CORRELATION OF SERUM VITAMIN C LEVEL AND SERUM URIC ACID WITH VITAMIN D LEVEL IN A SAMPLE OF IRAQI RHEUMATOID ARTHRITIS PATIENTS

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Abstract. Rheumatoid arthritis (RA) is an autoimmune disease of an unknown etiology and, according to recent studies, vitamin D, vitamin C, and uric acid may all play an important role in the pathophysiology of RA. This cross-sectional study aims to investigate the correlation between the levels of vitamin C and uric acid with vitamin D level in 110 patients with RA who were divided into three groups depending on their serum 25-hydroxyvitamin D (25(OH)D) level. The results revealed that only 27.27% of our RA patients had sufficient serum 25(OH)D (≥ 30 ng/mL), whereas 72.73% of RA patients had deficient or insufficient vitamin D levels (< 30 ng/mL). In females, the percentage of those with vitamin D level < 30 ng/mL was higher (63.75%) than that in males (36.25%). According to different levels of vitamin D in RA patients' groups, a significant decrease in the level of vitamin C ($p = 0.0001$) was observed while a non-significant difference was found in the level of serum uric acid ($p = 0.527$). Meanwhile, no significant correlations were observed ($P > 0.05$) between levels of vitamin C and uric acid with vitamin D level in patients with RA. On the other hand, a negative correlation between serum vitamin C level and uric acid level was found ($P = 0.0001$), which indicates RA patients suffered from vitamin C deficiency regardless of the level of vitamin D and they had hyperuricemia which had a negative correlation with vitamin C.

Keywords: rheumatoid arthritis, vitamin D, vitamin C, uric acid.

List of Abbreviations

RA – Rheumatoid arthritis
25(OH)D – 25-hydroxyvitamin D
r – coefficient of correlation

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder disease (Azzam *et al.*, 2023) that affects up to 1% of the global population, mainly women (Mohammed *et al.*, 2022; Oleiwi & Zgair, 2023). The immune system attacks the joints causing chronic inflammation (Rija *et al.*, 2021; Mohammed *et al.*, 2022) and leading to organ damage where the dysregulation of the immune response is the major cause of RA (Yousif *et al.*, 2020; Al Ghuraibawi *et al.*, 2023). The immune system is a complex and integrated thing and needs specific micronutrients of vitamins and minerals to be at normal levels to maintain immune functions within the normal range (Barrea *et al.*, 2021). Vitamin D is the most important vitamin which has an important immunomodulatory effect due to its action on all immune system cells via cytokine generation (Renke *et al.*, 2023). Hypovitaminosis D is the most highly prevalent globally, especially in Asia and the Middle East region (Bassil *et al.*, 2013; Chakhtoura *et al.*, 2018). In Iraq, vitamin D deficiency is reported in several pathological conditions (Mustafa *et al.*, 2017; Hamdi *et al.*, 2018; AlRayahi *et al.*, 2021; Mijbel & Ibrahim, 2023) and it has been related to an increased risk of autoimmune disorders mainly RA (Hwaidi & Hasan, 2019; Hasan, 2020; Al-Cekal *et al.*, 2021). Another vitamin that boosts the immune system to function optimally is vitamin C (Moore & Khanna, 2023). Meanwhile, one of the induced inflammatory responses is elevated uric acid which leads to increased inflammation (Tian *et al.*, 2023). Therefore, the current study aims to investigate the correlation between levels of vitamin C and uric acid with vitamin D level in RA patients' sera.

Materials and Methods

Study design and participants

A cross-sectional study was conducted from November to December 2022 with 110 RA patients aged 40–60 years who were newly diagnosed with RA by a rheumatologist at the Rheumatology outpatient clinic in Baghdad Teach-

ing Hospital, Department of Rheumatology (Baghdad, Iraq). All participants who had received vitamin D supplements in the previous 3 months were excluded from this study.

Blood sample collection

Five milliliters of blood were collected from each participant in a gel tube. The tube was incubated for 5 minutes in an incubator (37°C) and then centrifuged at (3000 x g) for 15 min to obtain serum which was kept frozen at −20°C until used.

Determination of serum vitamin D concentration

A total of 25-hydroxyvitamin D (25(OH)D) concentrations was determined in serum by electrochemiluminescence binding assay using Roche Cobas e411 immunoassay analyzer according to the manufacturer's instructions (REF: 07464215 190, Roche Diagnostics GmbH, Mannheim, Germany). A vitamin D binding protein is used in this assay that binds to both 25-hydroxyvitamin D2+ 25- hydroxyvitamin D3. The assay was performed in three incubation steps and the concentration was expressed as nanograms per milliliter (ng/ml).

Determination of serum vitamin C concentration

Serum vitamin C concentration was determined by the colorimetric method as reported in Nino & Shah (1986), Aburahma & Kadhim (2023).

Determination of serum uric acid concentration

The concentration of the uric acid in serum was determined by colorimetric method using a commercially available kit (Uric Acid liquicolor assay kit) using the manufacturer's instructions (Ref. 10690, Human Diagnostic, Germany). The concentration was expressed as milligrams per deciliter (mg/dl).

Statistical analysis

Statistical analysis was conducted using SPSS 26 (IBM SPSS software). And presented as mean (standard deviation). One-way analysis of variance (ANOVA) was used to compare the mean values of the three groups by using the least significant difference as a Post Hoc Tukey test to make individual comparisons and the *P*-value was considered significant if it was < 0.05.

The Bivariate Pearson correlation was performed among the different studied groups, with the coefficient of correlation (r) used as an indicator for the strength of the relationship between vitamin D and other parameters. The correlations between the different serum vitamin D levels and other variables were detected using the Bivariate Pearson correlation. In all cases, a value of $p < 0.05$ was considered significant.

Ethical approval

The study was performed in accordance with the ethical guidelines of the Declaration of Helsinki and approved by the local ethics committee at College of Science, University of Baghdad.

Results

Baseline characteristics

The participants' baseline characteristics and level of serum 25(OH)D are shown in Table 1. This study included 110 participants diagnosed with RA. Their mean age was 50.15 ± ± 5.53 years, and 60.9% of them were females. The mean serum 25(OH)D level was 22.30 ± ± 10.92 ng/mL. When comparing female and male participants, no significant differences in mean of age and the level of serum 25(OH)D have been observed among them $p > 0.05$.

According to Endocrine Society guidelines (Holick *et al*., 2011), RA patients were categorized into three groups depending on their serum 25(OH)D level as follows (Table 2):

- Deficient group (25(OH)D ≤ 20 ng/mL; n = 50).
- Insufficient group (25(OH)D = = 21-29.9 ng/mL; n = 30).
- Sufficient group (25(OH)D ≥ 30 ng/mL; n = 30).

To investigate the effect of vitamin D levels on both vitamin C and uric acid levels in these patients' sera, a sufficient group (25(OH)D ≥

≥ 30 ng/mL) was used as a control in the current study.

The results in Table 2 demonstrated that serum 25(OH)D level in 72.73% (n = 80) among the total 110 RA patients revealed either vitamin D deficiency or insufficiency where 45.46% (n = 50) had vitamin D deficiency, and 27.27% (n = 30) had vitamin D insufficiency. Females were represented with 63.75% of them. While the vitamin D level was sufficient in only 27.27% (n = 30) out of 110 of the RA patients. Meanwhile there was no significant difference in the mean age between these groups of RA patients (p = 0.480).

Serum levels of vitamin C and uric acid

When vitamin C levels were measured in the RA patients the results in Table 3 showed that the mean serum vitamin C level in RA patients was 0.301 ± 0.051 mg/dl and there was no significant difference in this level between female and male participants (p = 0.108). When comparing the RA patients according to the levels of serum 25(OH)D level, the mean serum vitamin C level was significantly decreased in both RA groups with vitamin D-deficient and insufficient compared to those with the vitamin D-sufficient group (0.278 ± 0.04 and 0.305 ± ± 0.04 vs. 0.335 ± 0.04 mg/dl, respectively; p = = 0.0001, p = 0.031). Also, when comparing the mean value of serum vitamin C levels in vitamin D-deficient and vitamin D-insufficient groups, it was found there was a significant decrease in serum vitamin C levels between these two groups p = 0.027.

The results of uric acid level measurement were presented in Table 4 and the level was (6.98 ± 1.65 mg/dl) in the total number of the patients included in the current study. Meanwhile, there was a significant difference in this level between female and male participants (p = = 0.024). While no significant differences were found among the different levels of vitamin D groups in the RA patients (p = 0.527).

To understand the relationship between vitamin C levels and uric acid levels with vitamin D levels in RA patients, a Pearson correlation analysis between the two variables was performed. As shown in Figure 1, serum 25(OH) D levels were correlated with vitamin C levels (P = 0.0001) and Pearson's correlation coefficient indicated that this correlation was positive (r = 0.456, P = 0.0001). While there was no significant correlation between 25(OH) D levels and uric acid levels (P = 0.263).

Table 1

Baseline characteristics of the participants. Data were expressed as Mean ± SD and n (%) in categoric variables, respectively

Characteristic	Total	Female	Male	*P*-value
Sex, n (%)	110	67 (60.9%)	43 (39.1%)	–
Age (years)	50.15 ± 5.53	50.78 ± 5.38	49.19 ± 5.68	0.142
Serum 25(OH)D (ng/mL)	22.30 ± 10.92	23.11 ± 10.78	21.04 ± 10.99	0.335

Table 2

Baseline characteristics and serum 25 (OH) D level in different groups of serum 25 (OH) D level

Parameters	Vitamin D deficient group ≤ 20 ng/mL	Vitamin D insufficient group 21–29.9 ng/mL	Vitamin D sufficient group ≥ 30 ng/mL	*P*-value
Participants, n (%)	50 (45.46%)	30 (27.27%)	30 (27.27%)	–
Female, n (%)	35 (70%)	16 (53.33%)	16 (53.33%)	–
Male, n (%)	15 (30%)	14 (46.67%)	14 (46.67%)	–
Age (years)	50.64 ± 5.27	50.33 ± 5.14	49.1 ± 6.44	0.480
Serum 25(OH)D (ng/mL)	12.24 ± 4.91	24.94 ± 2.42	36.56 ± 4.04	0.0001**

**: refers to a high significant difference p < 0.01

Table 3

Mean ± SD level of vitamin C in RA patients with different vitamin D level

Characteristic	Vitamin C (mg/dl)	*P*-value
All participants (n = 110)	0.301 ± 0.051	–
Female (n = 67)	0.307 ± 0.05	0.108
Male (n = 43)	0.291 ± 0.05	
Vitamin D deficient group (n = 50)	0.278 ± 0.04^{**a*c}	0.0001**
Vitamin D insufficient group (n = 30)	0.305 ± 0.04^{*b}	
Vitamin D sufficient group (n = 30)	0.335 ± 0.04	

[a]: refers to significant differences between vitamin D deficient group and the vitamin D sufficient group;
[b]: refers to significant differences between the vitamin D insufficient group and the vitamin D sufficient group;
[c]: refers to significant differences between the vitamin D deficient group and the vitamin D insufficient group;
[**]: refers to high significant difference $p < 0.01$;
[*]: refers to significant difference $p < 0.05$.

Table 4

Mean ± SD level of uric acid in RA patients with different vitamin D level

Characteristic	Uric acid (mg/dl)	*P*-value
All participants (n = 110)	6.98 ± 1.65	–
Female (n = 67)	6.69 ± 1.58	0.024*
Male (n = 43)	7.42 ± 1.68	
Vitamin D deficient group (n = 50)	7.17 ± 1.69	0.527
Vitamin D insufficient group (n = 30)	6.83 ± 1.66	
Vitamin D sufficient group (n = 30)	6.79 ± 1.60	

*: refers to significant difference $p < 0.05$

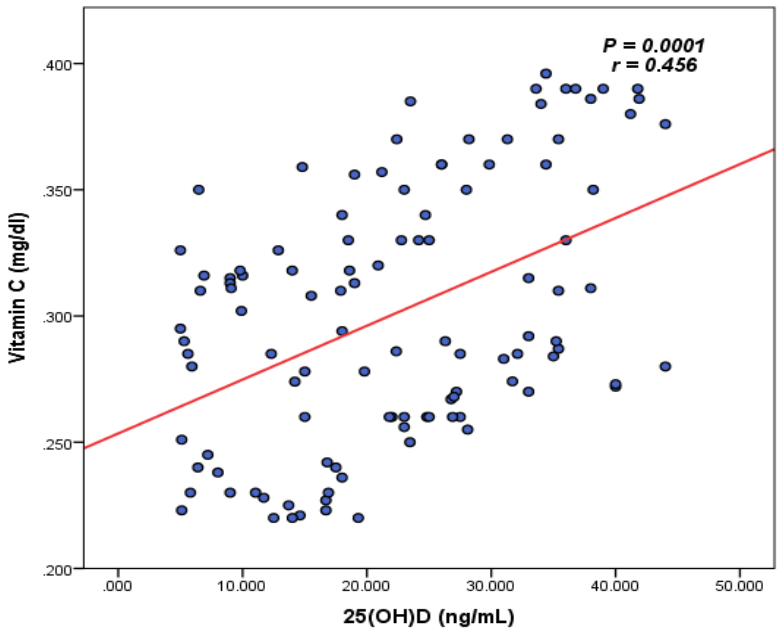

Fig. 1. Correlation between serum 25(OH) D levels and vitamin C levels

In contrast, there was a correlation between vitamin C levels and uric acid levels in the serum of all RA participants (P < 0.05) and Pearson's correlation coefficient indicated that this correlation was negative (r = -0.756, *P* = = 0.0001) (Fig. 2).

When comparing the correlations of vitamin C levels or uric acid levels according to the different levels of vitamin D, the results in Table 5 illustrated that there were no significant correlations (P > 0.05).

A negative correlation was observed between serum vitamin C levels and uric acid levels in all studied groups of RA patients as shown in Table 6 and Figure 3 (Group 1: *r* = -0.684, *P* = 0.0001; Group 2: *r* = -0.876, *P* = 0.0001; Group 3: *r* = -0.948, *P* = = 0.0001).

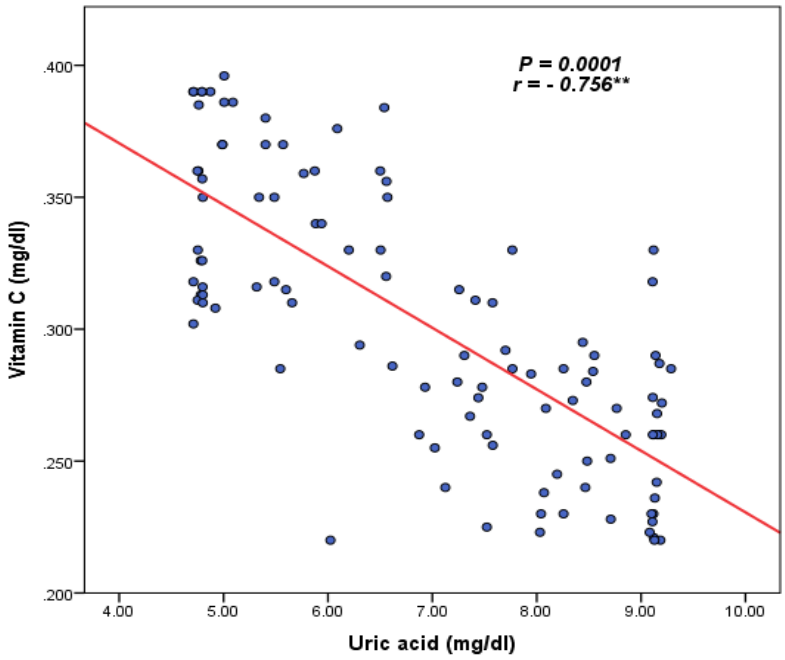

Fig. 2. Correlation between vitamin C level and uric acid level in serum of all participants

Table 5

Correlation analysis between the different level of serum 25(OH) D levels and levels of vitamin C and uric acid

Parameters	**25 hydroxyvitamin D levels**					
	Vitamin D deficient group (Group 1)		Vitamin D insufficient group (Group 2)		Vitamin D sufficient group (Group 3)	
	Pearson correlation		Pearson correlation		Pearson correlation	
	r	*P*-value	*r*	*P*-value	*r*	*P*-value
Vitamin C (mg/dl)	0.001	0.992	0.011	0.953	0.174	0.359
Uric acid (mg/dl)	-0.058	0.687	-0.11	0.955	-0.242	0.198

Table 6

Correlation analysis between uric acid level and serum vitamin C level

Parameter	Vitamin C levels					
	Vitamin D deficient group (Group 1)		Vitamin D insufficient group (Group 2)		Vitamin D sufficient group (Group 3)	
	Pearson correlation		Pearson correlation		Pearson correlation	
	r	*P*-value	*r*	*P*-value	*r*	*P*-value
Uric acid level	-0.684**	0.0001	-0.876**	0.0001	-0.948**	0.0001

**: correlation is significant at the 0.01 level (2-tailed)

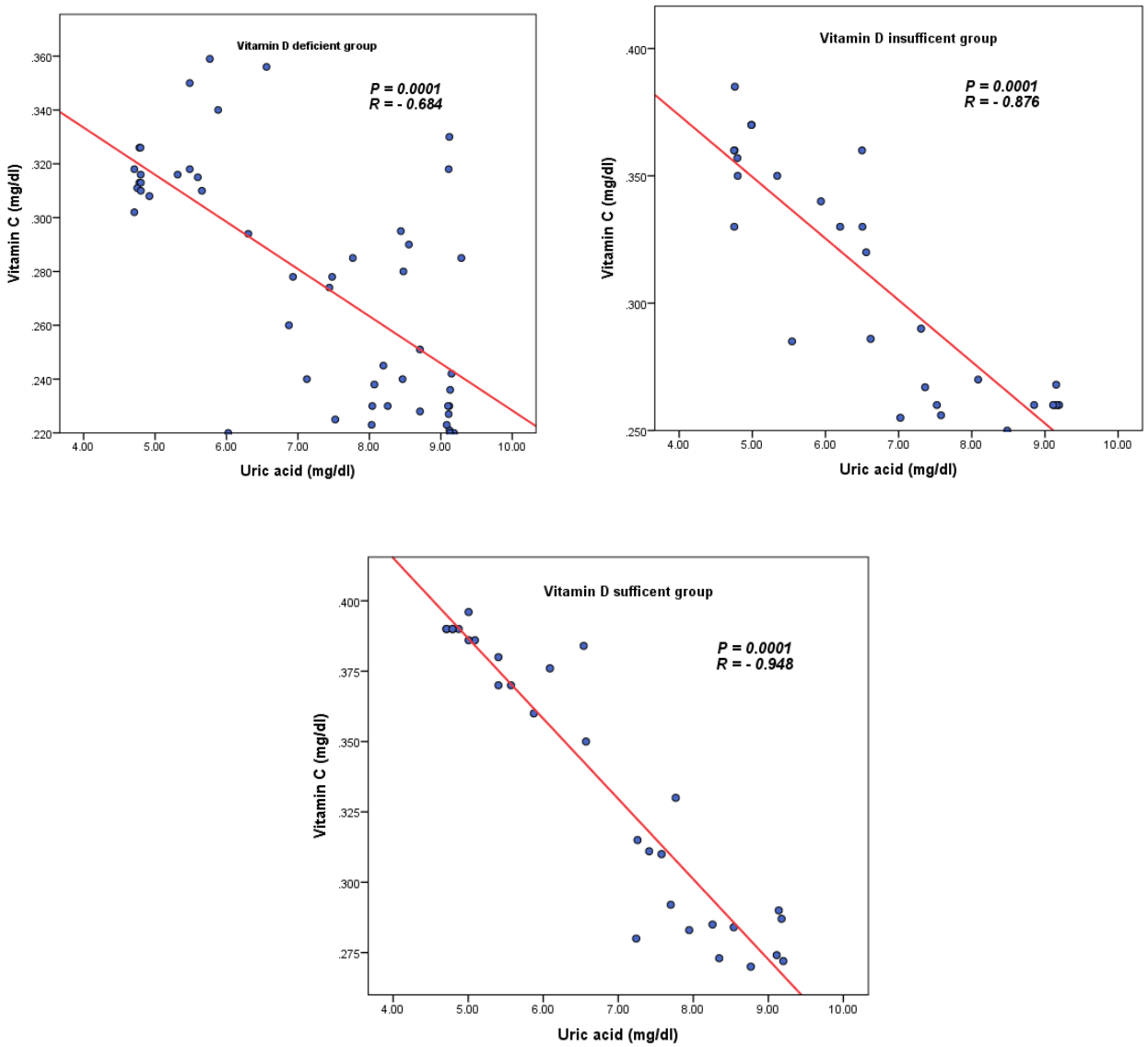

Fig. 3. Correlations between vitamin C level and uric acid level in the serum of the studied groups using Pearson's correlation coefficient

Discussion

In this study, the vitamin D level of the participants was variable. Only 27.27% of our RA patients had sufficient serum 25(OH)D (≥30 ng/mL), whereas 72.73% of RA patients had deficient or insufficient vitamin D levels (< 30 ng/mL). In females the percentage of those with vitamin D level < 30 ng/mL was higher (63.75%) than that in males (36.25%). Similar previous research has indicated that vitamin D insufficiency, or deficiency is common in patients with RA (Cecchetti *et al*., 2016; Lee & Bae, 2016; Hwaidi & Hasan, 2019; Qadir & Shnawa, 2022; Kaur & Sarao, 2023). For example, the prevalence of vitamin D level < 30 ng/mL in patients with RA was reported to be 59.5 % in France (Cecchetti *et al*., 2016), 76.5% in Iraq (Hwaidi & Hasan, 2019), and 80.6% in Saudi Arabia (Alharbi *et al*., 2023). Many patients with autoimmune diseases including RA have vitamin D insufficiency, however, it is unclear how and if low serum vitamin D contributes to RA risk (Gioia *et al*., 2020).

Humans have two types of immunity: innate (born) immunity and adaptive (acquired) immunity (Parkhe *et al*., 2023). Mazur *et al*. recently reported that vitamin D is one of the primary nutrients in the course of autoimmune disorders treatment (Mazur *et al*., 2022).

Vitamin D can modulate both immune responses, it has been shown to alter the innate and adaptive immune systems predominantly through toll-like receptors and the development of T-cells, primarily Th17 cells, which play a significant role in the pathophysiology of RA (Higgins *et al*., 2013). Moreover, vitamin D receptors are expressed in immune cells that are all capable of synthesizing the active form of vitamin D (Alpert, 2017). Based on research by Deluca and Cantorna in animals, vitamin D when present in appropriate concentrations, acts as an immunosuppressant significantly suppressing autoimmune disorders (Deluca & Cantorna, 2001).

Besides vitamin D, vitamin C also serves to enhance the immune system, reducing the risk of autoimmune disorders; it is one of the most famous immune-boosting vitamins (Schoor, 2019) so as an antioxidant and anti-inflammatory measure, serum vitamin C was determined and an interesting result was that all of RA patients in the current study had low values (Table 3), less than the normal range (0.6-2 mg/dl) (Nino & Shah, 1986) and this was observed even between female and male RA patients. Numerous conditions involving physiological stress, infections, surgery, traumas, and burns, alter vitamin C metabolism, and vitamin C levels may decline substantially (Hemilä & Chalker 2019). The present findings were in agreement with several studies that reported a low level of vitamin C in RA patients such as the studies conducted by Mateen *et al* in India in their study on ROS formation (Mateen *et al*., 2016) and Das *et al* in Bangladesh in their study a different biochemical parameter in RA patients (Das *et al*., 2021). Thus, the decrease observed in the level of vitamin C in the present study can be explained as the following: the etiology of rheumatoid arthritis has been linked to inflammation and tissue injury-related oxidative stress. Generally, at the site of inflammation and tissue damage, free radicals become extremely high. Since in such a condition, inflammatory cytokines delay neutrophil apoptosis, this leads to an increased generation of reactive oxygen species which causes bone and joint damage (Vijayakumar *et al*., 2006). And since vitamin C is one of the most important endogenous antioxidants and it is the first antioxidant oxidized upon leukocyte stimulation as well as it protects plasma lipids from peroxidative damage caused by aqueous peroxyl radicals or activated polymorphonuclear cells (Jaswal *et al*., 2003). All these will result in decreased vitamin C level. Vitamin C also is important to vitamin D function through acting as a co-factor of hydroxylating enzymes which are important for the transformation of vitamin D_3 into active metabolites as well as, it is required for forkhead box P3 (Foxp3) protein expression to maintain immunological homeostasis (Weister *et al*., 1988; Cantatore *et al*., 1991; Sasidharan *et al*., 2016).

Another important powerful antioxidant in human body fluid is uric acid which presents in high concentrations in plasma (Esnafoglu & Ertürk, 2023; Kondo & Okada, 2023). The re-

sult of the present study Table 4 showed that uric acid levels even though high in the vitamin D deficiency group are not statistically significant $p = 0.527$. This agreed with several studies that have confirmed an association between vitamin D deficiency and hyperuricemia (Peng *et al*., 2013; Isnuwardana *et al*., 2020; Zhang *et al*., 2020; Nimitphong *et al*., 2021). The mechanism of these observations is unknown. *In vivo*, hyperuricemia has been demonstrated to inhibit 1-hydroxylase, decreasing vitamin D levels (Chen *et al*., 2014). Furthermore, a deficiency of vitamin D may stimulate the parathyroid, leading to a release of parathyroid hormone, which was considered to increase serum uric acid levels (Zhang *et al*., 2020).

The present findings concerning the negative correlation between vitamin C level and serum uric acid level (Table 6, Fig. 3) were in agreement with the previous findings of Das et al. that in rheumatoid arthritis patients, high levels of uric acid provide antioxidant protection against free radicals, while low levels of vitamin C are related to its urate radical repairing and free radical scavenging action (Das *et al*., 2014). Vitamin C in the plasma is essential for uric acid's antioxidant activity (Sautin & Johnson, 2008). Kuzkaya *et al*. demonstrated that in the extracellular space, uric acid is a unique peroxynitrite scavenger but it cannot scavenge superoxide, and both vitamin C and thiols is essential for complete peroxynitrite scavenging (Kuzkaya *et al*., 2005). On the other hand, at higher concentrations, urate acts as a pro-oxidant, depleting vitamin C, inducing vitamin E depletion, and increasing lipid peroxidation and then hyperuricemia may raise the risk of several conditions associated with increased oxidative stress via this pro-oxidant mechanism (Benzie & Strain, 1996). Maple and Mason demonstrated that vitamin C not only scavenges reactive oxygen species but also repairs the urate radical generated via the free radical attacks on uric acid (Maples & Mason, 1988). As a result of the oxidative stress, the uric acid level increases while the vitamin C level decreases.

Conclusion

In conclusion, the result of this study indicated that the RT patients suffered from vitamin C deficiency regardless of the level of vitamin D. Meanwhile they had hyperuricemia which had a negative correlation with vitamin C. Therefore, they should be examined holistically, and vitamins should be at normal levels as well as pharmacological therapy could be enhanced by adding a complementary therapy of vitamins to ensure proper immune system functioning.

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