Implementing High Vitamin C Treatments to Decrease Blood Uric Acid Levels in Hyperuricemic Saudi Patients

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Abstract: This study was conducted to determine the effects of high vitamin C intake from diet and supplements on serum uric acid concentrations during 2 months. A group of 30 Saudi adults, nonsmokers, hyperurecemic, from both genders and aged between 20-70 yrs. Participants were divided into 3 groups; control group (low purine diet with normal vitamin C intake), high dietary vitamin C with purine restricted diet and high vitamin C supplements with purine restricted diet. The high vitamin C dose was 500mg/day. All participants have been followed-up for two months and reviewed at least two times a week. Uric acid, creatinine and estimated glomerular filtration rate were measured before and during the study. The overall mean reduction of uric acid for dietary treated group was -0.77 mg/dl and for supplemented group was -0.28 mg/dl. In the control group, the average uric acid was incremented after 2 months by 0.51 mg/dl. Reduction in serum uric acid was statistically significant for dietary treated group but not for supplemented one. This study suggests that inclusion of 500 mg/day of vitamin C for 2 months reduced risk factors associated with hyperuricemia. Dietary treatment was more effective in reduction serum uric acid than supplements.
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1. Introduction

Vitamin C is an essential water soluble micronutrient that participates in a number of important enzymatic reactions. It also acts as a antioxidant to prevent oxidative damage by free radicals, which protects tissue from oxidative stress (**Rolfes *et al.*, 2009**).

Uric acid is a waste product normally present in the blood as a result of the breakdown of purines. Excessive amounts of serum uric acid is known as hyperuricemia (serum uric acid more than 7 mg/dl males and more than 6 mg/dl females), which can cause crystals to form in the joints and cause gout (**Eustice, 2005**). Although hyperuricemia alone is not sufficient to cause gout, a dose-response relationship between serum uric acid and the risk of developing gout is well documented (**Campion *et al.*, 1987**).

In previous studies, vitamin C exerts a uricosuric effect that may be beneficial for hyperuricemic patients (**Mitch *et al*., 1981**). By increasing urinary excretion of uric acid, vitamin C may reduce serum concentrations of uric acid that at high levels could become crystallized in the joint and kidney and lead to gout and kidney stones (**Berger *et al*., 1977; Combs, 2008; Choi *et al*., 2009**).

All studies have been used high vitamin C tablets to decrease blood uric acid. However, no detailed studies on the effect of high vitamin C intake from diet on blood uric acid levels. Therefore, this study is occurred to determine the effects of high vitamin C intakes from diet and supplements on serum uric acid concentrations during 2 months period, and finding out the relationship of different vitamin C treatments on blood uric acid, creatinine levels and glomerular filtration rate (GFR).

2. Material and Methods

Subjects

A group of 30 Saudi adults, nonsmokers, equally from both genders, aged between 20-70 years old with hyperuricemia (serum uric acid higher than 6 mg/dl for females and 7 mg/dl for males) or diagnosed with gout before at least one year were recruited from Al-Noor Hospital in Makkah (Saudi Arabia). Exclusion criteria were; smoking, history of dialysis, patients less than 20 yrs. old, alcohol consumption, pregnant or lactating women and patients used drugs that reduce uric acid. Approval of Ethics Committee for this research was obtained from the University of Umm Al-Qura Ethics Committee of Research Projects.

Study Protocol

Eligible persons were randomly and equally assigned to one of the three study groups: 1) control group (Purine Restricted Diet Group (PRD), 2) vitamin C supplements group (High Vitamin C Supplements-Purine Restricted Diet Group (CS-PRD), and finally 3) vitamin C-rich diet group (High Dietary Vitamin C-Purine Restricted Diet Group (CD-PRD). Patients in the control group (PRD) took normal vitamin C requirements according to RDA with low purine diet. In the second group (CS-PRD), they took 500 mg/day vitamin C chewable tablets with low purine diet. While, the third study group (CD-PRD) took 500 mg/day vitamin C-rich fruits and vegetables with low purine diet. All participants have been followed-up for

two months and each subject had been reviewed weekly.

At the beginning of the study, a basic information questionnaire was completed by each participant, which include; personal information, educated level, medical and drug history information, anthropometric measurements, and the rate of vitamin C consumption during the study period. Nutritional counseling about their disease, servings size from each food pyramid group, portion size, food type and preparation method, the relation between vitamin C and disease, avoidance of high purine foods, medical conditions that could affect their health status and other nutritional recommendations all were explained to the patients by expert nutritionists.

As mentioned before, high vitamin C was intervened to patients by diets and drugs. Chewable tablets contain 500 mg vitamin C were purchased from local pharmacy. On the other hand, the vitamin C-rich fruits and vegetables were purchased from local supermarket every two weeks and delivered to the patient's houses. With regard to diet treated group, 500 mg vitamin C from fruits, vegetables and juices were calculated from USDA Food Composition Data, Release 18 (**USDA, 2005**), as well as Food Composition Table (**Rolfes *et al.*, 2009**). As seen in Table 1, seven different packages with different foodstuffs each equal about 500 mg vitamin C were admitted to subjects participated in CD-PRD study group. Each package was consumed every day.

The 500 mg vitamin C intervention dose was recommended in this study as concluded results from researches as the superior dose that reduced uric acid efficiently (**Gao *et al.*, 2008; Choi *et al*., 2009**).

Blood Sample Collection

Subjects have been accepted for participating in the study after completing the consent form. Three blood samples were taken from each patient during the study period; at the beginning before the intervention, retested after the first month and collected again after two months. Twelve hours fasting blood samples have been collected from patients. Six mg blood sample was withdrawn with special needle. The blood samples were allowed to clot for no more than 15 minutes and saved in icebox.

Biochemical Analysis

The blood samples were centrifuged at 4500 rpm for 6 minutes at room temperature by normal centrifuge. Serum specimens were portioned and stored at -30 ^{o}C for biochemical tests. Serum uric acid and creatinine concentrations were analyzed by specific kits using Dimension Vista System (SIEMEMS**,** Camberley, UK**)**. Estimated GFR in ml/min/1.73 m^2 was calculated according to the Modification of Diet in Renal Disease equation by **Levey *et al*. (1999)** as:

$$GFR = 186 \times (\text{serum creatinine in mg/dl})^{-1.154} \times \text{age}^{-0.203} \times 0.742 \text{ (if female)} \times 1.21 \text{ (if African origin)}.$$

Statistical Analysis

Statistical analysis was performed with SPSS (Statistical Package for Social Sciences) software version 17. Paired test was used for determining the significances between means. P-value less than 0.05 consider statistically significant.

3. Results

All subjects completed the study duration and treatments. The average intake of vitamin C in mg/day for the RPD, CS-PRD and CD-PRD groups were (mean ± S.D) 60.8±25.1, 507.7±12.7 and 445.5±91.3, respectively. No significant difference was shown between the last two groups.

Table 2 shows the characteristics of the study groups. Five males and 5 females in each group were recruited in this study. No significant differences in mean age and BMI between groups. According to the BMI, participants in dietary treated group (CD-PRD) were under obese category, while other two groups were under overweight. High percent of chronic diseases were found in study groups. Renal problems and hypertension were the most observed chronic diseases.

Uric Acid, creatinine and estimated GFR levels during 60 days study period are found in Table 3. Uric acid of the control group increased after 60 days by about 5.25%, while it decreased 12.85% and 3.67% for the dietary treated group (CD-PRD) and supplements treated (CS-PRD), respectively. The decreasing was statistically significant ($P < 0.05$) in CD-PRD group but not in the CS-PRD (Figure 1). After 30 days, the reduction percent in uric acid was similar between treated groups (about 11% each), whereas after 60 days the reduction in uric acid further increment in CD-PRD group but diminished in the other group. From the same table, creatinine levels of vitamin C treated groups decreased remarkably but not significantly after 60 days. Control group also showed slightly decreased in creatinine concentration. On the other hand, estimated GFR increased meaningfully in treated groups after 60 days, and weakly increased in the control group.

Table 4 demonstrates average differences in uric acid for the groups after 2 months. For the control group, uric acid was increased by a mean of 0.51 mg/dl, and the increment was higher in women than men participants. In contrast, the average changes in uric acid for CS-PRD and CD-PRD were -0.28 mg/dl and -0.77 mg/dl, respectively. The reduction was higher in females than males.

Table 1: Packages of 500 mg/day vitamin C food items

Food item	NDB_No*	Common measure	Vitamin C (mg)	Total vitamin C
Package 1				
Oranges, raw	09200	1 orange	69.7	502.7 mg
Tangerine, raw	09218	1 tangerine	22.4	
Tomatoes, red, ripe, raw	11529	2 tomatoes	31.2	
Papayas, raw	09226	1 papaya	187.9	
Strawberries, raw	09316	1 cup	97.6	
Grapefruit juice, pink, raw	09404	1 cup	93.9	
Package 2				
Kiwi fruit, fresh, raw	09148	1 medium	70.5	500.6 mg
Molokhia**	---	100 g	77.4**	
Lemon raw without peel	09150	1 lemon	30.7	
Mango, raw	09176	1 mango	57.3	
Orange juice, raw	09206	1 cup	124.0	
Turnip green, cooked, boiled, drained, without salt	11569	1 cup	39.5	
Peppers, sweet, green, cooked, boiled, drained, without salt	11334	1 cup	101.2	
Package 3				
Arugula leaves, raw***	8683****	1 cup	27	500.8 mg
Grapefruit, raw, pink and red	09112	1 grapefruit	76.8	
Pineapple, raw	09226	1 cup	56.1	
Guava, raw***	987****	1 guava	156	
Oranges, raw	09200	1 cup	95.8	
Kohlrabi, cooked, boiled, drained, without salt	11242	1 cup	89.1	
Package 4				
Raspberries, raw	09302	1 cup	32.2	499.0 mg
Broccoli, raw	11090	1 cup	78.5	
Peas, edible-podded, boiled, drained, without salt	11301	1 cup	76.6	
Watermelon, raw	09326	1 wedge	23.2	
Pears, raw	09252	2 pears	14	
Pepper, sweet, green, raw	11333	1 cup	119.8	
Lemon raw without peel	09150	1 lemon	30.7	
Orange juice, raw	09206	1 cup	124.0	
Package 5				
Cabbage, raw	11109	1 cup	22.5	499.7 mg
Melon, cantaloupe, raw	09181	1 cup	58.7	
Pepper, sweet, red, raw	11821	1 cup	283.7	
Grapes, red or green	09132	1 cup	17.3	
Broccoli, cooked, boiled, drained, without salt	11091	1 cup	101.2	
Celery, raw	11143	1 stack	1.2	
Lettuce, iceberg, raw	11252	1 head	15.1	
Package 6				
Brussels sprouts, cooked, boiled, drained, without salt	11099	1 cup	96.7	499.1 mg
Tomatoes, red, ripe, raw	11529	2 tomatoes	31.2	
Lemon juice, canned or bottled	09153	1 cup	60.5	
Kiwi fruit, fresh, raw	09148	1 medium	70.5	
Strawberries, raw	09316	1 cup	97.6	
Pineapple, raw	09226	1 cup	56.1	
Papayas, raw	09226	1 cup	86.5	
Package 7				
Cauliflower, cooked, boiled, drained, without salt	11136	1 cup	56.3	499.2 mg
Mango, raw	09176	1 mango	57.3	
Orange juice, raw	09206	1 cup	124.0	
Grapefruit, raw, pink and red	09112	1 grapefruit	76.8	

Pepper, sweet, green, raw	11333	1 cup	119.8
Melon, cantaloupe, raw	09181	1 cup	58.7
Apple, raw, with skin	09003	1 apple	6.3

* NDB_No is codes for USDA Nutrition Database.
* *Molokhia (*Corchorus olitorius)* vitamin C content is obtained from Zighichi *et al* (2003).
*** Data obtained from Food Composition Table.
**** Code Numbers are DA+ code for Wadsworth Diet Analysis Program.

Table 2: Baseline Characteristics of the Study Participants

Characteristic \ Group	PRD (n=10)	CS-PRD (n=10)	CD-PRD (n=10)
Age (year)	58 ± 12.03	44.18 ± 15.99	42.04 ± 8.23
Education beyond high school %	50.4%	37.2%	62.1%
Weight (Kg)	81 ± 18.74	71.05 ± 26.25	81.89 ±18.85
Height (m)	1.65 ± 0.09	1.55 ± 0.09	1.57 ± 0.1
BMI (Kg/m^2)	29.23 ±3.27	28.88 ± 10.09	33.22 ± 9.62
Family history with hyperuricemia %	25.0%	18.2%	7.7%
Chronic diseases* %	70.5%	86.4%	76.2%

- Results are considered as Mean ± S.D.
- PRD; Purine Restricted Diet, CS-PRD; High Vitamin C Supplements-Purine Restricted Diet, CD-PRD; High Dietary Vitamin C-Purine Restricted Diet, BMI; Body Mass Index.

* Chronic diseases; Diabetes mellitus, Hypercholesterolemia, Renal problems, Hypertension and/or Cardiovascular diseases

Table 3: Uric Acid, creatinine and estimated GFR for groups during the study period

Parameter \ Group	PRD (n=10)	CS-PRD (n=10)	CD-PRD (n=10)
Uric acid (mg/dl)			
At zero time	8.85 ± 2.13	8.18 ± 1.70	7.73 [a] ± 3.27
After 30 days	9.24 ± 2.33 (4.22%)*	7.36 ± 1.52 (-11.14%)*	6.96 ± 3.57 (-11.06%)*
After 60 days	9.34 ± 2.41 (5.25%)*	7.89 ± 1.45 (-3.67%)*	6.85 [b] ± 2.72 (-12.85%)*
Creatinine (mg/dl)			
At zero time	1.67 ± 0.56	3.11 ± 2.74	2.12 ± 1.54
After 30 days	1.58 ± 0.3	2.57 ± 2.22	1.76 ±1.18
After 60 days	1.60 ± 0.50	2.37 ± 2.17	1.75 ± 1.14
Estimated GFR**			
At zero time	46.41 ± 17.44	46.84 ± 38.97	55.22 ± 45.03
After 30 days	47.47 ± 15.60	50.48 ± 36.72	59.68 ± 43.29
After 60 days	48.21 ± 17.70	61.19 ± 55.40	65.63 ± 54.0

- Results are considered as Mean ± S.D.
- Means with different superscripts are significantly different at $P < 0.05$.
- PRD; Purine Restricted Diet, CS-PRD; High Vitamin C Supplements-Purine Restricted Diet, CD-PRD; High Dietary Vitamin C-Purine Restricted Diet, GFR; glomerular filtration rate.

* Percentage of changes in uric acid as compared with zero time within each group. Negative results are mean percent reduction in uric acid.

** Estimated GFR in ml/min/1.73 m^2 was calculated according to the Modification of Diet in Renal Disease equation.

Table 4: Average changes in uric acid levels (mg/dl) after 2 months

Parameter \ Group	PRD (n=10)	CS-PRD (n=10)	CD-PRD (n=10)
Average difference in uric acid for men (n=5)	0.27 ± 1.17	-0.03 ± 1.68	-0.72 ± 0.21
Average difference in uric acid for women (n=5)	1.23 ± 0.08	-1.02 ± 1.82	-0.80 ± 1.38
Average difference in uric acid for total (n=10)	0.51 ± 1.068	-0.28 ± 1.98	-0.77 ± 0.98

- Negative results are mean reduction in uric acid.
- PRD; Purine Restricted Diet, CS-PRD; High Vitamin C Supplements-Purine Restricted Diet, CD-PRD; High Dietary Vitamin C-Purine Restricted Diet.

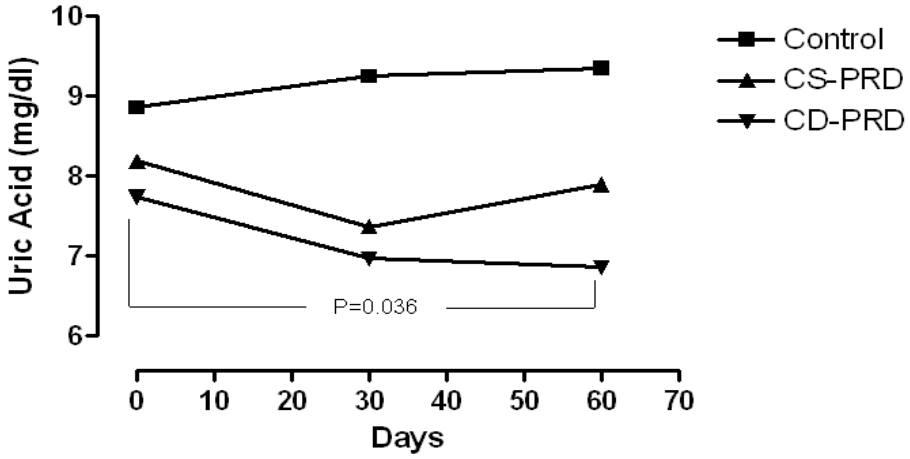

Figure 1: Uric acid pattern during 60 days

4. Discussion

In this study, the researchers used 500 mg intervention dose of vitamin C because the results of **Choi and his collegue (2009)** demonstrated that it was the minimum dose that reduced uric acid efficiently in gout patients, and higher doses used up to 1500 mg vitamin C showed as same uric acid reduction as the 500 mg dose. Other researchers also confirmed the previous finding (**Gao *et al*., 2008**) to the effect that an inverse dose-response association was observed through vitamin C intake of 400–500 mg/d with serum uric acid level, and then reached a plateau. Adjusted mean uric acid concentrations across total vitamin C intake categories (<90, 90–249, 250–499, 500–999, or ≥1000 mg/d) were 6.4, 6.1, 6.0, 5.7, and 5.7 mg/dl, respectively.

At the end of this study, the reduction of uric acid in CD-PRD group was -0.77 mg/dl and in CS-PRD group was -0.28 mg/dl. For the control group, there was an increase in uric acid (mean change 0.51 mg/dl). These results were in accordance with Huang *et al*. (2005) results which concluded that serum uric acid levels were significantly reduced in the hyperuricemic group treated with 500 mg vitamin C/ day (mean change -0.5 mg/dl), but not in the placebo group (mean change 0.09 mg/dl).

The uricosuric effect of vitamin C may be the main mechanism that reduced blood uric acid. From the results, high vitamin C intake from diet and supplement increased GFR with time. Several reasons for that increase in GFR as a consequence of megavitamin C therapy include an antioxidant effect that reduces micro vascular ischemia in glomeruli and leads to increased blood flow at the site, as well as dilation of afferent arterioles (Stein *et al*., 1976). Other possible mechanism is the competition for renal reabsorption via an anion exchange transport system at the proximal tubules (**Choi *et al*., 2009**), because ascorbic acid is the major interfering electroactive species to uric acid, which oxidizes at a potential similar to that of uric acid (**Fujishima *et al*., 2005**). Finally, the antioxidant property of vitamin C could reduce oxidative stress and inflammation, and could, therefore, be related to lower uric acid synthesis (**Gao *et al*., 2008**).

After 2 months of this study, the reduction in serum uric acid was higher in dietary treated group than supplements one, which could be related to other

functional ingredients in foods that diminished serum uric acid efficiently. A matter which needs further investigations.

Conclusion

The study demonstrates that about 500 mg/day vitamin C intake for 60 days considerably reduced serum uric acid. Dietary vitamin C was shown to be more effective than vitamin C tablets in reduction of serum uric acid concentration.

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