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The role of vitamin C in orthopedic practices

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Abstract

Ascorbic acid, or vitamin C, is a significant antioxidant that has been widely used in the orthopedics community. Vitamin C's involvement in bone and tendon physiology, joint replacement, and postoperative pain are all being studied in current research. The majority of research, both in the lab and on humans, links vitamin C consumption to better tendon repair and bone health. The use of vitamin C to enhance functional results, reduce postoperative pain, and avoid complex regional pain syndrome after orthopedic surgeries is somewhat supported by recent research. Investigations are also ongoing about the perioperative usage of vitamin C in individuals undergoing anterior cruciate ligament reconstruction and joint replacement surgery. All things considered, high-quality human trials are required to verify whether vitamin C can enhance the results of orthopedic surgeries and to establish the ideal dosage and mode of administration to optimize its suggested advantages. This review's objectives were to provide an overview of vitamin C's use in orthopedic procedures and suggest possible research topics.

Keywords: Ascorbic acid, Vitamin, Orthopedic

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Introduction

Scurvy is most frequently linked to a vitamin C (ascorbic acid) deficit. Vitamin C is a significant antioxidant. In addition to being essential for the synthesis of collagen in connective tissue and bone, vitamin C has also been linked to enhanced collagen synthesis and subsequent tendon healing (1). Moreover, it eliminates free radicals, which lessens inflammation and oxidative stress (2,3).

Orthopedic patients have also been treated with vitamin C supplements. Increased bone mineral density and a lower incidence of osteoporosis and bone fractures have both been related to vitamin C (4). Moreover, recent data points to a possible protective function for vitamin C against osteoarthritis. Vitamin C has been shown to enhance functional results and lower the incidence of complex regional pain syndrome (CRPS) from the standpoint of postoperative recovery. Some of these findings about vitamin C's medicinal effects are still up for debate, though (5,6).

This review aims to provide an overview of vitamin C's function in orthopedic procedures and provide possible directions for further research.

Pain control throughout surgery

Studies assessing the function of vitamin C supplementation in CRPS prevention and postoperative recovery have been conducted recently (7). The use of vitamin C to prevent chronic restless pain syndrome (CRPS), which is an uncommon chronic illness marked by inexplicable pain and swelling, hot flashes, and limited joint mobility, after distal radius fracture (DRF) is supported by moderate evidence (8). While case series investigations have demonstrated the analgesic impact of vitamin C, the precise mechanism responsible for its antinociceptive effect is still being studied. It is thought that vitamin C's antioxidant qualities are mainly responsible for its analgesic effects. Reactive oxygen species (ROS) are produced less frequently when vitamin C is present, which protects tissues—including nerves—from oxidative damage. The production of peptide hormones and neurotransmitters, especially amidated opioid peptides, depends on vitamin C as a cofactor (9,10). Lastly, the expression of genes and transcription factors that control the analgesic effects of vitamin C is linked to it. To fully understand how vitamin C works as an analgesic in the context of pain production at certain body sites—particularly in the postoperative setting—more research is required.

Malay et al. confirmed the function of vitamin C supplementation in the prevention of CRPS by using the Hill criteria in already completed clinical studies (8). Three of the four clinical studies examined in this review involved patients with DRF, while the fourth study focused on patients having foot and ankle surgery (8). Six out of the nine Hill criteria were satisfied, according to the authors, pointing to a possible link between vitamin C and the ability to prevent CRPS in patients following DRF and foot/ankle surgery. Despite acknowledging the need for additional research to determine the mechanism by which vitamin C can lower the incidence of CRPS, Malay et al.(8) concluded that the AAOS's suggestion to supplement with vitamin C to prevent CRPS following DRF has "practical merit." Malay et al. did admit, though, that selection bias and the potential impact of confounding variables limited the examined studies.

However, in a randomized controlled trial (RCT) on the effect of vitamin C postoperative pain following DRF repair, Ekrol et al. (11) reported no therapeutic benefit from vitamin C treatment. 336 adult patients were randomly randomized to receive 500 mg of oral vitamin C or a placebo tablet for 50 days after their fracture. There were no appreciable differences observed in the DASH scores (preoperatively, at 6 weeks, and a year postoperatively), the rate of CRPS, or any functional outcomes (wrist and finger motion, grip and pinch strength, and discomfort) between the vitamin C-treated DRFs and the control group (11). At six weeks, the vitamin C group was having more problems than the control group. One limitation of the clinical trial, according to Ekrol et al. (11), was that the patient dropout rate was 26% higher than in previous studies. Conversely, a meta-analysis carried out

by Chen and associates demonstrated a significant reduction in CRPS upon vitamin C administration (12). The authors concluded that while more clinical trials are needed to determine the optimal dosage and enhance the quality of evidence about vitamin C's efficacy, there is "high-level evidence" to suggest perioperative vitamin C supplementation at a dose of 1 g/day for 50 days after DRF to avoid CRPS. Similar to what Malay et al. did (8), Chen et al. identified selection bias and confounding results as potential limitations of the evaluated study (12).

Other research has looked at how vitamin C affects pain in people having spinal and distal lower extremity surgery (6). 123 adult patients who had Posterior Lumbar Interbody Fusion (PLIF) were enrolled in an RCT by Lee et al. and given the option of receiving a placebo tablet or 500 mg of oral vitamin C daily for 45 days after the procedure (6). The main end measure was the degree of lower back discomfort, which was assessed using a visual analogue scale (VAS) at 1, 3, 6 months, and 1 year following surgery. Complications, fusion rate, and the Oswestry Disability Index (ODI) were among the secondary outcomes. Throughout the follow-up period, there was no discernible difference between the two groups' VAS scores, fusion rates, or complications. In the third postoperative month, the vitamin C group's ODI score was noticeably greater than the control group. According to Lee et al., the use of a visual analogue scale across time, a small sample size, and a restricted number of follow-up time points were the study's limitations (6).

Similarly, Jain et al. looked into the relationship between vitamin C supplementation and pain relief after foot and ankle surgery (13). Six weeks after the procedure, 60 adult patients who had a closed fracture of the foot or ankle were randomly assigned to receive 500 mg of oral vitamin C or a placebo tablet twice a day. At the first, second, sixth, and three-month follow-ups, the functional result, analgesia required, and VAS score were evaluated. In comparison to the control group, the vitamin C group had higher VAS ratings at two and six weeks postoperatively. Furthermore, compared to the control group, the vitamin C group showed better functional outcomes at three months and a reduced mean quantity of analgesia needed at the end of six weeks. A small patient population, a brief follow-up period, and the use of VAS scores—a subjective pain measurement—were limitations of the Jain et al. research (13).

When weighed against NSAIDs and opioids, vitamin C supplementation is comparatively inexpensive and safe. High-dose vitamin C (1.5–2 g/day) has been linked to gastrointestinal distress and an increased risk of kidney stones, according to certain studies (14). A safe upper limit of 2000 g/day of vitamin C has been established, despite conflicting findings about its impact on kidney stone formation (8). Supplementation below this cutoff is thought to be a low-risk nutritional intervention (15).

Supplementing with vitamin C may help with postoperative healing, particularly after PLIF and foot/ankle surgery, according to moderate evidence. Notwithstanding their limitations, the previously described clinical trials offer a strong foundation for upcoming research examining the impact of perioperative vitamin C administration of 0.5–1 g for 40–50 days on the short-, mid-, and long-term outcomes of patients after spinal and lower-extremity surgeries. In the meanwhile, encouraging but sparse and often contradictory data suggests that vitamin C may help avoid chronic regional pain syndrome (CRPS) after orthopedic surgeries. Nonetheless, until more high-level data is available, administering 500–1 gg/day of perioperative vitamin C for 50 days seems like a fair course of action. In general, additional prospective clinical trials are needed in these domains to establish the ideal dosage and mode of administration for vitamin C and to offer more proof of its efficacy.

Bone metabolism

Animal models have been used to study the function of vitamin C in bone healing throughout the past ten years. The effects of intraperitoneal vitamin C supplementation on bone healing following rat tibia fracture were studied by Giordano et al. They found no histological changes between groups A (vitamin C) and B (saline) (16). At six weeks in this trial, every participant in both groups had a fully fused bone. In a different study, vitamin C restored the ovariectomy-induced alterations in the rates of various bone properties, such as reduced antioxidant capacity

and bone quality (17). In ovariectomized (OVX) Wistar rats, Choi et al. recently discovered that vitamin C can prevent osteoporosis by encouraging osteoblast development and preventing osteoclastogenesis via various signaling pathways (4). Additionally, their findings showed that vitamin C administration enhanced bone volume and mineral density (BMD) in OVX rats, as well as the number and expression of osteoblast and osteoclast genes (4). Similarly, Zheng et al. found that by enhancing osteoblast development, reducing inflammation, and fostering angiogenesis, combined magnesium and vitamin C supplementation can mitigate steroid-associated osteonecrosis in Sprague-Dawley rats (18). The fact that none of the aforementioned animal research involved human participants placed restrictions on them. However, according to the information above, vitamin C supplements may promote bone regeneration and lessen the impact of degenerative bone diseases such as osteoporosis, osteoarthritis (OA), and osteonecrosis. However, further human studies are required to support these claims.

Studies on humans have recently looked into the relationship between vitamin C and fracture risk. An analysis of the relationship between antioxidant consumption and hip fracture risk in senior Chinese individuals was conducted by Sun et al. There were 726 hip fracture patients and 726 control participants in the study (19). The scientists measured different antioxidant intakes using a food frequency questionnaire and in-person interviews. They found a substantial inverse link between vitamin C intake and hip fracture risk. Sun et al. did note, however, that prospective dietary alterations could have limitations, such as recall bias and assumptions made in the estimation of food antioxidant levels (19). Low serum vitamin C concentrations were associated with an increased incidence of hip fracture in senior patients, according to a similar study by Torbergson et al. This association may be explained by the vitamin's involvement in bone turnover mechanisms. The fact that Torbergson et al. failed to consider patient fall risk, which may have contributed to the variation in hip fracture risk between the two groups, limited the scope of their investigation (20).

A study by Finck et al., in contrast to the other two, focused on the impact of vitamin C on heel bone ultrasonography measures and hip/spine fracture risk. Out of the total number of patients in the study, 25,639 had fractures. The researchers found that plasma vitamin C content was associated with a decreased risk of fracture in men and that dietary vitamin C was significantly associated with higher heel bone ultrasonography measurements. Finck et al. noted that a weakness of the study was the approximately 3-year interval between diet/plasma data and those of the ultrasonography, indicating that further research is needed to elucidate vitamin C's inconsistent association with bone health parameters (21). A robust statistical link between dietary vitamin C and a lower incidence of hip fracture was discovered in a subsequent meta-analysis involving 10,807 patients (7908 controls and 2899 instances of hip fracture). More specifically, for every 50 mg/day increase in dietary vitamin C intake, the incidence of hip fracture dropped by 5%. To support these findings, the authors did concede that additional carefully planned RCTs were necessary (22).

Studies conducted on humans have also assessed the relationship between vitamin C and the risk of osteoporosis. Kim et al. looked at the relationship between postmenopausal women's BMD and their dietary vitamin C intake. The results of their investigation showed that, among postmenopausal women, dietary vitamin C intake showed a substantial positive association with bone mineral density (BMD) and a strong negative correlation with the risk of osteoporosis. These correlations were most pronounced in patients who were vitamin D deficient and aged 50–59 or older than 70. Kim et al. identified two feasible constraints: the low incidence of fractures and the dearth of information on serum vitamin C concentrations (23). An additional research team assessed the impact of vitamin C consumption and physical exercise on the risk of osteoporosis in Korean individuals over the age of fifty. The 3047 participants in the study were divided into two groups based on BMD results: those with osteoporosis and those without it. The findings indicated that in Korean adults with low levels of physical activity, increased vitamin C intake was associated with a lower risk of osteoporosis; however, no correlation was observed between the two in those with high activity levels. One possible drawback that was brought up was the difficulty

of determining causality (24).

Studies conducted in labs and on humans have generally linked vitamin C use to better bone health. This is because long-term dietary consumption of the antioxidant may help to improve parameters like bone mineral density and reduce fracture risk, while shorter-term supplementation may attenuate degenerative bone conditions like osteonecrosis and OA. To gain a deeper understanding of vitamin C's specific effects on bone health, more human trials assessing the vitamin in isolation are necessary.

Anterior cruciate ligament reconstruction and arthroplasty

The ACL is the most frequently torn ligament in the knee, and over 100,000 reconstructive ACL procedures are thought to be performed annually in the US. According to certain research, individuals with ACLs may have a higher chance of getting osteoarthritis (OA) in the years after reconstruction (25). OA is the most frequent cause of pain and disability in the US, with the knee joint being most typically affected. Because vitamin C can protect chondrocytes through downstream signaling pathways, it has been proposed that vitamin C may slow down the course of OA. However, there is currently little data from laboratory research supporting this theory (26). Through their ability to increase oxidative stress on human cartilage tissue, several ROS, including hydrogen peroxide (H2O2), hypochlorite ion, hydroxyl radical, and superoxide anion, have been linked to the pathophysiology of OA. Degeneration of cartilage and chondrocyte dysfunction has been linked to increased oxidative stress (27). The extant literature mostly attributes the chondroprotective effect of vitamin C to its potent antioxidant capabilities (26).

The potential of vitamin C supplementation to improve patient outcomes after total knee arthroplasty (TKA) and ACL repair has been investigated in recent research (28). Barker et al. investigated the impact of vitamin C supplementation before surgery on inflammation after ACL reconstruction. Twenty patients following ACL surgery were divided into two groups: the antioxidant group received a matched placebo or 500 mg of vitamin C and 200 IU of vitamin E twice a day. During the 12-week trial, the researchers found that antioxidant supplementation decreased the rise in a proinflammatory cytokine that occurred 90 minutes after surgery and counteracted drops in plasma vitamin C concentrations. Barker et al. also discovered, though not statistically significant, that antioxidant treatment increased the injured limb's 12-week strength improvement relative to the control. One plausible restriction mentioned by the authors was the insufficient frequency of blood draws after the tourniquet was removed during surgery (28). Cheng et al. investigated the impact of vitamin C irrigation saline on graft healing in rats after ACL reconstruction, which was comparable to the research on AT healing. 114 rats were divided into four groups for this 6-week trial, and each group received 10 milliliters of either saline solution or saline enriched with vitamin C at concentrations of 3, 10, or 30 mg/ml. On Day 1 post-operation, all vitamin C groups showed reduced inflammatory response; at 6 weeks post-operation, the 3 mg/ml group showed improved anterior-posterior knee laxity and less graft degradation than the control group (29). In comparison to saline irrigation alone, the authors found that irrigation with saline plus vitamin C was linked to improved anterior posterior knee laxity and a decrease in serum C-reactive protein after surgery. The impact of vitamin C irrigation on human ACL repair graft recovery has not been investigated in any research.

In a similar vein, some research has assessed how vitamin C supplementation affects the results of individuals having knee replacement surgery. Behrend et al. looked into the potential effects of vitamin C administration during surgery on knee range of motion and arthrofibrosis (AF) risk after total knee arthroplasty (TKA) (30). 95 TKA patients were split into two groups for this study: the placebo group received a daily pill that contained a placebo, and the vitamin C group received 100 mg of oral vitamin C every day (30). The supplementation period for both groups was 50 days, beginning the day before the surgery. After TKA, the vitamin C serum concentration dropped in the vitamin C group but not in the placebo group, according to the authors. Patients who had decreases of more than 30 µmol/L had a higher risk of developing atrial fibrillation one year later. Behrend et al. recognized that the study was constrained by an insufficient sample size and a lack of measurable

biomarkers related to inflammation. Shah et al. monitored vitamin C and inflammatory cytokine levels in TKA patients concurrently. Ten patients had pre- and postoperative blood samples taken. After TKA, the authors saw a marked rise in inflammation but no discernible changes in serum vitamin C levels. It was accepted that the short study period and limited sample size were limitations (31).

There is still a lack of data to adequately support the perioperative use of vitamin C in patients having knee joint surgeries, and its significance after total knee arthroplasty (TKA) and ACL reconstruction is unclear. Further studies may be necessary to determine whether vitamin C supplements can improve patient outcomes after ACL repair and lower the incidence of OA and AF. Verification of the decrease in vitamin C and its proposed advantages following TKA requires more human trials.

Tendon regeneration

Both sedentary and active people are susceptible to tendon injury (32). Ruptures or inflammations of the biceps, rotator cuff, Achilles, or patellar tendons are examples of common tendon ailments. Collagen makes up over 75% of the dry weight in tendons, making it a crucial component (33). To strengthen tendons and reduce injury, dietary and exercise interventions have been suggested as a way to induce collagen synthesis. Numerous research works have investigated the effects of vitamin C supplementation on tendon health and repair as well as collagen synthesis (34). Vitamin C promotes local angiogenesis and increases the diameter of collagen fibrils and fibroblasts at the site of injury to enhance tendon recovery. Furthermore, in an animal model, vitamin C has been demonstrated to decrease peritendinous adhesions (35).

The majority of research conducted on laboratory animals supports the use of vitamin C alone or in conjunction with other therapies, such as magnesium, HA, and stem cells, to promote tendon health and recovery. Furthermore, a study connected the application of irrigation saline enhanced with vitamin C to improved graft healing after anterior cruciate ligament (ACL) restoration. Nonetheless, as previously stated, superior human clinical trials are required to support vitamin C's efficacy in this regard.

Conclusions

The field of musculoskeletal research on vitamin C's role in molecular pathways associated with bone and tendon regeneration is relatively new. Supplementing with vitamin C has been linked to better functional results, less pain after surgery, and a lower chance of developing chronic regional pain syndrome after orthopedic surgeries. All things considered, high-quality human trials are required to verify if vitamin C can enhance the results of orthopedic treatments and to establish the best dosages and modes of administration for obtaining its suggested advantages.

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Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Contributions

Research concept and design: **ŞY**

Data analysis and interpretation: **ŞY**

Collection and/or assembly of data: **ŞY**

Writing the article: **ŞY**

Critical revision of the article: **ŞY**

Final approval of the article: **ŞY**

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