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Full Length Research Paper

Relationship between vitamin D and disease activity in some rheumatic diseases

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Most people are aware that vitamin D deficiency in young children can lead to rickets, a condition where the bones become weak and soft. Many of the benefits of vitamin D relate to its role in the modulation of immune system. So, vitamin D may play role in autoimmune rheumatic diseases. There are two groups: patients group and control group. The control group included 20 healthy volunteers. Patients group included 100 rheumatic patients, 30 with rheumatoid arthritis (RA), 20 with systemic lupus erythematosus (SLE), 30 with osteoartheritis (OA), 10 with Behcet's disease, 10 with ankylosing spondylitis (AS). Venous blood samples were taken for determination of erythrocyte sedimentation rate (ESR), serum 1. 25(OH) 2 D3 levels and serum C reactive protein (CRP) levels. The disease activity in different target groups was assessed using Disease Activity Score including 28 joint counts (DAS28) in RA patients, SLE disease activity index (SLEDAI) in SLE patients, Western Ontario and McMaster Universities Arthritis Criteria (WOMAC) in OA patients, The American College of Rheumatology (ACR) criteria in Behcet's patients and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) in A.S. patients. The mean value of vitamin D serum levels were significantly lower in each of RA, SLE, Behcet's disease and AS patients (mean ± SD) (13.47 ± 8.17, 19.32 ±10.67, 17.64 ±8.79 and 17.81 ±8.11 respectively) in comparison to control group (26.61 ± 6.44, p-value ≤0.05). While, There is no significance difference between the OA (22.95 ±9.3) and control groups, as p-value of 0.178. As regard the comparison of vitamin D serum level between the active RA, SLE, OA, Behcet's disease and AS patients and the inactive groups, the difference was found to be statistically insignificant (p-value >0.05). In the patients group DAS28 in RA patients, SLEDAI in SLE patients, WOMAC in OA patients, ACR criteria in Behcet's patients and BASDAI in AS were significantly higher in active groups as compared with inactive groups. In the present study no association was observed between vitamin D levels and disease activity scales DAS28, SLEDAI, WOMAC, and ACR. While there is a significant negative correlation between vitamin D levels and BASDAI. Vitamin D deficiency occurs at a higher rate in patients with RA, SLE, Behcet's disease and A.S. While, no association was observed between vitamin D levels and disease activity scales in the RA, SLE, OA, and Behcet's disease patients.

Key words: Vitamin D, immune system, rheumatic autoimmune diseases, activity and severity.

INTRODUCTION

Vitamin D is one of the fat soluble vitamins derived from Cholecalciferol (7-dehydrocholesterol, pro-vitamin D_3) in humans and from ergosterol (pro-vitamin D_2) in yeast and plants, both forms are bioactive. The main source of

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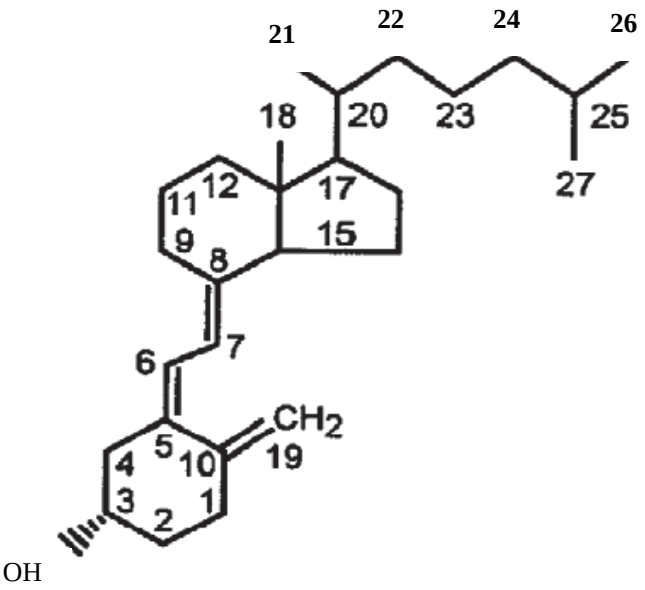

Vitamin D_3

Figure 1. Cholecalciferol (D3) (Adams, and Hewison, 2010).

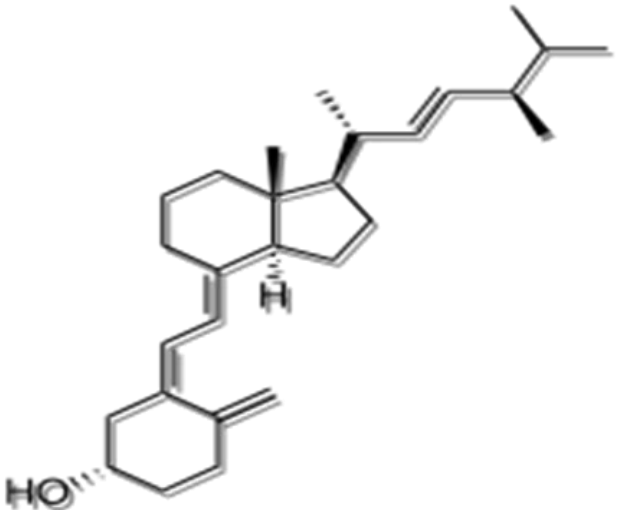

Figure 2. Ergocalciferol (D2) (Joshi et al., 2010).

vitamin D is de novo synthesis in the skin. Vitamin D_3 is produced in the skin of vertebrates after exposure to ultraviolet B light from the sun (Koyyalamudi et al., 2009) Figure 1 and 2. Vitamin D_3 (cholecalciferol) is hydroxylated in the liver at position 25 forming 25-hydroxycholecalciferol (calcidiol). This reaction is catalyzed by the microsomal enzyme vitamin D 25-hydroxylase, which is produced by hepatocytes. Once made, the product is stored in the hepatocytes until it is needed and then can be released into the plasma where it will be bound to an α-globulin (Cheng et al., 2004).

Calcidiol is then converted in the kidneys (by the enzyme 25(OH)D-1α-hydroxylase) into calcitriol (1,25-$(OH)_2D_3$), a secosteroid hormone that is the active form of vitamin D. It can also be converted into 24-hydroxycalcidiol in the kidneys via 24-hydroxylation. This product is a potent ligand of the vitamin D receptor (VDR) which mediates most of the physiological actions of the vitamin (Arnson et al., 2007) Figure 3.

The binding of calcitriol to the VDR allows the VDR to act as a transcription factor that modulates the gene expression of transport proteins (such as TRPV6 and calbindin), which are involved in calcium absorption in the intestine. The vitamin D receptor belongs to the nuclear receptor superfamily of steroid/thyroid hormone receptors, and VDRs are expressed by cells in most organs, including the brain, heart, skin, gonads, prostate, and breast. VDR activation in the intestine, bone, kidney, and parathyroid gland cells leads to the maintenance of calcium and phosphorus levels in the blood (with the assistance of parathyroid hormone and calcitonin) and to the maintenance of bone content (Holick, 2004) Figure 4.

Lack of vitamin D activity leads to reduced intestinal absorption of calcium and phosphorus. Early in hypovitaminosis D, hypophosphatemia is more marked than hypocalcemia. With persistent hypovitaminosis D, hypocalcemia causes a secondary hyperparathyroidism that leads to phosphaturia, demineralization of bones, and without treatment, to osteomalacia in adults and rickets in children. Glucocorticoids, when used chronically in high doses, inhibit the intestinal vitamin D dependent calcium absorption and therefore cause osteomalacia. Sub clinical vitamin D deficiency (or vitamin D insufficiency) is extremely common and may contribute to the development of osteoporosis. Vitamin D stores decline with age, especially in the winter. Controlled trials have demonstrated that vitamin D and calcium supplementation can reduce the risk of falls and fractures in the elderly (Misra et al., 2008).

1,25-dihydroxyvitamin D_3, the biologically active metabolite of Vitamin D_3, not only regulates bone and calcium metabolism but also exerts immunomodulation via the nuclear VDR expressed in antigen-presenting cells and activated T/B cells (Van Etten and Mathieu, 2005). The effect of vitamin D on the immune system is an enhancement of innate immunity coupled with multifaceted regulation of adaptive immunity (Adorini and Penna, 2008). The discovery of the vitamin D receptors (VDR) in the cells of the immune system and the fact that several of these cells produce vitamin D hormone suggested that it could have immunoregulatory properties (Sigmundsdottir et al., 2007) Figure 5, Table 1.

However, vitamin D insufficiency is emerging as a clinical problem of global proportions and epidemiology has linked vitamin D status with autoimmune disease susceptibility and severity, epidemiological evidence indicates a significant association between vitamin D deficiency and an increased incidence of a variety of autoimmune rheumatic diseases such as rheumatoid

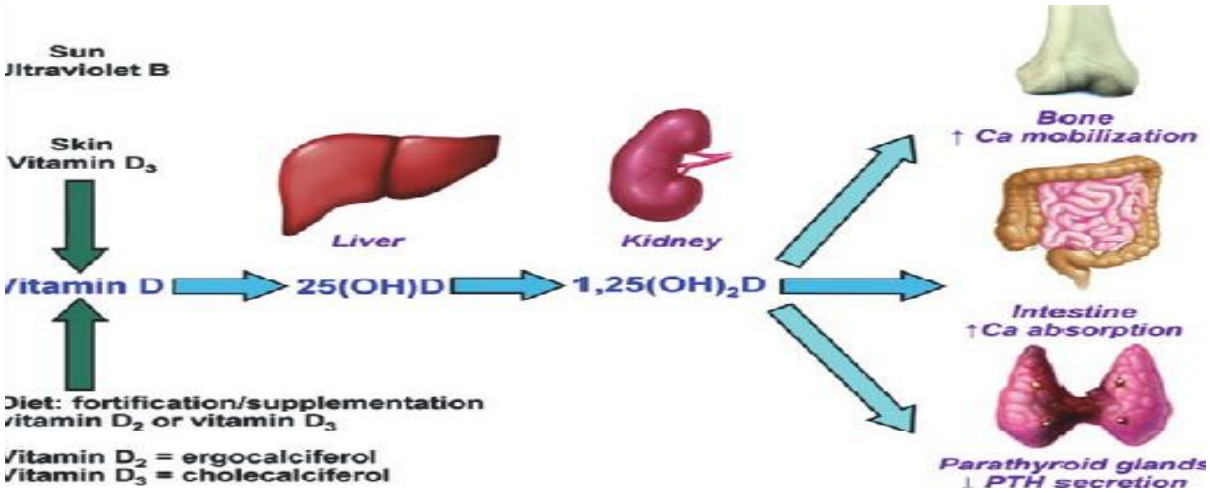

Figure 3. Mechanism of synthesis of vitamin D: 1, 25 dihydroxyvitamin D (Cheng et al., 2004).

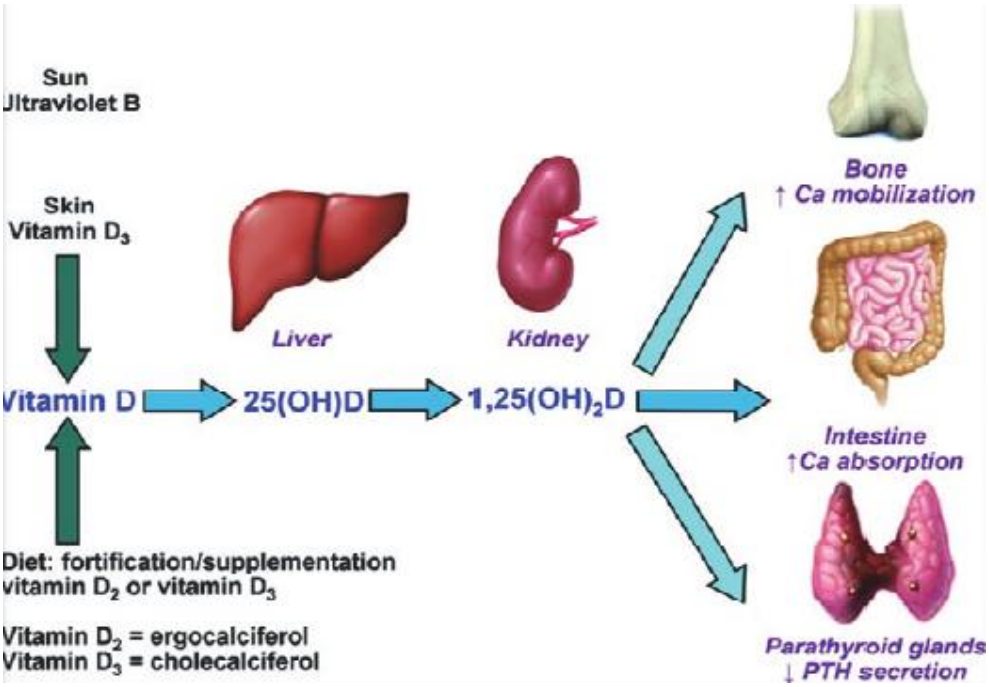

Figure 4. Role of synthesis and metabolism of Vitamin D in the regulation of calcium and bone mineralization (Holick et al., 2007).

arthritis (RA) and SLE (Adorini and Penna, 2008). Observational studies in humans suggest an association between vitamin D deficiency and many rheumatological and non-rheumatological disorders listed in Table 2.

Low serum levels of vitamin D_3 might be partially related, among other factors, to prolonged daily darkness (reduced activation of the pre-vitamin D by the ultraviolet B sunlight), different genetic background (that is, vitamin D receptor polymorphism) and nutritional factors, and explain to the latitute-related prevalence of autoimmune diseases such as RA, by considering the potential immunosuppressive roles of vitamin D. Treatment of vitamin D deficiency could be particularly important in SLE patients due to concomitant insults on their tissues such as bone, and in view of the discovered immuno-modulatory effects exerted by vitamin D (Cutolo, 2008). Low sun exposure and reduced body mass index (BMI) are well established risk factors for vitamin D deficiency in RA patients (Rossini et al., 2010). Few studies have examined dietary or nutritional intake prior to RA onset,

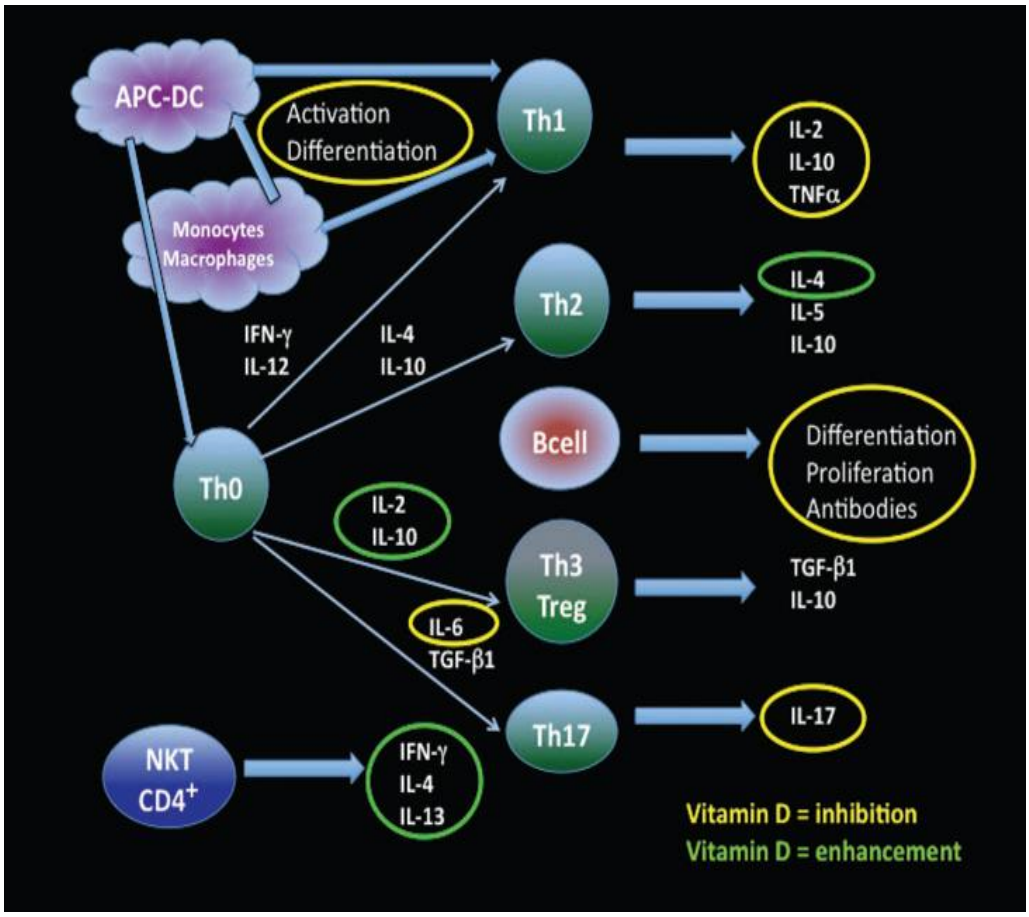

Figure 5. Mechanisms involved in vitamin D modulation of the immune responses. Dendritic cells (DCs) are primary targets for the immunomodulatory activity of 1,25(OH)2D3, as indicated by inhibited DC differentiation and maturation, together with inhibition of differentiation of monocyte precursors into immature DCs. 1,25(OH)2D3 suppresses Th1 (and Th17) driven cytokine responses, induces Treg cells, induces IL-4 production (Th2) and enhances NKT-cell function. Differentiation and maturation of B cells is also inhibited. Th are CD4þ helper cell subsets (Th1, Th2, Th3-Treg, Th17) originating from naı¨ve T cell (Th0). Thin arrows (left) indicate cytokines that induce differentiation of Th0 cells and thicker arrows (right) indicate cytokines produced by activated Th cell subsets. All T cells that have been tested express the VDR. B cells and NKT cells are also reported.The yellow circles indicate the cytokines/activities inhibited by vitamin D. On the contrary, the green circles indicate the cytokines enhanced by vitamin D. (Sigmundsdottir et al., 2007).

and none have assessed the association of vitamin D with disease onset. Merlino et al. (2004) found that greater intake of total daily vitamin D was inversely associated with risk of RA. Inverse associations were apparent for both dietary and supplemental vitamin D.

Several studies have demonstrated a higher prevalence of vitamin D deficiency in SLE patients when compared to individuals with other rheumatologic diseases and healthy controls (Borba et al., 2009). The inflammatory activity in ankylosing spondylitis (AS) itself plays a major role in the pathophysiology of bone loss; this may be mediated in AS by substances regulating both the inflammatory process and bone turnover. High levels of pro-inflammatory cytokines such as interleukin-1 and tumor necrosis factor α (TNFα) are thought to play a major role in chronic inflammation and act on osteoblasts and osteoclasts (Lange et al., 2005). Osteoporosis is frequent in AS and high disease activity assessed by Bath ankylosing spondylitis disease activity index (BASDAI) is associated with an alteration in vitamin D metabolites and increased levels of bone resorption (Braun-Moscovici et al., 2008) .

Zold et al. (2008) demonstrated the presence of a seasonal variation in the levels of 1.25(OH)2 D3 in patients with undifferentiated connective tissue disease (UCTD) and that those levels were lower in this population than in the control population. In the same study, 21.7% of patients with UCTD and vitamin D deficiency developed established connective tissue disease (especially RA, SLE, Sjogren's syndrome, and mixed connective tissue disease); their mean 1. 25(OH)2 D3 was lower than that of patients who remained with undifferentiated disease, 14.7 ± 6.45 ng/ml versus 33.0 ± 13.4 ng/ml, P = 0. 0001, respectively.

Table 1. Demographic data and duration of illness in the patients group.

Parameter	RA group (n=30) Mean±SD	SLE group (n=20) Mean±SD	OA group (n=30) Mean±SD	Behcet disease group (n=10) Mean±SD	AS group (n = 10) Mean±SD	P-value	Statistical Significance
Age (years)	42.30±12.97	37.65±12.37	62.27±10.35	40.30±7.83	41.90±11.70	<0.001	Sig
Age of onset (years)	32.57±8.23	27.35±8.80	49.30±15.67	26.70±5.03	33.20±8.28	<0.001	Sig
Duration of illness(years)	9.40±6.41	10.30±5.91	12.93±7.32	11.60±4.48	8.70±4.69	0.975	N.S.

Table 2. Disorders that have been linked to 1. 25(OH) 2 D3.

Rheumatological disorders	Non Rheumatological disorders
1. Rheumatoid Arthritis "RA".	1. Multiple Sclerosis "MS".
2. Undifferentiated Connective tissue UCTD.	2. Insulin dependent Diabetes Mellitus
3. Systemic lupus erythematosus SLE.	"IDDM".
4. Scleroderma.	3. Allergic asthma in children.
5. Ankylosing spondylitis"AS" .	4. Allergic rhinitis.
6. Behcet's disease.	5. Grave's disease.
7. Psoriasis.	
8. Fibromylgia .	

(Cutolo and Otsa 2008).

Prospective studies available for the 4 major autoimmune diseases: RA, SLE, MS, and type 1 diabetes mellitus (DM), have demonstrated the beneficial effects of vitamin D supplementation in modulating the components of the immune system responsible for the inflammation, such as the expression of cytokines, growth factors, nitrous oxide, and metalloproteinase (Marques et al., 2010).

The aim of this work is to estimate the level of $1,25(OH)_2D_3$ in different rheumatic diseases to find the relation between $1,25(OH)_2D_3$ level and rheumatic diseases and to establish its relation to the rheumatic diseases activity and severity.

MATERIALS AND METHODS

This study was done on 100 patient selected from the outpatient clinic of rheumatology department faculty of medicine, Alazher university, Assuit branch as patients group, their age ranged between 16 to 65 years old. The disease duration ranged from 1 to 20 years. The following patients were excluded from the study: patients who had parathyroid disorder, patients who had renal disorder, patients who had hepatic disorder, patients who had gastrointestinal and metabolic disorders, patients who had diabetes and patients who received vitamin D supplementation. The study also included 20 healthy volunteers as control group who matched the patients group in age and socio-economic status. The study has been approved by the relevant research and ethics committee after informed consent for each of patients and control groups. Patients group was subdivided into: 30 patients suffering from RA, 30 patients suffering from OA, 20 patients suffering from SLE, 10 patients suffering from Behcets disease and 10 patients suffering from ankylosing spondylitis. The following iwere done for each patients and control groups:

1. Medical history, general clinical examination, body joint examination to determine joint tenderness, arthritis, tenosynovitis, deformity or functional limitation of the affected joints, muscular examination for atrophy, tenderness and weakness.

2. Venous blood samples were taken for determination of complete blood count using automated cell counter, ESR using westergren tubes method, serum $1,25(OH)_2D_3$ level, serum calcium (total and ionized), serum phosphorus, serum parathormone, blood urea and serum

Table 3. Demographic data and duration of illness in the patients group.

	R.A. group *(n = 30)* Mean ± S.D	SLE group *(n =20)* Mean ± S.D	O.A Group *(n = 30)* Mean ± S.D	Behcet disease group *(n = 10)* Mean ± S.D	A.S group *(n = 10)* Mean ± S.D	P-value	Statistical Significance
Age (years)	42.30± 12.97	37.65 ± 12.37	62.27± 10.35	40.30 ± 7.83	41.90 ± 11.70	0.000	Sig
Age of onset (years)	32.57 ± 8.23	27.35 ± 8.80	49.30 ± 15.67	26.70 ± 5.03	33.20 ± 8.28	0.000	Sig
Duration of illness(years)	9.40 ± 6.41	10.30 ± 5.91	12.93 ± 7.32	11.60 ± 4.48	8.70 ± 4.69	0.975	N.S.

NS = non significant.

Table 4. Statistical comparison of vitamin D serum level, ESR and CRP between the target R.A. patients and control group.

Characteristic	R.A. group *(n = 30)* Mean ± S.D	Control group *(n = 20)* Mean ± S.D	P-value	Statistical Significance
Vitamin D serum level in ng/mL	13.47± 8.17	26.61± 6.44	0.000	Sig.
CRP mg/dL	4.34±3.70	0.80± 0.00	0.000	Sig.
ESR mm/hr.	53.00± 24.17	24.05± 10.38	0.000	Sig.

creatinine, liver function tests (aspartate aminotransferase and alanine aminotransferase, AST and ALT), rheumatoid factor using latex agglutination test, anti-nuclear antibodies (ANA) and anti double stranded DNA and anti Sm ab, fasting and post prandial blood glucose level and complete urine analysis by microscopic examination.

3. Radiology: Plain X-ray of hands and feet (postero-anterior view).

4. Plain X-ray of other affected joints.

5. The disease activity in different target groups was assessed using disease activity score 28 (DAS28) in RA patients, SLE disease activity index (SLEDAI) in SLE patients, bath ankylosing spondylitis disease activity index (BASDAI) in AS patients, The Western Ontario and McMaster Universities Arthritis Index (WOMAC osteoarthritis index) in OA patients and American College of Rheumatology (ACR) criteria in Behcet patients.

Assessment of $1,25(OH)_2D_3$ sufficiency by *in vitro* quantitative determination of $1,25(OH)_2D_3$ in human serum was done by using the electrochemiluminescence immunoassay ECLIA (Leino et al., 2008). ECLIA is a highly innovative technology that offers distinct advantages over other detection techniques including: extremely stable non-isotopic label which allows liquid reagent convenience, enhanced sensitivity in combination with short incubation times, means high quality assays and fast result turnaround, large measuring range of five orders of magnitude minimizes dilutions and repeats, reducing handling time and reagent costs and applicable for the detection of all analytes providing a solid platform for menu expansion (Weir 2010). ECLIA is based on competition principle. Total duration of assay is 18 min.

1st incubation: $1,25(OH)_2D_3$ in the sample (35 µl) competes with the biotin labeled vitamin D in the complex contained in R2 (biotin-vitamin D/polyclonal $1,25(OH)_2D_3$ - specific ruthenium labeled antibody). The remaining amount of the complex (biotin-vitamin D/polyclonal $1,25(OH)_2D_3$ - specific ruthenium labeled antibody) is dependent upon the analyte concentration in the sample.

2nd incubation: After addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and strepavidin. The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier. Results are determined via a calibration curve which is instrument-specifically generated by 2-point calibration and a master curve provided via the reagent barcode (Roth et al., 2008). The analyzer automatically calculates the analyte concentration of each sample (either in ng/ml or nmol/L).

Conversion factors: nmol/l × 0.40 = ng/ml

or ng/ml × 2.50 = nmol/L

Data were expressed as mean ± standard deviation. Comparisons were performed for normal distributed data using t-test for independent groups. P-value considered insignificant if > 0.05, significant if ≤ 0.05, highly significant if ≤ 0.001, the statistical analysis were done using statistical package for social sciences (SPSS) V11.0 program Table 3 to 13, Figure 6 to 15.

RESULTS AND DISCUSSION

In the current study, thirty patients with RA fulfilling ACR criteria for the classification of rheumatoid arthritis and twenty healthy controls were included. The mean value of vitamin D serum level (ng/ml) was found to be low in RA group (mean ± SD) (13.47 ± 8.17) in comparison to the control group (26.61 ± 6.44). This difference was statistically significant. The comparison of vitamin D level

Table 5. Statistical comparison of serum vitamin D, CRP and ESR levels between the target SLE patients and control groups.

Characteristic	SLE group (n=20) Mean±SD	Control group (n = 20) Mean±SD	P-value	Statistical Significance
Vitamin D ng/mL	19.32± 10.67	26.61± 6.44	0.019	Sig.
CRP mg/dL	3.60±3.04	0.80± 0.2	<0.001	Sig.
ESR mm/hr.	51.30± 19.15	24.05± 10.38	<0.001	Sig.

Table 6. Statistical comparison of serum vitamin D, CRP, ESR and SLEDAI levels between the active SLE group and the inactive SLE group.

Characteristic	Active SLE group (n=5) Mean±SD	Inactive SLE group (n=5) Mean±SD	P-value	Statistical significance
Vitamin D ng/ml	18.33± 3.1	21.87± 2.07	0.346	N.S.
CRP mg/dl	5.88± 0.69	1.16± 0.28	<0.001	Sig
ESR mm/hr.	64.00± 5.27	38.47± 4.3	0.003	Sig.
SLEDAI	4.98±0.62	1.62±0.27	<0.001	Sig.

Table 7. The relation between vitamin D values and disease activity parameters in the SLE group.

Characteristic	r	P-value	Statistical Significance
CRP mg/dL	0.35	0.35	N.S
ESR mm/hr.	- 0.12	0.75	N.S
SLEDAI	- 0.22	0.56	N.S

Table 8. Statistical comparison of serum vitamin D, CRP and ESR between the target OA patients and control group.

Characteristic	OA group (n = 30) Mean ± S.D	Control group (n = 20) Mean ± S.D	P-value	Statistical significance
Vitamin D ng/mL	22.95± 9.30	26.61± 6.44	0.178	N.S.
CRP mg/dL	1.25±0.80	0.80± 0.00	<0.001	Sig.
ESR mm/hr.	35.00±13.72	24.05± 10.38	0.006	Sig.

Table 9. Statistical comparison of serum vitamin D, CRP, ESR and WOMAC levels between the active OA and the inactive OA group.

Characteristic	Active Behcet disease group (n=5) Mean±SD	Inactive Behcet disease group (n=5) Mean±SD	P-value	Statistical Significance
Vitamin D ng/ml	21.874±2.07	24.89±2.65	0.38	NS
CRP mg/dl	1.60±0.70	0.95±0.32	0.003	Sig.
ESR mm/h	43.93±10.45	27.19±11.39	<0.001	Sig.
WOMAC	1.31±0.17	0.72±0.11	0.013	Sig.

between the active RA group and the inactive RA group did not show any statistically significant difference. This finding was matched with Gail et al. (2011) who reported that in elderly male RA patients $1,25(OH)_2D_3$ insufficiency

Table 10. The relation between vitamin D values and disease activity parameters in the OA group.

Characteristic	r	P-value	Statistical Significance
CRP mg/dL	0.35	0.35	Sig.
ESR mm/hr.	- 0.12	0.75	Sig.
WOMAC	- 0.22	0.56	Sig.

Table 11. Statistical comparison of vitamin D serum level, ESR and CRP between the target Behcet's disease patients and control group

Characteristic	Behcet's disease group *(n = 10)* Mean ± S.D	Control group *(n = 20)* Mean ± S.D	P-value	Statistical Significance
Vitamin D ng/mL	17.64± 8.79	26.61± 6.44	0.006	Sig.
CRP mg/dL	1.85±1.76	0.80± 0.2	<0.001	Sig.
ESR mm/hr.	38.70±18.51	24.05± 10.38	0.041	Sig.

Table 12. Statistical comparison of serum vitamin D, CRP, ESR and ACR levels between the active Behcet's disease and the inactive Behcet's disease group:

Characteristic	Active Behcet's disease group *(n = 5)* Mean ± S.D	Inactive Behcet's disease group *(n = 5)* Mean ± S.D	P-value	Statistical Significance
Vitamin D ng/mL	14.74± 7.70	20.54± 9.66	0.465	N.S
CRP mg/dL	2.72± 2.23	0.98± 0.35	0.081	N.S
ESR mm/hr.	53.80± 11.03	23.60± 8.88	0.009	Sig.
ACR	3.72 ± 0.60	1.53 ± 0.20	<0.001	Sig.

Table 13. The relation between vitamin D values and disease activity parameters in the Behcet's disease group:

Characteristic	r	P-value	Statistical Significance
CRP mg/dL	0.07369	0.85	N.S
ESR mm/hr.	-0.05468	0.89	N.S
ACR	-0.2797	0.47	N.S

Table 14. Statistical comparison of vitamin D serum level, ESR and CRP between the target AS patients and control group

Characteristic	A.S group *(n = 10)* Mean ± S.D	Control group *(n = 20)* Mean ± S.D	P-value	Statistical Significance
Vitamin D ng/mL	17.81± 8.11	26.61± 6.44	0.008	Sig.
CRP mg/dL	1.76±1.05	0.80± 0.00	<0.001	Sig.
ESR mm/hr.	38.50±14.70	24.05± 10.38	0.010	Sig.

activity and disability scores are inversely related to $1,25(OH)_2D_3$ levels.

This study was incompatible with Cutolo et al. (2009) who reported that no significant differences were found

Table 15. Statistical comparison of serum vitamin D, CRP, ESR and BASDAI levels between the active AS and the inactive AS group

Characteristic	Active A.S group *(n = 10)* Mean ± S.D	Inactive A.S group *(n = 10)* Mean ± S.D	P-value	Statistical Significance
Vitamin D ng/mL	14.1± 1.07	18± 2.13	0.121	N.S
CRP mg/dL	2.43± 0.14	1.32± 0.15	<0.001	Sig.
ESR mm/hr.	47.8± 3.65	26.48± 2.59	<0.001	Sig.
BASDAI	5.61 ± 0.76	3.28 ± 0.56	0.018	Sig.

Table 15. The relation between vitamin D values and disease activity parameters in the AS group.

Characteristic	r	P-value	Statistical Significance
CRP mg/dL	-0.17	0.66	N.S
ESR mm/hr.	- 0.07	0.84	N.S
BASDAI	- 0.72	0.03	Sig.

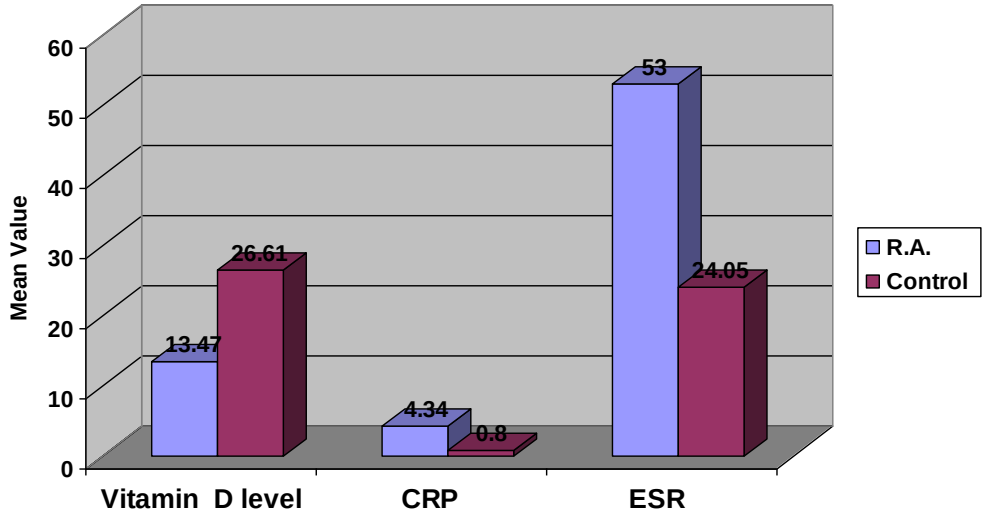

Figure 6. Statistical comparison of vitamin D serum level, ESR and CRP between the target R.A. patients and control group.

was highly prevalent. On the other hand, there was a conflicting report by Rossini et al. (2010) who reported that vitamin D deficiency is quite common in RA patients, but similar to that found in control subjects; and disease concerning $1,25(OH)_2D_3$ serum level between RA patients and their controls in both North and South European RA patients, in addition, $1,25(OH)_2D_3$ values showed a significant negative correlation with RA clinical status (DAS28), suggesting possible effects of vitamin D among other factors on disease activity.

In the current study, twenty SLE patients with mean age of 37.65 ± 12.37 years and twenty control cases were studied. The study shows vitamin D deficiency in SLE patients as the mean value of vitamin D level was (19.32 ± 10.67) in the SLE group, while in the control group it was (26.61 ± 6.44). This difference in the mean value of vitamin D level between the target SLE group and control group was found to be statistically significant, as p-value of 0.019 and the difference in the mean value of vitamin D level between the SLE active group and inactive group was found to be statistically insignificant, as p-value of 0.470.

This finding was matched with the study done by Souto et al. (2011). Their objectives were to determine the prevalence of vitamin D insufficiency in Brazilian lupus patients and study the relationship between vitamin D insufficiency and disease activity, the study included 159 SLE patients and showed that the prevalence of vitamin D insufficiency and deficiency were 37.7 and 8.2%, respectively, levels of $1,25(OH)_2D_3$ were not associated with lupus activity score which is compatible with our study. Similar study done by Bonakdar et al. (2011)

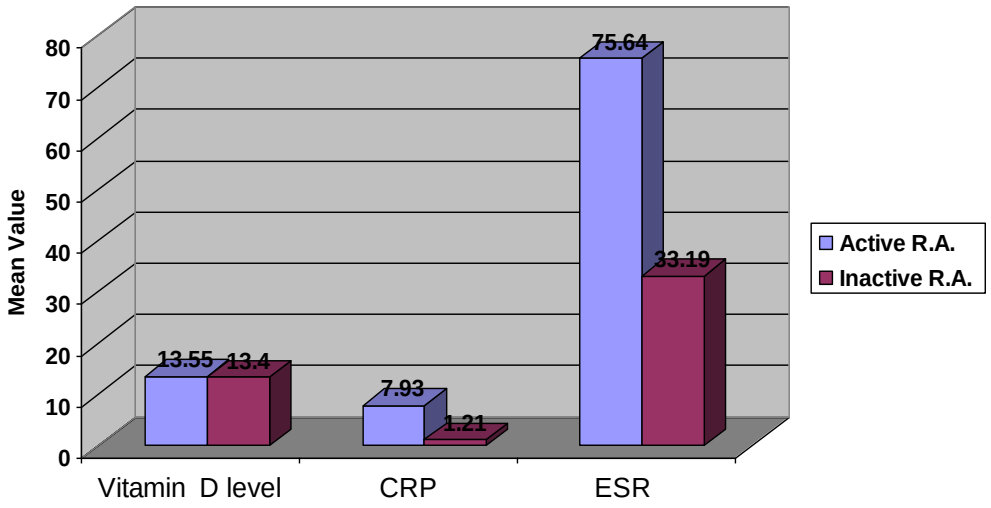

Figure 7. Statistical comparison of vitamin D serum level, ESR and CRP between the active R.A. group and the inactive RA group.

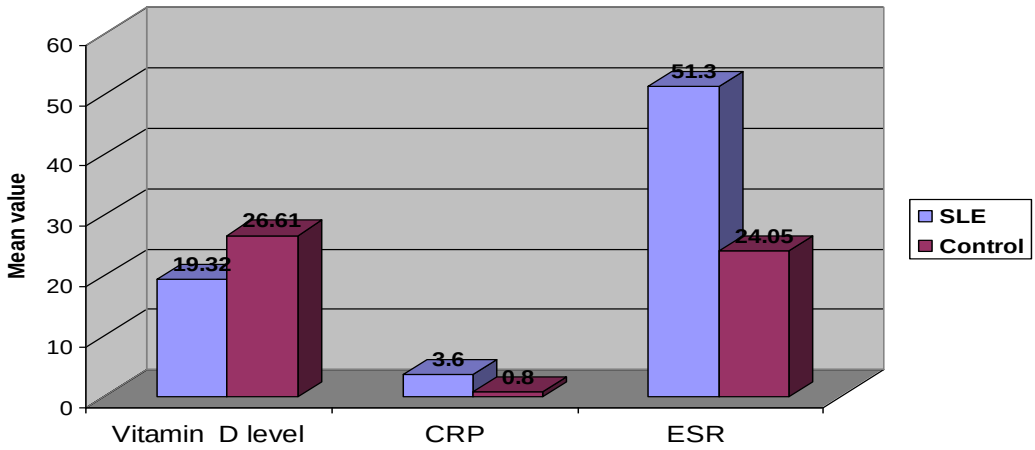

Figure 8. Statistical comparison of vitamin D serum level, ESR and CRP between the target SLE patients and control group.

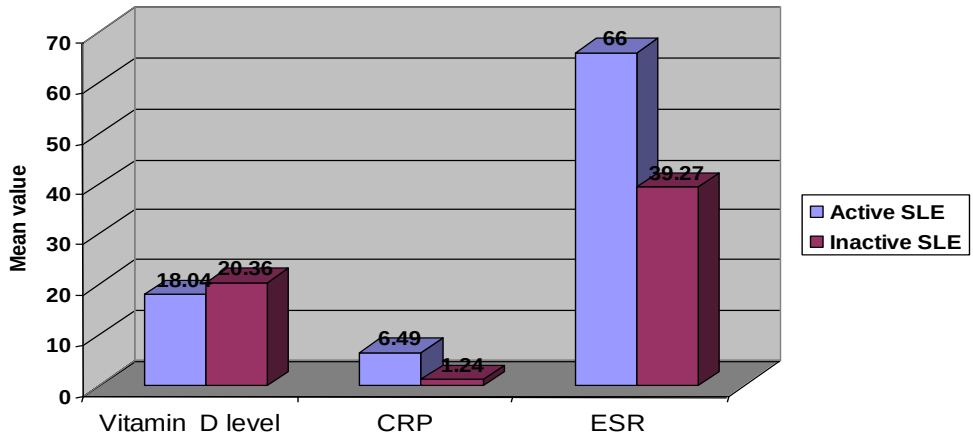

Figure 9. Statistical comparison of vitamin D serum level, ESR and CRP between the active SLE group and the inactive SLE group.

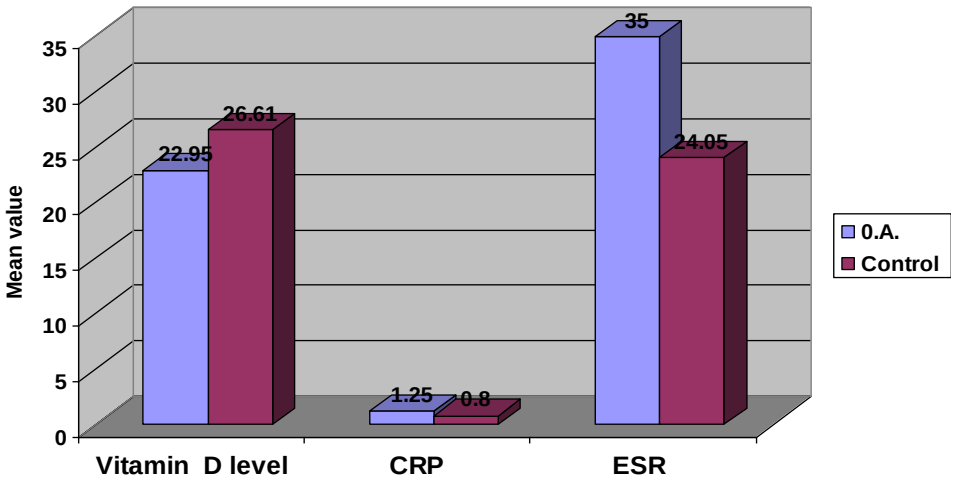

Figure 10. Statistical comparison of vitamin D serum level, ESR and CRP between the target 0.A. patients and control group.

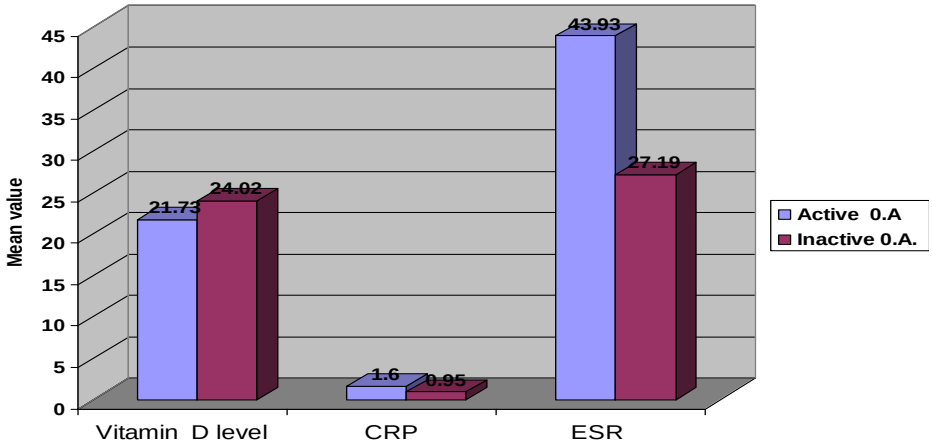

Figure 11. Statistical comparison of vitamin D serum level, ESR and CRP between the active OA and the inactive OA group.

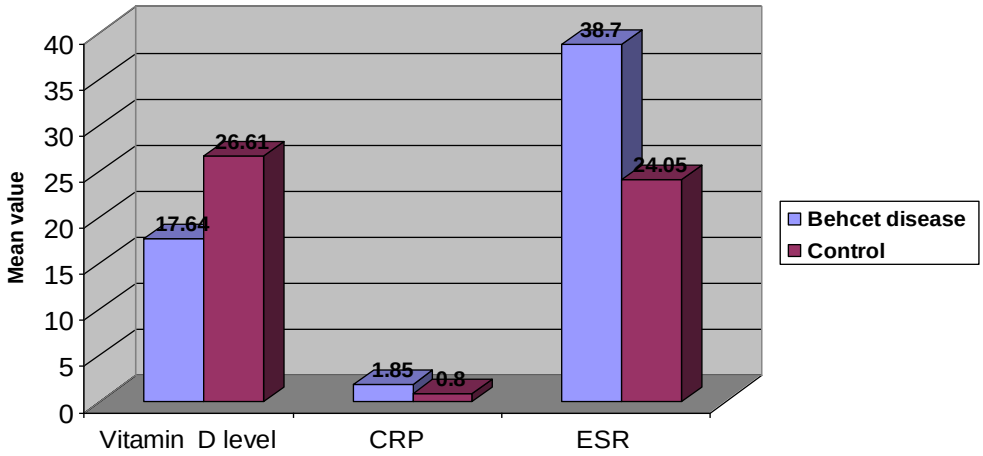

Figure 12. Statistical comparison of vitamin D serum level, ESR and CRP between the target Behcet disease patients and control group.

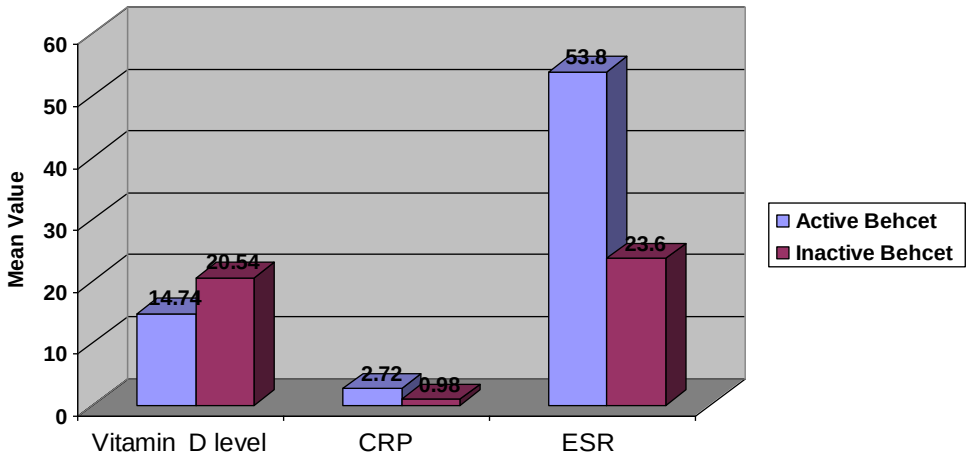

Figure 13. Statistical comparison of vitamin D serum level, ESR and CRP between the active Behcet disease and the inactive Behcet disease group.

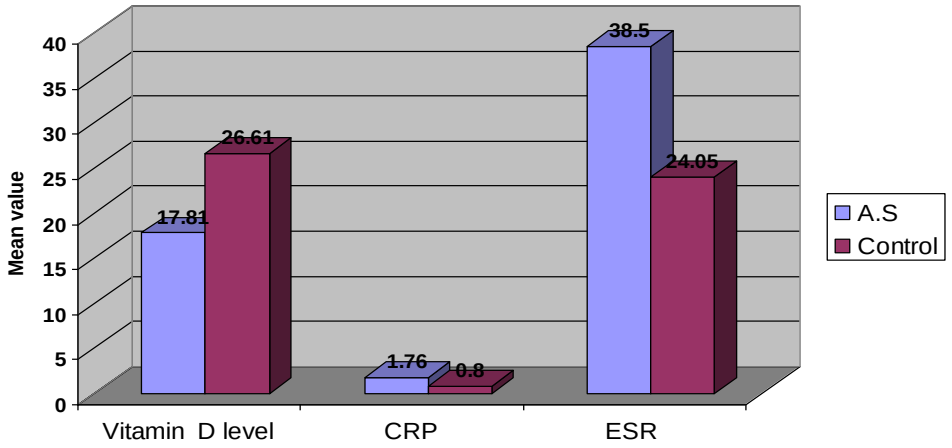

Figure 14. Statistical comparison of vitamin D serum level, ESR and CRP between the target AS patients and control group.

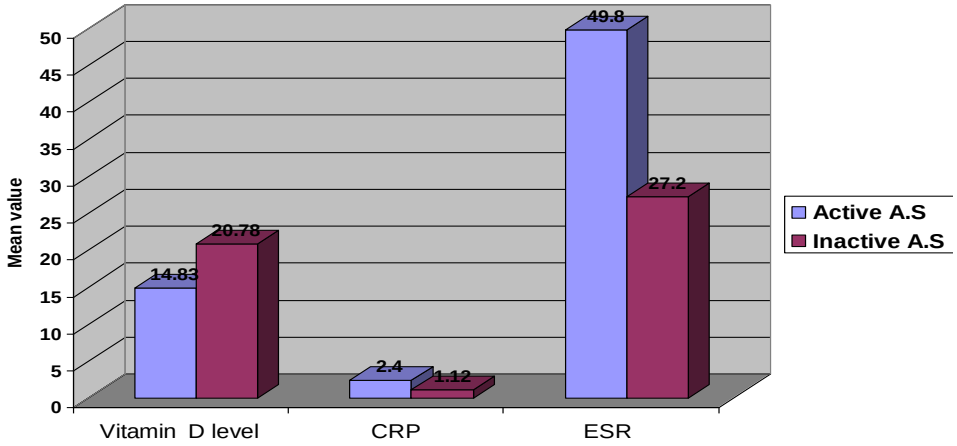

Figure 15. Statistical comparison of vitamin D serum level, ESR and CRP between the active A.S and the inactive A.S group.

showed that most of the SLE patients have vitamin D deficiency at the time of diagnosis that is associated with a higher disease activity. Another study was done by Borba et al. (2009); the association between vitamin D deficiency and disease activity was demonstrated and levels of $1,25(OH)_2D_3$ were lower (17.4 ± 12.5) in patients with high disease activity when compared to those with mild disease activity and the control group.

In a Spanish study done by Ruiz-Irastorza et al. (2008) on 92 SLE patients, there were low levels of vitamin D (< 30 ng/ml) in 75% of the patients and deficiency (< 10 ng/ml) in 45% of them. 45% of the patients with low levels and 35% of those with deficiency were on calcium and vitamin D supplementation at the time of the evaluation. In this current study, the relation between vitamin D serum level and the disease activity in patients with ankylosing spondylitis (AS) was investigated in ten patients with AS and twenty healthy individuals included in the study. The study showed that in the patient group, the vitamin D serum levels were lower than the control group (17.81 ± 8.11) and (26.61 ± 6.44), respectively. This was found to be statistically significant, with p-value of 0.008. The difference in the mean value of vitamin D serum level between the AS active group and inactive group was found to be statistically insignificant as p-value of 0.17. This finding was compatible with Bedriye et al. (2010) who found out that the vitamin D serum levels were lower in AS patients than in the control group.

In this current study, ten patients with Behçet's disease and twenty matched healthy controls were included. The diagnostic criteria for Behçet's disease proposed by the American college of rheumatology were used for diagnosis. In this study, the mean value of vitamin D serum level in the Behçet's disease group was low in comparison to vitamin D serum level in the control group (17.64 ± 8.79) and (26.61 ± 6.44), respectively. The difference in the mean value of vitamin D serum level between the target Behcet disease group and control group was found to be statistically significant, with p-value of 0.041. In comparison with vitamin D serum level between the active Behçet's disease and the inactive Behcet disease group, there was no statistically significant difference as the mean value of vitamin D serum level was (14.74 ± 7.70) in the Behcet disease active group, while in the Behçet's disease inactive group it was (20.54 ± 9.66) and p-value 0.465. This is compatible with Saliha et al. (2011) who reported that $1,25(OH)_2D_3$ serum levels are decreased in patients with Behçet's disease.

This study is also compatible with Christina et al. (2010) who reported that vitamin D deficiency occurs at a higher rate in patients with Behçet's disease, thus appropriate supplementation should be indicated. In the current study, thirty OA patients with mean age of 62.27 ± 10.35 years and twenty control cases were studied. The difference in the mean value of vitamin D serum level between the target OA group and control group was found to be statistically insignificant, with p-value of 0.178 as the mean value of vitamin D serum level was (22.95 ± 9.30) in the OA group, while in the control group it was (26.6 1 ± 6.44). The difference in the mean value of vitamin D serum level between the OA active group and inactive group was found to be statistically insignificant, with p-value of 0.430.

This finding was incompatible with the study done by Changhai et al. (2009) who reported that the serum level of $1,25(OH)_2D_3$ levels are associated with decreased knee cartilage loss (assessed by radiograph or MRI) in subjects with radiographic OA and knee pain. Also, it was not matched with Bergink et al. (2009) who reported that low vitamin D serum level and low dietary vitamin D intake increases the risk of progression of knee OA. Thus, improving the vitamin D status in the elderly could protect against the development and worsening of knee OA, especially in those with low bone mineral density (BMD).

Conclusion

Vitamin D is recognized as an important immunomodulatory factor involved in autoimmune rheumatic diseases. These immunomodulatory and anti-inflammatory activities might be particularly efficient in the treatment of rheumatic patients and support a therapeutic role of $1,25(OH)_2D_3$ in such diseases. Vitamin D deficiency occurs at a higher rate in patients with autoimmune disorders such as RA, SLE, Behcet disease and AS. Routine screening for vitamin D deficiency in early rheumatic diseases is recommended. A much higher oral vitamin D intake than recommended in current guidelines is safe and necessary to maintain adequate circulating $1,25(OH)_2D_3$ levels especially in the absence of UVB radiation to the skin. Further studies should be performed on a larger number of rheumatic patients to the role of vitamin D in rheumatic diseases and its relation to disease activity.

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