Research Article

Clinical, Laboratory and Radiographic Effects of Vitamin-D Therapy in Primary Knee Osteoarthritic Patients

Youstina Abd El-Massih[1†], Nivine Darwish[1], Radwa El-Khouly[1], Amal El Bendary[2], Mohamed Mowafy[1]

ABSTRACT

Aim: To study the effect of vitamin D therapy in clinical, laboratory, and radiographic findings in primary knee osteoarthritic patients.

Patients and Methods: Study included 40 cases with primary knee Osteoarthritis (OA) and suffered from vitamin D insufficiency (equal or less than 50 nmol/L or 30 ng/ml). Patients were divided into 2 groups; group 1 received meloxicam in a dose of 15 mg daily in cases of marked knee OA for 2 months, in addition to home exercise program. group 2 received the same previous treatment in addition to vitamin D3 supplementations orally 50,000 IU/week for 6 months.

Results: There was significant improvement of degree of knee (pain, tenderness and effusion grading) and WOMAC index in group 2 after 6 months whereas the improvement in group 1 was insignificant. Regarding ultrasonographic assessment of knee cartilage degeneration, after 6 months there was insignificant difference in both groups. As regards ultrasonographic assessment of knee effusion, after 6 months there was significant improvement in group 2. As regards serum vitamin D level, after 6 months there was significant improvement in group 2 (85% had normal serum vitamin D level).

Conclusion: Before treatment, there was significant correlation between vitamin D level and age, clinical, functional parameters, and ultrasonographic findings (synovial membrane thickness and knee effusion). After vitamin D therapy there was significant improvement of serum vitamin D level and this improvement was correlated to VAS and WOMAC index.

Keywords: Vitamin D; Osteoarthritis; Ultrasound

Introduction

Osteoarthritis (OA) is a progressive joint disease which represents failed joint damage repair. Abnormalities in the articular cartilage, subchondral bone, ligaments, menisci, periarticular muscles, peripheral nerves or synovium can cause joint damage. The effect is a deterioration of cartilage and bone, which results in symptoms of pain, stiffness and functional impairment [1].

Numerous rheumatic disorders such as rheumatoid arthritis, systemic lupus erythematosus, osteoarthritis, and multiple sclerosis were associated with vitamin D deficiency [2].

Vitamin D may have direct effects on chondrocytes; Chronic vitamin D inadequacy in adults was found to have adverse effects on calcium metabolism, osteoblast activity, matrix osification and bone density and could therefore impair the bone's ability to respond optimally to OA pathophysiological processes. In addition, low levels of vitamin D are associated with decreased muscle strength and muscle mass in older men and women, which may be associated with increased knee OA risk [3].

Clinical, epidemiological and experimental studies indicate; the possible role that vitamin D can play in the clinical and functional improvement of various autoimmune diseases [4].

[1]Physical Medicine, Rheumatology and Rehabilitation, Tanta University, Tanta, Egypt

[2]Clinical Pathology, Tanta University, Egypt

[†]Author for correspondence: Youstina Abd El-Massih, Physical Medicine, Rheumatology and Rehabilitation, Medicine, Tanta University, Tanta, Egypt, E-mail: kyoustina26@gmail.com

Patient and Methods

This study was carried out on 40 cases with primary knee OA diagnosed according to clinical and radiographic findings parameters of ACR for Primary knee OA [5]. All the cases suffered from vitamin d insufficiency (equal or less than 50 nmol/L or 30 ng/ml. Causes of secondary OA, as (obesity, diabetes mellitus, fracture, trauma and operation) and other causes of vitamin D deficiency not related to arthritis as (chronic renal failure, malignancy, and patients with one of the fat malabsorption syndromes), and Patients on medications including anticonvulsants and primary hyperparathyroidism were excluded from the study. Informed consent was obtained from all subjects and the study was approved by the local ethics committee. Patients were divided into 2 groups:

■ Group 1

Received meloxicam in a dose of 15 mg daily in cases of marked knee OA for 2 months, in addition to home exercise program in form of ROM and strengthening exercises which were done 3 times daily during the period of the study

Strengthening exercise. The patients were asked to perform the following isometric quadriceps contraction (quadriceps drill) in full knee extension maintained for 5 seconds, followed by a 5-second rest; the exercise was performed for 20 repetitions per session. Straight leg raising exercise in a crock lying position (the patients were asked to tense the quadriceps muscle, elevate the limb to 45° and maintain it for 6 seconds, and lower the limb slowly and then relax for 6 seconds; the exercise was performed for three sets of 10 repetitions per session.

■ Group 2

Received the same previous treatment in addition to vitamin D3 supplementations orally 50,000 IU/week for 6 months.

Patients were subjected to full history taking, clinical examination, assessment of Knee pain by VAS (The scale was represented at 10 cm line. Its ends means the extreme pain from zero to maximum pain at 10, each patient was asked to make point on this scale representing his /her degree of pain intensity) [6], Knee tenderness by grading Scale for tenderness [7], effusion according by grading scale of the knee joint [8] and functional assessment was done using WOMAC index [9]. Laboratory investigations included Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), Complete Blood Count (CBC), liver function tests, renal function tests and serum 25(OH) vitamin D level by Enzyme-Linked Immunosorbent Assay (ELISA) [10]. Osteoarthritis severity was determined using knee plain x-ray at the start of the study evaluated according to the Kellgren and Lawrence (K and L) grading system [11].

All participants underwent sonographic examination at ultra-sound unit of physical medicine, rheumatology and rehabilitation department of Tanta University Hospital using SAMSUNG MEDI-SON (UGEO H60), with linear array transducers (7.5 Mhz-16 MHz).

■ Technique

The anterior aspect of the knee was exarnined with the patient supine. A knee flexion of 20-30 degree obtained by placing a pillow under the popliteal space. The suprapatellar synovial recess lied deep to the quadriceps tendon and the suprapatellar fat pad and superficial to the prefemoral fat. Knee effusion recorded in the supra-patellar recess and was assessed semi quantitatively [12]. The Synovial thickening was measured in millimeters [13]. Femoral trochlea was assessed with full knee flexion, the femoral V-shaped trochlea andthe overlying articular cartilage were examined on the axial planes. Cartilage degeneration of the knee joints was graded into (0, 1, 2A, 2B, 3) in the knee joint [13].

- **Grade 0:** The cartilage were subjectively evaluated as normal if they showed a monotonous anechoic band having a sharp hyperechoic anterior and posterior interfaces
- **Grade 1:** Degenerative changes (mild) were loss of the normal sharpness of cartilage interfaces and/or increased echogenicity of the cartilage (one point for each observation site, thus maximum of three points if the findings were present in both condyles and in sulcus)
- **Grade 2A:** Degenerative changes (moderate) were in addition to above changes, clear local thinning (less than 50%) of the cartilage was observed
- **Grade 2B:** Degenerative changes were: local thinning of the cartilage more than 50%

but less than 100% (two points at each observation site, maximum of six points

- **Grade 3:** Degenerative change (severe) was 100% local loss of the cartilage tissue (three points, maximum of nine points

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The Kolmogorov Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level. The used tests were: Chi-square test For categorical variables, to compare between different groups, Fisher's Exact or Monte Carlo correction for Correction for chi-square when more than 20% of the cells have expected count less than 5, Student t-test for normally distributed quantitative variables, to compare between two studied groups, Mann Whitney test.

For abnormally distributed quantitative variables, to compare between two studied groups ANOVA with repeated measures for normally distributed quantitative variables, to compare between more than two periods or stages, and Post Hoc test (LSD) (Bonferroni adjusted) for pairwise comparisons.

Results

Comparison between the two studied groups according to the different demographic data presented in **Table 1** showed that there was insignificant difference between the two studied groups at the start of the study as regards gender, age, occupation, duration of the disease and BMI. Comparison between the two studied groups as regards pain (VAS) at the start and after 6 months of the study that presented in **Table 2** showed that there was significant improvement in group 2 whereas the improvement in group 1 was insignificant.

Table 1: Comparison between the two studied groups according to the different demographic data (gender, age, occupation, duration of the disease and Body Mass Index (BMI).

	Group 1 (n=20)		Group 2 (n=20)		Test of Sig	p-value
	N	%	N	%		
Gender						
Male	3	15	3	15	χ^2=0.00	FEp=1.000
Female	17	85	17	85		
Age (years)						
Min.-Max.	40.0-73.0		40.0-63.0		t=0.319	0.752
Mean ± SD.	49.0 ± 8.62		49.80 ± 7.19			
Median		45.5	51			
Occupation						
Housewife	8	40	9	45	χ^2=0.150	0.928
Manual worker	6	30	5	25		
Office worker	6	30	6	30		
Duration of the disease (in years)						
Min.-Max.	1.0- 9.0		1.0-10.0		U=193.50	0.862
Mean ± SD.	3.55± 2.33		3.80 ±2.63			
Median	3		3.5			
BMI (Kg/m²)						
Min.-Max	25.0-30.0		25.0-30.0		t=0.747	0.459
Mean ± SD.	27.60 ± 1.79		28.05 ± 2.01			
Median	28		28.5			

χ2: Chi Square Test; FE: Fisher Exact; MC: Monte Carlo; t: Student t-test; U: Mann Whitney Test

As regards WOMAC total comparison between the two studied groups that presented in **Table 2** showed that after 6 months treatment there was significant improvement in group 2 whereas the improvement in group 1 was insignificant.

As regards effusion either detected clinical or by ultrasonography, comparison between the improvement of effusion grading in each group between the start and after 6 months of the study presented in **Tables 2 and 3** showed that After 6 months there was significant improvement in group 2 whereas the improvement in group 1 was insignificant regarding effusion.Correlation between serum vitamin d level with clinical, functional and ultrasonographic findings for both groups studied at the start of the study that presented in **Table 4** showed that before treatment, there was significant negative

Table 2: Comparison between the two studied groups as regards pain (VAS), Womac total and Effusion grading at the start and after 6 months of the study.

		Group 1 (n=20)		Group 2 (n=20)		Test of Sig	p-value
VAS	**Start of the study**						
	Min-Max	2.0-9.0		1.0-9.0		U=132.0	0.068
	Mean ± SD	6.80 ± 2.28		5.40 ± 2.56			
	Median	7		5.5			
	After 6 months						
	Min-Max	1.0-9.0		0.0-4.0		U=32.50*	<0.001*
	Mean ± SD	6.55 ± 2.48		1.90 ± 1.41			
	Median	7		2			
	Change	0.25 ± 0.55		3.50 ± 2.06		U=21.50*	<0.001*
	Zp1	0.059		<0.001*			
Womac total	**Start of the study**						
	Min-Max	14.0-64.0		18.0-63.0		U=187.0	0.738
	Mean ± SD	37.70 ± 13.27		39.40 ± 12.81			
	Median	38		37.5			
	After 6 months						
	Min-Max	13.0-66.0		0.0-40.0		U=57.0*	<0.001*
	Mean ± SD	37.20 ± 15.05		18.35 ± 11.20			
	Median	33.5		20.5			
	Change	0.50 ± 6.44		21.05 ± 13.30		U=18.50*	<0.001*
	Zp1	0.824		<0.001*			
Effusion grading	**Start of the study**						
	0	4	20	6	30	χ^2=1.722	MCp=0.715
	1	5	25	3	15		
	2	6	30	8	40		
	3	5	25	3	15		
	After 6 months						
	0	4	20	8	40	χ^2=5.223	MCp=0.16
	1	5	25	6	30		
	2	7	35	6	30		
	3	4	20	0	0		
	MHp	0.317		0.008*			

U: Mann Whitney Test; Z: Wilcoxon Signed Ranks Test; X^2: Chi Square Test; MC: Monte Carlo; MH: Marginal Homogeneity Test; P: P Value for Comparing Between The Studied Groups; P1: P Value for Comparing Between Start of the Study and After 6 Months; *: Statistically Significant at P ≤ 0.05

Table 3: Comparison between the improvement of effusion grading by ultrasonography in each group between the start and after 6 months of the study.

Effusion grading	Start of the study		After 6 months		Test of sig.	p-value
	No.	%	No.	%		
Group 1						
0	4	20	4	20	MH=1.414	0.157
1	6	30	8	40		
2	9	45	7	35		
3	1	5	1	5		
Group 2						
0	6	30	12	60	MH=3.638*	<0.001*
1	5	25	8	40		
2	9	45	0	0		
3	0	0	0	0		

Z: Wilcoxon Signed Ranks Test; P: P-Value for Comparing Between Start of the Study and After 6 Months;*: Statistically Significant

Table 4: Correlation between serum vitamin D level with clinical, functional and ultrasonographic findings for both groups studied at the start of the study.

	Vitamin D (Start of the study)	
	rs	p-value
Age	-0.377	0.016*
BMI (Kg/m²)	-0.95	<0.001*
Duration (in years)	-0.425	0.006*
VAS	-0.604	0.005*
Tenderness grading	-0.402	0.010*
Effusion grading	-0.583	<0.001*
WOMAC total	-0.458	0.043*
Effusion grading by ultrasonography	-0.649	<0.001*
Synovial thickness(in mm)	-0.649	<0.001*

Rs: Spearman Coefficient; *: Statistically Significant At P ≤ 0.05

correlation between vitamin D level and age , BMI, duration of the disease , WOMAC total, VAS, tenderness grading , effusion grading , effusion grading by ultrasonography and synovial thickness.

Discussion

Knee OA is a degenerative disease caused by biomechanical stresses which affects the articular cartilage and subchondral bone of the knee [14]. Many studies reported that vitamin D deficiency was associated with rheumatic diseases as OA, rheumatoid arthritis, systemic lupus erythematosus and multiple sclerosis [15]. Musculoskeletal ultrasonography is a promising technique for assessing soft tissue abnormalities [13]. This study included 40 cases with primary knee OA diagnosed according to clinical and radiographic findings parameters of ACR for Primary knee OA [5].

This study aimed to study the effect of vitamin D therapy in clinical, laboratory, and radiographic findings in primary knee osteoarthritic patients . In this study the age of group 1 ranged from 40.0-73.0 years with mean value of 49.0 ± 8.62 years while in group 2 the age ranged from 40.0-63.0 years with mean value of 49.80 ± 7.19. This study showed that serum vitamin D was significantly correlated with age before treatment in both groups.

These results were supported by many studies that severity and progression of OA increased with age. This concides with the results of Huskisson [16] who showed that the disease becomes symptomatic in around 15% of all adults more than 40 years of age

Ding et al. [17] showed that age was positively associated with cartilage defect of the knee. The association of aging and OA is also explained by Heijink et al. [18] who studied morphological changes in articular cartilage that was related to age and found that there is little to no division of cells in the adult articular cartilage and that with aging chondrocytes would be less sensitive to growth factors. The prevalence of cartilage defects of the knee were found in 54% of subjects after the age of 45 years, whereas the prevalence was 31% in subjects before the age of 45 years, suggesting that knee cartilage defects are cornmon in older patients. Regarding occupation, most of our patients had activities that required kneeling or squatting, heavy lifting

such as housewives and manual workers (70%) while (30%) were office workers. There was no significant difference between group 1 and group 2 as regards occupation.

Yucesoy et al. [19] described occupational factors that cause the risk of developing OA, as the common occupational risk factor for OA; is heavy physical work load, frequent exposure to several biomechanical stressors such as bending of the knee, kneeling or squatting, standing for long hours (2 hour) per day and heavy lifting. The mean values of BMI were (27.60 ± 1.79, 28.05 ± 2.01) in group 1 and group 2, respectively. There was significant positive correlation between vitamin D deficiency and BMI before treatment.

Lagari et al. [20] found an inverse correlation between serum 25(OH) D levels and fat mass index among women, suggesting that higher supplementation with vitamin D is needed as weight increases.

This may be explained on the basis that vitamin D deficiency increases the expression of the hepatic mRNA levels of TLR-2, TLR-4, and TLR-9 in tissue which are surface trans-membrane receptors, which has the important role in the pathogenesis of obesity. Their expression are increased in adipose tissue [21,22].

In our study it was found that after 6 months there was significant improvement regarding. VAS and tenderness grading in group 2 whereas the improvement in group 1 was insignificant. Many studies reported significant improvement of pain and tenderness grading after vitamin D therapy [23,24].

Heidari et al. [24] studied the effect of 50.000 IU oral cholecalciferol weekly for at least two months on patients with knee OA with deficiencies of the serum 25-OHD. At the end of the study period, knee pain decreased significantly based on VAS scores as well as WOMAC index whereas serum 25-OHD and quadriceps muscle strength increased significantly as compared with baseline. These findings indicated that correction of vitamin D deficiency in patients with knee OA exerts a significant favorable effect on knee pain and quadriceps muscle strength.

This was explained by; several lines of evidence link vitamin D to pain processes. First, vitamin D possesses immune regulatory properties that can downregulate proinflammatory cytokines and upregulate antiinflammatory cytokines, and thereby may have pain-reducing benefits. And second, vitamin D deficiency has been suggested to promote skeletal muscle hypersensitivity, resulting in enhanced pain [25].

It was found that after 6 months there was significant improvement as regards effusion grading either clinically or by ultrasonography in group 2 whereas; the irnprovement in group 1 was insignificant.

The results of our study were in agreement with Wang et al. [26] who examined the role of vitamin D supplementation for 24 months in effusion and synovitis in patients with osteoarthritic knee and low vitamin D levels and found that vitamin D supplementation could retard the progression of effusion- synovitis that can potentially benefit patients with inflamrnatory OA as vitamin D supplementation reduces the expression of pro-inflammatory cytokines in osteoarthritic patients.

Barker et al. [27] who found that after muscular injury; the anti inflammatory cytokines have increased in patients who have sufficient level of vitamin D.

In our study it was found that after 6 months there was significant improvement regarding WOMAC index in group 2 whereas the improvement in group 1 was insignificant. Our results were supported by Gao et al. [28] who found that vitamin D supplementation improved WOMAC pain and function in knee osteoarthritic patients. Manoy et al. [29] studied the effects of six months intake of vitamin D2 supplementation in a dose of 40,000 IU per week on muscle strength and physical performance in osteoarthritic patients with low levels of serum 25(OH) D (<30 ng/mL) and found that osteoarthritic patients who received vitamin D2 supplementation reduced oxidative protein damage by; decreasing levels of protein carbonyl , decreased VAS , improved life quality, and irnproved grip strength and physical perforrnance. As vitamin D supplementation reduced oxidative protein damage so it leads to cellular dysfunction and a decline in muscle function.

Conclusion

Before treatment, in primary knee osteoarthritic patients there was significant reduction of serum vitamin D level (deficiency or suboptimal values).

This reduction was significantly correlated with age, clinical, functional parameters, and ultrasonographic findings (synovial membrane thickness and knee effusion). After vitamin D therapy there was significant improvernent of serum vitamin D level and this improvement was correlated to VAS and WOMAC index. After vitamin D therapy there was significant improvement in all clinical, functional parameters in addition to improvement of degree of knee effusion assessed by ultrasonography. In primary knee osteoarthritic patients who didn't receive vitamin D therapy there was no significant differences between the baseline and final assessment of all clinical, functional and ultrasonographic parameters studied.

Conflict of Interest

None

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Ferri FF. Ferris clinical advisor 2019: 5 books in 1 (1st Edition). Elsevier (2019).
2. Munger K, Levin L, Hollis B, et al. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. Jama 296, 2832-2838 (2006).
3. Jin X, Jones G, Cicuttini F, et al. Effect of vitamin D supplementation on tibial cartilage volume and knee pain among patients with symptomatic knee osteoarthritis: a randomized clinical trial. Jama 315, 1005-1013 (2016).
4. Schoindre Y, Terrier B, Kahn J, et al. Vitamin D and autoimmunity. Second part: Clinical aspects. Rev Med Interne 33, 87-93 (2012).
5. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 29, 1039-1049 (1986).
6. Crichton N. Visual analogue scale (VAS). J Clin Nurs 10, 697-706 (2001).
7. Magee DJ. Orthopedic physical assessment (6th edition). WB Saunders Philadelphia (2014).
8. Sturgill L, Snyder-Mackler L, Manal T. Interrater reliability of a clinical scale to assess knee joint effusion. J Orthop Sports Phys Ther 39, 845-849 (2009).
9. McConnell S, Kolopack P, Davis A. The western Ontario and McMaster universities osteoarthritis index (WOMAC): A review of its utility and measurement properties. Arthritis Rheumatol 45, 453-461 (2001).
10. Zerwekh JE. Blood biomarkers of vitamin D status. Am J Clin Nutr 87, 1087S-1091S (2008).
11. Kellgren JH, Lawrence JS. Radiological assessment of osteoarthrosis. Ann Rheum Dis 16, 494-502 (1957).
12. El Miedany Y. Musculoskeletal ultrasonography in rheumatic diseases. Springer (2015).
13. Oo W, Bo M. Role of ultrasonography in knee osteoarthritis. JCR J Clin Rheumatol 22, 324-329 (2016).
14. Bonnin M, Chambat P. Osteoarthritis of the knee. Springer, Paris (2008).
15. Hawker GA, Stewart L, French MR, et al. Understanding the pain experience in hip and knee osteoarthritis-an OARSI/OMERACT initiative. Osteoarthr Cartil 16, 415-422 (2008).
16. Huskisson E. Modern management of mild-to-moderate joint pain due to osteoarthritis: A holistic approach. J Int Med Res 38, 1175-1212 (2010).
17. Ding C, Garnero P, Cicuttini F, et al. Knee cartilage defects: Association with early radiographic osteoarthritis, decreased cartilage volume, increased joint surface area and type II collagen breakdown. Osteoarthr Cartil 13, 198-205 (2005).
18. Heijink A, Gomoll AH, Madry H, et al. Biomechanical considerations in the pathogenesis of osteoarthritis of the knee. Knee Surg Sports Traumatol Arthrosc 20, 423-435 (2012).
19. Yucesoy B, Charles L, Baker B, et al. Occupational and genetic risk factors for osteoarthritis: A review. Work 50, 261-273 (2015).
20. Lagari V, Gomez-Marin O, Levis S. The role of vitamin D in improving physical performance in the elderly. JBMR 28, 2194-2101 (2013).
21. Caricilli A, Nascimento P, Pauli J, et al. Inhibition of toll-like receptor 2 expression improves insulin sensitivity and signaling in muscle of mice fed a high-fat diet. J Endocrinol 199, 399-406 (2008).
22. Canto C, Houtkooper R, Pirinen E, et al. The NAD+ precursor nicotinamide riboside enhances oxidative metabolism and protects against high-fat diet-induced obesity. Cell Metab 15, 838-847 (2012).
23. Sanghi D, Mishra A, Sharma A, et al. Does vitamin D improve osteoarthritis of the knee: A randomized controlled pilot trial. Clin Orthop Relat Res 471, 3556-3562 (2013).
24. Heidari B, Javadian Y, Babaei M, et al. Restorative effect of vitamin D deficiency on knee pain and quadriceps muscle strength in knee osteoarthritis. Acta Med Iran 53, 466-470 (2015).
25. Schlogl M, Chocano-Bedoya P, Dawson-Hughes B, et al. Effect of monthly vitamin D on chronic pain among community-dwelling seniors: A randomized, double-blind controlled trial. J Am Med Dir Assoc 20, 356- 361 (2019).
26. Wang X, Cicuttini F, Jin X, et al. Knee effusion-synovitis volume measurement and effects of vitamin D supplementation in patients with knee osteoarthritis. Osteoarthr Cartil 25, 1304-1312 (2017).
27. Barker T, Martins T, Hill H, et al. Vitamin D sufficiency associates with an increase in anti-inflammatory cytokines after intense exercise in humans. Cytokine 65, 134-137 (2014).
28. Gao X, Chen Y, Deng W. The effect of vitamin D supplementation on knee osteoarthritis: A meta-analysis of randomized controlled trials. Int J Surg 46, 14-20 (2017).
29. Manoy P, Yuktanandana P, Tanavalee A, et al. Vitamin D supplementation improves quality of life and physical performance in osteoarthritis patients. Nutrient 9, 799-811 (2017).