	157.1±34.0	(98.7–235.9)	143.9±42.4	(85.3–252.5)	0.2
QIK60PT/BW (%)	180.6±38.1	(109.7–259.8)	166.4±34.5	(111.1–258.6)	0.18
QIK180PT (N-m)	93.8±22.7	(57.9–128.0)	88.3±26.1	(52–157)	0.33
QIK180PT/BW (%)	107.9±26.8	(67–152)	102.1±21.5	(67.8–160.9)	0.53
QIK180TW (J)	97.0±29.6	(51.9–136.8)	95.8±22.3	(58.7–135.2)	0.73
BIK60PT (N-m)	86.4±15.3	(55.4–125.6)	81±20.4	(49.3–120)	0.15
BIK60PT/BW (%)	100.1±21.4	(61.6–145.7)	95±21.8	(56.8–142.9)	0.42
BIK120PT (N-m)	68.6±16.5	(42.1–117.9)	61.7±14.0	(41.2–93.3)	0.11
BIK120PT/BW (%)	79.8±21	(40.5–114.4)	72.5±15.5	(53.6–99.3)	0.03
BIK120TW (J)	43.2±11.0	(23.7–67.5)	35.4±10.1	(20.2–62.2)	0.21

QIM 60 PT: quadriceps isometric 60° peak torque; QIM 60 PT/BW: quadriceps isometric 60° peak torque/body weight; BIM45 PT: biceps isometric 45° peak torque; BIM 45 PT/BW: biceps isometric 45° peak torque/body weight; QIK 60 PT: quadriceps isokinetic 60° peak torque; QIK 60 PT/BW: quadriceps isokinetic 60° peak torque/body weight; QIK 180 PT: quadriceps isokinetic 180° peak torque; QIK 180 PT/BW: quadriceps 180° peak torque/body weight; QIK 180 TW: quadriceps isokinetic 180° total work; BIK 60 PT: biceps isokinetic 60° peak torque; BIK 60 PT/BW: biceps isokinetic 60° peak torque/body weight; BIK 120 PT: biceps isokinetic 120° peak torque; BIK 120 PT/BW: biceps isokinetic 120° peak torque/body weight; BIK 120 TW: biceps 120° total work

Table 3. Association of pain scale results and objective muscle strength measurements in myalgia group (n=17)

	QIM60PT		QIM60PT/BW		QIK180TW		BIK120PT/BW	
	r	p	r	p	r	p	r	p
VAS	–0.519	0.033	–0.591	0.012				
PPI					–0.512	0.035		
PRI							–0.515	0.034
MSP	–0.546	0.024	–0.558	0.02				

QIM 60 PT: quadriceps isometric 60° peak torque; QIM 60 PT/BW: quadriceps isometric 60° peak torque/body weight; QIK 180 TW: quadriceps isokinetic 180° total work; BIK 120 PT/BW: biceps isokinetic 120° peak torque/body weight

lationship between the pain scale results and vitamin D levels were analyzed by correlation analysis, but there was no statistically significant relationship between them.

The analysis of the factors affecting the severity of pain was performed using logistic regression analysis. A model where the dependent variable is VAS and independent variables are age, BMI, BFR, type of statin, dose of statin, exposure time to statin, and 25-OH vitamin D levels was constructed. No statistically significant relationship was found between these variables and VAS.

The results of the grip strength measurements and isometric and isokinetic measurements performed for the knee extensor and elbow flexor muscles were summarized in Table 2. There was no statistically significant difference between the groups in the means of these measurements except for the biceps' isokinetic PT/BW.

In the statin-induced myalgia group, the correlation between muscle strength measurements and pain scales were analyzed. As a result, an inverse relationship was found between the following parameters: VAS and QIM60PT-QIM60PT/BW, PPI and QIK180TW, PRI and BIK120PT/BW, and MSP and QIM60PT-QIM60PT/BW (Table 3).

Discussion

There are a number of studies performed on the mean vitamin D status of the Turkish population, but the results of these studies are quite different. In a study by Erkal et al. (27), the 25-OH vitamin D levels of 85 males aged 21–66 years and 242 females aged 17–69 years from different parts of Turkey were analyzed. The results were 18.8 and 14.4 ng/mL, respectively. Alagöl et al. (28) performed a similar study in a group of females aged 25–30 years living in İstanbul. In this study the mean vitamin D levels were as follows: 22.4 ng/mL for women clothed in a modern style, 12.8 ng/mL for women using a headscarf, and 4 ng/mL for veiled women. On the other hand, Guzel et al. (29) evaluated 25-OH vitamin D levels of 60 females living in Adana, in the southern part of Turkey. The mean age of the study group was 25 years, and the time of the study was the end of summer. The results were 33.2 ng/mL for the veiled or head scarfed ones, whereas 54 ng/mL for the ones with modern clothes. The different results of the studies mentioned above are attributable to the differences in age, gender, clothing style, and residence of the patients involved in the studies. In our study, the mean 25-OH vitamin D levels of both groups were above the sufficiency

level. This is partly because of the season when the analyses were performed and partly because of the study population, which comprises young, active working males performing at least 1 h of outdoor activities daily.

In 2007, Goldstein (8) was the first to emphasize 25-OH vitamin D deficiency as a risk factor for statin-induced myalgia by referring to a case with fatal myopathy due to simvastatin, which was published by Boltan et al. (30). After that, in a case with a history of persistent intolerance of five different statin types, 25-OH vitamin D concentration was found to be 17 ng/mL, and vitamin D deficiency was considered to be the reason (9). In a study by Duell and Connor (10), 99 patients receiving statins were analyzed. The mean value of 25-OH vitamin D was 20.5 ng/mL in the group with myalgia, whereas it was 30.1 ng/ml in the group without myalgia. In a case series reported by Lee et al. (7), 25-OH vitamin D levels were below the sufficiency level (<30 ng/mL) in all of the 11 patients with statin-induced myalgia. Furthermore, Ahmed et al. (11) reported similar results in their study comprising 621 statin-treated patients. In this study, the mean value of serum 25-OH vitamin D level was lower in the group with myalgia (28.6±13.2 ng/mL) than in the group without myalgia (34.2±13.8 ng/mL) ($p<0.0001$). Eighty-two patients who were vitamin D deficient and had myalgia were orally administered 50000 IU of vitamin D once a week for 12 weeks, and subsequently, the resolution of myalgia occurred. Similarly, symptomatic myositis–myalgia in a group of 150 patients with hypercholesterolemia who were unable to tolerate statins was treated with 50000 IU of vitamin D twice a week for three weeks, and 131 of the 150 patients were free of myalgia thereafter (31). More recently, in 2014, in a retrospective study comprising 450 patients receiving 80 mg simvastatin daily, Mergenhagen et al. (32) found that 25-OH vitamin D levels of the myalgic group were approximately 10 ng/mL, which were lower compared with the group without myalgia. Furthermore, according to this study, myalgia was statistically more likely to occur in younger patients and in patients with a previous history of myalgia. In a retrospective study of 5526 patients, the relationship between statin-induced myalgia and vitamin D level at statin initiation was investigated and levels ≤15 ng/mL were found to have a high predictive accuracy for statin-induced myalgia. (33) In contrast, in a paper including 6808 statin users, Kurnik et al. (34) did not find any association between low 25-OH vitamin D levels and statin-induced myalgia. Riphagen (35) and Eisen (36), in 2014, also investigated the relationship between statin-induced myopathy and vitamin D deficiency and reported that myopathy and 25-OH vitamin D were unrelated. Our results are consistent with the last three papers mentioned above.

In the statin-induced myalgia group, the intensity and pattern of pain was evaluated using VAS and McGill–Melzack pain questionnaire. To the best of our knowledge, this is the only study in the literature wherein VAS and McGill–Melzack pain questionnaire were used to asses pain characteristics in patients with statin-induced myalgia.

In the literature, only Traustadóttir et al. (37) studied the objective muscle strength before and after treatment with high dose simvastatin for 12 weeks, and they did not find a statistically significant difference. These results are compatible with our study results. In our study, the objective muscle strength was measured using a hand dynamometer and isokinetic system. Only BIK120PT/BW was significantly lower in the statin-induced myalgia group; however, this result was ignored. In contrast, an inverse relationship was expectedly found between the muscle strength measurements and pain scale results: VAS and QIM60PT-QIM60PT/BW, PPI and QIK180TW, PRI and BIK120PT/BW, and MSP and QIM60PT-QIM60PT/BW.

The most important limitations of this study are the number of patients and the cross-sectional design. Future prospective, randomized, controlled studies in large patient groups should be performed to generalize the results.

Conclusion

According to our results 25-OH vitamin D levels were within the sufficiency limits (>30 ng/mL) both in patients with statin-induced myalgia and without myalgia; therefore, vitamin D deficiency may not be a risk factor for statin-induced myalgia.

Moreover, there is no statistically significant difference between the objective muscle strength measurements of patients with and without statin-induced myalgia. The muscle strength measurements are inversely related with the pain parameters in the myalgia group.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Hacettepe University.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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