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EFFECT OF ASCORBIC ACID ON SERUM CALCIUM LEVELS IN HYPERPARATHYROID INDIVIDUALS WITH AND WITHOUT PHYSICAL ACTIVITY

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Abstract

Parathyroid hormone (PTH) produced by parathyroid glands which are oval shaped, two sets of four glands present in the bottom of neck. In some cases, PTH glands secrete or release too much PTH hormones and become overactive and cause a condition known as hyperparathyroidism (HPT). In HPT the calcium level in body rises in the blood and can cause different health problems. In United States of America every year around 100000 people develop HPT. To decrease the levels of PTH and prevent the problems produced by HPT, one of the important methods is to reduce the levels of PTH by increasing the levels of ascorbic acid or also known as Vitamin C (Vit. C). Studies showed that ascorbic acid combined with physical activity is an important modifier and can affect the expression and production of PTH by changing the calcium and phosphate levels. The aim of this study was to observe the effect of ascorbic acid on serum calcium levels in hyperparathyroid individuals with and without physical activity. Overall, 240 patients selected randomly at baseline in which 94 patients were men and 146 were women. Different baseline biochemical tests were performed and SPSS 24 was used for statistical analysis. Results showed that those individuals who received ascorbic acid and ascorbic acid with 45 minutes duration of physical activity each day had a significant rise in mean serum calcium concentration. We concluded that in HPT patients the levels of PTH reduced with supplements of ascorbic acid combined with physical activity and that is beneficial for HPT patients because it decreases the serum calcium levels.

Keywords: *Ascorbic acid, Hyperparathyroidism, Physical activity, Vitamin C*

INTRODUCTION

Parathyroid (PT) are oval shaped, two sets of four glands present in the bottom of neck found close to the lobes of thyroid glands. They are small glands, and each one gland normally are about the size of pea (1). Parathyroid hormone (PTH) produced by PT glands, and it plays a significant role in the blood by managing the regulation of calcium levels, because in the human body accurate calcium levels are important as minor modifications can affect nerve and muscle complications. PTH also stimulates the different functions in human body such as stimulation of bones released calcium into the blood, stimulation of calcium absorption from food by the intestines, and stimulate the calcium preservation by the kidneys, and stimulate the cells of kidney to convert the vitamin D at absorbing calcium from weaker to the strongest form from the digestive organs (2).

Hormones of PT is produced and expressed by the chief and oxyphil cells off PT glands and the regulation of PTH done by a gene on chromosome 11 (short arm) (3). The chief target organs for PTH are

kidney and skeleton. In some cases, PTH glands secrets or release too much PTH hormones and become overactive and causes a condition known as Hyperparathyroidism (HPT) (4). In HPT the calcium levels in body rises in the blood and can cause different health problems with the high levels of calcium in the blood. The body with overproduction of PTH can respond by releasing more calcium from bones into bloodstream which can weakens the bones and increases the risk of bone fracture. It can also affect the digestive tract of human by absorbing more calcium from the food. It can cause kidney related problems such as by returning the retaining calcium into your blood instead of clearing it out in urine which can cause kidney stones (5, 6).

Extreme PTH levels also considered as uremic toxins which can accelerate the absorption and reabsorption of bone and can cause demineralization of bone and renal osteodystrophy (7, 8). The demineralized bones are physically fragile, can simply be broken and not resistant to any shock and in this stage the bones of body are in higher risk of fractures (4, 9). In hyperparathyroidism, Euparathyroidism is associated with improved bone dynamics and having a normal PTH level (10).

In America every year around 100000 people develop HPT. Women are at (two to three times) higher risk of getting HPT compared to men specially woman above 60 years and older and every year 1/500 develop HPT (11). HPT patients can show severe symptoms or no symptoms at all. Some common symptoms are weakness, depression, pain, and serious symptoms include loss of appetite, nausea, constipation, vomiting, loss of memory, frequent urination, and fractures (12).

HPT can increase the risk of osteoporosis, gallbladder related diseases, gallstone, kidney stones and kidney failure etc. Post-menopausal older women are at greater risk of getting HPT. This condition also impacts the life expectancy of patients by about five to six years (8). Mainly there are two types of HPT.

PRIMARY HYPERPARATHYROIDISM (PHPT)

PHPT also known as hypercalcemia, in which the glands (one, two or all) of parathyroid produces too much PTH which can increase the levels of calcium in blood. This condition is more common in obese or heavy weight people and to those who have chronically low intake of calcium (13).

SECONDARY HYPERPARATHYROIDISM (SHPT)

In SHPT The parathyroid glands over activate as a response to other conditions e.g., severe calcium deficiency or chronic kidney failure, which can cause calcium loss and over activity of parathyroid glands is an effort by your body to maintain the normal levels of calcium (12, 14).

To decrease the levels of PTH and prevent the problems produced by HPT, it is essential to analyze and examined different methods and one of important method is to reduce the levels of PTH by increasing the levels of ascorbic acid or also known as Vitamin C (Vit. C).

INCREASE LEVELS OF ASCORBIC ACID

For humans' ascorbic acid is an important nutrient (15) and based on studies it was apparent that Ascorbic acid improved the absorption of the intestinal calcium and by enhancing levels of ascorbic acid with dietary supplements the level of PTH decreases as an outcome (16, 17). Investigations have shown that to decrease the levels of PTH (with less side effects) supplements of ascorbic acid is used which increases the levels of ascorbic acid in body and as a result the levels of PTH reduced (18, 19). In receptors, ascorbic acid decreases the levels of PTH as a result of increasing the adenosine monophosphate response to PTH (20).

PHYSICAL ACTIVITY (PA) EFFECT ON PTH LEVELS

The functions of PTH during physical activity have been studied frequently (21). PA can be defined as any intentional movement of body which requires energy such as activities of daily living or exercise. It is very important to understand the clear effect of PA on the production of PTH to see how body adapts to physical exercise depending upon strength and time duration. Studies showed that PA is an important modifier and can affect the expression and production of PTH by changing the calcium and phosphate levels. HPT can be prevented and controlled by those individuals who have a more active lifestyle. Those People are at lesser risk of getting HPT who incorporate high level of regular PA compares to those who have a very sedentary lifestyle and are in greater risk of getting HPT (22-24).

MATERIALS AND METHODS

STUDY DESIGN

From October, 2020 to September, 2021; two hundred and forty adult patients of HPT (94 men and 146 women) were randomly recruited in the trial which was done at the Bolan Medical Complex Hospital, Quetta. All 240 patients experienced a 15-weeks treatment program. Members of this research were enrolled on the basis of advanced criteria of inclusion/exclusion. All 240 patients were divided in to 4 groups equally.

- In Group 1 there were (55) patients who received 0.5 g supplements of ascorbic acid for each day in morning and not took part in any physical activity.
- In Group 2 (55) patients who received 0.5 g supplements of ascorbic acid for each day with 45 minutes of PA in early morning or in the evening.
- In Group 3 there were (55) patients who received 1 placebo (Inactive drug) of ascorbic acid or each day without any PA.
- Group 4 consists of (55) patients who received one placebo of ascorbic acid for each day with 45 minutes duration of PA.

All the supplements were in same shape and size and were obtained from Drug Testing Lab., Health Department, Balochistan, Quetta.

COLLECTION OF DATA

A standardized questionnaire was designed in this study to gather the data from the patients also they were interviewed to acquire the medical history of bp, cancer, obesity, diabetes, cholesterol etc.

INCLUSION/EXCLUSION CRITERIA

The inclusion criteria were an age of 18 years and higher which includes both men and women and have PTH level of 200 pg/ml to 550 pg/ml. The exclusion criteria included those patients using any medication for weight loss, any active infections, use of supplements of ascorbic acid (Vit. C & D), cancer, human immunodeficiency virus, high TG levels (>400 mg/dl), or high or low blood pressure.

ASSESSMENT OF PA AND SOCIODEMOGRAPHIC FACTORS

In this study patients were asked to report and specify the average time spent each week in any of the following activities mentioned below. The PA time of all the patients should be more than or equal to 5 hours each week. PAs include: running or jogging, sports such as (squash, badminton, and tennis etc.), swimming, aerobic activities, climbing/hiking and exercise.

Patients' height (m) and weight (kg) were assessed while standing without shoes. As a measure of relative weight, the body mass index (BMI) was computed as weight/height squared (kg/m2). Overweightness was defined as a BMI of more than 30 kg/m2 in both men and women. The patients' blood pressure (bp) was examined as per the present European standards for bp testing (25,26).

BIOCHEMICAL TESTS

After 15 weeks of intervention (10 cc) of fasting blood samples (FBS) were obtained at baseline. Fasting samples were collected after 12 hours (overnight) of fasting and further the serum levels of fasting plasma glucose (FPG), ascorbic acid , low density lipoprotein cholesterol (LDL-C), total cholesterol levels (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), serum calcium level, and levels of PTH were analyzed. Model-vidas analyzer (Biomerux, Italy) was used to evaluate the ascorbic acid (Vit C) levels. Samples of FPG were collected by enzymatic colorimetric technique using glucose oxidase on the day of blood collection. Enzymatic colorimetric tests were used to analyze the concentration of serum triglycerides and TC with cholesterol oxidase, glycerol phosphate oxidase and cholesterol esterase by utilizing protocol of standard kits. After the precipitation of the apolipoprotein B containing lipoprotein with phosphotungstic acid, HDLC was measured and LDL-C was computed from TG, HDL-C & TC serum

based on appropriate formula (27). Original kit (perfect plus 400 autoanalyzer (Mindary, UK) was used to measure the serum PTH levels.

STATISTICAL ANALYSIS

SPSS version 24 (Statistical Package for the Social Sciences) was used in this study for statistical analysis. Chi-square test and ANOVA was used to test the demographic and medical history of patients. A P value of less than 0.05 was used to determine significance.

RESULTS

Overall, 240 hyperperathyroid patients were selected randomly at baseline in which 94 patients were men and 146 were women. Ultimately, 192 patients completed the study, and 48 patients were excluded from the study because of different reasons such as not taking ascorbic acid supplements properly, pregnancy and some of them didn't finish the study. Table I shows the baseline physical characteristics of the study patients in the current investigation.

Table I. Baseline characteristics of all the patients included in this study

	Group (n=192)				
Variables	**Vitamin C + PA (n=46)[3]**	**Ascorbic acid (Vit. C) (n=52)[4]**	**Placebo + PA (n=44)[5]**	**Placebo (n=50)[6]**	**p value[2]**
Female (%)	16.3 (70)	16.4 (62)	13.2 (59)	12.3 (48)	0.71
Age	40.77 ± 5.7	41.20 ± 5.7	41.60 ± 6.3	42.59 ± 5.7	0.125
Weight (kg)	79.71 ± 13.6	81.03 ± 13.2	74.83 ± 12.7	82.33 ± 13.8	6 0.467
Married (%)	21 (83)	22 (85)	17 (77)	21 (84)	0.155
Waist circumference (cm)	107.8 ± 8.8	108.2 ± 10.5	111.4 ± 10.3	107.6 ± 9.7	0.563
Body mass index (kg/m2)	32.33 ± 5.7	31.97 ± 6.1	30.12 ± 4.6	32.82 ± 4.4	0.654
Family history of hypertension (%)	13 (57)	12 (47)	9 (41)	15 (60)	0.326
Personal history of obesity (%)	15 (65)	17 (65)	11 (50)	19 (76)	0.427
Personal history of diabetes mellitus (%)	8 (35)	12 (46)	9 (41)	15 (60)	0.754
Systolic blood pressure (mmHg)	130.1 ± 11.8	130.1 ± 11.8	125.6 ± 14.6	128.9 ± 11.4	0.806
Diastolic blood pressure (mmHg)	79.3 ± 7.2	81.3 ± 8.4	82.5 ± 5.8	80.0 ± 6.8	0.523
Triglycerides (mg/dl)	176.1 ± 87.2	*268.4 ± 107.1	161.6 ± 70.2	147.3 ± 42.8	0.001
Total cholesterol (mg/dl)	178.2 ± 29.8	174.7 ± 41.6	194.0 ± 35.8	185.9 ± 39.1	0.771
Fasting plasma glucose (mg/dl)	103.9 ± 13.7	106.6 ± 19.8	106.2 ± 18.2	110.6 ± 17.3	0.635
LDL-C (mg/dl)	135.5 ± 32.7	‡114.4 ± 47.5	153.5 ± 38.4	150.4 ± 39.9	0.027
HDL-C (mg/dl)	†37.61 ± 11.1	33.06 ± 13.5	40.81 ± 16.6	30.04 ± 8.6	0.004
PTH (pg/ml)	52.6 ± 11.3	59.3 ± 10.7	54.7 ± 17.4	49.2 ± 12.4	0.806
Calcium (mg/dl)	9.15 ± 1.1	9.56 ± 1.3	9.63 ± 1.1	9.33 ± 1.3	0.498
Ascorbic acid (Vit C) (ng/ml)	0.78 ± 0.28	0.8j6 ± 0.38	0.92 ± 0.35	0.95 ± 0.32	0.367

[1]Mean data ± standard deviation (SD)
[2]ANOVA or chi-square test obtained, where proper and appropriate
[3]Per Day of getting ascorbic acid (Vit. C) (0.5 g) with 45 minutes of PA
[4]Per Day of getting ascorbic acid (Vit. C) (0.5 g)
[5]Per Day of getting placebo with 45 minutes of PA
[6]Per Day of getting placebo
*By utilizing Tukey's test (P<0.05), equated with other groups
†By utilizing Tukey's test (P<0.05), equaled with placebo group
‡By utilizing Tukey's test (P<0.05), equated with placebo with PA group

Different characteristics such as status of marriage, age, gender and family history of diabetes, overweightness or high blood pressure were evaluated in study groups so it would not change the findings after the intervention at the baseline. Amongst intervention groups there were not any difference in demographic features of the patients and as a result, the assessment of different factors at the end of the research does not need to be corrected for these variations. Our findings demonstrated that there was no major difference in baseline serum levels of ascorbic acid across the research groups and the p value was 0.367. Furthermore, when compared to those who took placebo or "placebo with 45-minutes of PA each day", patients who took ascorbic acid supplements had greater serum levels of TG and the p value for all was 0.05.

The variation in quantified variables amongst the research groups (after 15 weeks of intervention) is demonstrated in Table II. Patients who got either ascorbic acid or "ascorbic acid with 45 minutes duration of PA each day" had substantially higher mean serum calcium concentrations as shown in table II than those who got placebo or "placebo with 45 minutes duration of PA each day" and the p value for all was 0.001. Patients who got either ascorbic acid or placebo with 45 minutes duration of PA each day had substantial decrease in mean calcium serum levels compared to those who got placebo with no physical activity. Also, there was substantial decrease in levels of PTH to those who got ascorbic acid or ascorbic acid with 45 minutes duration of PA each day compared to those who got placebo and the p value for all was less than 0.05. Results showed that PTH levels were decreases more when ascorbic acid took with 45 minutes of physical activity compared to those who only took ascorbic acid with no physical activity.

Table II. 15 weeks of intervention, variation in the assessed variables amongst the groups

		Variables		
		Ascorbic acid (Vit. C) (ng/ml)	**PTH (pg/ml)**	**Calcium (mg/dl)**
Ascorbic acid (Vit. C[3]) + PA (n=46)	Before Mean± SD	0.78 ± 0.28	52.6 ± 11.3	9.15 ± 1.1
	After Mean ±SD	1.66 ± 0.34	1.66 ± 0.33	8.82 ± 1.7
P value		0.001	0.001	0.028
Ascorbic acid (Vit C[4]) (n=52)	Before Mean± SD	0.86 ± 0.37	0.86 ± 0.37	9.56 ± 1.2
	After Mean ±SD	1.36 ± 0.27	1.36 ± 0.27	9.41 ± 0.8
P value		0.001	0.006	0.319
Placebo[5] +PA (n=44)	Before Mean± SD	0.92 ± 0.33	54.7 ± 17.4	9.63 ± 1.0
	After Mean ±SD	1.07 ± 0.29	52.8 ± 11.0	9.23 ± 0.5
P value		0.144	0.406	0.015
Placebo[6] (n=50)	Before Mean± SD	0.95 ± 0.32	49.2 ± 12.4	9.33 ± 1.3
	After Mean ±SD	0.88 ± 0.36	54.61 ± 8.7	9.61 ± 1.1
P value		0.475	0.021	0.041

[1]Mean data ± standard deviation (SD)
[2]Obtained from paired sample T test
[3]Per Day of getting ascorbic acid (Vit C) (0.5 g) with 45 minutes of PA
[4]Per Day of getting ascorbic acid (Vit C) (0.5 g)
[5]Per Day of getting placebo with 45 minutes of PA
[6]Per Day of getting placebo
*Significant (P<0.05)
PA: Physical activity

Table III demonstrates the mean values at the end of testing ascorbic acid, PTH and calcium levels for the research groups. In comparison to the other groups, we analyzed that after invention there was a substantial increase in mean serum ascorbic acid concentration in those patients who got ascorbic acid or ascorbic acid with 45 minutes of physical activity each day and the p value was less than 0.001. Also, there

was a substantial decrease in mean serum calcium concentration in those patients who got ascorbic acid, ascorbic acid with 45 minutes of PA in each day and placebo with 45 minutes of physical activity each day and the p value was less than 0.001. There was a major decrease in means serum levels of PTH in those patients who got ascorbic acid or ascorbic acid with 45 minutes of PA per day compared to other groups and the p value was less than 0.001.

Table III. Ascorbic acid, calcium, and PTH levels at the end of the experiment were compared amongst research groups

Variables	Ascorbic acid (Vit C) + PA[3] (n=46)	Ascorbic acid (Vit C) [4] (n=52)	Placebo + PA[5] (n=44)	Placebo[6] (n=50)	p-value[2]
PTH (pg/ml)	46.83 ± 8.4	54.32 ± 10.7	52.81 ± 11.1	54.61± 8.7	0.001
Ascorbic acid (Vit C) (ng/ml)	1.66 ± 0.34	1.36 ± 0.29	1.07 ± 0.30	0.88 ± 0.36	0.001
Calcium (mg/dl)	8.82 ± 1.7	9.41 ± 0.9	9.23 ± 0.5	9.61 ± 1.1	0.001

[1]Mean data ± standard deviation (SD)
[2]Obtained from ANOVA
[3]Per Day of getting ascorbic acid (Vit C) (0.5 g) with 45 minutes of PA
[4]Per Day of getting ascorbic acid (Vit C) (0.5 g)
[5]Per Day of getting placebo with 45 minutes of PA
[6]Per Day of getting placebo
*Significant (P<0.05)
PA: Physical activity

Table IV shows the changes in levels of calcium, PTH and ascorbic acid, in various groups. Compares to other group's patients who took ascorbic acid with 45 minutes of PA each day had more changes in ascorbic acid levels and the P value was less than 0.001. Also, there was a major change observed in which a significant increase in concentration of PTH and serum calcium levels were observed in placebo group compared to others and p value for all was less than 0.001. In the end, results showed that for decreasing the level of PTH a few interventions are helpful in increasing the ascorbic acid level in body and decreases the calcium level in patient of hyperparathyroidism.

Table IV. Ascorbic acid, calcium, and PTH levels changes in various groups

Variables	Ascorbic acid + PA[3] (n=46)	Ascorbic acid[4] (n=52)	Placebo + PA[5] (n=44)	Placebo[6] (n=50)	p-value[2]
PTH (pg/ml)	-5.78 ± 7.29	-4.99 ± 9.54	-1.90 ± 0.63	*5.40 ± 0.64	0.001
Ascorbic acid (Vit C) (ng/ml)	*0.89 ± 04	0.49 ± 92	0.14 ± 96	0.14 ± 97	0.001
Calcium (mg/dl)	-0.33 ± 0.94	-0.15 ± 0.05	-0.41 ± 0.05	0.27 ± 0.97*	0.001

[1]Mean data ± standard deviation (SD)
[2]Obtained from ANOVA
[3]Per Day of getting ascorbic acid (Vit. C) (0.5 g) with 45 minutes of PA
[4]Per Day of getting ascorbic acid (Vit. C) (0.5 g)
[5]Per Day of getting placebo with 45 minutes of PA
[6]Per Day of getting placebo
*Significant (P<0.05)
PA: Physical activity

DISCUSSION

Our data showed and suggested that taking ascorbic acid with PA on a regular basis had a greater effect on PTH levels than taking ascorbic acid alone. Patients who got either ascorbic acid or ascorbic acid with 45 minutes duration of PA on each day had substantially higher mean serum ascorbic acid concentration than those who got placebo or placebo with 45 minutes duration of PA each day. It is shown in studies that administration of intravenous ascorbic acid in visibly reduced level of PTH, and in our body PA changes calcium homeostasis (17, 28).

It's also been recommended that raising ascorbic acid levels through food supplementation causes PTH levels to drop. This study does not indicate that more of ascorbic acid should be used to treat SHPT. Further studies, however, may reveal a significant connection between ascorbic acid and the PTH-linked signaling pathways, as well as treatment strategies (19).

Results showed that those individuals who received ascorbic acid or ascorbic acid with 45 minutes duration of PA each day had a significant rise in mean serum ascorbic acid concentration. According to study severe duration of PA seems to improve blood levels of ascorbic acid and the researchers recommended that PA could cause ascorbic acid to be released from the adrenal glands into the blood circulation (29). In our investigation, patients who received ascorbic acid, ascorbic acid with 45 minutes duration of PA on each day, or placebo with 45 minutes duration of PA on each day had significantly lower mean blood calcium concentrations.

A study done by Peake JM showed that PA generally causes a temporary rise in circulating ascorbic acid in the hours following exercise. However, a drop below pre-exercise levels in the days after continuous PA might explain two different patterns in ascorbic acid levels in the presence of PA. Increased PA suggested oxidative stress might be the cause of these alterations. It's uncertain if regular PA boosts ascorbic acid metabolism based on changes in ascorbic acid levels in the blood. The fact that athletes and nonathletes had related food intakes and effects to supplementation recommends that regular PA does not raise the need for ascorbic acid in athletes (30)

According to the studies a few interventions are effective in lowering PTH levels by increasing ascorbic acid levels in the body and lowering calcium levels in HPT patients, as demonstrated in a study where PTH responded by increasing the ascorbic acid at receptors, boosting cyclic adenosine monophosphate, and reducing PTH (31). Another study done by Pravina P has found a direct link between PTH and calcium, which is in close agreement of our findings, which demonstrate that lowering PTH lowers calcium levels (32).

CONCLUSION

It has been concluded that in HPT patients the levels of PTH reduced with supplements of ascorbic acid combined with physical activity and that is beneficial for HPT patients because it decreases the serum calcium levels.

Conflict of Interest

The authors declare no conflict of interest.

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