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Vitamin D_3, C, E and Sialic acid in Serum of Hyperuricemia Patients

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Abstract:
Hyperuricemia is commonly diagnosed with abnormal purine metabolism. Prolonged hyperuricemia often associated with gout, which is a vital risk factor for joint dysfunction. Our study aimed to determine the bidirectional association between vitamins (D_3, C, E) and sialic acid in hyperuricemia patients, which assessed the association between serum uric acid and vitamins measured in this study. Materials and methods: The study was conducted on 98 blood samples were collected from males and females at a ratio (1:1), 48 of which were control subject and 48 of which were from patients with hyperuricemia, whose age ranged from (25 years and above), during a period from September to December 2021, from Al-Salam Teaching Hospital in Mosul city, Iraq, serum samples were separated and stored in capped tubes, then we measured the level of (D_3, C, E) and sialic acid. The results indicated that the level of vitamin D_3 and E decreased in hyperuricemia patients (the differences between control subjects and hyperuricemia patients were significant at ($p \leq 0.05$), but vitamin C and sialic acid increased significantly at ($p \leq 0.05$) compared to control subject.
Keywords: hyperuricemia, vitamin D_3, vitamin C, vitamin E, uric acid, sialic acid.

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Introduction

Uric acid is the final product of purine metabolism in humans. Hyperuricemia is a metabolic disease that results from either an increased formation or decreased excretion of uric acid in the blood. Studies show that elevated blood uric acid is closely related to the generation of reactive oxygen species (ROS). In the human body, xanthine oxidoreductase (XOR) catalyzes the oxidative hydroxylation of hypoxanthine to xanthine to uric acid, with reactive oxygen species (ROS) production [1]. Normal levels of uric acid in human blood are usually defined as higher than (7.0 mg/dl) in men and higher than (5.7 mg/dl) [2] or (6.0 mg/dl) [3] in women, or higher than (7.7 mg/dl) in men and higher than (6.6 mg/dl) in women [4]. When the levels of uric acid in the blood exceed the normal limits monosodium urate begins to crystallize and deposit in the joints and surrounding tissues to cause gout or gouty arthritis, tophi, kidney stones and urate nephropathy [5]. Hyperuricemia is associated with many chronic diseases such as high blood pressure, diabetes mellitus, metabolic syndrome, kidney and cardiovascular diseases [6].

Vitamins

Vitamins are complex organic compounds and are essential and required in small amounts for normal metabolic processes. The absence or deficiency of these nutrients causes disorders, while the resupply of these nutrients can treat the symptoms of deficiency. Vitamins are divided into two main classes: water-soluble vitamins, which

include a group of B and C vitamins, and fat-soluble vitamins, which include fat-soluble vitamins A, D, E, and K. Fat-soluble vitamins bind to fats and are absorbed along with dietary fats [7].

Vitamin D_3

It is a group of fat-soluble vitamins traditionally known for its role in maintaining the balance of calcium and phosphorous in the body. Vitamin D is found in two common forms, vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol). Vitamin D3 is produced in the skin by exposure to sunlight and can be found in foods of animal origin. Vitamin D2 is found in plants, especially in mushrooms and yeast [8]. Studies have shown an inverse relationship between the level of 1, 25-dihydroxy vitamin D (cholchalceferol) and the level of uric acid in the blood [9].

Vitamin C

Vitamin C, or ascorbic acid, is a water-soluble vitamin that works in the body as an antioxidant and cofactor for many enzymes. Vitamin C performs several functions, as it can directly scavenge ROS, such as superoxide and peroxynitrite, thus preventing damage to cellular proteins. It can also reactivate other ROS scavengers, such as glutathione (GSH) and alpha-tocopherol, by donating a single electron to these compounds [10]. Studies have indicated that vitamin C supplementation has an effect on lowering serum uric acid concentrations, which may be beneficial for the prevention of gout [11].

Vitamin E

It is one of the fat-soluble vitamins and is considered one of the main antioxidants in the body. One of the most important functions of vitamin E is to fight free radicals as well as protect the body from the harmful effects of active oxygen compounds (ROS) resulting from metabolism or to which the body may be exposed to from the environment [12,13]. A study conducted in the United States evaluating the relationship between vitamin E supplementation and hyperuricemia demonstrated an association between increased vitamin E intake and a decrease in hyperuricemia [14].

Sialic acid

Sialic acids are a subgroup of acidic polysaccharides with a carbon skeleton of nine carbon atoms containing approximately fifty derivatives of neuraminic acids. The term "sialic acid" first appeared in 1952 to describe N-acetylneuraminic acid, a major product released by the mild acid hydrolysis of glycolipids in brain or salivary mucins [15]. The most recently described property of sialic acid is its antioxidant and free radical scavenging effect, which can be particularly important on the endothelium of blood vessels [16]. Increased sialic acid has been observed in many diseases such as myocardial infarction, diabe tes, tumors, and alcoholism. Serum sialic acid also increases during inflammatory processes because of elevated concentrations of sialylated-rich glycoproteins in the acute phase [17].

Material and methods

Subjects

During this study, 98 blood samples were collected from males and females at a ratio of (1:1), 48 of which were as control group and 48 of which were from patients with hyperuricemia in the blood, whose ages ranged from

(25 years and over). During a period from September to December 2021, from Al-Salam Teaching Hospital in Mosul city, Iraq.

Collection of blood serum samples

Five ml of blood were drawn from the subjects. Serum samples were separated, and then kept in clean and tightly covered tubes at a temperature of -20 ^{o}C until use.

Estimation of biochemical parameters

Uric acid level was estimated by following the enzymatic method (Uricase Enzyme), using kit manufactured from the French company Bio Labo [18, 19]

Vitamin D_3 concentration was estimated by using Cobas e 411 device, which operates on the principle of electrochemiluminescence, and using the kit manufactured specially for the device, which is based on the principle of competitive protein binding assay [20]

Vitamin C level was determined by oxidation of ascorbic acid with copper to form dihydro ascorbic acid (DHAA) and (Diketo Glonic Acid), then these products reacted with (2, 4- dinitro phenyl hydrazine) and by adding thiourea A derivative (Bis-2, 4-Dinitro Phenyl Hydrazine) is formed and in the presence of sulphuric acid a product is formed that gives an absorption band at a wavelength of (520 nm) [21].

Vitamin E level was estimated using a method based on redox reactions called (Emmeric- Engle Reaction), this method is based on the reduction of the ferric ion to ferrous by tocopherol and then the ferric ion reacts with α- ά-Dipyridyl solution to form a red-orange complex whose absorbance is measured at 520 nm [22].

Sialic acid concentration was determined by the modified method of Mittinen and Luukkainen (1959) [23].

Statistical analysis

The data analysis is performed using SPSS 26. All results are expressed as the mean ± standard error (SE). The results have been analyzed statistically using t-test to find the significant differences between the study groups and the probability level $P \leq 0.05$ is considered significantly as well as the correlation coefficient is used (Person's moment correlation) for the purpose of determining the existence of an effective correlation between the studied variables.

Results and discussion

The level of biochemical variables measured in blood serum of patients with Hyperuricemia in the blood compared to control group:

The results shown in Table 1 indicate that there is a significant increase in the level of uric acid at the level of probability ($p \leq 0.05$) in patients with hyperuricemia (8.55 ± 0.16) mg/100 ml compared to control group (4.86 ± 0.14) mg/100 ml . The reason for the increase in the level of uric acid is attributed to an increase in the intake of foods rich in purines or more commonly, a decrease in its secretion, as the increase in absorption or decrease in the secretion of uric acid in the renal tubules leads to an increase in its levels in the blood [24]. The results in Table 1 also show that there is a significant decrease in the level of vitamin D_3 concentration and at the level of probability ($p \leq 0.05$) in the blood serum of patients with high uric acid (21.07 ± 0.75) ng/ml. This can be explained by the fact that the increase in uric acid can lead to the inhibition of 1α-hydroxylase, which prevents the conversion of the (1, 25 hydroxy vitamin D) form of vitamin D into the active form cholecalciferol (1, 25 dihydroxy vitamin D) and thus an increase in the level of (1, 25 hydroxy vitamin D) but a decrease in the active form of cholecalciferol (1, 25 dihydroxy vitamin D) [25], this result agrees with the finding of authors (Y.-Y. Zhang et al., 2020) [26].

A significant increase shown in the level of vitamin C (0.76± 0.02) mg/dl at the probability level ($p \leq 0.05$) ,Vitamin C works as an antioxidant and a scavenger for free radicals, and the reason for its rise may be due to taking vitamin C supplements by patients in order to reduce uric acid levels in the blood, where the authors (Liu et al., 2021) found that taking vitamin C supplements plays an important role in reducing uric acid levels in the blood [27], also a significant decrease was found at the probability level ($p \leq 0.05$) in the level of vitamin E (0.37± 0.03) mg/l in patients, This is probably due to the protective role of vitamin E against oxidative stress in humans, as it is a

fat-soluble antioxidant and has a strong efficacy in scavenging free radicals in the body [28]. There was also a significant increase at the probability level ($p \leq 0.05$) in sialic acid (6.28 ± 1.79) µg/ml as shown in Table 1. The reason for the high concentration of sialic acid is attributed to its role as an antioxidant as a scavenger of hydrogen peroxide H_2O_2. Sialic acid rises during inflammatory processes because of increased concentrations of glycoproteins rich in sialylates. High sialic acid is an indicator of inflammatory conditions [29].

Table 1 Level of biochemical parameters measured in the blood serum of patients with hyperuricemia compared to healthy subjects

Biochemical Parameters	Control group n=48		Patient group n=48		P-value
	Mean	SE	Mean	SE	
Uric acid(mg/dl)	4.86	0.14	8.55	0.16	0.05*
Vitamin D_3 (ng/ml)	38.88	0.92	21.07	0.75	0.05*
Vitamin C (mg/dl)	0.56	0.01	0.76	0.02	0.05*
Vitamin E (mg/L)	0.75	0.05	0.37	0.03	0.05*
Sialic acid (µg/ml)	4.21	0.12	6.28	1.79	0.05*

* Indicates that there is a significant difference at the probability value $p \leq 0.05$

Correlation between uric acid and biochemical parameters measured in the serum of patients with hyperuricemia: The relationship of uric acid with the biochemical variables measured in the blood serum of patients with hyperuricemia shown in Table 2 was studied by finding the linear correlation coefficient (r).

Table 2 Correlation between uric acid level and biochemical parameters measured in the serum of patients with hyperuricemia

Biochemical Parameters	Patients group n=48	
	r-value	p- value
Vitamin D_3 (ng/ml)	0.256	P≥0.05
Vitamin C (mg/dl)	0.007	P≥0.05
Vitamin E (mg/L)	-0.223	P≥0.05
Sialic acid (µg/ml)	0.437**	P≤0.01

** Indicates that there is a significant difference at the probability value $p \leq 0.01$

A direct significant relationship at the level of probability ($P \leq 0.01$) shown in Table 2 between the concentration of uric acid and the level of sialic acid concentration, where it is shown that with an increase in the concentration of uric acid, the concentration of sialic acid increases. Some studies showed that sialic acid has an antioxidant role as it is a scavenger for hydrogen peroxide H_2O_2 [30], and the reason for this positive relationship may be due to this property of sialic acid. Moreover, there are no significant correlations between uric acid level and other measured biochemical parameters.

The effect of sex on the level of biochemical parameters measured in the blood of patients with Hyperuricemia: The effect of sex factor was studied on the level of all biochemical parameters that were measured in serum of patients with hyperuricemia, as shown in the Table 3 and Figure 1, there is a significant decrease in the concentration of vitamin D_3 in male patient compared to female patients, And no significant differences shown between male and female groups in other biochemical parameters.

Table 3 The effect of sex on the level of biochemical parameters measured in the blood of patients with Hyperuricemia

Biochemical Parameters	Male n=24		Female n=24		P-value
	Mean	SE	Mean	SE	
Uric acid(mg/dl)	8.85	0.21	8.27	0.26	p≥0.05
Vitamin D_3 (ng/ml)	19.60	1.06	22.55	0.99	p≤0.05*
Vitamin C (mg/dl)	0.77	0.03	0.76	0.02	p≥0.05
Vitamin E (mg/L)	0.34	0.05	0.41	0.05	p≥0.05
Sialic acid (µg/ml)	6.52	0.48	6.06	0.20	p≥0.05

* Indicates that there is a significant difference at the probability value $p \leq 0.05$

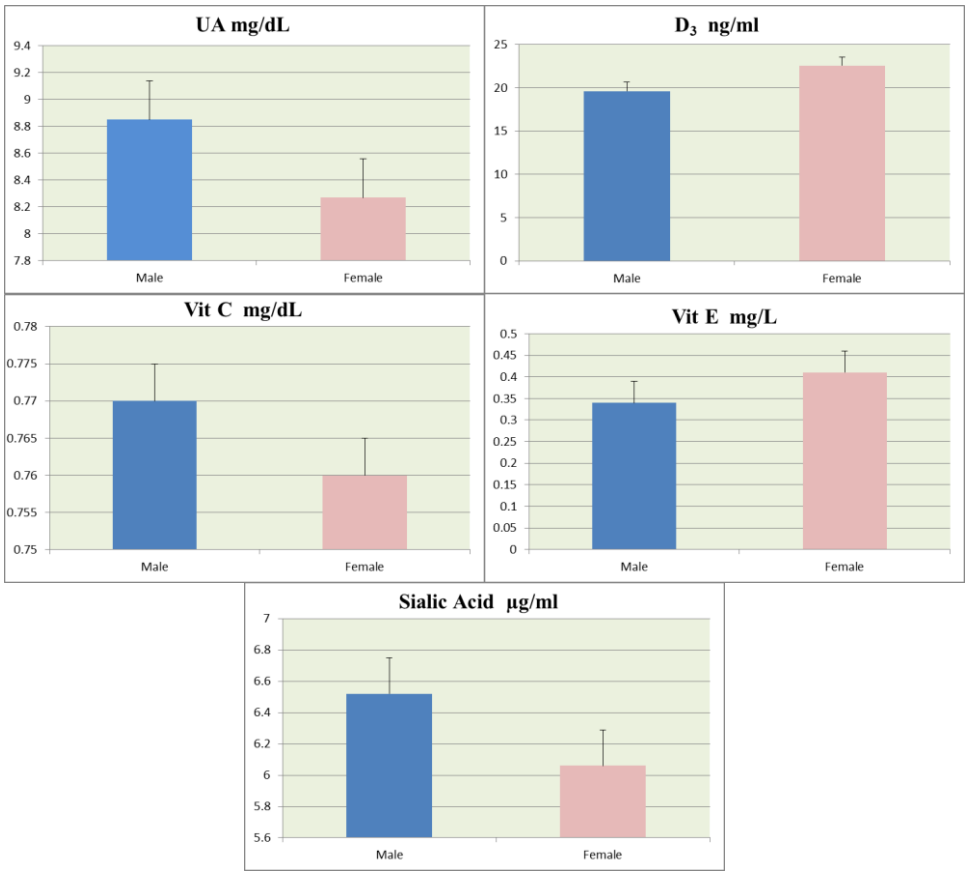

Figure 1: Effect of sex on level of (uric acid, vitamin D3, C, E and sialic acid) in serum of hyperuricemia patients

Conclusion

By this study, we concluded that vitamin D_3 deficiency is associated with high concentration of uric acid in serum of patients with hyperuricemia also decreased level of vitamin E as a result of increased oxidative stress within the cell and this is due to increased uric acid concentration in the blood.

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