Glutamine: Indicated in Cancer Care?

Georgia M. Decker, MS, RN, CS-ANP, AOCN®, CN

Little was known about L-glutamine (commonly referred to as glutamine) until research in the 1930s found it to be the most prevalent amino acid in the human body. Approximately 20 amino acids, classified as essential or nonessential, make up dietary protein (see Figure 1). Glutamine is a nonessential amino acid (i.e., the body is able to synthesize it) contained in most dietary proteins. A healthy person consumes 5–10 grams of dietary glutamine daily and, therefore, usually does not need supplemental glutamine (Lebow & Souba, 2000; Miller, 1999; Smith & Wilmore, 1990).

High concentrations of this amino acid are found in the skeletal muscle, liver, brain, lungs, and stomach (Miller, 1999; Souba, 1993). Glutamine has a role in multiple bodily functions and serves as an essential amino acid, leading to protein catabolism. For example, depletion of skeletal muscle glutamine because of tumor growth results in cachexia (Klimberg & McClellan, 1996). Researchers believe that a tumor becomes a glutamine trap and worsens glutamine loss in patients with cancer and that glutamine has the potential to stall or halt tumor growth because of its immunomodulatory action (Klimberg & McClellan).

Glutamine in Cancer Care

The use of glutamine in oncology has been researched in animals and humans, but the results often have conflicted (Miller, 1999). Researchers became concerned about an increase in tumor growth with glutamine supplementation in patients with cancer after in vitro studies revealed an increase in cellular growth with glutamine supplementation (Kang, Feng, & Hatcher, 1994). However, subsequent in vivo studies showed the opposite effect: a reduction in tumor growth (Bartlett, Charland, & Torosian, 1995; Fahr, Kornbluth, Blossom, Schaeffer, & Klimberg, 1994).

Researchers focused on assessing its role in alleviating side effects. In a randomized, double-blind, crossover study, oral glutamine (16 g/day) or a placebo was given to 18 patients receiving 5-fluorouracil chemotherapy for gastrointestinal cancers. The glutamine was well tolerated with no apparent adverse effects but failed to have any significant effect on oral mucosa as assessed by the patients and researchers (Jebb et al., 1994). In a larger double-blind study, 66 patients were randomized to receive oral glutamine or a placebo in conjunction with oral cytotherapy and 5-fluorouracil chemotherapy. No significant differences were found in subjective and objective mucositis scores between the two groups (Okuno et al., 1999).

Other studies have found some benefits to glutamine supplementation. In a randomized, an enteral diet containing glutamine increased muscle glutamine in rats by 60% without increasing tumor growth or tumor glutamine use. Glutamine supplementation in rats receiving methotrexate chemotherapy was found to increase tumor methotrexate concentration; reduce methotrexate-induced side effects, including mucositis; and improve survival (Fox et al., 1988). Glutamine supplementation also was found to prevent mucosal ulceration in rats subjected to abdominal radiation (Klimberg, Souba, Salloum, et al., 1990). Such promising results from laboratory and animal studies led to clinical studies of glutamine supplementation.

Alleviating the Side Effects of Chemotherapy

Most studies of glutamine supplementation in patients receiving chemotherapy have focused on assessing its role in alleviating side effects. In a randomized, double-blind, crossover study, oral glutamine (16 g/day) or a placebo was given to 18 patients receiving 5-fluorouracil chemotherapy for gastrointestinal cancers. The glutamine was well tolerated with no apparent adverse effects but failed to have any significant effect on oral mucosa as assessed by the patients and researchers (Jebb et al., 1994). In a larger double-blind study, 66 patients were randomized to receive oral glutamine or a placebo in conjunction with oral cytotherapy and 5-fluorouracil chemotherapy. No significant differences were found in subjective and objective mucositis scores between the two groups (Okuno et al., 1999).

Other studies have found some benefits to glutamine supplementation. In a randomized,
double-blind, crossover study of 24 patients receiving mucositis-inducing chemotherapy, patients received either glutamine (1 g/m² four times daily for 14 days) followed by a placebo (for 14 days) or a placebo followed by glutamine. Patients completed diaries to record mouth pain and oral intake. Paired data indicated that the severity and duration of mouth pain were significantly less when chemotherapy was supplemented with glutamine (Anderson, Schroeder, & Skubitz, 1998).

In a randomized study of 24 patients receiving 5-fluorouracil chemotherapy, half received glutamine supplementation at a dose of 2 g/m² twice daily. The gastrointestinal (GI) mucosa was assessed by endoscopic examinations and measurement of villus height/ crypt depth ratios. In the group receiving glutamine, a significant reduction in ulcerations of the gastric duodenal mucosa and higher villus ratios were documented after the third course of chemotherapy. However, no significant differences in incidence and severity of clinical side effects were recorded (Decker-Baumann et al., 1999).

The effect of glutamine on chemotherapy-induced diarrhea also has been explored. Oral glutamine (18 g/day for 15 days) was given to half of 70 patients with colorectal cancer prior to fluorouracil chemotherapy; the remaining half of the patients received a placebo. The duration of diarrhea was 1.9 days for the group receiving glutamine, compared with 4.5 days for the placebo group. The patients receiving glutamine also took fewer loperamide tablets to manage the diarrhea (Daniele et al., 2001). However, glutamine supplementation had no effect on chemotherapy-induced diarrhea in a study of 65 women with breast cancer (Bozzetti et al., 1997). Glutamine also has been used anecdotaly to treat late-onset irinotecan-induced diarrhea (Savarese, Al-Zoubi, & Boucher, 2000).

Improvement in vincristine-, cisplatin-, and paclitaxel-induced peripheral neuropathies first was documented in rats receiving glutamine supplements (Boyle, Wheeler, & Shenfield, 1996, 1999). In a nonrandomized study using cohort samples, the severity of peripheral neuropathy in 33 patients receiving high-dose paclitaxel was compared to the severity experienced by 12 patients who received the same chemotherapy with glutamine supplementation (10 g/day for three days). Patients receiving glutamine had a significant reduction in the development of dyesthesias and numbness of the fingers and toes. However, researchers noted a need for randomized, placebo-controlled clinical trials of the effectiveness of glutamine in reducing this side effect (Vahdat et al., 2001). Improvement in paclitaxel-induced myalgias and arthralgias also has been anecdotally attributed to glutamine supplementation (30 g/day) (Savarese, Boucher, & Corey, 1998); however, further research is needed.

Use in Patients Undergoing Transplantation

Oral glutamine was compared with protein and dextrose supplementation in a study of patients undergoing autologous stem cell transplantation (SCT). None of the supplements was effective in preventing GI toxicity, and 59% of the patients who received oral glutamine (20 g/day) required total parenteral nutrition (TPN) for GI toxicity (Canovas et al., 2000). In a study of people undergoing allogeneic or autologous SCT, 58 patients were randomized to receive glutamine (30 g/day) or a placebo. No significant differences were found between the groups in nutritional status, number of days of TPN required, or severity or duration of mucositis (Dickson et al., 2000). In a study conducted by Schloerb & Skikne (1999), glutamine supplementation in 66 patients undergoing allogeneic or autologous SCT also failed to demonstrate benefit; no differences existed in length of stay, mucositis incidence and severity, or neutrophil recovery time between patients who received glutamine and those who did not. An earlier randomized, double-blind study comparing glutamine to a placebo also found no differences in mucositis incidence and severity, TPN use, or length of hospitalization (Anderson, Ramsay, et al., 1998).

One study that found glutamine to be beneficial was a retrospective analysis of consecutive patients who received high-dose paclitaxel and melphalan as the preparative regimen for autologous SCT. Researchers revealed that those who were given oral glutamine (24 g/day) every four hours around the clock did not require patient-controlled analgesia (PCA) morphine, whereas those who did not receive glutamine required five days of PCA. The severity and duration of mucositis also were lower in the glutamine-treated group (Cockerham, Weinberger, & Lerchie, 2000).

Glutamine supplementation (0.57 g/kg per day) was credited with decreasing infection rates (based on stool and throat culture results) and shortening hospital stays by one week for patients undergoing bone marrow transplantation (Ziegler et al., 1992). However, these findings recently were disputed by Buchman (2001), who acknowledged that although hospital stays decreased, it was not clear whether this was a result of fewer negative throat and stool cultures, less severe negative nitrogen balance, or the glutamine supplementation.

Use in Radiation Therapy

The influence of oral glutamine on radiation-induced mucositis was examined in a randomized study of 17 patients undergoing radiation therapy to the head and neck area. Patients received 16 g of oral glutamine or a placebo. The duration of objective oral mucositis was shorter for patients who received glutamine, but it did not reduce the duration or severity of subjective oral mucositis for patients with grades 1 and 2 mucositis. Patients with grade 3 mucositis receiving glutamine reported less severe mucositis, but patients in both groups required analgesia, and no changes were recorded in mean body weights between the groups (Huang et al., 2000).

Evidence or Lack of Evidence for Using Glutamine?

In an era of evidence-based practice, published studies of glutamine supplementation must be examined critically. Many of the early studies did not use a randomized, placebo-controlled design, and only a few published studies were double-blind. Most study samples were small, and in some studies, the control groups were much larger than the treatment groups. In addition, various doses and dosing intervals of glutamine were evaluated. Outcome measures also were varied and diverse. Certain outcome measures, such as length of hospitalization or infection rates, can be affected by a multitude of factors and were not necessarily a reflection of glutamine supplementation. In most of the placebo-controlled studies, glycine was used as the placebo, and data suggest that glycine might have immunologic and antioxidant properties of its own (Hall, Heel, & McCauley, 1996). Buchman (2001) reviewed what he termed the “human data” on glutamine and challenges many of the research findings. He asserted that “on the basis of currently available clinical data, it is inappropriate to recommend glutamine for therapeutic use in any condition.”
(Buchman, p. 2). Ziegler (2001) noted that, given the available data, randomized, double-blind controlled clinical trials of glutamine supplementation during cancer treatment are indicated to define the utility of this amino acid as adjuvant therapy.

**Dosage and Administration**

Dosing parameters for oral and enteral glutamine supplementation vary. Decke-Baumann et al. (1999) used endoscopic visualization and villus height measurements to determine that 14–22 g of parenteral glutamine per day decreased gastroduodenal mucositis. A dose of 0.5 g of glutamine per kilogram of body weight per day is thought to be adequate for metabolic stress conditions (Savy, 2000). The majority of studies of glutamine supplementation in humans have examined doses of oral and enteral glutamine at 30 g per day (10 g three times daily), sometimes beginning prior to the initiation of therapy.

Pharmaceutical-grade glutamine powder, granules, and capsules are available commercially without a prescription, are almost tasteless, and may be added to any beverage or soft food or dissolved in water for administration through a feeding tube. Savy (2000) also noted that no reports have documented glutamine causing clogged feeding tubes.

Glutamine-containing solutions are not stable for long periods of time and, therefore, should be used as soon as possible after mixing. Some authors consider parenteral glutamine supplementation to be costly and difficult to produce (Savy, 2000), although others assert that cost savings occur with its use (MacBurney, Young, Ziegler, & Wilmore, 1994).

**Summary**

Glutamine is a nonessential amino acid contained in most dietary proteins and provides immune functions and fuel for the small intestine. For healthy people, dietary glutamine (from protein) usually is considered adequate. Results of research evaluating the potential benefits of glutamine during cancer therapy are encouraging but remain inconclusive.

Some researchers have suggested recently that glutamine may, in fact, be a conditionally essential amino acid (Buchman, 2001). Decreases in glutamine levels after trauma or major burns, postoperatively, and in patients with diseases such as inflammatory bowel disease, AIDS, and cancer are widely recognized and acknowledged (Medina, 2001; Miller, 1999). The interpretation of data suggesting that glutamine supplementation is of benefit in almost any clinical situation is controversial. Additional research is needed to confirm the mechanism of action and efficacy of glutamine as adjuvant therapy in patients receiving cancer treatment.

**Author Contact:** Georgia M. Decker, MS, RN, CS-ANP, AOCN®, CN, can be reached at jorja@worldnet.att.com.

**References**


Osteoporosis Related to Androgen Suppression


Study Summary

The purpose of this study was to describe the long-term risk of skeletal fracture in men on androgen suppression for prostate cancer and to identify risk factors for skeletal fracture. Data collection involved chart reviews and interviews of 181 men with prostate cancer on androgen suppression therapy. The median patient age at prostate cancer diagnosis was 72 years, and the median duration of androgen suppression was 47 months. Sixty-two percent of the patients had metastatic prostate cancer at the initiation of androgen suppression therapy. Results indicated that 96% of the patients were fracture-free at five years with androgen suppression therapy and 80% were fracture-free at 10 years with androgen suppression therapy. Of those patients with fractures (n = 9), four had hip fractures, one had a hip and extremity fracture, three had extremity fractures, and one had a spinal fracture. Multivariate analyses revealed that African American men and men with an increased body mass index were at a lower risk for skeletal fractures associated with androgen suppression therapy. A significant correlation was found between the duration of androgen suppression therapy and the risk of skeletal fracture. Factors not found to be associated with skeletal fractures included stage of disease, pretreatment prostate-specific antigen, Gleason score, androgen-independent prostate cancer, type of androgen suppression, and primary treatment administered. In comparison to normal-aged match controls, patients with prostate cancer who were treated with androgen suppression therapy were at a five-fold increased risk of androgen suppression-related skeletal fractures.

Applications to Patient Care

- Study findings suggest that African American men and men with increased body mass index are at low risk for androgen suppression-associated skeletal fractures. Conversely, slender, Caucasian men on prolonged duration of androgen suppression therapy are at greater risk for skeletal fractures.

These findings can assist oncology nurses in identifying patients with prostate cancer on androgen suppression therapy that may be at risk for skeletal fractures. Nurses should obtain medical and family histories on all patients at the initiation of androgen suppression therapy to identify other risk factors for osteoporosis. Patients on androgen suppression therapy with increased numbers of risk factors may need frequent evaluations for osteoporosis. If osteoporosis is identified, treatment should be initiated to prevent skeletal fractures.

- The median patient age for this study was 72 years, and 62% of the patients had metastatic prostate cancer.

The major site for metastatic disease in prostate cancer is bone. Both advanced age and compromised bone structure can predispose men with prostate cancer on androgen suppression therapy to skeletal fractures. Oncology nurses should provide education to these patients regarding methods to decrease the risk of fractures. This includes information regarding a fracture-free environment to minimize the risk of falls or other accidents. Nurses should instruct patients to remove clutter from walk areas, secure rugs, install handrails in showers and tubs, light stairwells and hallways, and wear sturdy, low-heeled shoes. Nurses also should instruct patients to report any symptoms of vertigo, lightheadedness, or loss of balance that may place them at increased risks of falls.

Author Contact: Diane Cope, PhD, ARNP-BC, AOCN®, can be reached at ecope@attglobal.net.