

# L-Arginine & Cancer

Arginine and Cancer. Does arginine promote or retard cancer growth?  
Should cancer patients be cautioned against 5 grams arginine per day?

I reviewed the pubmed database using the search terms "L-arginine" and "Cancer" and retrieved over 1,000 articles. Many actually referred to specific nitric oxide studies in lab animals and in vitro cancer cell lines, and overall were too difficult to summarize. Such statements as "NO causes metastasis" would be contradicted in the next article by the statement "NO prevents metastasis and causes tumor regression." I found about 50 articles which actually referred to the use of L-arginine and its inhibitors which seemed useful to the question at hand.

Theoretical concerns include:

- Increased blood flow may feed the tumor
- Increased growth hormone due to supplementation with arginine may cause tumor growth
- Arginine itself may feed auxotrophic tumors, those which cannot manufacture arginine themselves, such as melanoma and hepatocellular carcinoma.

## **BLOOD FLOW**

As you know, L-arginine can be utilized by the body to make arginine derived nitric oxide (ADNO). Nitric oxide synthase (eNOS, or NOS I) is the enzyme responsible for this in the endothelium. The nitric oxide dilates blood vessels. But will that increase blood flow to tumors? There is one study documenting diminished blood flow to tumors after NOS inhibitor was used. While inhibition of ADNO production diminishes tumor blood flow <sup>1</sup>, it is not clear that the enhanced blood flow due to arginine supplementation would enhance tumor growth. In fact, L-arginine has been used in cancer therapy. Read on.

## **GROWTH HORMONE**

L-arginine supplementation can<sup>2 3</sup> (but does not always<sup>4</sup>) increase serum growth hormone concentrations in humans.

One well-designed study compared men to women with various growth hormone secretagogues, including arginine (30 grams IV), exercise, growth hormone releasing hormone, somatostatin rebound, compared to rest and saline for each individual. The impressive thing is that the **exercise** stimulus was roughly equivalent to **30 grams of intravenous L-arginine**, a dose several times more and via a different route than we are advocating. (Even my own husband, a Cardiococktail junky, takes only 20 grams at most each day, and he does not yet mainline the stuff.) If you enjoy a well-designed, well-executed study, you'll enjoy reading this article. The link to the full text is in the footnotes.<sup>5</sup>

In another randomized, placebo-controlled study in healthy men, placebo was compared to Arginine alone, placebo +exercise, or Arginine + exercise. The dose was 7 grams oral Arginine. The **exercise** yielded a greater growth hormone response than exercise + Arginine or Arginine alone.<sup>6</sup>

It is true that patients who received growth hormone injections in the past are considered at a higher risk of various cancers, including leukemia. What is not known is whether the growth hormone which may be secreted after arginine supplementation will trigger the same potential for tumor support as a recombinant injection. And since the growth hormone produced in response to oral arginine would be less than exercise stimulation, are we going to tell them **not to exercise** because the growth hormone produced by the **exercise might promote cancer**?

## **SPECIAL CASES: MELANOMA AND HEPATOCELLULAR CARCINOMA**

These are the only group of people whom I think should be warned against using L-arginine. Melanoma, hepatocellular carcinoma and possibly leukemic cells<sup>7</sup> require L-arginine to be supplied for their growth. They lack the enzymes necessary to convert L-citrulline into L-arginine, and sometimes from L-arginine into nitric oxide.<sup>8 9</sup> This particular characteristic has already

been exploited in tumor research with good results. Interestingly, in a mouse model if these cell types are transgenically infected with the enzymes to convert L-arginine into nitric oxide they LOSE THE ABILITY TO METASTASIZE.<sup>10</sup> Yet NOS activity is higher in melanoma than melanocyte cell lines in vitro.<sup>11</sup>

A number of trials have used arginase (an enzyme responsible for changing arginine to ornithine) to treat hepatocellular carcinomas. These have resulted in responses with regression in both metastasis and the primary tumor.<sup>12</sup> An arginine diiminase (another enzyme which breaks down arginine) from Mycoplasma has been used in multiple trials. One trial shrank a tumor from an unresectable to a surgically resectable size. Other studies show inhibition of hepatocellular carcinoma and malignant melanoma cells both in vitro and in vivo.<sup>13</sup>

## **Human Studies**

What happens if we give L-arginine to real, live cancer patients? Many studies have utilized L-arginine as a component in perioperative nutrition and immunomodulation, and some have even used it as an adjunct to chemotherapy. After explaining immunonutrition and the immune dysfunction in cancer, I'll talk about some specific cancer studies using L-arginine supplementation.

**Immunonutrition** is the concept of optimizing the immune system through giving proper nutrients, nutrients known to improve blood components known to fight cancer or infection, such as IgG and IgM, Natural Killer (NK), Lymphokine-Associated Killer (LAK), and T-cytotoxic cells, while diminishing the circulating components known to undermine host defenses such as T suppressor cells and IL-6. L-arginine appears again and again as a beneficial component of these formulations. These studies support the safety of formulae containing L-arginine, reveal the improvement of patients' immune markers over control groups who did not receive immunonutrition, and a few even suggest a trend toward better survival in cancer patients.

It is known that there is **immune dysfunction in cancer**; it is believed that poor immune function allows cancer to thrive in the body. How does this happen? And how does L-arginine interact with the immune system in cancer?

### **Myeloid cells**

Immature myeloid cells actually protect tumors. When exposed to the environment of the tumor, they become myeloid suppressor cells resulting in poor function of immune system. They develop increased **arginase** activity, breaking down arginine, and making it unavailable to T-cells. Arginine is directly responsible for T-lymphocyte cell cycle progression<sup>14</sup>, T-cell proliferation, and production of cytokines. Since macrophages in tumors are known to secrete Arginase I,<sup>15</sup> it is not surprising that in cancer, T-cells have a decreased ability to proliferate and decreased production of cytokines. Arginase I also decreases expression of T-cell receptor "CD3zeta chain",<sup>16 17</sup> and impairs T-cell responses. In fact Arginase I is increased in tumors relative to surrounding normal tissues, and often in cancer patients' serum in general.<sup>18</sup> **Addition of excess arginine restores T-cell proliferation, cytokine production and CD3zeta receptor expression.**<sup>19</sup>

### **General Cancer Studies**

In one study, Arginine, glutamine and omegas were supplemented in trauma, burn and cancer patients. All patients had increased lymphocytes, CD4, CD8 cells, Complement 3, IgG, and IgA; with decreased CRP.<sup>20</sup> Three studies (2 were double blinded) studied a mixtures of Arginine, glutamine, omega3, omega 6, RNA, vitamins E, C, A. 3 studies showed **decreased infection rate** in surgical patients (down 75%!), and hospital **length of stay was 20% shorter.**<sup>21</sup>

Arginine 25 grams daily was compared to glycine 43 grams of supplement in 30 cancer patients undergoing surgery. Positive mean nitrogen balance, although moderate, was achieved only in the arginine group. The **immune effect was much more noticeable**, with improvements in T-lymphocyte response to stimulation and increase in CD4 phenotype.<sup>22</sup> However, in

advanced gastric cancer 30 grams daily of L-arginine for a week did not stimulate lymphocyte function. It was found to be safe in this patient population.<sup>23</sup>

Another study in patients undergoing major surgery for cancer found no difference in lymphocyte proliferation or monocyte function between Control groups, compared to groups given arginine or to arginine plus omegas.<sup>24</sup>

Thymic hormone (thymulin) levels, known to be low in cancer patients, are improved by lysine-arginine mix. The levels ultimately were **higher than in age-matched controls, and the patients had increased numbers of peripheral T-cell subsets.**<sup>25</sup>

### **Head and Neck:**

A number of head and neck cancer studies evaluated perioperative nutrition via several regimens. L-arginine was found to be safe in all cases, and generally well-tolerated. These all are supportive of the use of L-arginine in a general nutritional regimen. The entire regimen did not prolong life, but did reduce wound complications, fistulae, hospital stays and hospital costs. One study of supplementation revealed better protein levels<sup>26</sup>. Another randomized study revealed increased lymphocytes, CD4, CD4/8 ratios on day 4 and CD3, CD4, CD4/8 on PO8. In a malnourished subgroup in the same study, the arginine supplemented group had decreased incidence of postoperative and wound complications and length of stay in the hospital.<sup>27</sup> Other studies showed decreased fistulae<sup>28 29 30</sup>, in the groups receiving L-arginine supplements. The studies had differing result regarding length of stay in the hospital.

Other studies showed no difference in nutritional or inflammatory markers between groups,<sup>31</sup> and no difference regarding nutritional status, complications, but a trend toward better survival in Arginine supplemented group.<sup>32</sup>

### **Breast cancer patients:**

Although L-arginine supplementation inhibits growth of tumors in animals, it seems to stimulate tumor protein synthesis in tumors of humans supplemented with L-arginine.<sup>33</sup> Nevertheless, multiple studies have been done and are currently underway using L-arginine supplementation for cancer patients. Generally, L-arginine supplementation or IV regimens have been well-tolerated and seem to improve prognosis.<sup>34</sup>

In a double-blinded, randomized, controlled study using 30 grams/day for 3 days in addition to standard chemotherapy vs placebo, no significant change was noted in response rate. However, for tumors less than 6 cm in size at diagnosis, 88% response rate was noted vs. 52% (p=0.04) Two other studies using the same protocol with CHOP regimen chemotherapy noted smaller and delayed onset immunosuppression, improved NK and LAK cytotoxicity<sup>35</sup> and in tumors >4 cm a **95% response rate. For 18% there was no tumor left at the time of resection.**<sup>36</sup>

### **GI cancer:**

Again, formulations with supplemental L-arginine are well-tolerated. They are usually combined in this group with other immunomodulatory components like omega-3 fatty acid mixtures, and/or glutamine. While one study of both benign and malignant peri-operative supplementation showed no difference in complication, mortality or length of hospital stay, the majority of studies in cancer showed distinct benefit.<sup>37</sup> These formulations have been associated with cost savings,<sup>38,39</sup> decreased late complications,<sup>36</sup> improved CD4 counts, CD4/8 ratios, IL-2 levels, increased proteins<sup>40</sup> and immunoglobulin<sup>41,40</sup>; as well as lowered IL-6 and TNF alpha.<sup>42 43 44</sup>

One formula with Arginine, Omega-3, and RNA had better wound healing and fewer wound complications.<sup>45</sup> Another study of this same formula in GI surgery patients (benign and malignant disease) found no benefit.<sup>46</sup>

One study compared arginine to glutamine to a control population. While the arginine group had a higher albumin, the glutamine group had decreased postoperative morbidity.<sup>47</sup>

**A meta-analysis of 1269 pts receiving various immunonutrients including L-arginine revealed positive effect on post operative infection ( $p < 0.00001$ ), Length of stay in the hospital ( $p < 0.00001$ ), and improved immune function, without side effects.<sup>48</sup>**

Yet another study of patients with cachexia, more than 5% wt loss, and stage IV solid tumors were studied. The protocol called for either a control formula of nonessential amino acids, or a formula containing 3g/d beta-hydroxy-beta-methylbutyrate, and 14 g/d each of L-arginine and L-glutamine for 24 weeks. The mixture of HMB/Arg/Gln increased weight by increasing fat-free mass in these patients.<sup>49</sup> Another study of the same mixture revealed reversed muscle wasting and improved Hgb, Hct, lymphocytes, eosinophils, improved emotional profile, and decreased feeling of weakness in randomized cancer and HIV patients.<sup>50</sup>

### **Summary**

In summary, arguments that growth hormone produced by L-arginine might feed a tumor fall apart under close scrutiny. Blood flow is inhibited by the inhibition of NOS, but it is not known whether supplemental L-arginine actually would tilt the balance in favor of the tumor. Most importantly, **L-arginine is used extensively in the management of cancer.** It is an **essential nutrient** for T-cells, NK, and LAK cells, whose job it is to defend the body against cancer. I think L-arginine should not be withheld from patients with cancer. The only possible exception is in the case of malignant melanoma and hepatocellular carcinoma.

## Resources:

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- 1) **Effect of nitric-oxide synthesis on tumour blood volume and vascular activity: a phase I study.** [Lancet Oncol.](#) 2007 Feb;8(2):111-8.  
[Ng QS](#), [Goh V](#), [Milner J](#), [Stratford MR](#), [Folkes LK](#), [Tozer GM](#), [Saunders MI](#), [Hoskin PJ](#).

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**BACKGROUND:** Nitric oxide has been implicated in tumour angiogenesis and in the maintaining of vasodilator tone of tumour blood vessels. The tumour vascular effects of inhibition of nitric-oxide synthesis have not been investigated in patients with cancer.

**METHODS:** Seven women and 11 men (12 with non-small-cell lung cancer, five prostate cancer, and one cervical cancer) were recruited onto a phase I dose-escalation study and received a single dose of the nitric oxide synthase inhibitor, N-nitro-L-arginine (L-NNA). Dose escalation was done by a modified Fibonacci scale with three patients at each dose level, starting with 0.1 mg/kg. Changes in dynamic contrast-enhanced CT measures of tumour relative blood volume and transfer constant (K) were measured at 1 h and 24 h after L-NNA administration.

**FINDINGS:** In the 18 patients, toxic effects were self-limiting cardiovascular changes: three patients had Common Toxicity Criteria version 2.0 grade 1 hypertension; two had grade 1 sinus bradycardia; and one had grade 1 palpitation. L-NNA area under the curve (AUC) increased linearly with dose from 163 micromol min<sup>(-1)</sup> L<sup>(-1)</sup> at 0.1 mg/kg L-NNA to 2150 micromol min<sup>(-1)</sup> L<sup>(-1)</sup> at 0.9 mg/kg L-NNA. In eight patients that underwent dynamic CT scanning, tumour blood volume decreased 1 h after L-NNA treatment (mean 42.9% [range 12.0-62.1]; paired t test p=0.0070), which was sustained for up to 24 h (mean 33.9% [range 6.5-64.9]; p=0.035). This decrease in blood volume was associated with an increase in the number of non-perfused pixels from 7.3% (SD 5.5) at baseline to 25.1% (15.3; p=0.0089) at 1 h, and 18.2% (12.9; p=0.050) at 24 h. There was a significant correlation between L-NNA plasma AUC and the reduction in tumour blood volume at 24 h after L-NNA (r=0.83; p=0.010).

**INTERPRETATION:** We have shown in vivo in patients with cancer that nitric oxide has a role in maintaining tumour blood supply, and we provide early clinical evidence that inhibition of nitric-oxide synthesis has tumour antivasular activity.

- 2) **Endocrine and lipid effects of oral L-arginine treatment in healthy postmenopausal women.** [J Lab Clin Med.](#) 2000 Mar;135(3):231-7.



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[Blum A](#), [Cannon RO](#), [Costello R](#), [Schenke WH](#), [Csako G](#).

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As a substrate for nitric oxide synthesis, L-arginine may give the same protection as estrogen, but its other biologic effects may adversely affect atherogenesis. Therefore, possible endocrine and lipid effects of L-arginine were investigated in a double-blind, placebo-controlled, single crossover study. After randomization, oral L-arginine (9 g) or placebo was given daily for 1 month, with crossover to the alternate therapy after a 1-month washout period, to 10 postmenopausal women receiving no estrogen. Compared with placebo, L-arginine increased growth hormone (1.5+/-1.8 mg/L vs. 0.6+/-0.6 mg/L, P = .04) but had no effect on insulin and catecholamines. Total cholesterol, triglyceride, apolipoprotein E, and low-, very-low-, and high-density lipoprotein cholesterol levels were also unaffected. Lipoprotein(a) measured by an immunoturbidimetric method was increased by L-arginine in 9 of 10 women relative to placebo (0.46+/-0.35 g/L vs. 0.38+/-0.30 g/L, P = .053), and the changes in lipoprotein(a) levels significantly correlated with the relative increase in growth hormone (r = 0.85, P = .03). However, lipoprotein(a) measured by an enzyme-linked immunosorbent assay failed to demonstrate significant changes. Lack of an increase by L-arginine in lipoprotein(a) with a verifiable apolipoprotein(a) isoform-independent method, despite an increase in growth hormone, questions the validity of previous observations for growth hormone-induced increases in lipoprotein(a). The observed lack of effect on major endocrine hormones and lipid profile support the safety of oral L-arginine administration.

**3) Growth hormone responses to varying doses of oral arginine.** [Growth Horm IGF Res.](#) 2005 Apr;15(2):136-9. Epub 2005 Jan 26  
[Collier SR](#), [Casev DP](#), [Kanaley JA](#).

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Intravenous (IV) arginine invokes an increase in growth hormone (GH) concentrations, however, little is known about the impact of oral arginine ingestion on the GH response. OBJECTIVE: The purpose of this study was to determine the dose of oral arginine that elicits an optimal GH response and to determine the time course of the response. DESIGN: Eight healthy males (18-33

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years - 24.8±1.2 years) were studied on 4 separate occasions. Following an overnight fast at 0700 h, a catheter was placed in a forearm vein. Blood samples were taken every 10 min for 5 h. Thirty minutes after sampling was initiated, the subject ingested a dose of arginine (5, 9 or 13 g) or placebo (randomly assigned). RESULTS: Mean resting GH values for the placebo, 5, 9 and 13 g day were 0.76, 0.67, 2.0 and 0.79 microg/L (n=6), respectively. Integrated area under the curve was not different with 13 g (197.8±65.7 min microg/L), yet it increased with 5 and 9 g compared with the placebo (301.5±74.6, 524.28±82.9 and 186.04±47.8 min microg/L, respectively, P<0.05). Mean peak GH levels were 2.9±0.69, 3.9±0.85, 6.4±1.3 and 4.73±1.27 microg/L on each day for the placebo, 5, 9 and 13 g days. CONCLUSION: In conclusion, 5 and 9 g of oral arginine caused a significant GH response. A 13 g dose of arginine resulted in considerable gastrointestinal distress in most subjects without augmentation in the GH response. The rise in GH concentration started approximately 30 min after ingestion and peaked approximately 60 min post ingestion.

**4) Influence of chronic supplementation of arginine aspartate in endurance athletes on performance and substrate metabolism - a randomized, double-blind, placebo-controlled study.** [Int J Sports Med.](#) 2005 Jun;26(5):344-9.

[Abel T](#), [Knechtle B](#), [Perret C](#), [Eser P](#), [von Arx P](#), [Knecht H](#).

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The intake of arginine aspartate has been shown to increase anabolic hormones like human growth hormone (hGH) and glucagon. The aim of our study was to investigate whether daily intake of two different dosages of arginine aspartate during four weeks affects selected parameters of overtraining syndrome like performance, metabolic and endocrine parameters. Thirty male endurance-trained athletes were included in a randomized, double-blind, placebo-controlled study and divided into three groups. During four weeks, they ingested either arginine aspartate with a high concentration (H) of 5.7 g arginine and 8.7 g aspartate, with a low concentration (L) of 2.8 g arginine and 2.2 g aspartate or placebo (P). VO<sub>2</sub>peak and time to exhaustion were determined on a cycling ergometer in an incremental exercise test before and after supplementation. Before and after each incremental exercise test, concentrations of hGH, glucagon, testosterone, cortisol, ferritine, lactate, and urea were measured. Compared to placebo, no significant differences on endurance performance (VO<sub>2</sub>peak, time to exhaustion), endocrine (concentration of hGH, glucagon, cortisol, and testosterone) and metabolic parameters

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(concentration of lactate, ferritin, and urea) were found after chronic arginine aspartate supplementation. The chronic intake of arginine aspartate during four weeks by male endurance athletes showed independent of dosage no influence on performance, selected metabolic or endocrine parameters. Consequently, there seems to be no apparent reason why the supplementation of arginine aspartate should be an effective ergogenic aid. The practice of using arginine aspartate as potential ergogenics should be critically reevaluated. Further investigations with higher dosage and extended supplementation periods should be performed.

**5) Contributions of gender and systemic estradiol and testosterone concentrations to maximal secretagogue drive of burst-like growth hormone secretion in healthy middle-aged and older adults.** [J Clin Endocrinol Metab.](#) 2004 Dec;89(12):6291-6.

[Veldhuis JD](#), [Patrie JT](#), [Brill KT](#), [Weltman JY](#), [Mueller EE](#), [Bowers CY](#), [Weltman A](#).

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To test whether concentrations of estradiol and testosterone predict GH responses to mechanistically distinct secretagogues in healthy older adults, we studied 16 volunteers (n = 10 men, n = 6 women, age 49-72 yr) in each of six randomly ordered sessions as follows: 1) saline; 2) l-arginine; 3) aerobic exercise; 4) GHRH; 5) GH-releasing peptide (GHRP)-2; and 6) somatostatin-induced rebound. Statistical comparisons disclosed that stimulus type ( $P < 0.001$ ) and the interaction between gender and stimulus type ( $P = 0.023$ ) determine GH secretion. In women, each secretagogue, except exercise and somatostatin-induced rebound, stimulated GH secretion by 2.6- to 6.4-fold over saline/rest ( $P < 0.023$ ). In men, somatostatin-induced rebound drove GH secretion by 4.6-fold ( $P = 0.004$ ), exercise by 16-fold ( $P < 0.001$ ), and other secretagogues by 18- to 109-fold over saline/rest (each  $P < 0.001$ ). Gender comparisons disclosed greater GH secretion in men than women after somatostatin-induced rebound ( $P = 0.008$ ) and GHRP-2 injection ( $P < 0.001$ ) and conversely greater GH secretion in women than men after saline ( $P = 0.013$ ). Regression analysis showed that individual concentrations of estradiol ( $r = 0.80$ ,  $P = 0.002$ ) and testosterone ( $r = 0.63$ ,  $P = 0.008$ ) and their combination ( $r = 0.86$ ,  $P < 0.001$ ) strongly predict responses to GHRP-2 only. We conclude that among healthy middle-aged and older adults, the action of GHRP is uniquely determined by gender and physiological concentrations of testosterone and estradiol.

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**6) Oral arginine attenuates the growth hormone response to resistance exercise.**

[J Appl Physiol](#). 2006 Sep;101(3):848-52. Epub 2006 Jun 1

[Collier SR](#), [Collins E](#), [Kanaley JA](#).

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This study investigated the combined effect of resistance exercise and arginine ingestion on spontaneous growth hormone (GH) release. Eight healthy male subjects were studied randomly on four separate occasions [placebo, arginine (Arg), placebo + exercise (Ex), arginine + exercise (Arg+Ex)]. Subjects had blood sampled every 10 min for 3.5 h. After baseline sampling (30 min), subjects ingested a 7-g dose of arginine or placebo (blinded, randomly assigned). On the exercise days, the subject performed 3 sets of 9 exercises, 10 repetitions at 80% one repetition maximum. Resting GH concentrations were similar on each study day. Integrated GH area under the curve was significantly higher on the Ex day (508.7 +/- 169.6 min.ng/ml;  $P < 0.05$ ) than on any of the other study days. Arg+Ex (260.5 +/- 76.8 min.ng/ml) resulted in a greater response than the placebo day but not significantly greater than the Arg day. The GH half-life and half duration were not influenced by the stimulus administered. The GH secretory burst mass was larger, but not significantly, on the Arg, Ex, and Arg+Ex day than the placebo day. Endogenous GH production rate (Ex > Arg+Ex > Arg > placebo) was greater on the Ex and Arg+Ex day than on the placebo day ( $P < 0.05$ ) but there were no differences between the Ex and Arg+Ex day. Oral arginine alone (7 g) stimulated GH release, but a greater GH response was seen with exercise alone. The combined effect of arginine before exercise attenuates the GH response. Autonegative feedback possibly causes a refractory period such that when the two stimuli are presented there will be suppression of the somatotrope.

**7) Single amino acid (arginine) deprivation: rapid and selective death of cultured transformed and malignant cells.** [Br J Cancer](#). 2000 Sep;83(6):800-10.

[Scott L](#), [Lamb J](#), [Smith S](#), [Wheatley DN](#).

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The effects of arginine deprivation (-Arg) has been examined in 26 cell lines. Less than 10% of

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those with transformed or malignant phenotype survived for > 5 days, and many died more rapidly, notably leukaemic cells. Bivariate flow cytometry confirmed that vulnerable cell lines failed to move out of cell cycle into a quiescent state (G0), but reinitiated DNA synthesis. Many cells remained in S-phase, and/or had difficulty progressing through to G2 and M. Two tumour lines proved relatively 'resistant', A549 and MCF7. Although considerable cell loss occurred initially, both lines showed a 'cell cycle freeze', in which cells survived for > 10 days. These cells recovered their proliferative activity in +Arg medium, but behaved in the same manner to a second -Arg episode as they did to the first episode. In contrast, normal cells entered G0 and survived in -Arg medium for several weeks, with the majority of cells recovering with predictable kinetics in +Arg medium. In general, cells from a wide range of tumours and established lines die quickly in vitro following -Arg treatment, because of defective cell cycle checkpoint stringency, the efficacy of the treatment being most clearly demonstrated in co-cultures in which only the normal cells survived. The findings demonstrate a potentially simple, effective and non-genotoxic strategy for the treatment of a wide range of cancers. Copyright 2000 Cancer Research Campaign.

**8) Integrity and stability of the citrulline-arginine pathway in normal and tumour cell lines.** [Cancer Lett.](#) 2005 Sep 28;227(2):141-52.

[Wheatley DN](#), [Kilfeather R](#), [Stitt A](#), [Campbell E](#).

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Arginine catabolizing enzymes have been used on cancers for over 60 years. In the last 5 years the ability of arginine catabolizing enzymes, not only to inhibit proliferation, but to kill tumour cells has been reinvestigated. Selectivity of action lies in the inability of many tumours to circumvent arginine deprivation by recycling precursors through the urea cycle. While this offers an immediate window of opportunity to treat, e.g. melanomas and hepatocellular carcinomas (HCC) that have poor citrulline converting ability, it is possible that the deprivation can be applied to many other types of cancer. The problem of deficiency of the urea cycle enzymes in a wider range of normal and malignant cell lines has been addressed, and shown to be variable throughout several different tumour types. We also need to know how fickle recycling enzyme activity can be in both normal and tumour cells, and found to be remarkable stable. Increasing interest is shown in the amino acid (arginine) deprivation protocol because it has already moved into the clinic. Initial findings on a named-patient basis have been encouraging, and the

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development of a new rational approach to the systemic treatment of melanomas, HCCs and leukemias seems imminent. This is the more attractive because arginine deprivation protocols can also 'stage' tumour cells for combination therapy in cases where they might not be killed outright by deprivation alone.

**9) Arginine deprivation, growth inhibition and tumour cell death: 3. Deficient utilisation of citrulline by malignant cells.** [Br J Cancer](#). 2003 Aug 4;89(3):573-6. [Wheatley DN](#), [Campbell E](#).

Department of Cell Pathology, University of Aberdeen, MacRobert Building, 581 King Street, Aberdeen AB24 5UA, UK.

Arginine deprivation causes death of up to 80% of cancer cell lines in vitro, but in the body, citrulline would be available as a convertible source of this amino acid in vivo. Some tumour cell lines, notably the vast majority of melanomas and hepatocellular carcinomas, tend to be deficient in argininosuccinate synthetase (EC 6.5.4.3.), and therefore cannot recycle citrulline to arginine. Argininosuccinate synthetase is present at levels that convert enough citrulline to arginine to allow limited growth in about half of a modest range of malignant cell types analysed in this study. Attempts to rescue cells that are unable to utilise citrulline with the immediate downstream product, argininosuccinate, had very limited success in a few tumour cell lines. Particularly noteworthy is the demonstration that argininosuccinate was totally incapable of rescuing cells that utilise citrulline efficiently, consistent with tight channelling (coupling) of argininosuccinate synthetase and argininosuccinate lyase in the urea cycle. The findings suggest that an excellent opportunity exists for further exploitation of arginine deprivation in the selective killing of tumour cells.

**Activation of nitric oxide synthase gene for inhibition of cancer metastasis.**

[J Leukoc Biol](#). 1996 Jun;59(6):797-803

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The process of cancer metastasis consists of multiple sequential and highly selective steps. The vast majority of tumor cells that enter the circulation die rapidly and only a few survive and proliferate to form distant metastases. This survival is not random. Metastases are clonal in origin and are produced by specialized subpopulations of cells that preexist in a heterogeneous primary tumor. Metastatic cells of the murine K-1735 melanoma survive in the circulation to produce experimental lung metastases, whereas nonmetastatic cells do not. After incubation with different cytokines or LPS, nonmetastatic cells exhibit a high level of inducible nitric oxide synthase (iNOS) activity and nitric oxide (NO) production, whereas metastatic cells do not. To provide direct evidence for the inverse correlation between the production of endogenous NO and the ability of K-1735 cells to produce metastasis in syngeneic mice, highly metastatic clone 4 cells (C4.P), which express low levels of iNOS, were transfected with a functional iNOS (C4.L8), inactive mutated iNOS (C4.S2), or neomycin resistance (C4.Neo) genes in medium containing 3 mM NMA. C4.P, C4.Neo3, and C4.S2.3 cells were highly metastatic, whereas C4.L8.5 cells were not. Moreover, C4.L8.5 cells produced slow-growing subcutaneous tumors in nude mice, whereas the other three cell lines produced fast-growing tumors. In vitro studies indicated that the expression of iNOS in C4.L8.5 cells was associated with apoptosis. Multiple intravenous injections of liposomes containing a synthetic lipopeptide upregulated iNOS expression in murine M5076 reticulum sarcoma cells growing as hepatic metastases. The induction of iNOS was associated with the complete regression of the lesions. Collectively, these data demonstrate that the expression of iNOS in tumor cells is associated with apoptosis, suppression of tumorigenicity, abrogation of metastasis, and regression of established hepatic metastases.

### **Nitric oxide synthase activity is up-regulated in melanoma cell lines: a potential mechanism for metastases formation.**

[Melanoma Res.](#) 1996 Apr;6(2):121-6.

[Joshi M](#), [Strandhoy J](#), [White WL](#).

Department of Dermatology, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC 27157, USA.

Nitric oxide (NO) may be an important mediator of tumour angiogenesis and metastasis formation. Tumour cell derived NO may be important in the regulation of angiogenesis and vasodilatation of the blood vessels surrounding a tumour. The aims of the present study were,

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firstly, to determine whether malignant melanoma cells and normal melanocytes had nitric oxide synthase (NOS) activity (measured by the conversion of L-arginine to L-citrulline) and, secondly, to determine whether there was a difference in NOS activity between malignant and normal cell types. This paper assays NOS activity directly in lysates from normal human melanocyte and malignant melanoma cell lines. The enzyme activity was not inducible with bacterial lipopolysaccharide and could be heat denatured. The activity of NOS was demonstrated to be both NADPH- and calcium-dependent and it was inhibitable in a dose-dependent manner by the NOS inhibitor Nw-nitro-L-arginine methyl ester. We conclude that melanoma and melanocyte cells express a constitutive form of NOS. Finally, nitric oxide synthase activity in melanoma cell lines was found to be significantly greater than in normal melanocytes. These findings suggest that NO synthesis is elevated in malignant melanoma. An elevated NO concentration in melanoma is expected to promote metastases by maintaining a vasodilator tone in the blood vessels in and around the melanoma.

**Remission of hepatocellular carcinoma with arginine depletion induced by systemic release of endogenous hepatic arginase due to transhepatic arterial embolisation, augmented by high-dose insulin: arginase as a potential drug candidate for hepatocellular carcinoma.**

[Cancer Lett.](#) 2005 Jun 16;224(1):67-80. Epub 2004 Dec 25

[Cheng PN](#), [Leung YC](#), [Lo WH](#), [Tsui SM](#), [Lam KC](#).

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Hepatocellular carcinoma (HCC) is auxotrophic for the semi-essential amino acid arginine, depletion of which leads to tumor death. In humans, arginine is not an essential amino acid since many adult somatic cells can re-synthesize it from other sources, such as citrulline. Enzymes capable of depleting arginine in vitro include the urea cycle enzyme arginase, which is found in abundance in human liver. For over three decades, arginase has not been considered as a potential drug candidate because of its low substrate affinity, short circulatory half-life and sub-optimal enzymatic activity at physiological pH, though its in vitro anti-tumor activities in certain tumors have been amply reported. Arginine deiminase, a bacterial enzyme from *Mycoplasma hominus* has been shown to induce HCC remission through the mechanism of arginine depletion. We report here an innovative treatment approach for the treatment of locally advanced and metastatic HCC with transhepatic arterial embolisation (TAE) of the liver tumor with lipiodol



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and gel foam as a means of inducing a leakage of hepatic arginase from the liver into the circulation. Hepatic arginase released into the systemic circulation rapidly depleted plasma arginine. High-dose insulin was included to induce a state of hypoaminoacidaemia to augment arginine depletion. With this protocol, we have treated seven patients with locally advanced and/or metastatic HCC. Five patients achieved arginine depletion, ranging from 0 to 20 microM (normal plasma level 100-120 microM); all had varying degrees of tumor remission in their primary tumors and extra-hepatic sites in the lymph nodes, lungs and bones, suggesting systemic anti-cancer effect of arginine depletion. The two non-responders did not show significant reduction in plasma arginine. Based on our findings, we propose that the urea cycle enzyme, arginase, is a good drug candidate for the treatment of HCC.

**Pegylated arginine deiminase (ADI-SS PEG20,000 mw) inhibits human melanomas and hepatocellular carcinomas in vitro and in vivo.**

[Cancer Res.](#) 2002 Oct 1;62(19):5443-50.

[Ensor CM](#), [Holtsberg FW](#), [Bomalaski JS](#), [Clark MA](#).

Department of Biology, T. H. Morgan Building and Phoenix Pharmacologics, Inc., Lexington, Kentucky 40503, USA.

Some murine melanomas and hepatocellular carcinomas (HCCs) have been shown to be auxotrophic for arginine. Arginine deiminase (ADI; EC 3.5.3.6.), an arginine-degrading enzyme isolated from Mycoplasma, can inhibit growth of these tumors. We found that ADI was specific for arginine and did not degrade other amino acids. Although arginine is not an essential amino acid for most cells, all human melanomas and HCCs tested were found to be inhibited by ADI in vitro. Arginine is synthesized from citrulline in two steps by argininosuccinate synthetase and argininosuccinate lyase. Melanomas and HCCs did not express argininosuccinate synthetase mRNA but did express argininosuccinate lyase mRNA, suggesting that the arginine auxotrophy of these cells was a result of an inability to produce argininosuccinate synthetase. Human melanomas and HCCs were transfected with an expression plasmid containing argininosuccinate synthetase cDNA. The transfected cells were much more resistant to ADI than the parental cells in vitro and in vivo. Initial attempts to use ADI in vivo indicated that this enzyme had little efficacy, consistent with its short circulation half-life. Formulation of ADI with polyethylene glycol to produce ADI-SS PEG(20,000 mw) resulted in an enzyme with a much longer circulation half-life that, and although equally effective in vitro, was more efficacious in the treatment of mice implanted with human melanomas and HCCs. These data indicate that

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sensitivity of melanoma and HCC is due to the absence of argininosuccinate synthetase in these cells and that an effective formulation of ADI, which causes a sustained decrease in arginine, may be a useful treatment for arginine auxotrophic tumors including melanoma and HCC.

**L-arginine availability regulates T-lymphocyte cell-cycle progression.**

[Blood](#). 2007 Feb 15;109(4):1568-73. Epub 2006 Oct 5.

[Rodriguez PC](#), [Quiceno DG](#), [Ochoa AC](#).

Tumor Immunology Program, Stanley S. Scott Cancer Center, Louisiana State University Health Sciences Center, Department of Pediatrics, New Orleans 70112, USA. prodri1@lsuhsc.edu

L-arginine (L-Arg) plays a central role in several biologic systems including the regulation of T-cell function. L-Arg depletion by myeloid-derived suppressor cells producing arginase I is seen in patients with cancer inducing T-cell anergy. We studied how L-Arg starvation could regulate T-cell-cycle progression. Stimulated T cells cultured in the absence of L-Arg are arrested in the G0-G1 phase of the cell cycle. This was associated with an inability of T cells to up-regulate cyclin D3 and cyclin-dependent kinase 4 (cdk4), but not cdk6, resulting in an impaired downstream signaling with a decreased phosphorylation of Rb protein and a low expression and binding of E2F1. Silencing of cyclin D3 reproduced the cell cycle arrest caused by L-Arg starvation. The regulation of cyclin D3 and cdk4 by L-Arg starvation occurs at transcriptional and posttranscriptional levels. Signaling through GCN2 kinase is triggered during amino acid starvation. Experiments demonstrated that T cells from GCN2 knock-out mice did not show a decreased proliferation and were able to up-regulate cyclin D3 when cultured in the absence of L-Arg. These results contribute to the understanding of a central mechanism by which cancer and other diseases characterized by high arginase I production may cause T-cell dysfunction.

**Arginase I production in the tumor microenvironment by mature myeloid cells inhibits T-cell receptor expression and antigen-specific T-cell responses.**

[Cancer Res](#). 2004 Aug 15;64(16):5839-49

[Rodriguez PC](#), [Quiceno DG](#), [Zabaleta J](#), [Ortiz B](#), [Zea AH](#), [Piazuelo MB](#), [Delgado A](#), [Correa P](#), [Brayer J](#), [Sotomayor EM](#), [Antonia S](#), [Ochoa JB](#), [Ochoa AC](#).

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T cells infiltrating tumors have a decreased expression of signal transduction proteins, a diminished ability to proliferate, and a decreased production of cytokines. The mechanisms causing these changes have remained unclear. We demonstrated recently that peritoneal macrophages stimulated with interleukin 4 + interleukin 13 produce arginase I, which decreases the expression of the T-cell receptor CD3zeta chain and impairs T-cell responses. Using a 3LL murine lung carcinoma model we tested whether arginase I was produced in the tumor microenvironment and could decrease CD3zeta expression and impair T-cell function. The results show that a subpopulation of mature tumor-associated myeloid cells express high levels of arginase I, whereas tumor cells and infiltrating lymphocytes do not. Arginase I expression in the tumor was seen on day 7 after tumor injection. Tumor-associated myeloid cells also expressed high levels of cationic amino acid transporter 2B, which allowed them to rapidly incorporate L-Arginine (L-Arg) and deplete extracellular L-Arg in vitro. L-Arg depletion by tumor-associated myeloid cells blocked the re-expression of CD3zeta in stimulated T cells and inhibited antigen-specific proliferation of OT-1 and OT-2 cells. The injection of the arginase inhibitor N-hydroxy-nor-L-Arg blocked growth of s.c. 3LL lung carcinoma in mice. High levels of arginase I were also found in tumor samples of patients with non-small cell carcinoma. Therefore, arginase I production by mature myeloid cells in the tumor microenvironment may be a central mechanism for tumor evasion and may represent a target for new therapies.

### **Role of immature myeloid cells in mechanisms of immune evasion in cancer.**

[Cancer Immunol Immunother.](#) 2006 Mar;55(3):237-45. Epub 2005 Jul 27

[Kusmartsev S, Gabrilovich DI.](#)

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Tumor affects myelopoiesis by inhibiting the process of differentiation/maturation of antigen-presenting cells from their myeloid precursors and by stimulating an accumulation of immature myeloid cells in cancer patients and tumor-bearing mice. These immature myeloid cells can contribute greatly to tumor progression and promote tumor evasion from immune attack: i) by inhibiting development of adaptive immune responses against tumor in lymphoid organs; ii) by migrating into tumor site and differentiating there into highly immune suppressive tumor-associated macrophages. Immature myeloid cells and tumor-associated macrophages utilize

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different JAK/STAT signaling pathways and different mechanisms to control T cell responses, which include increased production of TGF-beta, reactive oxygen species, peroxynitrites, as well as enhanced L-arginine metabolism. Understanding of precise mechanisms, which tumors use to affect differentiation of APC from myeloid cell precursors and inhibit T cell responses, could help to develop new approaches for cancer therapy and substantially improve efficiency of existing cancer vaccination strategies.

**Arginase-producing myeloid suppressor cells in renal cell carcinoma patients: a mechanism of tumor evasion.** [Cancer Res.](#) 2005 Apr 15;65(8):3044-8.

[Zea AH](#), [Rodriguez PC](#), [Atkins MB](#), [Hernandez C](#), [Signoretti S](#), [Zabaleta J](#), [McDermott D](#), [Quiceno D](#), [Youmans A](#), [O'Neill A](#), [Mier J](#), [Ochoa AC](#).

Stanley S. Scott Cancer Center, Department of Immunology and Microbiology, Louisiana State University Health Sciences Center, New Orleans, LA 70112, USA.

Myeloid suppressor cells with high arginase activity are found in tumors and spleen of mice with colon and lung cancer. These cells, described as macrophages or immature dendritic cells, deplete arginine and impair T cell proliferation and cytokine production. Although arginase activity has been described in cancer patients, it is thought to originate from tumor cells metabolizing arginine to ornithine needed to sustain rapid cell proliferation. The goal of this study was to determine whether myeloid suppressor cells producing high arginase existed in renal cell carcinoma patients. Peripheral blood mononuclear cells from 123 patients with metastatic renal cell carcinoma, prior to treatment, were found to have a significantly increased arginase activity. These patients had a markedly decreased cytokine production and expressed low levels of T cell receptor CD3zeta chain. Cell separation studies showed that the increased arginase activity was limited to a specific subset of CD11b+, CD14-, CD15+ cells with a polymorphonuclear granulocyte morphology and markers, instead of macrophages or dendritic cells described in mouse models. Furthermore, these patients had low levels of arginine and high levels of ornithine in plasma. Depletion of the CD11b+, CD14- myeloid suppressor cells reestablished T cell proliferation and CD3zeta chain expression. These results showed, for the first time, the existence of suppressor myeloid cells producing arginase in human cancer patients. In addition, it supports the concept that blocking arginase may be an important step in the success of immunotherapy.

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**Arginase in patients with breast cancer.** [Clin Chim Acta](#). 2003 Feb;328(1-2):105-11

[Porembaska Z](#), [Luboiński G](#), [Chrzanowska A](#), [Mielczarek M](#), [Magnuska J](#), [Barańczyk-Kuźma A](#).

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The mean arginase activity in breast cancers (n = 80) was significantly higher than in control tissues and it accounted for 0.31 +/- 0.23 U/g wet tissue and 0.083 +/- 0.061 U/g (P < 0.05), respectively. With the cutoff value of 0.1 U/g wet tissue, raised arginase activity was observed in 74% of tumors. The preoperative arginase activity in blood serum from women with breast cancer was 11.2 +/- 7.9 U/l (n = 115), and it was significantly higher than in 70 healthy controls, where it was 5.7 +/- 2.4 U/l (P < 0.05). With the cutoff value for normal serum arginase activity above 8.0 U/l, the activity was raised in 10% of control individuals, and in 63% of women with breast cancer. The sensitivity and specificity of the arginase test in blood serum were 63% and 60%, respectively. Two isoforms immunologically identical to human kidney arginases (L-arginine amidinohydrolase) were found in both normal and cancerous breast tissues. The level of anionic form was similar in control and cancerous tissues, whereas the cationic isoform predominated in breast cancer. The cationic isoform was the only one present in serum of both ill and healthy women, and its level was higher in patients with breast cancer. Thus, it can be concluded that the cationic isoform is responsible for the increase of arginase activity in serum of patients with breast cancer. Copyright 2002 Elsevier Science B.V.

**L-arginine consumption by macrophages modulates the expression of CD3 zeta chain in T lymphocytes.** [J Immunol](#). 2003 Aug 1;171(3):1232-9.

[Rodriguez PC](#), [Zea AH](#), [DeSalvo J](#), [Culotta KS](#), [Zabaleta J](#), [Quiceno DG](#), [Ochoa JB](#), [Ochoa AC](#).

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L-Arginine plays a central role in the normal function of several organs including the immune

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system. It is metabolized in macrophages by inducible nitric oxide synthase to produce nitric oxide, important in the cytotoxic mechanisms, and by arginase I (ASE I) and arginase II (ASE II) to synthesize L-ornithine and urea, the first being the precursor for the production of polyamines needed for cell proliferation. L-Arginine availability can modulate T cell function. Human T cells stimulated and cultured in the absence of L-arginine lose the expression of the TCR zeta-chain (CD3zeta) and have an impaired proliferation and a decreased cytokine production. The aim of this work was to test whether activated macrophages could modulate extracellular levels of L-arginine and alter T cell function, and to determine which metabolic pathway was responsible for this event. The results show that macrophages stimulated with IL-4 + IL-13 up-regulate ASE I and cationic amino acid transporter 2B, causing a rapid reduction of extracellular levels of L-arginine and inducing decreased expression of CD3zeta and diminished proliferation in normal T lymphocytes. Competitive inhibitors of ASE I or the addition of excess L-arginine lead to the re-expression of CD3zeta and recovery of T cell proliferation. In contrast, inducible nitric oxide synthase or ASE II failed to significantly reduce the extracellular levels of L-arginine and modulate CD3zeta expression. These results may provide new insights into the mechanisms leading to T cell dysfunction and the down-regulation of CD3zeta in cancer and chronic infectious diseases.

### **Metabolic and immune effects of dietary arginine, glutamine and omega-3 fatty acids supplementation in immunocompromised patients.**

[J Med Assoc Thai](#). 1998 May;81(5):334-43.

[Chuntrasakul C](#), [Siltharm S](#), [Sarasombath S](#), [Sittapirochana C](#), [Leowattana W](#), [Chockvivatanavanit S](#), [Bunnak A](#).

Research Center for Nutritional Support, Siriraj Hospital.

To evaluate the nutritional, metabolic and immune effects of dietary arginine, glutamine and omega-3 fatty acids (fish oil) supplementation in immunocompromised patients, we performed a prospective study on the effect of immune formula administered to 11 severe trauma patients (average ISS = 24), 10 burn patients (average % TBSA = 48) and 5 cancer patients. Daily calorie and protein administration were based on the patient's severity (Stress factor with the range of 35-50 kcal/kg/day and 1.5-2.5 g/kg/day, respectively) Starting with half concentration liquid immune formula through nasogastric tube by continuous drip at 30 ml/h and increasing to maximum level within 4 days. The additional energy and protein requirement will be given either by parenteral or oral nutritional support. Various nutritional, metabolic, immunologic and

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clinical parameters were observed on day 0 (baseline), day 3, 7, and 14. Analysis was performed by paired student-t test. Initial mean serum albumin and transferrin showed mild (trauma) to moderate (burn and cancer) degree of malnutrition. Significant improvement of nutritional parameters was seen at day 7 and 14 in trauma and burn patients. Significant increase of total lymphocyte count (day 7,  $P < 0.01$ ), CD4 + count (day 7,  $p < 0.01$ ), CD8 + count (day 7,  $p < 0.0005$  & day 14,  $p < 0.05$ ), complement C3 (day 7,  $p < 0.005$  day 14,  $p < 0.01$ ), IgG (day 7, and 14,  $p < 0.0005$ ), IgA (day 7,  $p < 0.0005$  & day 14,  $p < 0.05$ ), in all patients. C-reactive protein decreased significantly on day 7 ( $p < 0.0005$ ) and day 14 ( $p < 0.005$ ). 3 cases of burn wound infection, one case of UTI and one case of sepsis were observed. Two cases of hyperglycemia in burn, 3 cases of hyperbilirubinemia in trauma, 10 cases of elevated LFT (5 trauma/5 burn), and one case of hyponatremia in cancer patients were observed. Two cases of nausea, 4 cases of vomiting, 5 cases of diarrhea (< 3 times/day), 2 cases of abdominal cramp, 1 case of distension were observed. The feeding of IMMUNE FORMULA was well tolerated and significant improvement was observed in nutritional and immunologic parameters as in other immunoenhancing diets. Further clinical trials of prospective double-blind randomized design are necessary to address the so that the necessity of using immunonutrition in critically ill patients will be clarified.

**Immunoenhancement via enteral nutrition.** [Arch Surg.](#) 1993 Nov;128(11):1242-5.

[Alexander JW.](#)

Department of Surgery, College of Medicine, University of Cincinnati, Ohio.

Arginine, glutamine, the long chain polyunsaturated omega-3 and omega-6 fatty acids, and, to a lesser extent, ribonucleic acid and the vitamins E, C, and A have pharmacologic effects when given in amounts in excess of what is needed to prevent nutritional deficiency. These effects are exerted primarily via the immune system, and immunoenhancing diets that embody the recently developed principles of nutritional pharmacology have been shown to reduce infectious complications by approximately 75% in surgical patients and hospital stay by more than 20% in surgical patients and patients in the intensive care unit in three independent, prospective, randomized studies, two of which were double-blinded. These findings suggest that specialized diets can be designed that will be of benefit to patients with cancer, atherosclerosis, intestinal diseases, autoimmune diseases, infections, and trauma. However, the interaction of these

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nutrients in pharmacologic amounts with standard pharmacologic drugs is largely unknown, as are the effects of long-term administration of specialized diets to treat these conditions.

### **Immune and metabolic effects of arginine in the surgical patient.**

[Ann Surg.](#) 1988 Oct;208(4):512-23.

[Daly JM](#), [Reynolds J](#), [Thom A](#), [Kinsley L](#), [Dietrick-Gallagher M](#), [Shou J](#), [Ruggieri B](#).

Department of Surgery, University of Pennsylvania School of Medicine, Philadelphia 19104.

Arginine enhances immune function and promotes nitrogen retention in animal models, but its immunomodulatory effects in surgical patients are unknown. This randomized, prospective trial evaluated the immune and metabolic effects of supplemental L-arginine (25 g/day, n = 16) or isonitrogenous L-glycine (43 g/day, n = 14) in 30 cancer patients undergoing major operation. Two groups of patients received either arginine or glycine for 7 days after surgery as a supplement to a graduated enteral diet. Nitrogen balance was measured daily, and immune parameters were determined both before and after surgery, on Days 1, 4, and 7. The T-lymphocyte response to concanavalin A (con A) and PHA and dual marker phenotype analysis of lymphocyte (CD2, CD4, CD4/DR, CD8, CD8/DR) and macrophage (M3/DR) subsets were determined. Mean age, degree of preoperative weight loss, disease stage, number of perioperative transfusions, and calorie and nitrogen intake were similar for the groups studied. Mean daily nitrogen balance (-2.3 g/day in the arginine group vs. -3.9 g/day in the glycine group) was not significantly different between the two groups, but positive mean nitrogen balance was achieved only in the arginine group between Days 5 and 7 after surgery. Supplemental arginine significantly enhanced the mean T-lymphocyte response (stimulation index) to con A from 45 +/- 26 on postoperative Day 1 to 72 +/- 47 and 87 +/- 49 on postoperative Days 4 and 7, compared with the values of 29 +/- 15, 27 +/- 20, and 33 +/- 34 in the glycine group at the same time points, respectively. Supplemental arginine increased mean CD4 phenotype (% T-cells) on postoperative Days 1 and 7 from 25 +/- 9 to 43 +/- 14, compared with the values of 30 +/- 14 and 29 +/- 13 in the glycine group (p less than 0.05). The beneficial effect of arginine on the immune system appeared distinct from its more moderate effect on nitrogen metabolism. As a nutrient substrate, arginine was nontoxic, and may benefit surgical patients who are at increased risk of infection.

**Can daily dietary arginine supplement affect the function and subpopulation of lymphocytes in patients with advanced gastric cancer?**



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[Digestion](#). 1993;54(2):118-24.

[Wu CW](#), [Chi CW](#), [Chiu CC](#), [Wu HS](#), [Liu WY](#), [P'eng FK](#), [Wang SR](#).

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Since arginine can stimulate lymphocyte proliferation in the healthy human, its effect on lymphocyte proliferation in vitro was studied in 7 patients with far advanced gastric cancer. These patients with normal nourishment were ambulatory and could consume a regular diet. A daily dietary supplement of 30 g arginine for 7 days did not alter the total lymphocyte counts or the T/B cell ratio in the peripheral blood. Enhancement of lymphocyte proliferation in response to mitogen stimulation was not observed. Furthermore, an in vitro study on the effect of arginine on phytohemagglutinin-stimulated lymphocyte proliferation showed that lymphocytes from gastric cancer patients had poorer responses than those obtained from normal subjects, despite the supplement in the culture medium with normal serum, patient serum, or fetal bovine serum. Arginine ingestion did not impair liver function and had no detectable side effects except transient nausea in 1 patient. These results indicate that dietary arginine supplement appears safe but does not stimulate lymphocyte function in far advanced gastric cancer patients. The suppressed immune function in gastric cancer patients may be the result of their intrinsic lymphocyte defect.

### **Preoperative oral supplement with immunonutrients in cancer patients.**

[JPEN J Parenter Enteral Nutr](#). 1998 Jul-Aug;22(4):206-11

[McCarter MD](#), [Gentilini OD](#), [Gomez ME](#), [Daly JM](#).

Department of Surgery, New York Hospital-Cornell University Medical College, NY 10021, USA.

**BACKGROUND:** Early postoperative enteral nutrition with immune-enhancing supplements has helped to restore immune function and reduce infectious complications in patients with cancer undergoing major gastrointestinal operations. The aim of this study was to evaluate the effectiveness of similar supplements (containing arginine and arginine plus omega-3 fatty acids) given preoperatively for 1 week before cancer surgery. **METHODS:** In this randomized, double-blinded study, patients scheduled to undergo elective resection of upper gastrointestinal tumors were given one of three different oral liquid supplemental diets (control, arginine, arginine plus omega-3 fatty acids) to be taken each day for 7 days before surgery. Blood samples were obtained upon enrollment, on the morning of surgery, and on postoperative day 1 for analysis of immunologic function. **RESULTS:** Mean serum ornithine (a metabolite of arginine) levels were significantly higher compared with controls, but no significant increase in mean

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serum arginine levels was noted on the morning of surgery for those patients who received arginine as part of the supplement. In conjunction with these findings, there were no differences among groups in mean lymphocyte mitogenesis, mean peripheral blood mononuclear cell production of cytokines, or clinical outcomes.

CONCLUSIONS: Use of oral liquid supplements in this fashion did not improve lymphocyte proliferation or monocyte functions in patients with cancer undergoing major surgery.

**Recovery of low thymic hormone levels in cancer patients by lysine-arginine combination.** [Int J Immunopharmacol.](#) 1990;12(4):365-71.

[Mocchegiani E](#), [Cacciatore L](#), [Talarico M](#), [Lingetti M](#), [Fabris N](#).

Immunology Centre, Gerontology Research Department, Italian National Research Centres on Ageing (INRCA), Ancona, Italy.

Thymic hormones are required for maturation and maintenance of the immune efficiency. It has been previously demonstrated that with advancing age there occurs a progressive reduction of the plasma level of one of the best known thymic peptides, i.e. thymulin, and that the administration of an amino acid combination (lysine-arginine, as present in the commercial preparation Lysargin, Baldacci, Italy) to elderly individuals is able to increase the synthesis and/or release of thymulin to values comparable to those recorded in young subjects. In the present paper we report evidence that cancer patients show much lower thymulin values than those recorded in healthy age-matched individuals and that the oral administration of the amino acid preparation is able to significantly increase thymulin levels even over the values of age-matched controls and to increase the number of peripheral T-cell subsets. It is suggested that such an effect is mediated through the known secretagogue activity of the amino acids on the pituitary release of growth hormone, which has a modulating effect on the thymic endocrine activity.

**A randomized clinical trial with oral Immunonutrition (omega3-enhanced formula vs. arginine-enhanced formula) in ambulatory head and neck cancer patients.** [Ann Nutr Metab.](#) 2005 Mar-Apr;49(2):95-9. Epub 2005 Mar 29

[de Luis DA](#), [Izaola O](#), [Aller R](#), [Cuellar L](#), [Terroba MC](#).

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**OBJECTIVE:** The aim of our study was to investigate whether oral ambulatory nutrition of head and neck cancer patients, using an omega3 fatty acid-enhanced diet (low ratio omega6/omega3 fatty acids) versus an arginine-enhanced diet, could improve nutritional variables as well as clinical outcome, postoperative infectious and wound complications. **RESEARCH METHODS:** A population of 73 ambulatory postsurgical patients with oral and laryngeal cancer were enrolled. At discharge from hospital the postsurgical head and neck cancer patients were asked to consume two units per day of either a specially designed omega3 fatty acid-enhanced supplement (group 1) or an arginine-enhanced supplement (group 2) for a 12-week period. **RESULTS:** No significant intergroup differences in the trend of the three serum proteins and lymphocytes were detected. Differences were detected in weight (group 1: 65.5 +/- 11.5 kg vs. 70.4 +/- 11.1 kg;  $p < 0.05$ ) with a significant increase in fat mass in group 1 (15.4 +/- 6.6 vs. 18.1 +/- 8.4 kg;  $p < 0.05$ ) and in tricipital skinfold. The postoperative infectious complications were similar in both groups (0 in group 1 and 8.57% in group 2; nonsignificant). No local complications were detected in the surgical wound. Gastrointestinal tolerance (diarrhea and vomiting episodes) of both formulas was good. **CONCLUSIONS:** At the dose taken, the omega3-enhanced formula improved fat mass and proteins in ambulatory postoperative head and neck cancer patients. The arginine-enhanced formula improved proteins. Further studies are required to examine the potential role of immune-enhanced supplements. Copyright (c) 2005 S. Karger AG, Basel.

### **Postoperative enteral immunonutrition in head and neck cancer patients.**

[Clin Nutr.](#) 2000 Dec;19(6):407-12.

[Riso S](#), [Aluffi P](#), [Brugnani M](#), [Farinetti F](#), [Pia F](#), [D'Andrea F](#).

Clinical Nutrition Service, Maggiore della Carita Hospital, Novara, Italy.

**AIMS:** to determine if postoperative feeding of head and neck cancer patients, using an enteral diet supplemented with arginine, improves immunological and nutritional status, and clinical outcome, i.e., reduces postoperative infectious/wound complications and length of stay, when compared with an isocaloric, isonitrogenous control diet. **METHODS:** at operation 44 patients

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were randomized into two groups to receive: a) an enriched diet (n=23);b) an isocaloric, isonitrogenous control diet (n=21). Thirteen patients with a history of significant weight loss (> or = 10% over the last 6 months) were considered malnourished. Preoperatively and on postoperative days 1, 4 and 8 the following parameters were evaluated: albumin, prealbumin, transferrin, total number of lymphocytes, lymphocyte subsets (CD3, CD4, CD8 and CD4/CD8 ratio) and immunoglobulins. Postoperative complications and length of stay were recorded. RESULTS: 'visceral' serum proteins and immunological parameters decreased on postoperative day 1 in both groups. However, only the enriched group demonstrated a significant increase (P<0.05) in the total number of lymphocytes, CD4, CD4/CD8 on postoperative day 4, and total number of lymphocytes, CD3, CD4, CD4/CD8 on postoperative day 8. In the malnourished subgroup the administration of the enriched formula significantly reduced both postoperative infectious/wound complications and length of stay compared with the control group (P<0.05). CONCLUSIONS: enteral immunonutrition of head and neck cancer patients improves postoperative immunological response. Significant clinical advantages were observed in malnourished patients. Copyright 2000 Harcourt Publishers Ltd.

### **Randomized clinical trial with an enteral arginine-enhanced formula in early postsurgical head and neck cancer patients.**

[Eur J Clin Nutr.](#) 2004 Nov;58(11):1505-8.

[de Luis DA](#), [Izaola O](#), [Cuellar L](#), [Terroba MC](#), [Aller R](#).

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OBJECTIVE: Patients with head and neck cancer undergoing surgery have a high incidence of postoperative complications. The aim of our study was to investigate whether postoperative nutrition of head and neck cancer patients using an arginine-enhanced formula could improve nutritional variables as well as clinical outcomes. DESIGN: Randomized clinical trial.

SETTING: Tertiary care. SUBJECTS: A population of 90 patients with oral and laryngeal cancer was enrolled. INTERVENTIONS: At surgery, patients were randomly allocated to two groups: (a) patients receiving an arginine-enhanced formula with arginine and fiber (group I) and (b) patients receiving an isocaloric, isonitrogenous formula with fiber enteral formula (group II).

RESULTS: No significant intergroup differences in the trend of the three plasma proteins (albumin, transferrin, prealbumin) and lymphocytes were detected. Gastrointestinal tolerance

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(diarrhea) was better in group II than I (40% group I and 13% group II:  $P<0.05$ ). The postoperative complications due to infections were similar in both groups (4% group I and 9% group II: ns). Fistula (wound complication) was less frequent in the enriched nutrition group (5% group I and 11% group II:  $P<0.05$ ); wound infection was similar in both groups. The length of postoperative stay was better in group I than II (25.8 $\pm$ 15 days vs 35 $\pm$ 24.6 days;  $P<0.05$ ).  
CONCLUSIONS: In conclusion, arginine-enhanced formula improves fistula rates in postoperative head and neck cancer patients and decreases length of stay.

### **Postsurgery enteral nutrition in head and neck cancer patients.**

[Eur J Clin Nutr.](#) 2002 Nov;56(11):1126-9.

[de Luis DA](#), [Aller R](#), [Izaola O](#), [Cuellar L](#), [Terroba MC](#).

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OBJECTIVE: Patients with head and neck cancer undergoing surgery have a high incidence of postoperative complications. The aim of our study was to investigate whether postoperative nutrition of head and neck cancer patients, using an arginine-enriched diet, could improve nutritional variables as well as clinical outcomes. DESIGN: Randomized clinical trial. SETTING: Tertiary care. SUBJECTS: A population of 47 patients with oral and laryngeal cancer were enrolled. INTERVENTIONS: At surgery patients were randomly allocated to two groups: (a) patients receiving an enteral diet supplemented with arginine and fiber (group I); (b) patients receiving an isocaloric, isonitrogenous enteral formula (group II). RESULTS: No significant intergroup differences in the trend of the three plasma proteins and lymphocytes were detected. Gastrointestinal tolerance (diarrhea) of both formulas was good (17.4% group I and 8.3% group II; NS). During the 3 months after hospital discharge five patients died; no differences were detected between groups (13% group I and 8.3% group II; NS). The incidences postoperative infection complications were similar (nine patients) in both groups (21.7% group I and 16.7% group II; NS). Fistula were less frequent in enriched nutrition group (0% group I and 20.8% group II;  $P<0.05$ ); wound infection was more frequent in group II, but without statistical difference (4.3% group I and 12.5% group II; NS). The length of postoperative stay was 22.8 $\pm$ 11.8 days in the enriched group and 31.2 $\pm$ 19.1 days in the control group ( $P=0.07$ ).  
CONCLUSIONS: In conclusion, enriched formula improves local wound complications in

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postoperative head and neck cancer patients. Our results suggest that these patients could benefit from an immunonutrient-enhanced enteral formula.

**Clinical and biochemical outcomes after a randomized trial with a high dose of enteral arginine formula in postsurgical head and neck cancer patients.**

[Eur J Clin Nutr.](#) 2007 Feb;61(2):200-4. Epub 2006 Aug 23

[de Luis DA](#), [Izaola O](#), [Cuellar L](#), [Terroba MC](#), [Martin T](#), [Aller R](#).

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**OBJECTIVE:** Patients with head and neck cancer undergoing surgery have a high incidence of postoperative complications. The aim of our study was to investigate whether postoperative nutrition of head and neck cancer patients, using a higher dose of arginine-enhanced diet (17 g/day) than previous studies, could improve nutritional variables as well as clinical outcomes, when compared with a control enteral diet. **DESIGN:** Randomized clinical trial. **SETTING:** Tertiary care. **SUBJECTS:** A population of 72 patients with oral and laryngeal cancer was enrolled. **INTERVENTIONS:** At surgery, patients were randomly allocated to two groups: (a) 35 patients receiving an arginine-enhanced formula with arginine (group I) and (b) 37 patients receiving an isocaloric, isonitrogenous enteral formula (group II). **RESULTS:** No significant intergroup differences in the trend of the three plasma proteins (albumin, transferrin, prealbumin) and lymphocytes were detected. Episodes of diarrhea rate were equal in both groups (22.8% group I and 21.6% group II: NS). The postoperative infections complications were equal in both groups (5.7% group I and 5.4% group II: NS). Fistula (wound complication) was less frequent in enriched nutrition group (2.8% group I and 18.9% group II:  $P < 0.05$ ), whereas wound infection was similar in both groups. The length of postoperative stay was similar in both (27.9 $\pm$ 21 vs 28.2 $\pm$ 12 days; NS). **CONCLUSIONS:** At this dose, arginine-enhanced formula improves fistula rates in postoperative head and neck cancer patients without a high rate of diarrhea.

**Immunoenhanced enteral nutrition, effect on inflammatory markers in head and neck cancer patients.** [Eur J Clin Nutr.](#) 2005 Jan;59(1):145-7.

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[de Luis DA](#), [Arranz M](#), [Aller R](#), [Izaola O](#), [Cuellar L](#), [Terroba MC](#).

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The aim of our study was to evaluate the effect of enteral nutrition supplemented with arginine in inflammatory markers in surgical head and neck cancer patients. A population of 29 patients with oral and laryngeal cancer were enrolled in a randomized trial. At surgery patients were randomly allocated to two groups: (a) patients receiving an enteral diet supplements with arginine (group I, n=14); (b) patients receiving an isocaloric, isonitrogenous enteral formula (group II, n=15). The mean age was 61.1+/-10.8 y (five females/24 males). Characteristics of the patients on enrollment were similar for the two groups. Prealbumin and transferrin improved in both groups. c-reactive protein (CRP) levels decreased in both groups, (group I: 134.5+/-62.5 vs 75.3+/-51 mg/dl:P<0.05) and (group II: 103.6+/-62 vs 43.8+/-34.4 mg/dl:P<0.05). Interleukin-6 (IL-6) improved in both groups (group I: 20.35+/-11.2 vs 6.7+/-3.1 pg/ml:P<0.05) and (group II:22.8+/-40 vs 9.9+/-17.7 pg/ml:ns). Tumoral necrosis factor alpha and lymphocytes did not change. In conclusion, both formulas improved IL-6 and CRP levels. Further studies are needed to determine whether type of formula is the key in these patients or genetic background play a main role in inflammatory response.

**Effect of perioperative nutrition, with and without arginine supplementation, on nutritional status, immune function, postoperative morbidity, and survival in severely malnourished head and neck cancer patients.** [Am J Clin Nutr](#). 2001 Feb;73(2):323-32.

[van Bokhorst-De Van Der Schueren MA](#), [Quak JJ](#), [von Blomberg-van der Flier BM](#), [Kuik DJ](#), [Langendoen SI](#), [Snow GB](#), [Green CJ](#), [van Leeuwen PA](#).

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BACKGROUND: Malnourished head and neck cancer patients are at increased risk of postoperative complications. OBJECTIVE: We studied the effect of perioperative, arginine-supplemented nutritional support on nutritional status, immune status, postoperative outcome,

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and survival in severely malnourished (weight loss >10% of body weight) head and neck cancer patients undergoing major surgery. DESIGN: Forty-nine patients were randomly assigned to receive 1) no preoperative and standard postoperative tube feeding, 2) standard preoperative and postoperative tube feeding, or 3) arginine-supplemented preoperative and postoperative tube feeding. RESULTS: Patients in both prefed groups received approximately 9 d of preoperative tube feeding, resulting in energy intakes of 110% and 113% of calculated needs (compared with 79% in the control group;  $P = 0.007$ ). Compared with no preoperative feeding, preoperative enteral nutrition did not significantly improve nutritional status or any of the studied biochemical or immunologic indexes. Major postoperative complications occurred in 53%, 47%, and 59% of patients in study groups 1, 2, and 3 (NS). A trend was seen toward better survival in the arginine-supplemented group ( $P = 0.15$ ). Secondary analysis showed that survivors had better human leukocyte antigen-DR expression on monocytes ( $P = 0.05$ ) and higher endotoxin-induced cytokine production ( $P = 0.010$  for tumor necrosis factor alpha and  $P = 0.042$  for interleukin 6) at the start of the study than did patients who died. CONCLUSIONS: Nine days of preoperative tube feeding, with or without arginine, did not significantly improve nutritional status, reduce the surgery-induced immune suppression, or affect clinical outcome in severely malnourished head and neck cancer patients. Patients supplemented with arginine-enriched nutrition tended to live longer. Some markers of immune function may distinguish patients with good or bad prognoses.

### **Protein metabolism in the cancer patient.**

[Biochimie](#). 1994;76(8):713-7.

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The 'flooding' method has been widely used for measuring protein synthesis in animal tissues in vivo and in vitro, employing radioactively labelled amino acids, because it minimises errors in determining the specific radioactivity of the direct precursor of protein synthesis. This approach has now been modified for measuring protein synthesis rates in tumours and healthy tissues of humans by injection of the stable isotopic labels, [1-(13)C]leucine or [2H5]phenylalanine, followed by tissue sampling during surgery. Based on the observation that rates of protein synthesis correlate with changes in the expression of cell proliferation markers, we have suggested that changes in protein synthesis in tumours can be used as indices of changes in



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tumour growth. Measurements in colorectal cancer patients have shown that protein synthesis is stimulated 80% by feeding, suggesting that the tumour is not a pure parasite, but responds to exogenous nutrients. Moreover, when the composition of the amino acids given to the patient was changed from a balanced mixture to one supplemented with branched chain amino acids, the response of the tumour to feeding was significantly diminished, suggesting that tumour growth might be modulated by diet composition. Dietary supplements of arginine have been shown previously to inhibit tumour growth in animals, probably by activating the immune system. However, in breast cancer patients arginine stimulated tumour protein synthesis, suggesting that arginine might have separate stimulatory effects on the tumour and the immune system, the outcome depending on which effect predominates.

**The nitric oxide pathway: is L-arginine a gate to the new millennium medicine?  
A meta-analysis of L-arginine effects.**

[J Med.](#) 1999;30(3-4):131-48.

[Fisman EZ](#), [Tenenbaum A](#), [Shapira I](#), [Pines A](#), [Motro M](#).

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BACKGROUND: During the past ten years, there has been a growing interest in L-arginine (LA), a semi-essential amino acid, which has recently been shown as a physiological precursor of nitric oxide (NO). AIM: The aim of this study is to determine the current role of LA in both cardiovascular and general medicine. METHODS: We performed MEDLINE searches covering a period of 33.5 years (January 1966 to July 1999) for "L-arginine" (unlimited search). Since we focused on the potential importance of LA for clinical medicine, we added the term "disease" to limit the search (limited search). RESULTS: During the period of interest 25883 articles devoted to the issue were found on unlimited search, whereas only 1656 on the limited one (mean annual rate 772 and 49 articles per year, respectively). Drastic elevation in annual rate both for unlimited and limited searches were found during the last 5 years - 2055 and 194 articles per year, respectively. The effects of LA dietary supplementation at relatively high doses have been studied extensively in several populations. LA exerts favorable effects in the prevention and treatment of cardiovascular disorders associated with endothelial dysfunction, atherogenesis and thrombosis. On the basis of the data from experimental and clinical studies, the long term oral LA supplementation has proven to be useful in avoiding endothelial damage and restoring

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injured endothelial function in patients with cardiovascular risk factors (hypercholesterolemia, smoking, diabetes, advanced age) or with several chronic cardiovascular disorders, such as coronary disease, peripheral and cerebral vascular disease, mild and moderate heart failure. Intravenous LA administration is likely to represent a potentially novel therapeutic strategy in hospitalized patients with critical limb ischemia, during angioplasty, coronary bypass grafting and cardiac transplantation. In addition, LA led to an improvement in interstitial cystitis symptoms, male reproductive activity, recovery from trauma and prognosis of chemotherapy in breast cancer. CONCLUSION: Our data clearly demonstrate a significant growth of interest in LA in clinical medicine. Arginine is gaining a prominent position as a part of the therapeutic arsenal in the management of LA-NO pathway-related disorders.

### **Natural cytotoxicity in breast cancer patients receiving neoadjuvant chemotherapy: effects of L-arginine supplementation.**

[Eur J Surg Oncol.](#) 1994 Aug;20(4):467-72.

[Brittenden J](#), [Heys SD](#), [Ross J](#), [Park KG](#), [Eremin O](#).

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Certain cytotoxic drugs have been shown to suppress host anti-cancer defence mechanisms. The amino acid L-arginine can significantly enhance natural killer (NK) and lymphokine-activated killer (LAK) cell cytotoxicity in patients with locally advanced breast cancer. In this study, the effect of L-arginine supplementation on natural cytotoxicity was determined in patients with breast cancer receiving CHOP chemotherapy. This cytotoxic regimen caused a transient immunosuppression, maximal on day 14 of each cycle ( $P < 0.001$ ); this was not cumulative during the four cycles of treatment. Those patients receiving L-arginine supplementation (30 g/day for 3 days prior to each course of chemotherapy) had a smaller and delayed onset of immunosuppression (day 14), compared with those patients who had CHOP only (day 9). L-Arginine was able to repeatedly stimulate NK and LAK cell cytotoxicity in patients who were receiving CHOP chemotherapy ( $P < 0.003$ ). In conclusion, further studies are required to determine the optimal use of chemotherapeutic agents, alone or in combination with immunostimulators, to avoid inhibition of host anti-cancer defence mechanisms.

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**Dietary supplementation with L-arginine in patients with breast cancer (> 4 cm) receiving multimodality treatment: report of a feasibility study.**

[Br J Cancer](#). 1994 May;69(5):918-21.

[Brittenden J](#), [Heys SD](#), [Miller I](#), [Sarkar TK](#), [Hutcheon AW](#), [Needham G](#), [Gilbert F](#), [McKean M](#), [Ah-See AK](#), [Eremin O](#).

Department of Surgery, University of Aberdeen, UK.

L-Arginine has been shown, in human breast cancers, to increase protein synthesis and the number of cells in the growth phase of the cell cycle. L-Arginine, therefore, may potentiate the response of breast cancers to cell cycle-specific cytotoxic agents. This phase II pilot study assessed the clinical, radiological and pathological responses in 44 patients with breast cancers > 4 cm in diameter (46 tumours: T2, n = 6; T3, n = 22; T4, n = 19), who received oral L-arginine 30 g day<sup>-1</sup> for 3 days prior to each cycle of CHOP chemotherapy, followed after 4-6 cycles by radiotherapy. Following this treatment, 95% of patients had a clinical response: complete response in 30% and partial response in 65%. Imaging, ultrasound and mammography revealed response rates of 91% and 76% respectively. Surgery was performed in 43 patients. Histological examination revealed that in 18% of cases there was no residual evidence of tumour. Furthermore, if residual tumour was identified, the degree of destruction was graded as 'severe' in 36% and 'moderate' in 30% of cases. Further studies are now required to evaluate the potential beneficial use of nutritional pharmacology in combination with existing treatment regimens.

**Immunonutrition in elective gastrointestinal surgery patients.**

[Scand J Surg](#). 2007;96(1):46-50.

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**BACKGROUND:** Previous trials have shown that perioperative immunonutrition could protect patients from infectious complications after gastrointestinal cancer operations. The purpose of this study was to determine whether perioperative immunonutrition decreases postoperative morbidity, especially infection complications, mortality and length of hospital stay in patients undergoing major gastrointestinal tract surgery. **METHODS:** One hundred patients with a

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planned elective operation for benign or malignant gastrointestinal illness were randomized into two groups: group 1) oral supplementation for five days before and five days after surgery with 900 mL/day of a formula enriched with arginine, gamma-3-fatty acid and RNA + liquid diet ad libitum on one and two postoperative day and then solid food (immunonutrition group; n = 50) or group 2) no artificial nutrition before and after surgery, on one and two postoperative day intravenous solution of 5% glucose and electrolytes and then normal diet (conventional group; n = 50). RESULTS: The groups were comparable for all key baseline and surgical characteristics. There were nine (18%) infectious complications in both groups. Overall complication rates were 28% (n = 14) in the immunonutrition group and 24% (n = 12) in the conventional group. No significant difference between the groups was found in complication rates, mortality or length of hospital stay. CONCLUSION: Routine perioperative immunonutrition to the patients undergoing major gastrointestinal surgery is not beneficial.

**Early postoperative enteral immunonutrition: clinical outcome and cost-comparison analysis in surgical patients.** [Crit Care Med.](#) 1997 Sep;25(9):1489-96.

[Senkal M](#), [Mumme A](#), [Eickhoff U](#), [Geier B](#), [Späth G](#), [Wulfert D](#), [Joosten U](#), [Frei A](#), [Kemen M](#).

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OBJECTIVE: To determine if early postoperative feeding of patients with upper gastrointestinal malignancy, using an enteral diet supplemented with arginine, dietary nucleotides, and omega-3 fatty acids (IMPACT, Sandoz Nutrition, Bern, Switzerland) results in an improved clinical outcome, i.e., reduced infectious and wound complications and decreased treatment costs when compared with an isocaloric, isonitrogenous control diet. DESIGN: A prospective, randomized, placebo-controlled, double-blind, multicenter trial of the clinical outcome and a retrospective cost-comparison analysis. SETTING: Surgical intensive care units in three different German university hospitals. PATIENTS: Of 164 patients enrolled in the study, 154 patients were eligible for analysis. They were admitted to the intensive care unit after upper gastrointestinal surgery for cancer and they received an enteral diet via needle catheter jejunostomy. Infectious complications were defined as sepsis or systemic inflammatory response syndrome, pneumonia, urinary tract infection, central venous catheter sepsis, wound infection, and anastomotic leakage. The complication events were prospectively divided into two groups: early (postoperative days 1 to 5) and late (after the fifth postoperative day) postoperative complications. The treatment costs

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of each complication were analyzed and compared in both groups. INTERVENTIONS: Patients were randomized to receive either the immunonutritional diet (n = 77) or an isocaloric and isonitrogenous placebo diet (n = 77). Enteral feeding was initiated 12 to 24 hrs after surgery, starting with 20 mL/hr and advanced to a target volume of 80 mL/hr by postoperative day 5. MEASUREMENTS AND MAIN RESULTS: Clinical examination and adverse gastrointestinal symptoms were recorded on a daily basis. Both groups tolerated early enteral feeding well, and the rate of tube feeding-related complications was low. Postoperative complications occurred in 17 patients in the immunonutrition group vs. 24 patients in the control group (NS). Further, in the early phase (postoperative day 1 to 5), complications occurred to a similar extent in both groups (12 patients in the immunonutritional group vs. 11 patients in the control group). However, in the late phase (after postoperative day 5), considerably fewer patients in the experimental diet group experienced complications compared with the control group (5 vs. 13, p < .05). In addition, the frequency rate of complicating events were recorded in each group. In the experimental diet group, a total of 22 complicating events were recorded vs. a total of 32 events in the placebo diet group (NS). However, the occurrence of late complicating events, i.e., complicating events after the fifth postoperative day, was significantly reduced in the immunonutrition group when compared with the control group (8 vs. 17 events, p < .05). The total costs for the treatment of the complications were 83,563 German marks in the experimental diet group vs. 122,430 German marks in the control group, resulting in a cost-reduction of 38,867 German marks. (At the end of December 1995, the conversion rate from German marks to U.S. dollars was 1.4365 German marks to \$1.00.) CONCLUSIONS: Early enteral feeding with an arginine, dietary nucleotides, and omega-3 fatty acids supplemented diet, as well as an isonitrogenous, isocaloric control diet (placebo) were well tolerated in patients who underwent upper gastrointestinal surgery. In patients who received the supplemented diet, a significant reduction in the frequency rate of late postoperative infectious and wound complications was observed. Thereby, the treatment costs were substantially reduced in the immunonutrition group as compared with the control group.

**Hospital resources consumed for surgical morbidity: effects of preoperative arginine and omega-3 fatty acid supplementation on costs. [Nutrition](#). 2005 Nov-Dec;21(11-12):1078-86.**

**[Braga M](#), [Gianotti L](#), [Vignali A](#), [Schmid A](#), [Nespoli L](#), [Di Carlo V](#).**

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**OBJECTIVE:** Costs related to postoperative complications continue to be a major burden on any health care system. The aim of the present study was to calculate hospital costs for postoperative complications and to evaluate whether preoperative supplementation with omega-3 fatty acids and arginine (specialized diet) might lead to cost savings in patient care. **METHODS:** Blind analysis of costs performed on data gathered from a randomized clinical trial carried out on 305 patients with gastrointestinal cancer showed that an oral preoperative specialized diet decreased postoperative morbidity compared with conventional treatment (no supplementation). Estimates of complication costs were based on resources used for treatment and on additional length of hospital stay. Cost-comparison and cost-effectiveness analyses were then carried out. **RESULTS:** The mean cost of postoperative complications was 4492 pounds sterling. The greatest amount of resources was consumed by 19 anastomotic leaks (159,803 pounds sterling), 18 abdominal abscesses (112,921 pounds sterling), and 18 pancreatic fistulae (106,516 pounds sterling). The mean costs per complication were 6178 pounds sterling in the conventional group and 4639 pounds sterling in the preoperative group ( $P = 0.05$ ). The mean total costs of patients with complications were 10,494 pounds sterling in the conventional group and 8793 pounds sterling in the preoperative group. The mean cost per randomized patient was 3122 pounds sterling in the conventional group versus 1872 pounds sterling in the preoperative group ( $P = 0.04$ ). Effectiveness values were 50.0% in the conventional group and 62.8% in the preoperative group ( $P = 0.03$ ). Total costs consumed 93% of the diagnosis-related group reimbursement rate in the conventional group and 78% in the preoperative group. **CONCLUSIONS:** The costs of postoperative morbidity consumed a large amount of the diagnosis-related group reimbursement rate. Preoperative supplementation with the specialized diet appears to be a cost-effective treatment.

**Benefits of early postoperative enteral feeding in cancer patients.** [Infusionsther Transfusionsmed.](#) 1995 Oct;22(5):280-4.

[Braga M](#), [Vignali A](#), [Gianotti L](#), [Cestari A](#), [Profili M](#), [Di Carlo V](#).

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**OBJECTIVE:** To evaluate the effect of the early postoperative administration of an enriched enteral diet in cancer patients. **DESIGN:** Randomised controlled study. **SETTING:** Surgical intensive care unit of a university hospital. **PATIENTS:** 77 consecutive patients undergoing curative surgery for gastric or pancreatic cancer. **INTERVENTIONS:** Patients were randomised into 3 groups to receive: a standard enteral formula ( $n=24$ ); the same formula enriched with arginine, RNA, and omega-3 fatty acids ( $n = 26$ ), isonitrogen isocaloric total parenteral nutrition

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(n = 27). Enteral nutrition was started within 12 h following surgery. Infusion rate was progressively increased reaching the full regimen on postoperative day (POD) 4. On admission and on POD 1 and 8, the following measurements were performed: serum level of total iron-binding capacity, albumin, prealbumin, retinol-binding protein (RBP), and cholinesterase. Delayed hypersensitivity response (DHR), IgG, IgM, IgA, lymphocyte subsets, and monocyte phagocytosis ability were also evaluated. Bioelectrical impedance analysis was performed preoperatively and on POD 2, 7, and 11. The rate and severity of postoperative infections and the length of hospital stay were evaluated. **RESULTS:** In all patients, a significant drop of nutritional and immunologic parameters was observed on POD 1. A significant increase of prealbumin ( $p < 0.02$ ), RBP ( $p < 0.005$ ), monocyte phagocytosis ability ( $p < 0.001$ ), and DHR ( $p < 0.005$ ) was found on POD 8 only in the group fed with the enriched diet. A significant reduction of severity of postoperative infections and length of postoperative stay was found in the group with the enriched diet compared to the other groups. **CONCLUSIONS:** These data are suggestive of an improvement of the nutritional and immunologic status and clinical outcome in cancer patients who receive an enriched enteral diet in the early postoperative course.

**Early postoperative enteral nutrition with arginine-omega-3 fatty acids and ribonucleic acid-supplemented diet versus placebo in cancer patients: an immunologic evaluation of Impact.** [Crit Care Med.](#) 1995 Apr;23(4):652-9.

[Kemen M](#), [Senkal M](#), [Homann HH](#), [Mumme A](#), [Dauphin AK](#), [Baier J](#), [Windeler J](#), [Neumann H](#), [Zumtobel V](#).

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**OBJECTIVE:** To evaluate the effect of early postoperative feeding with a nutritionally complete enteral diet supplemented with the nutrients arginine, ribonucleic acid (RNA), and omega-3 fatty acids on the immune function in patients undergoing surgery for upper gastrointestinal (GI) malignancies. **DESIGN:** Prospective, randomized, placebo-controlled, double-blind study. **SETTING:** Surgical intensive care unit (ICU) in a German university hospital. **PATIENTS:** Forty-two consecutive patients receiving an enteral diet via needle catheter jejunostomy after GI surgery for cancer. **INTERVENTIONS:** Patients were randomized to receive either the arginine, RNA, and omega-3 fatty acids supplemented diet or an isocaloric and isonitrogenous placebo diet. Early enteral nutrition was started on postoperative day 1 in the surgical ICU with 20 mL/hr

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and progressed to the optimal goal of 80 mL/hr by postoperative day 5. **MEASUREMENTS AND MAIN RESULTS:** Clinical examination and adverse GI symptoms were recorded on a daily basis. Body weight was determined twice weekly. Immunoglobulin concentrations were determined by laser nephelometry. Interferon-gamma concentrations were measured with a modified enzyme-linked immunosorbent assay method. Fluorescence-activated cell scan flow cytometry was performed to analyze B cells, T lymphocytes and their subsets. Clinical patient characteristics and mean caloric intake were similar between the two groups and both formulas were well tolerated. The number of T lymphocytes and their subsets, helper T cells (CD4) and activated T cells (CD3, HLA-DR), were significantly higher in the supplemented diet group on postoperative days 10 and 16 ( $p < .05$ ). Mean interferon-gamma concentration after phytohemagglutinin stimulation was higher in the supplemented diet group on postoperative day 16. In the supplemented diet group, mean immunoglobulin M concentrations were significantly higher on postoperative day 10 and mean immunoglobulin G concentrations were higher on postoperative day 16 ( $p < .05$ ) compared with the results in the placebo group. B-lymphocyte indices were significantly higher in the supplemented vs. the placebo diet group on postoperative days 7 and 10 ( $p < .05$ ). **CONCLUSIONS:** Supplementation of enteral diet with arginine, RNA, and omega-3 fatty acids in the early postoperative time period improves postoperative immunologic responses and helps to overcome more rapidly the immunologic depression after surgical trauma.

**Role of enteral immunonutrition in patients with gastric carcinoma undergoing major surgery.** [Asian J Surg.](#) 2005 Apr;28(2):121-4.  
[Chen DW](#), [Wei Fei Z](#), [Zhang YC](#), [Ou JM](#), [Xu J](#).

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**OBJECTIVE:** To evaluate the influence of postoperative immunonutrition on immune and nutritional parameters in patients with gastric carcinoma. **METHODS:** From September 2002 to August 2003, 40 patients with gastric carcinoma who had undergone major surgery were randomly divided into an immunonutrition group and standard nutrition group, each of 20 patients. On postoperative Day 2, patients in the standard nutrition group received a standard enteral formula, while those in the immunonutrition group received an enteral formula enriched with glutamine, arginine and omega-3 fatty acids. Nutritional support was continued for 7 days.



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Blood samples were obtained to determine plasma albumin, prealbumin and transferrin on Days 0, 5 and 9. On Days 0, 1 and 9, blood samples were collected to detect immunoglobulin (Ig) A, IgG, IgM, CD4 and CD8 cell counts, the ratio of CD4/CD8, interleukin (IL)-2, IL-6 and tumour necrosis factor (TNF)-alpha, respectively. RESULTS: There were no significant differences between the two groups in protein and immune parameters preoperatively and no significant differences in management perioperatively. No serious adverse effects were recorded with the two formulas. Postoperative procedures were smooth in both groups. On Day 9, serum levels of prealbumin and transferrin were higher in the immunonutrition group than in the standard nutrition group ( $p < 0.01$ ). After 7 days' nutritional support, patients in the immunonutrition group had higher levels of immunoglobulin, CD4 cell counts, CD4/CD8 ratio and IL-2 than those in the control group, whereas IL-6 and TNF-alpha levels were significantly lower in the immunonutrition group. CONCLUSION: Compared with standard enteral nutrition, enteral immunonutrition can improve defence mechanisms and modulate inflammatory action after major elective surgery for gastric carcinoma.

### **Modulation of postoperative immune response by enteral nutrition with a diet enriched with arginine, RNA, and omega-3 fatty acids in patients with upper gastrointestinal cancer.**

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OBJECTIVE: To find out whether an enteral diet supplemented with arginine, RNA, and omega-3 fatty acids modulated the production of interleukin-1 (IL-1), interleukin-2 (IL-2), IL-2 receptor, interleukin-6 (IL-6), and tumour necrosis factor alpha (TNF-alpha) after operations for upper gastrointestinal cancer. DESIGN: Prospective double blind clinical study. SETTING: University hospital, Germany. SUBJECTS: 42 patients randomised into two groups ( $n = 21$  each), one of which was given an isocaloric and isonitrogenous placebo diet and one of which was fed the same diet supplemented with arginine, RNA, and omega-3 fatty acids.

INTERVENTIONS: The cytokines were measured before operation and on postoperative days 1, 3, 7, 10, and 16. MAIN OUTCOME MEASURES: Comparison of concentrations of cytokines in the two groups. RESULTS: Among those receiving the placebo diet (after spontaneous stimulation) IL-6 concentrations were significantly higher on days 3 and 7 ( $p < 0.05$ ) and TNF-

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alpha concentrations on day 7. In contrast (after stimulation with phytohaemagglutinin) mean concentrations of IL-2 receptor were significantly higher on days 3 and 7, and of IL-1 beta and IL-2 on day 16 ( $p < 0.05$ ) in the group receiving the supplemented diet. **CONCLUSION:** Supplementation of an enteral diet with arginine, RNA and omega-3 fatty acids can modulate the acute phase reaction as indicated by the reduction in concentrations of TNF-alpha and IL-6 in the group fed the supplemented diet. Patients receiving the supplemented diet also showed accelerated recovery in the concentrations of IL-1 beta and IL-2 receptor.

### **Modulation of postoperative immune and inflammatory response by immune-enhancing enteral diet in gastrointestinal cancer patients.**

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**AIM:** To evaluate if the administration of an enteral diet supplemented with glutamine, arginine and omega-3-fatty acids modulates inflammatory and immune responses after surgery.

**METHODS:** A prospective randomized double-blind, clinical trial was performed. Forty-eight patients with gastrointestinal cancer were randomized into two groups, one group was given an isocaloric and isonitrogenous standard diet and the other was fed with the supplemented diet with glutamine, arginine and omega-3-fatty acids. Feedings were started within 48 hours after operation, and continued until day 8. All variables were measured before operation and on postoperative day 1 and 8. Immune responses were determined by phagocytosis ability, respiratory burst of polymorphonuclear cells, total lymphocytes lymphocyte subsets, nitric oxide, cytokines concentration, and inflammatory responses by plasma levels of C-reactive protein, prostaglandin E2 level. **RESULTS:** Tolerance of both formula diets was excellent. There were significant differences in the immunological and inflammatory responses between the two groups. In supplemented group, phagocytosis and respiratory burst after surgery was higher and C-reactive protein level was lower ( $P < 0.01$ ) than in the standard group. The supplemented group had higher levels of nitric oxide, total lymphocytes, T lymphocytes, T-helper cells, and NK cells. Postoperative levels of IL-6 and TNF-alpha were lower in the supplemented group ( $P < 0.05$ ).

**CONCLUSION:** It was clearly established in this trial that early postoperative enteral feeding is safe in patients who have undergone major operations for gastrointestinal cancer.

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Supplementation of enteral nutrition with glutamine, arginine, and omega-3-fatty acids positively modulated postsurgical immunosuppressive and inflammatory responses.

### **Effect of early postoperative enteral immunonutrition on wound healing in patients undergoing surgery for gastric cancer.**

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**BACKGROUND & AIMS:** One of the most frequent complications in patients with cancer and malnutrition is the surgical wound healing delay or failure. Some studies have shown that arginine improves wound healing in rodents and in healthy human beings. The main objective of this study was to assess the effect of early postoperative enteral immunonutrition on the wound healing process in patients undergoing surgery for gastric cancer. **METHODS:** Sixty six patients with gastric cancer were randomized to receive early postoperative enteral immunonutrition (formula supplemented with arginine, omega-3 fatty acids and ribonucleic acid (RNA)) or an isocaloric-isonitrogenous control. Assessment of wound healing process: (1) Quantification of hydroxyproline deposition in a subcutaneously placed catheter, (2) occurrence of surgical wound healing complications. **RESULTS:** Sixty patients were analyzed. Patients fed with immunonutrition (n=30) showed higher local hydroxyproline levels (59.7 nmol (5.0-201.8), vs. 28.0 nmol (5.8-89.6) P=0.0018) and significantly lower episodes of surgical wound healing complications (0 vs. 8 (26.7%) P=0.005) when compared to patients fed with the control formula (n=30). **CONCLUSIONS:** Early postoperative enteral nutrition with a formula supplemented with arginine, omega 3 fatty acids and RNA increased hydroxyproline synthesis and improved surgical wound healing in patients undergoing gastrectomy for gastric cancer.

### **Immunonutrition in elective gastrointestinal surgery patients.**

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**BACKGROUND:** Previous trials have shown that perioperative immunonutrition could protect patients from infectious complications after gastrointestinal cancer operations. The purpose of this study was to determine whether perioperative immunonutrition decreases postoperative morbidity, especially infection complications, mortality and length of hospital stay in patients undergoing major gastrointestinal tract surgery. **METHODS:** One hundred patients with a planned elective operation for benign or malignant gastrointestinal illness were randomized into two groups: group 1) oral supplementation for five days before and five days after surgery with 900 mL/day of a formula enriched with arginine, gamma-3-fatty acid and RNA + liquid diet ad libitum on one and two postoperative day and then solid food (immunonutrition group; n = 50) or group 2) no artificial nutrition before and after surgery, on one and two postoperative day intravenous solution of 5% glucose and electrolytes and then normal diet (conventional group; n = 50). **RESULTS:** The groups were comparable for all key baseline and surgical characteristics. There were nine (18%) infectious complications in both groups. Overall complication rates were 28% (n = 14) in the immunonutrition group and 24% (n = 12) in the conventional group. No significant difference between the groups was found in complication rates, mortality or length of hospital stay. **CONCLUSION:** Routine perioperative immunonutrition to the patients undergoing major gastrointestinal surgery is not beneficial.

### **[Comparative study of arginine and glutamine supplements in malnourished surgical patients]**

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Protein-calorie malnutrition is frequently diagnosed in patients with serious digestive conditions displaying obstructive symptoms, notably in esophageal cancer. In the present study a homogeneous group of subjects affected by esophageal cancer and candidates for elective surgery was randomly treated by one of the following oral supplements: arginine (group I), glutamine (group II), or mixed commercial amino acids (Group III-controls). The methods included nutritional measurements (biochemical and anthropometric assessment), immunologic survey (skin tests), and general clinical and surgical findings, with emphasis on surgical morbidity. Body weight remained stable throughout the study, whereas serum albumin, total

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lymphocytes and skin tests tended to improve in all groups, with statistical confirmation for albumin in arginine-treated cases (group II). Post-operative hospitalization was numerically shorter during glutamine supplementation, and this trend was statistically significant when total morbidity was compared between the groups. It is concluded that: 1) Malnutrition and energy were a major problem in this population, with equally severe post-operative morbidity; 2) Administration of arginine enabled serum albumin levels to improve; 3) Glutamine-treated subjects displayed reduced post-operative morbidity; 4) No side effects could be attributed to the therapy here employed.

### **Application of perioperative immunonutrition for gastrointestinal surgery: a meta-analysis of randomized controlled trials.**

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The aim of this study was to evaluate clinical and economic validity of perioperative immunonutrition and effect on postoperative immunity in patients with gastrointestinal cancers. Immunonutrition diet supplemented two or more of nutrients including glutamine, arginine, omega-3 polyunsaturated fatty acids and ribonucleic acids. A meta-analysis of all relevant clinical randomized controlled trials (RCTs) was performed. The trials compared perioperative immunonutrition diet with standard diet. We extracted RCTs from electronic databases: Cochrane Library, MEDLINE, EMBASE, SCI and assessed methodological quality of them according handbook for Cochrane reviewer in June 2006. Statistical analysis was performed by RevMan4.2 software. Thirteen RCTs involving 1269 patients were included. The combined results showed that immunonutrition had no significant effect on postoperative mortality (OR =0.91, p= 0.84). But it had positive effect on postoperative infection rate (OR =0.41, p<0.00001), length of hospital stay (WMD=-3.48, p<0.00001). Furthermore, it improved immune function by increasing total lymphocytes (WMD=0.40, p<0.00001), CD4 levels (WMD=11.39, p<0.00001), IgG levels (WMD=1.07, p=0.0005) and decreasing IL6 levels (WMD=-201.83, p<0.00001). At the same time, we did not found significant difference in CD8, IL2 and CRP levels. There were no serious side effects and two trials found low hospital cost. In conclusion, perioperative diet adding immunonutrition is effective and safe to decrease postoperative infection and reduce

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length of hospital stay through improving immunity of postoperative patients as compared with the control group. Further prospective study is required in children or critical patients with gastrointestinal surgery.

## **Reversal of cancer-related wasting using oral supplementation with a combination of beta-hydroxy-beta-methylbutyrate, arginine, and glutamine.**

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**BACKGROUND:** Cancer-related cachexia is caused by a diverse combination of accelerated protein breakdown and slowed protein synthesis. The hypothesis proposed in this study is that supplementation of specific nutrients known to positively support protein synthesis and reduce protein breakdown will reverse the cachexia process in advanced cancer patients. **METHODS:** Patients with solid tumors who had demonstrated a weight loss of at least 5% were considered for the study. Patients were randomly assigned in a double-blind fashion to either an isonitrogenous control mixture of nonessential amino acids or an experimental treatment containing beta-hydroxy-beta-methylbutyrate (3 g/d), L-arginine (14 g/d), and L-glutamine (14 g/d [HMB/Arg/Gln]). The primary outcomes measured were the change in body mass and fat-free mass (FFM), which were assessed at 0, 4, 8, 12, 16, 20, and 24 weeks. **RESULTS:** Thirty-two patients (14 control, 18 HMB/Arg/Gln) were evaluated at the 4-week visit. The patients supplemented with HMB/Arg/Gln gained 0.95 +/- 0.66 kg of body mass in 4 weeks, whereas control subjects lost 0.26 +/- 0.78 kg during the same time period. This gain was the result of a significant increase in FFM in the HMB/Arg/Gln-supplemented group (1.12 +/- 0.68 kg), whereas the subjects supplemented with the control lost 1.34 +/- 0.78 kg of FFM (P = 0.02). The response to 24-weeks of supplementation was evaluated by an intent-to-treat statistical analysis. The effect of HMB/Arg/Gln on FFM increase was maintained over the 24 weeks (1.60 +/- 0.98 kg; quadratic contrast over time, P <0.05). There was no negative effect of treatment on the incidence of adverse effects or quality of life measures. **CONCLUSIONS:** The mixture of HMB/Arg/Gln was effective in increasing FFM of advanced (stage IV) cancer. The exact reasons for this improvement will require further investigation, but could be attributed to the observed

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effects of HMB on slowing rates of protein breakdown, with improvements in protein synthesis observed with arginine and glutamine.

**Supplementation with a combination of beta-hydroxy-beta-methylbutyrate (HMB), arginine, and glutamine is safe and could improve hematological parameters.**

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**BACKGROUND:** Combining the amino acids arginine and glutamine with the leucine metabolite beta-hydroxy-beta-methylbutyrate (HMB) has been shown to reverse lean tissue loss in cancer and acquired immunodeficiency syndrome (AIDS) patients. Although each of these nutrients has been shown to be safe, the safety of this mixture has not been reported. Three double-blind studies examined the safety of the combination of HMB, arginine and glutamine on blood chemistries, hematology, emotional profile, and adverse events. **METHODS:** Study 1 was conducted in healthy adult males (n = 34), study 2 was in HIV patients with AIDS-associated weight loss (n = 43), and study 3 was in cancer patients with wasting (n = 32). Volunteers were assigned to either a placebo or a mixture of 3 g HMB, 14 g arginine, and 14 g glutamine per day. **RESULTS:** Across the 3 studies, HMB, arginine, and glutamine supplementation was not associated with any adverse indicators of health. The only significant changes noted were positive indicators of health status. HMB, arginine, and glutamine supplementation was associated with an improvement in emotional profile (p = .05), a decreased feeling of weakness (p = .03), and increased red blood cells, hemoglobin, hematocrit, lymphocytes, and eosinophils (p < .05) when compared with placebo-supplemented subjects. Blood creatinine levels were not changed. However, blood urea nitrogen increased (p = .01) with HMB, arginine, and glutamine supplementation, which was possibly caused by the additional nitrogen consumed or to the fact that ureagenesis is influenced by arginine and glutamine supplementation. **CONCLUSION:** These results show that HMB, arginine, and glutamine can be safely used to treat muscle wasting associated with AIDS and cancer.