



## Impact of vitamin C on parathormone secretion in patients on hemodialysis with secondary hyperparathyroidism

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Secondary hyperparathyroidism is a complication of chronic kidney disease, and it develops due to abnormal regulation of calcium and phosphate homeostasis (1). Various factors interact in its development. They consist of decrease kidney synthesis of 1,25-dihydroxyvitamin D, the, phosphorus retention and impaired calcemic response to parathyroid hormone (1,2). Hence, increasing of parathormone synthesis, and parathyroid cell hyperplasia will happen. High serum levels of parathormone, considered as a uremic toxin, which can stimulate accelerated bone absorption and reabsorption, and cause bone demineralization and kidney osteodystrophy (1-4). The bones which become demineralized are structurally fragile and easily broken, and they are not resistant to any shock. At this stage, there is higher risk of fractures (2-5). On the other hand, there is a risk factor for ectopic calcification and cardiovascular disease in patients on hemodialysis too (1-5). Secondary hyperparathyroidism often happens in stage three of chronic kidney disease, before the development of hyperphosphatemia. To prevent the various troubles originated by secondary hyperparathyroidism, it is mandatory to reduce high parathyroid hormone to an acceptable level in hemodialysis patients (3-6). Various, active vitamin D analogs, which can strongly suppress parathyroid hormone, have become available for treatment, however, their yield are limited (2-7). According to various investigations, phosphate binders frequently result in unfavorable side effects and imbalance in bone metabolism (4-7). Thus, new therapies with fewer side effects is reasonable. In fact, there is a potential association between the occurrence of secondary hyperparathyroidism and low vitamin C levels (8,9). Vitamin C supplementation is possibly a modality to reduce parathormone with less side effects, while several investigations have shown, increasing vitamin C levels by dietary supplementation resulted in reduction of parathormone in vitamin C-deficient individuals on regular hemodialysis with secondary hyperparathyroidism (8,9). Investigations, have shown, in low serum levels of vitamin C, calcium-sensing receptors may become resistant to parathormone effects. Vitamin C increases the response to parathormone at the receptor level, through increasing the cyclic adenosine

### ■ Implication for health policy/practice/research/medical education

Increased parathormone can stimulate bone demineralization and lead to high-turnover bone disease; a situation marked by accelerated rates of bone absorption and reabsorption. This condition defined as secondary hyperparathyroidism and requires treatment. Various studies have shown the contradictory effect of vitamin C on parathormone secretion, however some of the investigations showed its beneficial property to lower serum parathormone level. Patients on hemodialysis are at risk for low levels of serum vitamin C too. Vitamin C is a water-soluble substance which can be reduced by routine hemodialysis. This subject, however needs further investigation with larger samples, to fully define the impact of vitamin C on parathormone secretion.

monophosphate and reducing parathormone by it (8-10). Hemodialysis patients are particularly susceptible to vitamin C deficiency due to clearance of vitamin C during dialysis sessions, dietary restrictions, and malnutrition. A hemodialysis session may result in a 50% to 75% decrease in plasma vitamin C level (8,10). Daily intake of 60 mg to 100 mg of vitamin C is adequate in individuals with normal renal function. However, in patients on hemodialysis, it may not be sufficient. On the contrary, long-term high doses of vitamin C treatment in patients on hemodialysis might be a potential risk for the development of secondary oxalosis and must be tightly under observation (8-10). To better examine, the impact of vitamin C administration on the reduction of serum parathormone level in patients on hemodialysis, Sanadgol *et al.*, previously conducted a study on twenty-one patients on regular hemodialysis, with serum parathormone levels less than 550 pg/mL (but more than 200 pg/mL). Patients were administered intravenous vitamin C, 200 mg, 3 times/week for three months. Blood samples for assessment of parathormone were gathered at the beginning of the hemodialysis session every month for three months (11). The mean

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level of serum intact parathormone was  $333.3 \pm 141.3$  pg/mL (normal: 7 pg/mL to 82 pg/mL) at baseline, and it decreased to  $256.5 \pm 137.2$  pg/mL at first month ( $p=0.03$ ). The mean parathormone level was also lower than the baseline value at second months ( $260.1 \pm 123.2$  pg/mL,  $p=0.03$ ), while it increased to  $328.9 \pm 176.0$  pg/mL at third months, which was still, slightly lower than the baseline level. In 15 patient, serum levels of parathormone, were lower than the baseline at months one to two, while in the remaining six, it was higher than the baseline value (11). At this study, they concluded that, administration of intravenous vitamin C in hemodialysis patients markedly decreased level of parathormone, however its effect gradually lessened (11). Recently, Biniiaz *et al.* conducted a study to test, the association between serum level of vitamin C and parathyroid hormone in patients on hemodialysis with secondary hyperparathyroidism (12). Their study consist of a randomized, placebo-controlled, double-blind and parallel-group trial on 82 patients on regular hemodialysis with serum levels of parathormone more than 200 pg/mL. In intervention group, 250 mg vitamin C was injected three times a week for eight weeks in a row immediately at the end of each hemodialysis session through the intravenous route (12). In the control group, same term of placebo saline was injected. At baseline, the mean of serum parathormone was 699.81 ( $\pm 318.8$ ) and 596.03 ( $\pm 410.7$ ) pg/mL in intervention and control groups respectively (reference range, 6-66 pg/mL), and at the end of investigation it changed to 441.4 and 424.6 in the respected groups. They found, the values of serum calcium and phosphate did not significantly change during the study. They interpreted that, vitamin C has not implication on the secondary hyperparathyroidism in hemodialysis patients (12). To explain, the contradictory, result with the Sanadgol's study, they emphasized on sample size diversity (21 versus 76), use of placebo, randomization, and control group in the study of Biniiaz *et al.* Moreover, there was not measuring of plasma level of vitamin C before, and after the study of Biniiaz *et al.*, while, this can be a limitation of this study (12). However, it should be remember that, in Sanadgol's study, there was at gradual diminishing of influence of vitamin C on the parathormone secretion too. It is possible that, gradual reduction of vitamin C effects on parathormone secretion perhaps related to the decrease of calcium-sensing receptors sensitivity on parathyroid gland cells to vitamin C throughout the time (11,12). As mentioned, hemodialysis patients are particularly prone to vitamin C deficiency. Furthermore, chronic inflammation due to the release of inflammatory mediators in hemodialysis directed to less production of essential antioxidants and more oxidative stress, and, hence it causes an increase in free radicals associated with vitamin C insufficiency as an important antioxidant (8-13). Vitamin C also is able to improve the anemia of hemodialysis. However, impact of vitamin C injection on parathormone secretion requires further investigation with larger samples, to fully define this aspect of hemodialysis patients (11-15).

## Conclusion

Increased parathormone can stimulate bone demineralization and lead to high-turnover bone disease; a situation marked by accelerated rates of bone absorption and reabsorption. This condition is defined as secondary hyperparathyroidism and requires treatment. Various studies have shown the contradictory effect of vitamin C on parathormone secretion; however, some of the investigations showed its beneficial property to lower serum parathormone. Patients on hemodialysis are at risk for low levels of serum vitamin C too. Vitamin C is a water-soluble substance which can be reduced by routine hemodialysis. This subject, however needs further investigation with larger samples, to fully define the impact of vitamin C on parathormone secretion.

## Author's contribution

HN was the single author of the paper.

## Conflict of interests

The author declared no competing interests.

## Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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