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### Study the Relation between Vitamin D with Interleukins 12, 17 and 23 in Rheumatoid Arthritis Iraqi Women.

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#### ABSTRACT

##### Background

Rheumatoid arthritis(RA) which establishes as Continuous & progressive joint devastation is a public prolonged autoimmune illness with inflammation which leads to pain, stiffness, and the final result functional disability. The objective of this cross sectional study was to explore the function of serum Vitamin D (Vit D), interleukin (IL)12, IL-17 & IL-23 in Iraqi Women with RA, and to evaluate their relationship with disease action & joint severity.

The work involved 42 RA Iraqi women patients and 42 healthy control matched by age and sex. Serum concentrations of VIT. D, IL-12, IL-17, IL-23 and Anti-cyclic citrullinated peptide (ACCP) were estimated via commercially available ELISA kit. Serum levels of Vit. D, IL-12, IL-17, IL-23 and ACCP were importantly greater ( $P<0.001$ ) in RA cases as related to healthy control. There was an important negative link between Vit. D and IL-12, IL-17 and IL-23, while an important positive link between IL-12 with IL-23, IL-17 with IL-23 and ACCP. Substantial sign shows that RA cases have small concentration of Vit. D. The proinflammatory grade arising in RA is considered through stimulation of inflammatory cells, augmented concentrations of inflammatory intermediaries & the attendance of autoantibodies, compatible in prompting endothelial dysfunction.

#### Introduction

Rheumatoid arthritis (RA) is a chronic, autoimmune inflammatory disease with women prevalence, and is assessed to infect about 1% of the population [1]. The etiology of RA is unidentified; however genetic aspects are linked with the situation and its harshness, several environmental, way of life features have been exposed to be related with its development [1]

In RA, irritation of the synovium reaches to cartilage, bone damage, with the joints of the hand, feet actuality the first pretentious [2]. Many junctions in the body are then pretentious. RA cases are at augmented danger for cardiovascular disorders (CVD), implicating atrial fibrillation, stroke & mortality, as well as additional autoimmune illnesses [1]. The relationship with CVD is of significance for the attendance of both situations rise with age, the population is aging [2]. The situation is very varied: it can wax and decline, be in diminution for an extensive period of time, reoccur, or growth quickly leading to devastating joint damage [1].

Vitamin D is not actually a vitamin at completely; nevertheless, it is steroid hormone which can do by receptors originate on cells in numerous tissue structures, involving the immune system [3]. A research has briefly defined alterations in immunocyte purpose which Vit. D encourages *in vitro*, in animal models which are linked to the pathogenesis of autoimmune illness [4]. There is a Vit. D prompted capture of differentiation, development of populaces of dendritic cells, T cells, B cells, with a growth in the manufacture of IL-10, a decrease of IL-12, delaying dendritic cell growth and prompting apoptosis. Concentrations of the proinflammatory interleukin IL-17 are reduced. Lower serum and post-switch memory B cells are manufactured [5].

Vitamin D participated in the controlling of  $Ca^{+2}$  homeostasis, as it controls  $Ca^{+2}$  taking from the gastrointestinal system [6]. The vitamin is manufactured in the skin via the effect of ultraviolet radiation [7]. Vitamin D has extraskelatal properties

also [8]. The nonclassical activities of Vit. D are presently below debate. Vitamin D has been established to have immunomodulatory activities [9].

Interleukin-12, a 70-kDa heterodimer produced via stimulated dendritic cells and macrophages, encourages initial helper T cells to differentiate into Th1 cells, stimulates the growth and proliferation of Th1 cells by signal transducer and activator of transcription 4 (STAT4). IL-12 may encourage IFN- $\gamma$  manufacture in T helper type 1 (Th1) cells via IL-1 receptor-related kinase pathway together with IL-18, resulting in nuclear translocation of the NF- $\kappa$ B complex [10]. As a result, IL-12 stimulated production of IFN- $\gamma$  and making of Th1 cells while it blocked development of Th2 cells [11]. IL-12 is documented as a chief controller of modification type 1 cell mediated immunity, the crucial route participate in preservation versus neoplasia and a lot of viruses. It binds to naive CD4<sup>+</sup> T-cells through its IL-12 $\beta$ 1/IL-12 $\beta$ 2 receptor and stimulates the manufacture of pro-inflammatory Th1 and Th17 cells [12]. It prevents IL-4, antagonizes Th2 replies and can reduce IL-2 production; therefore, it has been revealed to have a deleterious effect on Treg cells [13]. Besides its regulatory role, it has been stated that IL-12 expression is augmented in some inflammatory infections like RA [14]. Th17 cells selectively products the sign interleukins like IL-17, IL-21 & IL-22, have been established to exert a crucial function for the prolonged inflammatory reply and later tissue destruction in RA pretentious joints [15]. Interleukin-17 is extremely stated in the synovium and synovial liquid of cases with RA [16]. Interleukin (IL)-23 belongs to the IL-12 family which consists of the two subunits p19 and p40 [17]. IL-23 is mainly produced by macrophages and DCs, and through its interaction with the IL-23 receptor (IL-23R), adoption of the IL-12R $\beta$ 1 unit and the specific IL-23R unit, exert an essential part in inflammation including the initiation of Th17 cells. The cytokine IL-23 is created via dendritic cells, macrophages, and Th17 pro-inflammatory cells, which results in increased IL-17 production [18].

IL-23 has a function in prolonged irritation that is a public individual of several autoimmune infections. IL-23 stimulates the Th17 route, which has been revealed to be dynamic in the pathogenesis of various prolonged inflammatory illnesses, containing psoriasis, inflammatory bowel disease (IBD), and

MS. In IBD, encouragement of colonic leukocytes via IL-23 prompted the manufacture of IL-17 [19]. Therefore, closing the IL-23 might be beneficial for the controlling of IBD. Additional instance of this is with RA, IL-23 concentrations are importantly larger in the peripheral blood of RA cases than in healthy subjects [20].

This work was designed to assess Vit. D, IL-12, IL-17, IL-23 values and their function in the RA pathogenesis and to examine the association among these parameters and activity of disease, helping to identify novel investigative and/or therapeutic targets for arthritis RA cases.

### **Methods**

The study group contained of 42 RA cases. The cases come into the work as they came for assessment at the Al-Fallujah teaching hospital for over six months, from February to July 2018. A healthy subject involved 42 women, coordinated for age, ethnic background, and was evaluated as well. Anti-cyclic citrullinated peptide (ACCP), Vit. D, IL-12, IL-17 & IL-23 serum levels were conducted by ELISA enzyme-linked immunosorbent assay (ELISA) kits [MyBiosource, Inc, Southern California, San Diego (USA)] from the sera of subjects] [21].

### **Ethics Statement**

Written informed approval was gotten from whole subjects in accordance with Helsinki statement & the scrutiny was permitted via the Ethics board of the University of Anbar.

### **Results**

Patients with RA had importantly higher levels of anti-CCP (U/mL) Comparison with healthy subjects ( $54.02 \pm 15.36$  vs.  $7.93 \pm 3.64$ , respectively).

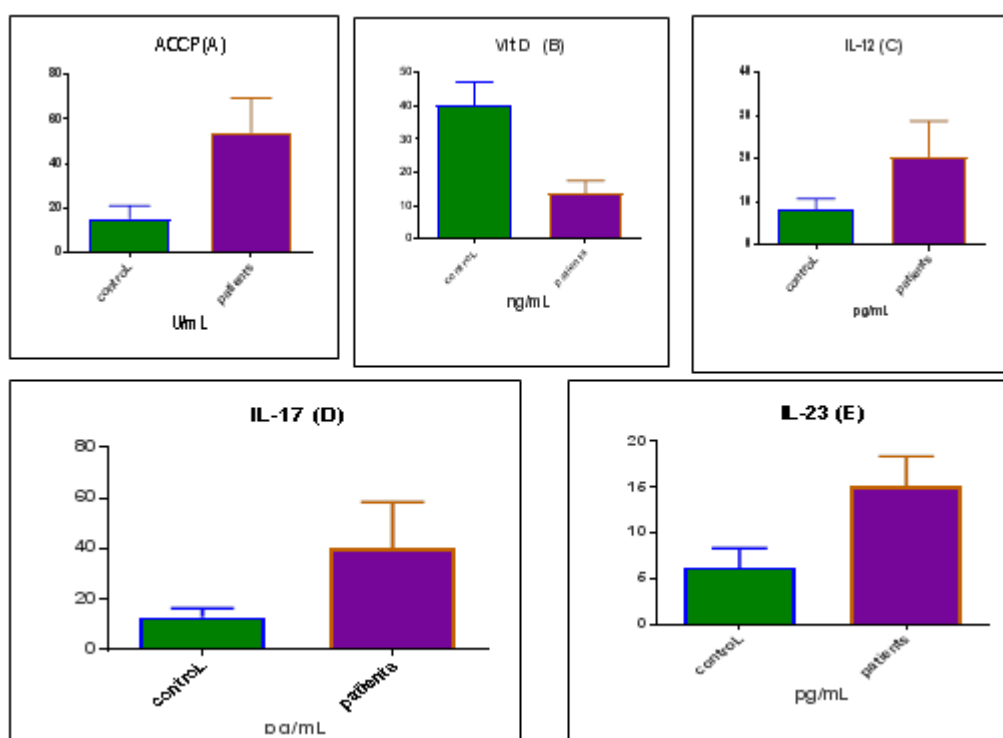
Vitamin D serum concentrations in RA cases were  $13.54 \pm 5.62$  ng/mL and  $40.30 \pm 6.93$  ng/mL in healthy subjects as in table no.1 (figure no.1 -A-).

Statistical analysis showed that Vit. D serum values were lower in RA cases than healthy controls ( $p < 0.001$ ), as established in table no.1 (figure no.1 -B-).

The mean serum IL-12, IL-17 & IL-23 were importantly greater among cases with RA ( $20.47 \pm 8.29$ ,  $40.18 \pm 18.25$  and  $15.07 \pm 3.33$  pg/mL respectively) compared to healthy controls ( $8.35 \pm 2.335$ ,  $12.88 \pm 3.52$  and  $6.13 \pm 2.18$  ng/mL respectively), as confirmed in table no.1 (figures no.1 -C-, -D- and -E-).

**Table (1): Comparison of various parameters between controls and RA cases**

factor		Mean ± S.D	S. Error Mean	T. test	p value
Age years	control	43.44±14.31	1.65	1.86	0.105
	patients	44.96±11.47	1.23		
Duration of disease years	control	-----	-----	-----	-----
	patients	7.93±3.64	0.65		
ACCP U/mL	patients	54.02 ± 15.36	2.31	14.960	0.000
	control	15.53 ± 2.34	0.88		
V D ng/mL	patients	13.54 ±5.62	0.61	-21.808	0.000
	control	40.30 ±6.93	1.10		
IL-12 pg/mL	patients	20.47 ± 8.29	1.31	8.896	0.000
	control	8.35 ± 2.335	0.37		
IL-17 pg/mL	patients	40.18 ± 18.25	2.88	9.287	0.000
	control	12.88 ± 3.52	0.55		
IL-23 pg/mL	patients	15.07 ± 3.33	0.52	14.18	0.000
	control	6.13 ± 2.18	0.34		



**Figure (1): Comparison between ACCP, Vit D, IL-12,IL-17 and IL-23 in studied groups**

Statically significant negative correlations among the concentrations of Vit. D with ACCP, IL-12, IL-17 & IL-23 [ $r = 0.439$ ,  $p < 0.01$ ;  $r = 0.429$ ,  $p < 0.01$ ;  $r = -0.385$ ,  $p < 0.05$  &  $r = -0.537$ ,  $p < 0.01$ , respectively] as confirmed in table no.2, a significant positive association of IL-17 levels with IL-23 [ $r = 0.393$ ,  $p <$

$0.05$ ] as demonstrated in table no. 2. There were weak statistically important associations between the values of IL-12 with ACCP, IL-12 with IL-23 and IL-17 with ACCP.

No statistically important associations between the values of other parameters in case or control groups.

**Table (2): Pearson correlation coefficients of serum studied parameters with each other.**

Factor	ACCP U/mL	IL-12 pg/mL	Vit D ng/mL	IL- 17 pg/mL	IL- 23 pg/mL
ACCP IU/mL	1	.294*	-.439-**	.267*	.241
IL- 12 pg/mL	.294*	1	-.429-**	.217	.289*
Vit D ng/mL	-.439-**	-.429-**	1	-.385-*	-.573-**
IL- 17 pg/mL	.267*	.217	-.385-*	1	.393*
IL- 23 pg/mL	.241	.289*	-.573-**	.393*	1

\*\* . Correlation is important at the 0.01 value (2-tailed).  
\* . Correlation is important at the 0.05 value (2-tailed).

## **Discussion**

Patients, reported that 25(OH)D values were negatively linked to infection action in RA. By dissimilarity, many studies did not discover a link among Vit. D insufficiency and infection action in RA [22, 23]. Vitamin D insufficiency is normally related with inflammatory illnesses; this relationship can be because of an augmented occurrence of provocative illnesses in low levels of Vit. D, while opposite causation cannot be omitted [24]. We detected a relationship among Vit. D values and inflammatory indicators such as IL-12, IL-17 and IL-23. Previous study stated that serum values of Vit. D reduction when an inflammatory injury and this decline seem to continue for many months [25].

In RA it has formerly been defined a relationship among Vit. D concentrations and erythrocyte sedimentation rate (ESR), infection movement marks, likewise with IL-17 & IL-23 serum concentrations [26]. Previous study established a relationship among Vit. D inadequacy and plasma concentrations of IL-17 in RA cases [27]. Furthermore, Vit. D and its similarities prevent IL-2, IFN- $\gamma$  construction and encourage the special properties of T-helper type 2 lymphocytes, connect to a decrease in MMPs, and obstruction atherosclerotic plate development [28].

Anti-Cyclic Citrullinated Peptide positive cases have an additional plain form of illness; certain researches have revealed that together ACCP & Rheumatoid factor (RF) antibodies are independent marker of illness development realized on X-rays, others have recommended lone ACCP antibodies are an freelance marker. Being positive for the anti-CCP antibody was related with a better response to the T cell co inspiration closing abatacept however, this antibody status was not linked with the ability of a tumor necrosis factor-inhibitor (TNFi) [29].

Several new papers have revealed that ACCP antibody can expect the harshness of both the medical & radiological result in cases with RA [30, 31]. Actually, usual proteins in the body become unusual via changing the amino acid arginine to citrulline and the immune system distinguishes the original citrillinated proteins as external materials and creates antibodies in contradiction of them. As a result, manufactured antibodies in the patient's joints collect and consequence in initiation of the complement system and irritation [32]. As the illness developments, terminating the antigen-antibody centers converts tougher for the immune system and extra of them persist in the joints. By the permanency and existence of these immune centers, regulatory cells could not be to control these responses, and the body will not return to homeostasis and equilibrium [33].

The cytokine IL-12 family memberships showed immunoregulatory effects because of their actions on T-cell differentiation and function. Both of IL-12 and IL-23 are pro-inflammatory interleukins; the previous can encourage Th1 cells however the last has a main

function in the initiation of Th17 cells. Additional, IL-27 showed a double purposeful phenotype accomplished of augmented pro - & anti-inflammatory responses [34]. It similarly prevents IL-4, antagonizes Th2 replies and can similarly reduce IL-2 production; therefore, it has been exposed to have an inverse impact on Treg cells, furthermore to its, prominent special monuments on the preparing of Th1 cell reactions and IFN- $\gamma$  making via T and NK cells, modern papers provision not only its crucial function as a third sign for CD8+ T-cell differentiation, but also its capacity to work as an vital issue in the recrudescence and persistence of memory CD4+ T-cells, this discovery is chiefly related in the repolarization of CD4+ T-cells from dysfunctional antitumor Th2 into Th1 cells in the cancer setting, besides its regulatory role, it has been stated that IL-12 expression is augmented in many inflammatory illnesses like RA [ 35,36].

Dysregulation of interleukin manufacture or activity is believed to require an essential part in the increase of RA. Formerly, RA had remained counted a Th1-cell- facilitated illness, consequently was assumed to be determined via a populace of T cells generating provocative interleukins like IL-2, TNF and interferons [37]. Previous study recommended that high levels of IL-17 and up-regulation of Th17 cells are public properties of RA [38].

Result of this work indicated that the calculation of serum values of IL-17 was expressively elevated in RA cases relating to healthy subjects, ( $p < 0.001$ ), and the IL-17 value elevated 3.5 times compared to control. In another work, the value of IL-17 amplified 5 times paralleled to the healthy subjects [39]. A study stated that the detection of IL-17 creating CD4+ T (Th17) cells as a distinctive T-helper cell line has studied the accepting of T-cell facilitated tissue damage [40]. Autoimmune illnesses like MS and RA, naturally assumed to be Th1 facilitated, are mainly determined via a Th17 immune reply. IL-17 (IL-17A, IL-17F, IL-21, IL-22) and perhaps similarly IL-9 manufactured via Th17 cells stimulate inflammation via straight producing tissue damage and increasing producing of pro inflammatory interleukins and chemokines via local cells. These outcomes in increased infiltration of leukocytes, in certain neutrophils to the pretentious tissue wherever they encourage organ irritation and damage. On synoviocytes, IL-1 $\beta$ , TNF- $\alpha$  and IL-17 were revealed to encourage manufacture of IL-6 and leukemia inhibitory factor (LIF) [41].

Interleukin -23 is a part of the IL-12 family and it is essentially formed via stimulated macrophages and dendritic cells (DCs). Closing IL-23, which is basic for Th17 growth and conservation, has similarly been tried as a possible treatment approach for autoimmune diseases [42]. The values of IL-17 and IL-23 are raised in the plasma and intestinal mucosa of RA cases, these values positively relate with the infection severity. There are further sections of

bolster for the calculated function of IL-23 in some autoimmune illnesses like RA. For instance, naive T cells do not direct the receptor for IL-23 (IL-23R), nonetheless this receptor is communicated on stimulated Th17 cells. Furthermore, IL-23 is central for the increase and preservation of Th17 cells. Continued IL-23 signaling in T cells is of significance for keeping current irritation [43]. Differentiated Th17 cells are sustained and extended mainly via IL-23. Subsequent researches demonstrated that IL-23 stimulates the growth of the original Th17 populace described via the manufacture of IL-17a and extra associated proinflammatory cytokine. Previous work stated that IL-23 has been categorized as a proinflammatory moderator in control for observance a equilibrium among effectors and controlling T-cell response, it is a necessary factor for the growth of T-cell-dependent inflammation. This study found that IL-23 levels inclined to be strongly higher (2.5 times) RA cases, serum IL-23 levels in RA, are strongly associated with Vit. D [44].

Results of this work propose that the function of IL-23 in recognized RA is restricted. But, IL-23 could be necessary in the primary autoimmune enlargement containing the manufacture of pathogenic autoantibodies, which is confirmed to be IL-23-needy [45]. Furthermore, IL-23 possibly could has a central role of illness deterioration in cases as recommended via investigational researches subsequently IL-23 exerts a function in recrudescence of memory T cells that are including in inflamed flares [46]. Consequently, impending research must disclose whether targeting the IL-23 signaling pathway in RA cases can avert an arthritic deterioration.

Therefore, this work was designed to existence results and differences of IL-12, IL-17 & IL-23 in RA and

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review new directed treatments of these cytokines that can be a irregular understanding foundation for further studies on interleukins in RA.

Study limitations included a small sample size; therefore, weak relations among outcomes and baseline factors cannot be detected. The study cannot accumulate statistics on parathyroid hormone concentrations or additional proxy actions of useful Vit. D deficiency. Moreover, the period of sunlight targeting in patients was not measured.

In conclusion, the circulating IL-12, IL-17 & IL-23 values were important in RA cases related with healthy subjects. There was an important inverse link among serum Vit. D values in RA cases and individual disease activity parameters, functional disability, and radiographic joint damage. Therefore, elevated serum IL-12, IL-17 and IL-23 values could be a suitable indicators to identify dynamic RA and disease progression RA cases. This study detected that anti-IL-23 could have a possible treatments function in the controlling of RA and evaluates the function of ustekinumab (anti-IL-23 drug) in RA cases, the statistics of this study afford more boost for a function of Vit. D as a medical bioindicator for RA. Starting point Vit. D can have possible as a predictor of disease severity in RA.

In this cohort, hypovitaminosis D was associated consistently over time to several specific symptoms, which could have therapeutic implications. Extra potential works are basic to explain the influence of Vit. D concentrations on these clinical variables of RA and to estimate whether Vit. D supplementation has a useful effect on disease course. Future works are required to demonstration if closing of IL-12, IL-17 & IL-23 signaling has a useful influence on Treg subsets in RA patients.

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## دراسة العلاقة بين فيتامين (د) مع الانترلوكينات 12، 17 و 23 في النساء العراقيات المصابات بالتهاب المفاصل

شاكرا فارس طلب الاعرجي

قسم الكيمياء ، كلية التربية للعلوم الصرفة ، جامعة الانبار ، رمادي ، العراق

### الملخص

التهاب المفاصل هو حالة مرضية مستمرة ومتقدمة للمفاصل وهو احد امراض المناعة الذاتية المزمنة مع الالتهاب الذي يؤدي إلى الألم، وتيبس للمفاصل، وبالنهاية العجز الوظيفي. هذا العمل يهدف لاستكشاف وتقييم المستويات المصلية لفيتامين د، والانترلوكينات 12، 17 و 23 في النساء العراقيات المصابات بالتهاب المفاصل ودراسة علاقتها مع فعل المرض ووخامة المفصل. تضمنت الدراسة 42 من النساء العراقيات المصابات بالتهاب المفاصل و 42 امرأة من الاصحاء المتطابقات بالعمر والخلفية العرقية. تم قياس التراكيز المصلية لفيتامين د ولانترلوكينات 12، 17، 23 وضد ببتيد السترونييند الحلقي من خلال استخدام عدد قياس تجارية وباستعمال تقنية الامتزاز المناعي المرتبطة بالانزيم. المستويات المصلية لفيتامين د ولانترلوكينات 12، 17، 23 وضد ببتيد السترونييند الحلقي كانت اعلى بشكل واضح ومهم احصائيا في مرضى التهاب المفاصل مقارنة بالاصحاء. توجد علاقة ترابطية سلبية ذات اهمية احصائية بين فيتامين د والانترلوكينات 12، 17، 23 وضد ببتيد السترونييند الحلقي في حين أظهر انترلوكين-12 مع انترلوكين-23 وانترلوكين-17 مع انترلوكين-23 و ضد ببتيد السترونييند الحلقي علاقة ترابطية ايجابية ذات اهمية احصائية. بينت الدراسة ان النساء المصابات بالتهاب المفاصل يملكن تراكيز قليلة من فيتامين د، وان العوامل التي تسبق الالتهاب تزداد في المرضى نظرا لنشاط الخلايا الالتهابية وزيادة التراكيز للوسيطات الالتهابية وتواجد الاجسام المضادة الذاتية التي تعزز تحفيز الاختلالات في الاغشية البطانية.