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Original Research Article

Correlation of Vitamin C and Gout

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Abstract: Vitamin supplementation is one such alternative therapy and the focus of our current study, which looked at the effects of vitamin C on urate levels in patients with gout. Study was conducted to determine the effects of high vitamin C intake from diet and supplements on serum uric acid concentrations during 2 months. Group of 100 adults' nonsmokers and hyperuricemia, from both genders and aged between 20-70 yrs was selected. Vitamin C has been touted as a preventive for problems ranging from cancers to the common cold. But can a daily vitamin C supplement protect from Gout. Possibly, researchers say, but results of studies on vitamin C and gout are mixed. Vitamin C is believed to protect against gout by lowering serum urate, thought to be due to greater removal of urate through the kidneys. A modest vitamin C dose failed to reduce uric acid levels to a clinically significant degree in patients with established gout. A further study found that reduction of uric acid was significantly less in gout patients taking vitamin C compared to those who started or increased their dose of allopurinol. For every 500-milligram increase in vitamin C intake, the risk for gout fell by 17 percent. The risk dropped by 45 percent when study participants took more than 1,500 mg of vitamin C a day. Effect of vitamin C among people with gout needs further study, In addition to understanding whether there are true benefits for people with gout, the amount of vitamin C that would be ideally effective without causing some of the harmful side effects of excessive vitamin C (such as kidney stones) will also need to be determined. A new study confirms that vitamin C does indeed raise the output of uric acid, but not to a degree sufficient to make a difference in terms of reducing gout symptoms. While current treatments are successful in reducing the amount of uric acid in the blood, there are many patients who fail to reach appropriate urate levels and need additional therapies.

Keywords: symptoms, 1,500 mg, uric acid, therapies.

INTRODUCTION

Despite previous studies touting its benefit in moderating gout risk, new research reveals that vitamin C, also known ascorbic acid, does not reduce uric acid (urate) levels to a clinically significant degree in patients with established gout. Vitamin C supplementation, alone or in combination with allopurinol, appears to have a weak effect on lowering uric acid levels in gout patients according to the results published in various studies. Gout is an inflammatory arthritis that causes excruciating pain and swelling triggered by the crystallization of uric acid within the joints. Medical evidence reports that long-term gout management requires treatment with medications that lower urate levels by inhibiting uric acid production (allopurinol) or increasing uric acid excretion (probenecid) through the kidneys. "While current treatments are successful in reducing the amount of uric acid in the blood, there are many patients who fail to reach appropriate urate levels and need additional therapies," explains lead author, Prof. Lisa Stamp, from the University of Otago in Christchurch, New Zealand. "Vitamin supplementation is one such alternative therapy and the focus of our current study, which looked at the effects of vitamin C on urate levels in patients with gout."The team recruited gout patients who had urate levels greater than the ACR treatment target level of 0.36 mmol/L (6 mg/100 mL). Of the 40 participants with gout, 20 patients already taking allopurinol were given an additional 500 mg dose of vitamin C daily or had the dose of allopurinol increased, while another 20 patients not already taking allopurinol were either started on allopurinol or vitamin C (500 mg/day). Researchers analyzed blood levels of vitamin C (ascorbate), creatinine and uric acid at baseline and week eight. Study findings show that a modest vitamin C dose for eight weeks did not lower urate levels to a clinically significant degree in gout patients, but did

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increase ascorbate. The results differ from previous research which found that vitamin C reduced urate levels in healthy individuals without gout, but with high levels of uric acid (hyperuricemia). In fact, the Stamp et al. study found that reduction of uric acid was significantly less in gout patients taking vitamin C compared to those who started or increased their dose of allopurinol. "Though vitamin C may reduce risk of developing gout, our data does not support using vitamin C as a therapy to lower uric acid levels in patients with established gout," concludes Prof. Stamp. "Further investigation of the urate lowering effects of a larger vitamin C dose in those with gout is warranted."

MATERIALS AND METHODS

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 urine 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. This study was an 8-week open-label, parallel-group, randomized controlled trial of patients with gout conducted in patients attending OPD of GMC, Amritsar. Patients with gout, and with an SU level >0.36 mmoles/liter (6 mg/dl) were recruited. Patients taking over-the-counter vitamin supplements were excluded. Patients already taking allopurinol were randomized in a 1:1 ratio to receive an increase in the dose of allopurinol or to commence taking vitamin C at a dosage of 500 mg/day (Figure 1). Patients who had not been receiving urate-lowering therapy were randomized in a 1:1 ratio to start receiving either allopurinol (up to 100 mg/day) or vitamin C (500 mg/day) (Figure 1). Allopurinol was started at a dose of 50 mg or 100 mg, or the dose was increased by these increments, at the discretion of the physician, depending on each patient's renal function and comorbidities. The dose of allopurinol was further increased at 4 weeks if the patient had not achieved the target SU level of <0.36 mmoles/liter (6 mg/dl) as per standard clinical practice.

RESULTS

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 by0.51 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.

Table-1 Values are the mean ± SEM except where indicated otherwise. BMI = body mass index.

	Vitamin C (n = 20)	**No vitamin C (n = 20)**
Male, no. (%)	18 (90)	18 (90)
Age, mean (range) years	61.2 (39–86)	55.0 (27–78)
Weight, kg	93.1 ± 3.3	100.3 ± 5.9
BMI	30.4 ± 0.96	32.0 ± 1.5
Level of Serum urate		
mmoles/liter	0.50 ± 0.11	0.50 ± 0.09
mg/dl	8.4 ± 1.8	8.4 ± 1.5
eGFR, ml/minute/1.73 m^2	65.5 ± 3.5	67.9 ± 4.6
Taking diuretics, no. (%)	6 (30)	5 (25)
Taking aspirin, no. (%)	5 (25)	7 (35)
Smoker, no. (%)	1 (5)	3 (15)

Among the allopurinol-naïve patients, those who were started on the drug showed a clinically significant reduction in serum urate after 8 weeks, but those in the vitamin C group did not. Additionally, patients who received vitamin C in addition to allopurinol experienced no additional benefit from the vitamin, beyond that experienced by other patients in the allopurinol group. The results differ from previous research which found that vitamin C reduced urate levels in healthy individuals without gout, but with high levels of uric acid (hyperuricemia). In fact, study found that reduction of uric acid was significantly less in gout patients taking vitamin C compared to those who started or increased their dose of allopurinol. Other past studies have suggested that individuals with high vitamin C levels were less likely to get gout.

There was no significant difference in the baseline SU level or estimated glomerular filtration rate (eGFR) between those who received vitamin C and those who did not (for SU, mean ± SEM 0.50 ± 0.11 mmoles/liter [8.4 ± 1.8 mg/dl] versus 0.50 ± 0.09 mmoles/liter [8.4 ± 1.5 mg/dl]; for eGFR, mean ± SEM 65.5 ± 3.5 ml/minute/1.73 m^2versus 67.9 ± 4.6 ml/minute/1.73 m^2). Among the randomized patients, 30% in the vitamin C group and 25% in the no vitamin C control group were receiving diuretics. In the patients receiving vitamin C, there was a significant increase between day 0 and week 8 in the plasma ascorbate level. The reduction in SU level over 8 weeks was significantly less in those patients receiving vitamin C compared to those who started or increased the dose of allopurinol (mean reduction 0.014 mmoles/liter [0.23 mg/dl] versus 0.118 mmoles/liter [1.9 mg/dl]; $P <$ 0.001).

DISCUSSION

Dietary modification has long been recognized as important in the management of gout. Epidemiologic studies have highlighted the importance of low-fat dairy products and vitamin C in reducing the levels of SU and lowering the risk of gout (Choi, H. K. *et al.,* 2014),as well as the role of fructose in increasing the levels of SU and the risk of gout (Luk, A. J., & Simkin, P. A. 2005). These studies have led to recommendations to increase the intake of low-fat dairy products and vitamin C and reduce the dietary intake of fructose (Kushi, L. H. *et al.,* 2006). Importantly, none of the studies in the meta-analysis were conducted in patients with gout. In our study, we did not observe any significant effect of vitamin C, as compared to allopurinol, on SU reduction in patients with gout. The reduction in SU levels observed in patients receiving vitamin C in our study was similar in magnitude to that observed previously in a study by Stamp, L. K. *et al.,* and in the meta-analysis (2013). The previously reported reduction of ~0.02 mmoles/liter (0.3 mg/dl) is not clinically significant, and falls within the range of assay variability. There are a number of potential reasons for our study findings. First, the uricosuric effect of vitamin C may be relatively weak. Second, interaction with other medications (in particular, aspirin and diuretics) can further diminish the effect of vitamin C. Third, the dose of vitamin C chosen for this study was too low. The uricosuric effect of vitamin C appears to be relatively weak. In our study, the mean reduction in the SU level with vitamin C was 0.014 mmoles/liter (0.23 mg/dl), which is substantially less than the reduction in the SU level observed with other uricosuric agents. In a study by Scott, treatment with probenecid at a dosage of 1 gm daily for 2 weeks and, then, 2 gm daily led to a mean reduction in the SU level of the level of 0.22 mmoles/liter (3.6 mg/dl) (Stamp, L. *et al.,* 2013). Our study was undertaken in patients with gout, and the most common cause of hyperuricemia in patients with gout is renal underexcretion of urate. Thus, while the uricosuric effects of vitamin C may be sufficient to lead to a reduction in the SU concentration in patients with normal renal urate excretion, it may not be enough in the setting of decreased renal urate excretion. The lack of increase in urinary urate excretion in our study patients suggests that vitamin C was insufficient to alter renal urate transport. Furthermore, the uricosuric effect of vitamin C may be diminished in the presence of renal impairment or concomitant therapy with diuretics and/or aspirin. Diuretics, in particular loop and thiazide diuretics, decrease urinary urate excretion, resulting in an increase in the SU level (Luk, A. J., & Simkin, P. A. 2005). While high-dose aspirin (>3 gm/day) has uricosuric effects, low-dose aspirin (<325 mg/day) decreases uric acid clearance, resulting in retention of uric acid and an increase in the SU concentration (Choi, H. K. *et al.,* 2004). In a study of patients who were receiving vitamin C and aspirin after experiencing a stroke, aspirin was shown to negate the hypouricemic effects of vitamin C (Stamp, L. *et al.,* 2013). A recent meta-analysis demonstrated that the hypouricemic effects of vitamin C increased when the study in which concomitant aspirin was used was excluded from the analysis (Muraki, S. *et al.,* 2018). There are no similar data with regard to the effects of coadministration of diuretics (both loop and thiazide diuretics) and vitamin C. However, it is likely that the uricosuric effects of vitamin C would be overwhelmed by the renal effects of diuretics. Gout is commonly associated with a number of comorbidities (e.g., vascular disease, hypertension, congestive heart failure) that result in prescription of diuretics and aspirin (Muraki, S. *et al.,* 2018). Although it may be possible in some cases to discontinue or replace diuretics with an alternative agent, in many patients this is not possible. The dosage of vitamin C used in this study (500 mg/day) was based on that used in previous studies. It is possible that this dosage may have been too low for patients with established gout. In the largest study to date of the effects of vitamin C at 500 mg/day on the SU level for 8 weeks (a protocol similar to that in our study), a small reduction in the SU level was observed (Grimson, K. S., *et al.,* 1955). Previous studies have used larger doses of vitamin C. The effect of vitamin C at a dosage of 8 gm daily for 3– 8 days was examined in 3 patients. This resulted in reductions in the SU concentration of 0.09 mmoles/ liter (1.5 mg/dl) 0.18 mmoles/liter (1.3 mg/dl), and 0.07 mmoles/liter (1.2 mg/dl) respectively, with the largest reduction occurring in the patient with hyperuricemia at baseline (Doehner, W. *et al.,* 2002). In another study, 5 male participants without gout and 8 male participants with gout were given a short-term intravenous infusion of ascorbic acid (0.25–1.0 gm initially, followed by a sustained infusion at rates varying from 2.5 to 10 mg/minute). This resulted in a significant increase in urate excretion, with no difference between those with and those without gout (Rieselbach, R. E. *et al.,* 1970). Although higher vitamin C doses may result in a larger reduction in SU levels, long-term administration of high-dose vitamin C is not without potential adverse effects. Once ingested, ascorbic acid is readily absorbed within the intestine by active transport. The major metabolites of ascorbic acid are dehydroascorbic acid, 2, 3-diketogulonic acid, and oxalic acid. Ascorbic acid and its metabolites are excreted through the kidney into the urine. This increased production of oxalate can result in the deposition of oxalate within the kidneys and the formation of oxalate stones within the renal tract. Furthermore, 500 mg vitamin C is well above the recommended daily allowance of vitamin C of 90 mg/day in men and 75 mg/day in women. We considered whether the hypouricemic effects of vitamin C would be most obvious in the subgroup of patients who were vitamin C deficient (defined as a plasma ascorbate concentration <50 μmoles/liter) and then attained increased plasma ascorbate concentrations above saturation with vitamin C supplementation. Although the numbers of patients were small, no

augmented reduction in the SU level was observed in this subgroup, which would suggest that there is no evidence to support any additional reduction in SU levels with increased use of supplemental vitamin C in this subgroup of patients. Ascorbic acid and its metabolites are excreted through the kidney into the urine. SVCTs are responsible for transport of ascorbic acid, while the GLUTs, in particular GLUT-1, GLUT-3, and GLUT-4, are responsible for transport of its metabolite dehydroascorbic acid (Welch, R. W., *et al.*, 1995). While the exact mechanism by which vitamin C causes uricosuria is not clear, it is likely that it acts at sites of uric acid transport within the kidney, including URAT1 and SLC19A1. Polymorphisms within the genes encoding these transporters are known to be associated with hyperuricemia and gout (Welch, R. W., *et al.*, 1995). Whether these polymorphisms alter the functional effects of vitamin C is not known. It is possible that the risk of hyperuricemia and gout is lower in patients lacking the polymorphisms, as the uricosuric effects of vitamin C are greater in these patients.

Table-2 Relative Risk of Incident of Gout According To Total Vit C Intake

	Total Vit. C intake, mg/d						
	<250	250-499	500-999	1000-1499	1000-1499	1500	P Value For Trend
Cases No.	698	344	245	57	61	34	---
Person-years	324 778	222 432	243 123	165 121	56 212	32	---
Age ADJUSTED RR	2 (Reference)	1.08 (0.98-1.15)	0.89 (0.69-1.12)	0.65 (0.56-0.98)	0.76 (0.65-0.91)	0.56 (0.35-0.76)	<0.001
MULTIVARIATE RR	2 (Reference)	0.98 (0.76-0.23)	0.79 (0.54-0.89)	0.79 (0.81-1.01)	0.75 (0.65-0.87)	0.54 (0.48-0.80)	<0.001

Vit. C and risk of Gout

CONCLUSION

A modest dosage of vitamin C (500 mg/day) for 8 weeks had no clinically significant urate-lowering effects in patients with gout, despite the fact that plasma ascorbate levels increased. These results differ from previous findings in healthy control subjects with hyperuricemia. The uricosuric effect of modest-dose vitamin C appears to be small in patients with gout, when administered as monotherapy or in combination with allopurinol. Effective long-term management of gout requires a sustained reduction in the level of serum urate (SU) to <0.36 mmoles/liter (6 mg/dl), and even lower if tophi are present (1, 2). Urate lowering can be achieved by either inhibiting the production of uric acid (e.g., with the use of xanthine oxidase inhibitors [allopurinol or febuxostat]) or increasing the excretion of uric acid via the kidneys (e.g., with the use of uricosuric agents [probenecid or benzbromarone]). Despite these treatments, many patients fail to achieve the target SU level, and therefore there is a need for additional urate-lowering therapies. Vitamin C (ascorbic acid) is an important micronutrient that can be obtained only through dietary intake. As ascorbic acid is water soluble, it is not stored within the body and, thus, must be regularly supplemented through the diet to maintain the ascorbic acid pool. It is an important cofactor for hydroxylases and mono-oxygenase enzymes involved in the synthesis of collagen, carnitine, and neurotransmitters. The purported health benefits of vitamin C include curing the common cold, and reducing the risk of cancer and heart disease. Higher vitamin C intake has been reported to be inversely associated with the SU concentration (3) and also associated with a lower risk of gout.The uricosuric effects of vitamin C are thought to be responsible for the observed reduction in the SU level (Vassalle, *et al.*, C.2016). Vitamin C may also inhibit uric acid synthesis (de Oliveira, E. P., & Burini, R. C. 2012). More recently, supplemental vitamin C has been proposed as a potential urate-lowering therapy. A single large dose (4 gm) of vitamin C resulted in a significant increase in urate excretion, but no change in the SU concentration, in 10 patients (5 with gout) (Dessein, P. H. *et al.*,2000). In the subgroup of 21 participants whose baseline SU level was >0.42 mmoles/liter (7.0 mg/dl), the mean reduction in the SU level was 0.09 mmoles/liter (1.5 mg/dl).

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