The Therapeutic Effect of Amino Acids in Prostate Cancer Patients

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CONTENTS:

1) OBJECTIVES

To review and determine the therapeutic effect of amino acids in prostate cancer patients.

To identify blood plasma amino acid patterns in prostate cancer patients in comparison to standardized optimal norms, administer a patient-specific orthomolecular therapeutic and observe the symptomatic and biochemical impact of the intervention.

2) BACKGROUND & REVIEW

NOTE: Due to the multidisciplinary nature of this study, the intent of this background and review is to provide the reader with the prerequisite knowledge base upon which to consider this study's findings, not to undertake an exhaustive, systematic science review.

Prostate Cancer Facts

Changes in plasma amino acid patterns reflect changes in protein metabolism that occur with different pathological conditions. Many cancer symptoms may be the repercussion of a disturbance/irregularity in protein. Prostate cancer patients demonstrate imbalances in blood plasma amino acid composition.

Prostate cancer is the most common cancer and the second leading cause of cancer deaths in men in the United States. There is an estimated lifetime risk of disease of 16.6% for Caucasians and 18.1%

for African-Americans and a lifetime risk of death of 3.5 and 4.3%, respectively[30]. It is estimated that in 2004, 230,110 men in the U.S. were diagnosed with prostate cancer and 29,900 died of the disease. Prostate cancer has the highest prevalence of any non-cutaneous cancer in the human body, with similar likelihood of neoplastic foci found within the prostates of men around the world regardless of diet, occupation, lifestyle, or other factors. Essentially all men with circulating androgens will develop microscopic prostate cancer if they live long enough.[33] More than 75% of men diagnosed with prostate cancer are over age 65.

Prostate cancer has a complex etiology; presently, age, ethnicity, and family history are the most consistently reported risk factors associated with disease.[15] The causal genetic, molecular, and biological distinctions between prostate tumors with recurrent and indolent clinical behavior remain largely unknown.[3]

Recently, attention in the United States has focused on the decline in mortality for prostate cancer during the past 5-10 years. The age-adjusted cancer mortality declined 0.5% per year on average during this period, which some observers attributed to better treatment of the more common cancers other than lung cancer. Although any reversal in the long-term upward trend in cancer mortality is welcome, the recent decline is really quite modest. Considering the decrease in mortality from heart disease and stroke over the past 25 years, and the enormous resources devoted toward reducing mortality from cancer during the same period, it is surprising that more progress has not been made.[13] Despite significant advances in therapy for early-stage cancer, the prognosis for most advanced-stage tumors remains little changed over the past 50 years.[1]

Another measure of the national burden of cancer is the estimated lifetime risk of having an invasive malignant disease. The most recent published data from the National Cancer Institute of Canada calculate this risk to be 40% for men and 35% for women.[6] The corresponding lifetime risks in the United States are 44% and 38%.[7] These figures are higher than the often quoted “1 in 3” and partly reflect the overall aging of the North American population. However, these lifetime risks carry with them a prospect of much suffering and distress for cancer patients and their families. This is the motivation to look for avoidable causes of cancer, along with the continued effort to improve treatment.

Prostate cancer epidemiology focuses on endogenous factors, including family history, hormones, race, aging and oxidative stress and exogenous factors including, diet, environmental agents, occupation and other factors, including lifestyle factors. Epidemiological studies suggest that environmental factors may mediate the transformation of latent prostate cancer into clinically apparent tumors and that diet appears to influence this progression. Close correlations between average per capita fat intake and prostate cancer mortality internationally generated interest in underlying mechanisms for this link, such as through serum levels of androgens, free radicals, pro-inflammatory fatty acid metabolites, or insulin-like growth factor. Much interest currently lies in the potential of HMG-CoA reductase inhibitors (statins) to play a chemo-preventative role in prostate cancer. Lycopene, a potent antioxidant found in tomatoes, may exert a protective effect in the prostate. Selenium and vitamin E have also been shown to decrease the risk of prostate cancer in some men. Calcium may support vitamin D-related anti-proliferative effects in prostate cancer. Certain soy proteins, common in the Asian diet, have been shown to inhibit prostate cancer cell growth. Finally, green tea may also have a chemo-preventive effect by inducing apoptosis. Despite

confounding factors present in clinical studies assessing the effect of diet on cancer risk, the data remain compelling that a variety of nutrients may prevent the development and progression of prostate cancer.[29]

Identifying and Treating Prostate Cancer

One of the major problems in management of prostate cancer is the lack of reliable genetic markers predicting the clinical course of the disease.[3] Our ability to accurately predict the risk of treatment failure for an individual patient with prostate cancer remains limited. The current tools we utilize to guide critical decisions, such as whether or how aggressively to treat prostate cancer, are based on serum PSA levels, biopsy Gleason score, and clinical stage.[5] These tools have had only limited success with respect to prostate cancer patients' stratification and demonstrated a significant variability in predictive value among different clinical laboratories and hospitals. Furthermore, best existing markers cannot reliably identify at the time of diagnosis a poor-prognosis group of prostate cancer patients who ultimately would fail therapy[3].

The diagnostic markers in many of these cancer tests may not have anything to do with cancer biology or etiology; they just happen to be there. The best and well-known example is the prostate-specific antigen (PSA) test for prostate cancer that measures PSA production (and hence its serum level) which is elevated in individuals with large prostate, enlarged prostate, or enlarging or inflamed prostate (by injury, infection, cancer, etc). Although patients with prostate cancer usually have elevated PSA levels, a majority of people with abnormally high serum PSA levels do not have prostate cancer.[8] In the latest study to question the value of prostate cancer screening, researchers have shown that evaluation with PSA testing or digital rectal examination does not reduce mortality.[67]

The treatment for prostate cancer may involve one or a combination of the following therapies:

- Watchful Waiting
- Surgery
- Radiation Therapy
- Hormonal Therapy
- Chemotherapy
- Gene Therapy
- Complementary & Alternative Therapies

Because many men with a slow-growing tumor have the same life expectancy as men who don't even have prostate cancer, it may not be necessary to treat these small, slow-growing tumors.

This is especially important since there still is no satisfactory drug for treatment of androgen-independent, metastatic human prostate cancer.

Prostate Cancer and Nutrition

North Americans' intake of the 40 essential micronutrients (vitamins, minerals, and other biochemicals that humans require) is commonly thought to be adequate in terms of the recommended dietary allowances (RDAs). The evidence suggests, however, that much chronic metabolic damage occurs at levels between the level that causes acute micronutrient deficiency disease and the RDAs.[5] In addition, the prevention of more subtle metabolic damage may not be addressed by current RDAs. When one input in the metabolic network is inadequate, repercussions

are felt on a large number of systems and can lead to degenerative disease. This may, for example, result in an increase in DNA damage (and cancer), or mitochondrial decay (and accelerated aging and degenerative diseases).[40]

Recent studies by the American Institute of Cancer Research on food, nutrition and cancer prevention indicate that differences in diet and lifestyle have pronounced effects on cancer incidence, prevalence and natural history.[21] The typical North American diet, for example, consists of significant excesses of fat and energy and deficiencies of micronutrients, fiber and other phytochemicals that may play an important role in cancer prevention[22].

Overt malnutrition is seen in about 40% of patients hospitalized for treatment of cancer. In patients whose primary treatment modality is surgical, morbidity and mortality is twice as high in the malnourished group as in the normally nourished patients. This clinically important malnutrition is a consequence of obligatory parasitism by the tumor, which grows at its own genetically determined rate and which competes effectively with the host for the limited available nutrients. Administration of extra nutritional support can alter the tumor-host nutritional balance so that host repletion may occur. Although the usefulness of nutritional support for correcting malnutrition in cancer patients is clear, the specificity and sensitivity and optimal choices of constituents for nutritional support continue to evolve.[18]

It has been estimated that 30–40 percent of all cancers can be prevented by lifestyle and dietary measures alone. Obesity, nutrient sparse foods such as concentrated sugars and refined flour products that contribute to impaired glucose metabolism (which leads to diabetes), low fiber intake, consumption of red meat, and imbalance of omega 3 and omega 6 fats all contribute to excess cancer risk. Intake of flax seed, especially its lignan fraction, and abundant portions of fruits and vegetables will lower cancer risk. Allium and cruciferous vegetables are especially beneficial, with broccoli sprouts being the densest source of sulforophane. Protective elements in a cancer prevention diet include selenium[66], folic acid, vitamin B-12, vitamin D, chlorophyll, and antioxidants such as the carotenoids (α-carotene, β-carotene, lycopene, lutein, cryptoxanthin). Ascorbic acid has limited benefits orally, but could be very beneficial intravenously. Supplementary use of oral digestive enzymes and probiotics also has merit as anticancer dietary measures. When a diet is compiled according to the guidelines here it is likely that there would be at least a 60–70 percent decrease in prostate cancer. Such a diet would be conducive to preventing cancer and would favor recovery from cancer as well.[9]

Most of the research on nutrition and cancer has been reductionist; that is, a particular food or a nutrient has been studied in relation to its impact on tumor formation/regression or some other end point of cancer at a particular site in the body. These studies are very helpful in seeing the details of the mechanisms of disease. However, they do not help give an overall picture of how to prevent cancer on a dietary level. Even less, they tell little of how to eat when a person already has a cancer and would like to eat a diet that is favorable to their recovery.

Cancer and Protein

Neoplastic transformation is accompanied by adaptive increases in nucleotide and protein synthesis. The high rates of protein synthesis in rapidly growing tumors require a continuous supply of both

essential and nonessential amino acids[39]. Tumours assimilate not only the nitrogen from the diet, but also the nitrogen from host proteins, raising the concept of tumors as "nitrogen traps," actively competing with the host for nitrogen compounds. Tumors use the incorporated amino acids for both oxidation and protein synthesis.[31] It appears that during disease, active metabolism and increased protein synthesis in central organs and in the immune system and wounds is a first priority. The substrate mix utilized for this process is crucially different from that used in the non-diseased state of starvation in healthy individuals.[59]

Whether infection, chronic disease or cellular stress directly alters the requirements for specific amino acids is not clearly understood, although it has been speculated that infection might specifically influence both aromatic amino acid[48] and sulfur amino acid[49] nutrition. The major factors affecting amino acid requirements are the stage of development, reproductive state, environmental factors, digestibility of dietary proteins, genotype of the individual, and pathological conditions. Remarkably, there are no conclusive data relative to changes in requirements induced by infection, injury, trauma, and chronic disease such as cancer. However, many chronic diseases are associated with deficiencies and imbalances of particular amino acids causing specific changes in requirements.[53]

At the most simple level, an individual's requirement for amino acids can be divided into those necessary for growth itself and those that must be supplied to maintain both the body protein equilibrium and optimum physiological functions. Both are sensitive to the adequacy of amino acid supply.[47]

The Optimal Amino Acid Level

The problem of defining amino acid requirements is inherently difficult. Few issues in nutritional science have aroused such long-standing and deep-seated controversies as protein and amino acid requirements.

The ideal optimal model should contain three main components:

1) the rates of the pathways that consume amino acids (and hence protein);
2) the factors, dietary and physiological, that regulate the bioavailability of the amino acids;
3) and the source, magnitude and regulation of the inefficiency of the utilization of bioavailable amino acids.[52] The bioavailability of dietary amino acids involves factors, such as intestinal amino acid use, that are not simple functions of the enzymatic digestion of protein, and the efficiency with which bioavailable amino acids are used involves important but poorly defined factors.

The most difficult problem in the calculation of amino acid dietary requirements is the definition of the quantities used in the maintenance of body protein equilibrium. This is critical because after about age 9 months, most dietary amino acids are used to maintain the physiological well-being of the individual. The magnitude of maintenance amino acid requirements (i.e., the essential amino acid requirements of adults) has been the subject of intense disagreement over the past 10 years.[50]

Ultimately, the key test of adequacy of either protein or amino acid intake must be the patient's long-term response. The optimal requirement would be determined by functional criteria such as good health, growth, resistance to disease, etc.

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In summary, changes in plasma amino acid patterns reflect changes in protein metabolism that occur with different pathological conditions. Many cancer symptoms may be the repercussion of a disturbance/irregularity in protein. Prostate cancer patients demonstrate imbalances in blood plasma amino acid composition.
Over a seven-year period in a clinical setting, hundreds of cancer patients have been administered patient-specific orthomolecular supplementation. This paper reviews the results of that supplementation.

3) METHODS

Case series clinical research evidence was gathered in several stages:

A) Initial blood test (no supplementation)
B) Initial blood plasma analysis for amino acids (no supplementation)
C) Self-administered, daily nutrient and amino acid supplementation
D) Iterative plasma analysis and amino acid supplementation

The concept of Case Series Research is "a retrospective analysis of clinical data that a practitioner has developed". The Office of Alternative Medicine of the National Institute of Health (USA) have suggested that Case Series Research methods are an effective means to determine whether a complementary anticancer therapy demonstrates potential efficacy. This study abided by all the essential elements of Case Series Research as identified by OAM.[68]

Setting

The setting, a medical center located in Ottawa, Ontario, Canada, with extensive experience in prostate and other cancers. Patients were recruited during their regularly scheduled visits and all data was analyzed on a confidential basis. This study followed the ethics policy of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans.[69]

There were two groups of participants: A) Prostate Cancer Patients and B) Non-Cancer Patients

Study Sample Characteristics

(A) Cancer subjects were 50 men, white, upper income and diagnosed with prostate cancer. The mean age of cancer study participants was 66 years (range 45 – 80 years).

Chart A: Cancer Study Participant Age Distribution (n=50)

Age	%age
45-50	4.0%
51-55	2.0%
56-60	16.0%
61-65	26.0%
66-70	28.0%
71-75	12.0%
76-80	12.0%
	100.0%

Patients were staged clinically from their medical charts by history, physical exam, digital rectal examination, and Gleason Score / serum PSA measurement. Additional studies, including CT scan, bone scan, and MRI, were reviewed as available. All cancer participants (n=50) were classified as Stage III or Stage IV. 64% had metastasis. The average Gleason score was 7.2 distributed as follows:

Chart B: Cancer Study Participant By Gleason Score Distribution

Gleason	%age
4	8.3%
6	33.3%
7	16.7%
8	16.7%
9	16.7%
10	8.3%
	100.0%

52% (n=50) of participants had undergone treatment (essentially surgical: 81% n=21) as follows:

Chart C: Cancer Study Participant By Treatment Distribution
S=surgery: R= radiation: C=Chemotherapy

Treatment	%age	
SRC	7.7%	
SC	15.4%	
S	11.5%	
SR	11.5%	
S	34.6%	80.8%
R	11.5%	
C	7.7%	
	52.0%	

Median time since diagnosis in this cohort of patients was 6.0 years and the mean was 6.1 years as follows:

Chart D: Cancer Study Participant By Date of Diagnosis Distribution

Date Diagnosed	%age
1990-1995	8.0%
1996-2000	40.0%
2001-2003	42.0%
2004-2005	10.0%
	100.0%

Both the median and mean time since commencing the supplementation program in this cohort of patients was 3.0 years as follows:

Chart E: Cancer Study Participant By Date Started
(an average of 5 plasma tests/patient with a range of 2-7 during their study involvement)

Date Started	%age
1999	6.0%
2000	8.0%
2001	2.0%
2002	22.0%
2003	30.0%
2004	20.0%
2005	12.0%
	100.0%

B) Non-Cancer Patients were 14 men, white, with no active known cancer. The mean age of male non-cancer study participants was 67 years (range 56 – 85 years). The median time since commencing the supplementation program in this cohort of patients was 2.0 years.

Collection of Blood Specimens
Blood samples for amino acid analysis were obtained after an overnight fast from all participants. A mean of 4.9 plasma tests were completed for a total of 244 tests on the cancer participants at intervals of between 1-3 months on average (n=50). An additional 56 tests were analyzed with a mean of 4/non-cancer participant (n=14). The samples were processed within 24 h after collection. Plasma was separated by centrifugation until the absence of platelets in the supernatant was confirmed. Plasma was separated from blood and deproteinized.

Through HPLC analysis, blood plasma concentrations of 28 amino acids were profiled. Individual profiles were referenced to standard amino acid norms[70].

To standardize nutritional variables, subjects uniformly and daily self-administered highly bio-available, pharmaceutical grade, pathogen-free, nutritional supplements. Capsules were vegetable gelatin and all products meet the highest USP and Pure Grade standards. The supplements consisted of:

1) a multi macronutrient, vitamin and minerals that are essential to human health as well as a variety of nonessential nutrients, such as certain phytochemicals, antioxidants and enzymes.
2) a broad-based prostate specific supplement containing various compounds including epigalocatechin (green tea extract), lycopene, saw palmetto and other enzymes and vitamins
3) flax seed oil

Patient-specific supplementation based on algorithms reflecting individual circumstances compared to standard norms were developed and included a daily total of 10grams of whey protein as a general source of amino acids along with additional patient-specific supplementation of deficient amino acids, typically; taurine, l-histidine and occasionally l-leucine, l-lysine, thiamin-HCL. This supplement was also self-administered by the participant on a daily basis. The amino acid make-up of the whey protein was:

Chart F: Amino Acid Composition of Whey Protein Supplement

Aspartic Acid	10.8%
Threonine	7.3%
Serine	4.8%
Glutamic Acid	17.2%
Glycine	1.6%
Alanine	4.8%
Valine	5.7
Isoleucine	6.6%
Leucine	10.2%
Tyrosine	2.9%
Phenylalanine	2.8%
Histidine	1.9%
Lysine	8.0%
Arginine	2.0%
Proline	7.1%
Cysteine	2.5%
Methionine	2.0%
Tryptophan	1.7%

Evaluation and Analysis Techniques
The above blood analysis/supplementation intervention cycle was repeated for each participant while cancer and collateral medical symptoms were qualitatively and quantitatively monitored through multiple case studies.

Data was collected on 50 male cancer and 14 male non-cancer participants. Qualitative and quantitative descriptive data analysis was performed on all subjects (n = 64). Patient age, sex, date of diagnosis, therapeutic interventions, clinical status, and biopsy reports were retrieved, as applicable, from the patients' charts. Medical treatments for prostate patients are increasingly being evaluated by quality of life (QOL) issues as well as life extension. Quality of life was qualitatively assessed using generic questionnaires filled out by each participant at the time of each blood test.

Statistical Descriptive analysis
Cancer and cancer-free groups were compared for initial blood plasma characteristics and follow-up blood samples.
All descriptive statistics are presented as means and standard deviations with their 95% confidence intervals for quantitative variables.

Third order, polynomial trend-lines provide a graphical representation of the movement and direction of amino acid concentrations from test to test. Coefficient of determination or R^2 values depict the reliability of the trend lines.

Safety
Administration of individual amino acids at low doses, which are consistent with the normal dietary intakes, does not require risk assessment since the absorption, metabolism, and disposition values are similar to the same amount consumed as part of a protein.[41]

4) RESULTS

Post-intervention, the following observations were made in 94% of the subjects:
(A) plasma amino acid profiles demonstrate correlative movement with intervention
(B) subjects demonstrate significant positive response rates in disease remission, stabilization, and improvement in quality of life without side effect or adverse events
(C) there is beneficial management of collateral damage from radiotherapy and chemotherapy

Observations:

- Several amino acids showed significant (confidence level 95%) starting and ending blood plasma concentrations. (Chart G).
- Initial taurine and histidine plasma levels in the cancer patients were varied but at the low-end or lower than standard norms
- The mean plasma taurine concentration in all 50 cancer participants was 56.4± 4.0 nmol/ml, which was significantly lower than the plasma taurine concentration of the non-cancer subjects ($P < 0.005$, Chart H and Chart I).
- Plasma levels of taurine and histidine significantly increased ($P<.001$) after supplementation and at a faster and more extreme rate of change than the non-cancer patients
- The mean plasma histidine concentration in all 50 cancer participants was 75.4± X.0 nmol/ml, which was significantly lower than the plasma histidine concentration of the non-cancer subjects ($P < 0.005$, Chart J).
- In several amino acids, blood plasma levels made an initial jump in concentration and then fluctuated before settling at either a higher or similar level.
    - The mean plasma glutamine concentration in all 50-cancer participants was 550± 20.0 nmol/ml, which was significantly lower than the final concentration post-supplementation ($P < 0.005$).
    - The mean plasma arginine concentration in all 50-cancer participants was 555± 21.0 nmol/ml, which was significantly lower than the final concentration post-supplementation ($P < 0.005$).
- Plasma amino acid levels were also measured for 27 other amino acids. Plasma level movement was detected in all cases with supplementation, however, except for those amino acids identified in Chart G, no statistically significant trends were observed. While initial concentrations varied, the mean was within the normal range.
- Survival: During the 7-year period in which patient testing has been undertaken, no patients have died from prostate cancer. Two patients died from pneumonia and one from an unrelated disease.
- Quality of Life: The experience of living with cancer, from the time of diagnosis and treatment decisions, through treatment itself and survival is fraught with psychological distress. In 94% of participant cases (n=47), prostate cancer participants indicated overall

improvement in three general types of measures: a qualitative measure of health, a measure of symptoms specific to prostate cancer, and psychosocial measures. Many indicated a reduction in the side effects of conventional treatment.

Chart G: Significant Starting/Ending Amino Acid Changes in Blood Plasma

units= nmol/mL	Starting	Ending	Difference
Taurine	56	93	36
Isoleucine	62	67	5
Leucine	122	133	11
Lysine	192	211	19
Arginine	88	86	-2
Histidine	75	80	5
Glutamine	557	573	16
Alanine	365	402	37
Glycine	198	227	29
Valine	226	245	19

Chart H: Blood Plasma Taurine in Cancer Patients

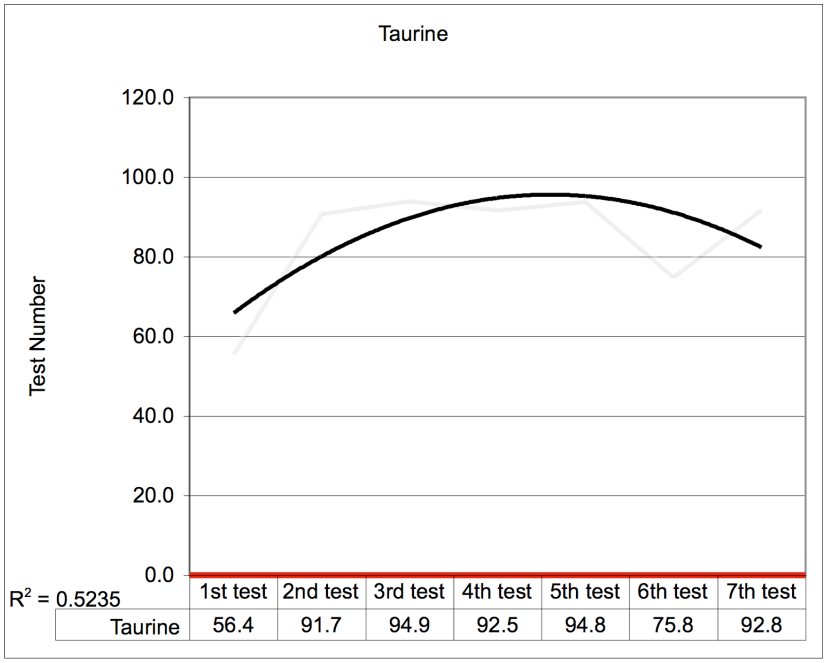


Chart I: Blood Plasma Taurine in Non-Cancer Patients

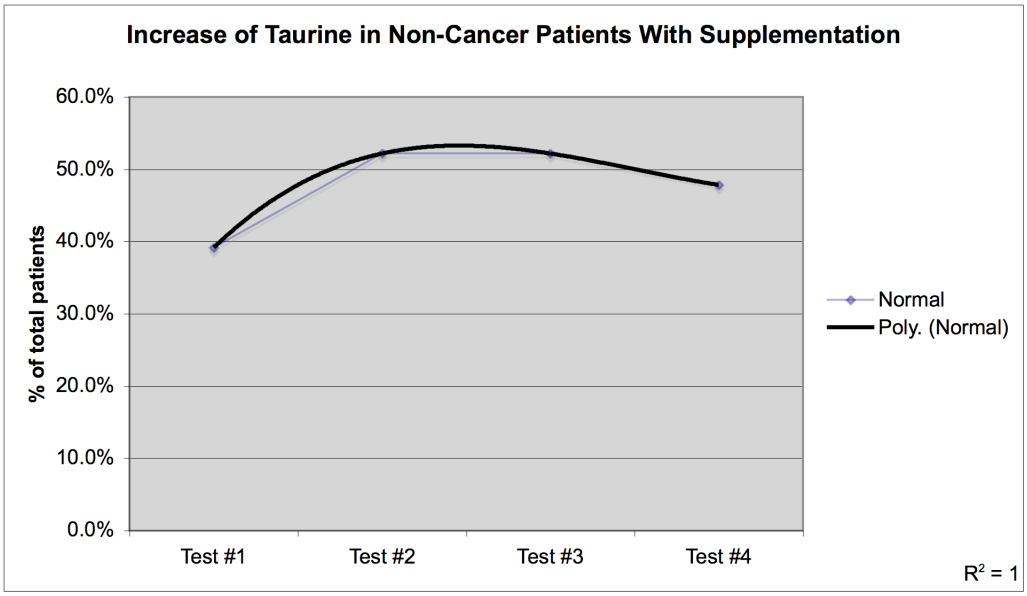
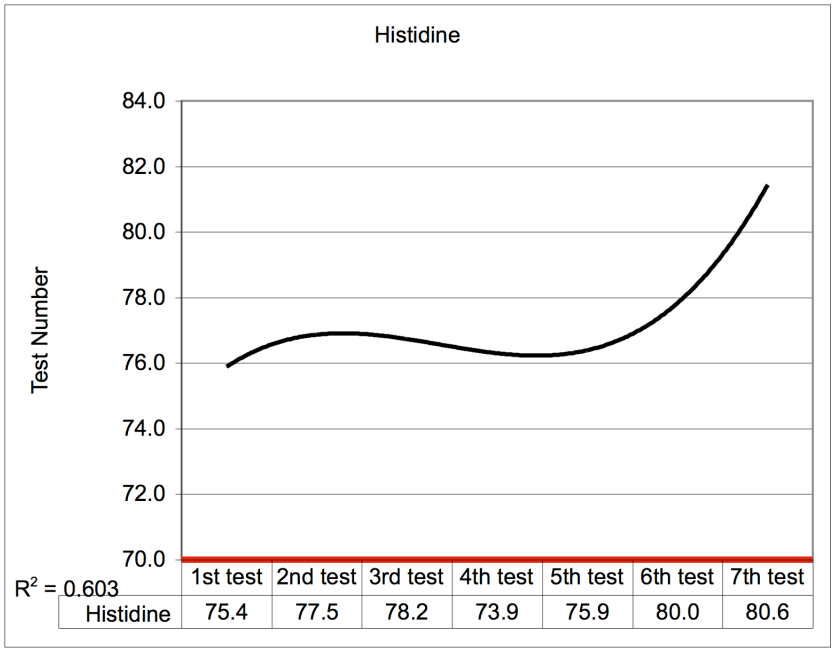


Chart J: Blood Plasma Histidine in Cancer Patients



5) LIMITATIONS

Several limitations to the study exist:

(A) The supplementation was self-administered by the participants. Compliance, while encouraged could not be mandated. Protein source, time of consumption, quantity, and composition are all factors that affect protein loads on food intake in men.[51] From clinical interviews, it was felt that most participants were reasonably compliant.

(B) While certain lifestyle recommendations were made to all participants, consistent with good standards of cancer management, there was no control of the environmental variables for each participant (i.e., eating habits, smoking, level of activity, etc). For example, fluctuations in the foods consumed not only influence the intake of particular bioactive components, but may alter metabolism and potentially influence the of action of both essential and nonessential amino acids.[16]

(C) It would be at least 10 to 15 years after the last patient was enrolled (and it would take many years to organize and subsequently recruit enough patients) before a possible conclusion could be drawn regarding one of the most important outcome criterion, survival. However, given the advanced disease stage of the cancer participant group under consideration and given that the SEER 5-Year Relative Survival rates of men diagnosed with distant stage prostate cancer is only 50% [65], it would appear that the supplementation intervention may have had an impact on extension of life of the subjects.

(D) An additional problem consists in the difficulty in quantitatively measuring endpoints such as remission, stabilisation or immune response.

(E) While all participants had the same base macronutrient supplementation, there will always be uncertainty surrounding how to assess the relative contribution of each nutritive product. There are numerous studies that demonstrate the progressive and synergistic effect on cancer progression of using multiple nutraceutical therapeutics.[71, 72]

(F) Amino acid adequacy is much better defined in growing and healthy organisms than during illness, because endpoints for growth and health are much easier to define than endpoints for amino acid adequacy during disease states. During disease, endpoints do not only indicate amino acid adequacy with respect to preserving the composition and function of the entire organism; more specifically, endpoints pertain to sustaining an adequate metabolic response to allow an organism to successfully deal with the disease process itself. Such an endpoint is difficult to assess, and no standards exist. For example, during critical illness, food handling by the gut is compromised, which may require adaptations to the route and mode of administration as well as the composition and quantities of food constituents. Similarly, in disease, metabolism appears to be specifically directed to generate a healing response rather than to preserve muscle mass; this influences amino acid requirements with respect to composition and quantity.[59]

6) DISCUSSION

Conferral with Other Human and Animal Studies
We have known for more than 30 years that metabolism during stress is crucially different from metabolism during pure starvation.[59]

(a) Taurine
Our initial low taurine results are consistent with several observations made by other researchers. In one study, the mean plasma taurine concentration in patients after chemotherapy was significantly lower than the plasma taurine concentration of the healthy control subjects. Plasma taurine deficiency after intensive chemotherapy or radiotherapy were uniformly low in all patients (20.0 +/- 6.4 mumol/L). Plasma taurine in 11 healthy volunteer control subjects was 45.0 +/- 20.3 mumol/L (P less than 0.001).[57]

This is also consistent with other studies where Taurine supplementation improves survival in mice after total body irradiation.[8] Additionally, taurine supplementation hastens the recovery from neutropenia in total-body-irradiated mice.[57] Neutropenia may be seen with viral infections and after radiotherapy and chemotherapy. Neutropenia lowers the immunologic barrier to bacterial and fungal infection.

Amino acid utilization and, therefore, demand differ between the healthy state and various disease states. In the healthy state most circulating amino acids are derived from dietary proteins that are stored and broken down in the gut and released gradually into the portal circulation, and from continuous turnover of body protein. In disease states, the amino acid composition of amino acids derived from peripheral protein breakdown and released in the circulation, is different, for example because a substantial part of the branched-chain amino acids is broken down to yield glutamine and alanine, which are released in the circulation.[59]

Another study documented this tendency of plasma Taurine to decrease with the worsening of metabolic and cardio-respiratory patterns as was also observed also in our study. The correlations between plasma taurine, other amino acid levels, and metabolic and cardio-respiratory variables were also assessed by this study. Levels of taurine were directly and significantly related to levels of glutamate, aspartate, ß-alanine and phosphoethanolamine (and unrelated to other amino acids). Levels of these amino acids increased simultaneously with increasing doses of leucine, isoleucine and valine. These results characterize the relationships between plasma taurine and other amino acid levels in sepsis, provide evidence of amino acid interactions that may support taurine availability and show more severe decreases in plasma taurine with the worsening of metabolic and cardio-respiratory patterns.[43]

The assessment of changes in plasma taurine levels with respect to levels of other amino acids seem relevant, given its unusual role; however, this aspect has remained unexplored. The results in this study and others both show that plasma taurine varies independently of changes in most other amino acid levels. Exceptions might be glutamate, aspartate, ß-alanine and phosphoethanolamine.[43]

(b) Glutamine

Several amino acids such as glutamine and cysteine (and taurine) are shown or suggested to be conditionally essential in disease, and to form substrate in the stressed patient for anabolic processes in liver, immune system, and injured sites.[59]

During catabolic stress or when tumors are proliferating, peripheral glutamine stores are rapidly diminished and the amino acid is preferentially shunted as a fuel source toward visceral organs or tumor tissue. This creates a glutamine-depleted environment, the consequences of which include enterocyte and immunocyte starvation.[58]

In relation to cancer, it seems that a supplementation of glutamine in the diet may be beneficial for several reasons. Tumor progression is associated with an avid consumption of host glutamine by tumor cells and a depression in the activity of natural killer cells due to a decrease in glutathione concentrations in these cells. Therefore, dietary supplementation of glutamine could have the beneficial effect of restoring the levels of glutathione inside natural killer cells. There are experimental data that seem to indicate that a dietary supplement diminishes tumor growth by restoring the function of natural killer cells and improves protein metabolism of the host or patient[10, 14]. Additionally, an oral supplement of glutamine can increase the selectivity of antitumor drugs[17, 24, 19] by protecting the patient from oxidative damage through an increase in glutathione contents [14]. Several groups have shown that glutamine can also protect against oxidative damage induced by radiotherapy [35, 36, 37]. It is now well documented that under appropriate conditions, glutamine is essential for cell proliferation, that it can act as a respiratory fuel and that it can enhance the function of stimulated immune cells. It is now clear that glutamine is utilized at high rates by isolated cells of the immune system such as lymphocytes, macrophages and neutrophils.[42]

However, there is no consensus on the usefulness of glutamine supplementation for cancer patients. For instance, a recent double-blind, randomized study on glutamine supplementation in cancer patients receiving chemotherapy concluded that glutamine did not have a significant effect on either tumor response or secondary effects of chemotherapy.[13, 38]

(c) Arginine

Arginine supplementation augments both specific and nonspecific anti-tumor mechanisms, retards tumor growth, and prolongs survival in some animal tumor models.[25] Arginine plays a role in protein synthesis, as a substrate for the urea cycle and the production of nitric oxide, and as a secretagogue for growth hormone, prolactin, and insulin. Whereas most amino acids are 16% nitrogen, arginine is 32% nitrogen. Arginine is synthesized primarily in the kidney from gut-derived citrulline via the urea cycle, which also detoxifies ammonia and facilitates excretion of nitrogen. Ornithine is a metabolite of arginine and is involved in the synthesis of polyamines, which are important for cellular division.[25] Strong evidence [33, 34] suggests that dietary supplementation with arginine enhances immunocompetence in adults in humans and in animal models.[26], [27] Immunonutritional formulas supplemented with arginine are widely used in acute and critical care units to enhance immune function in metabolically stressed patients.[25] Arginine has numerous roles in cellular metabolism that may influence the multistep process that results in cancer.[28]

(d) Histidine
Many of the study participants required histidine supplementation. There is little reference to histidine levels in any disease state. Long-term histidine deficient diet (1–8 wk) which could potentially be brought about through chemotherapy, leads to a significant decrease in plasma histidine concentrations.(73)

(e) Other
Researchers found that when they treated human prostate cells in the lab with whey protein, the levels of an antioxidant called glutathione rose dramatically. The results showed that both doses of whey protein increased glutathione levels by at least 60%. The more concentrated dose raised glutathione levels by 64%. Antioxidants like glutathione are thought to fight cancer-causing free radicals. Whey protein contains the amino acid cysteine, which is a key ingredient for producing glutathione in the body.(61)

A diet or supplementation with the amino acids glycine, alanine and glutamic acid has also been shown to help improve prostate symptoms, although it is not understood clearly what role these amino acids play in maintaining prostate health. Studies of L-glycine, L-alanine, and L-glutamic acid showed that these three amino acids relieved many of the symptoms of an enlarged prostate. For example patients taking these amino acids experienced reduced nighttime urination, reduced urgency, reduced frequency, and alleviation of delayed urination. Glycine, alanine and glutamic acid are three amino acids used in a preparation for a Japanese study involving men with chronic prostatitis. The researchers found, after four weeks, the amino acid preparation helped to reduce prostate swelling and alleviate symptoms of urinary discomfort(62). An early Spanish study found glycine, alanine and glutamic acid was effective in reducing symptoms of BPH and helped reduce the duration of the condition(63). Glutamic acid has also shown the ability to protect sperm and improve motility and fertilizing capacity.(64)

Biological Need and Dietary Requirement for Amino Acids in Prostate Cancer Patients
Biological Need defines the quantities of the nutrient in question that are consumed in its various metabolic pathways. From the perspective of protein and amino acid requirements, the biological need can be usefully divided into the needs for protein deposition and the needs for the maintenance of amino acid equilibrium. The latter category includes functions, such as immune and neuromuscular, that are not necessarily directly related to protein metabolism and turnover but are nonetheless of critical importance to adequate health.(47)

Similarly, Dietary Requirement defines the quantity of the nutrient that must be supplied in the diet to satisfy the biological need. The dietary requirement is, by definition, higher than the biological need because diets are not 100% bio-available and once absorbed into the body, are not used with 100% efficiency. Thus, the relationship between biological need and dietary requirement is a function of the diet.(47)

What is the Likely Mechanism of Therapeutic Supplementation
Infectious complications in critically ill patients can cause increased morbidity and mortality. Recent advances in nutritional support involved enhancing immune function through the beneficial effects and therapeutic actions of amino acids.(25)

By tracing the multi-step process of carcinogenesis at the levels of the cell, organ and experimental animal, researchers have been able to investigate the molecular mechanisms through which the nutrient and non-nutrient components of foods and botanical dietary supplements affect the development of cancer.[22]. Studies reveal that in epithelial neoplasms of prostate cancers, specific genetic polymorphisms may substantially affect the metabolic process that leads to cancer. A published symposium by AICR[23] on nutritional oncology acknowledges the extensive range of mechanisms through which dietary factors may influence and alter the risk of cancer. Dietary factors, which include dietary supplements, may affect multi-step carcinogenesis through many beneficial mechanisms. Such mechanisms include inhibiting carcinogen uptake, inhibiting the formation or activation of carcinogens and preventing dietary carcinogen-binding to DNA. Other supplements such as vitamin E scavenge oxygen radicals, whereas folic acid corrects DNA methylation imbalance. Many dietary constituents have the potential to operate through multiple mechanisms of action in the multi-steps of carcinogenesis as antiproliferative, antioxidative and anti-inflammatory agents that also modify carcinogen metabolism and induce differentiation and cell death.

For example, taurine has functional roles in stabilizing the membrane potential, in bile salt formation, growth modulation, osmoregulation, antioxidation, promotion of calcium transport, and calcium binding to membranes. It exerts positive ionotropic effects of the heart, as well as having antiarrhythmic and antihypertensive effects. It is involved in many metabolic responses in the central nervous system, has an anticonvulsant action, may have an insulinogenic action, and is required for eye function[54]. Taurine is capable of influencing programmed cell death in various cell types depending upon the initiating apoptotic stimulus.[55]

Both Taurine and glutathione have antioxidative roles, and both rely on similar substrates for synthesis. Actually, Glutamate and cysteine are precursors of glutathione and of taurine. This may lead to competition for substrate when demand for antioxidant protection increases; in effect, decreased plasma levels of sulfur amino acid in sepsis have been considered to be a consequence of amino acid utilization to enhance glutathione synthesis, and this same mechanism has been suggested to explain the fall in taurine.[44, 45, 46]

The goal of nutritional therapy is to exogenously furnish the specific amino acids that the previously healthy organism used to produce in excess before their acute illness. This may especially apply to patients who are unable to produce these substances themselves even when given adequate nutrition of conventional composition. It is likely that this is even more true in severely and chronically septic patients or in patients who have become depleted and lack the machinery to produce these amino acids.[59]

7) CONCLUSIONS

Prostate cancer symptoms correlate with disturbances in the host's protein metabolism. Normalization of imbalanced plasma amino acid profiles by the administration of patient-specific amino acid formulas may positively influence the clinical management of the cancer.

These data suggest that amino acid supplementation has important effects in prostate cancer patients, but the exact mechanisms to explain these events remain unknown, and more research is required to explain the apparent benefits of nutritional supplementation for prostate cancer.

Our results provide an insight into features of taurine that remain incompletely understood. More study is required to characterize fully taurine metabolism and interactions in prostate cancer. Beyond an improvement in understanding of patho-physiology, there are also therapeutic implications.

Because amino acid imbalances and antagonisms remain a major puzzle in understanding pathogenesis of disease, a joint concerted attack unraveling these problems may shed light on the secrets of the regulation of protein and amino acid metabolism, in health and disease.

This research could serve as the basis for future development of more specific anti-metastatic, anti-invasive, apoptosis-based therapies for human prostate cancer.

8) RELEVANCE TO PRACTICE

As a result of the broad application of measurements of PSA level in the blood for early detection of prostate cancer in the United States, an increasing proportion of prostate cancer patients are diagnosed with early-stage tumors that are apparently confined to the prostate gland, and many patients have seemingly indolent disease not affecting an individual's survival.[6]

Despite the plethora of confounding factors present in clinical studies assessing the effect of nutrition on cancer risk, the sum total of data remains compelling in regards to the potential for a variety of nutrients to potentially prevent the development and progression of prostate cancer.[32] Consequently, it can be argued that, management of prostate cancer may be highly influenced through the use of targeted supplementation. In other words, physicians now have an opportunity to add life to years, as well as adding years to life.[12]

Also, when the prostate cancer patient is receiving conventional treatment, he should also incorporate targeted supplementation in order to reduce the side effects of conventional treatment, improve the results, and possibly allow the patient to be able to discontinue the conventional treatments.

In general, there is little evidence of serious adverse effects in humans from most amino acid supplements.[20] On past experience, conventional medicine will only discover cures for chronic diseases slowly. It is therefore imperative for all concerned that other known to be safe avenues of approach to the problem are explored.

More than one third of recently diagnosed prostate cancer patients already utilize some form of CAM therapy, and the not all disclose their use to their physician(s). They tend to rely on anecdotal information for their CAM decision making. Dissemination of reliable CAM information is one key to helping men navigate this difficult arena. [34]

9) FOOTNOTES

This paper results from a paper presented at the IN-CAM Conference of Integrative Therapies held November 12, 2004, in Toronto, Ontario.

Conflict of interest: Chowdhury Zaman is the Medical Director and Dr Ken Lin is the Lab Director for Immune System Management Inc., the corporate entity that has sponsored this research. William O'Neill is CEO & Founder of ISM.

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11) REFERENCES

1. Bailar JC III, Gornik HL. Cancer undefeated. N Engl J Med. 1997;336:1569–1574.

2. James McKiernan1 and Mitchell C. Benson. Predicting the clinical course of prostate cancer J Clin Invest. 2004 March 15; 113(6): 806–808.

3. Gennadi V. Glinsky,1 Anna B. Glinskii,1 Andrew J. Stephenson,2 Robert M. Hoffman,3 and William L. Gerald2 Gene expression profiling predicts clinical outcome of prostate cancer J Clin Invest. 2004 March 15; 113(6): 913–923.

4. Thomas, G.V., and Loda, M. 2002. Molecular staging of prostate cancer. In Prostate cancer principles & practice. P.W. Kantoff, P.R. Carroll, and A.V. D'Amico, editors. Lippincott Williams & Wilkins. Philadelphia, Pennsylvania, USA. 287–303.

5. DeMarzo AM, Nelson WG, Isaacs WB, Epstein JI. Pathological and molecular aspects of prostate cancer. Lancet. 2003;361:955–964

6. Potosky A, Feuer E, Levin D. Impact of screening on incidence and mortality of prostate cancer in the United States. Epidemiol. Rev. 2001;23:181–186.

7. Sherbourne CD, Hays RD, Fleishman JA, Vitiello B, Magruder KM, Bing EG, McCaffrey D, Burnam A, Longshore D, Eggan F, Bozzette SA, Shapiro MF. Impact of psychiatric conditions on health-related quality of life in persons with HIV infection. Am J Psychiatry. 2000;157:248–254. doi: 10.1176/appi.ajp.157.2.248.

8. Hossein A. Ghanbari Cancer Diagnostics Integrated With Therapeutics: A Comprehensive Approach to Managing the Disease J Biomed Biotechnol. 2004; 2004(4): 175–176.

9. Michael S Donaldson Nutrition and cancer: A review of the evidence for an anti-cancer diet Nutr J. 2004; 3: 19.

10. Fahr MJ, et al.: Glutamine enhances immunoregulation of tumor growth. JPEN J Parenter Entral Nutr 1994 Nov-Dec;18(6):471-6.

11. Alex Hankey CAM Modalities Can Stimulate Advances in Theoretical Biology Evid Based Complement Alternat Med. 2005 March; 2(1): 5–12.

12. Stéphanie Boini, Serge Briançon, Francis Guillemin, Pilar Galan, and Serge Hercberg Impact of cancer occurrence on health-related quality of life: A longitudinal pre-post assessment Health Qual Life Outcomes. 2004; 2: 4.

13. Richard Clapp Review Environment and health: 4. Cancer CMAJ. 2000 October 17; 163(8): 1009–1012.

14. Rouse K, et al.: Glutamine enhances selectivity of chemotherapy through chenges in glutathione metabolism. Ann Surg 1995 Apr;22(4):420-6.

15. Kevin A. Nelson and John S. Witte Androgen Receptor CAG Repeats and Prostate Cancer Am J of Epidemiology, 2002 155(10):883-890

16. J. A. Milner Supplement: Nutrition and Gene Regulation Molecular Targets for Bioactive Food Components J. Nutr. 134:2492S-2498S, September 2004

17. Saverese D, et al: Glutamine Treatment of Paclitaxel-Induced Myalgias and Arthralgias. J Clin Oncol;Vol 16,No 12:3918-19, 1998.

18. Landel AM, Hammond WG, Meguid MM., Aspects of amino acid and protein metabolism in cancer-bearing states. Cancer. 1985 Jan 1;55 (1 Suppl):230-7.

19. Miller AL: Therapeutic considerations of L-glutamine: a review of the literature. Altern Med Rev 1999 Aug;4(4):239-48.

20. Peter J. Garlick Supplement: 3rd Amino Acid Workshop; The Nature of Human Hazards Associated with Excessive Intake of Amino Acids J. Nutr. 134:1633S-1639S, June 2004

21. World Cancer Research Fund/American Institute for Cancer Research Food, Nutrition, and Prevention of Cancer: A Global Perspective 1997 Banta Book Group Menasha, WI.

22. Heber D. Blackburn G. L. Go V.L.W. eds. Nutritional Oncology 1999 Academic Press New York, NY.

23. American Institute for Cancer Research Nutrition and Cancer Prevention 2000 Kluwer Academic/Plenum Press New York, NY. in press

24. Klimberg VS, et al.: Glutamine, Cancer, and its Therapy. Am J Surg 1996 nov;172(5):418-24.

25. Joyce K. Stechmiller, PhD, ARNP, Beverly Childress, MSN and Tricia Porter, BSN. Arginine Immunonutrition in Critically Ill Patients: A Clinical Dilemma American Journal of Critical Care. 2004;13: 17-23

26. Wu G, Meininger C, Knabe D, Bazer F, Rhoads J. Arginine nutrition in development, health, and disease. Curr Opin Clin Nutr Metab Care. 2000;3:59–66.

27. Barbul A. The use of arginine in clinical practice. In: Cynober LA, ed. Amino Acid Metabolism and Therapy in Health and Nutritional Disease. Boca Raton, Fla: CRC Press; 1995:361–372.

28. D. Scott Lind Supplement: Arginine Metabolism: Enzymology, Nutrition, and Clinical Significance J. Nutr. 134:2837S-2841S, October 2004

29. Sonn GA, Aronson W, Litwin MS. Impact of diet on prostate cancer: a review. Prostate Cancer Prostatic Dis. 2005 Aug 30

30. Klein EA, Thompson IM. Update on chemoprevention of prostate cancer. Curr Opin Urol 2004; 14: 143–149

31. Landel A. M., Hammond W. G. & Meguid M. M. (1985) Aspects of amino acid and protein metabolism in cancer-bearing states. Cancer 55:230-237

32. G A Sonn, W Aronson and M S Litwin Impact of diet on prostate cancer: a review Prostate Cancer and Prostatic Diseases advance online publication 30 August 2005; doi: 10.1038/sj.pcan.4500825

33. Bostwick DG, Burke HB, Djakiew D, Euling S, Ho SM, Landolph J, Morrison H, Sonawane B, Shifflett T, Waters DJ, Timms B. Human prostate cancer risk factors. Cancer. 2004 Nov 15;101(10 Suppl):2371-490.

34. Eng J, Ramsum D, Verhoef M, Guns E, Davison J, Gallagher R. A population-based survey of complementary and alternative medicine use in men recently diagnosed with prostate cancer Integr Cancer Ther. 2003 Sep;2(3):212-6.

35. Jensen GL, Miller RH, Talabiska DG, Fish J & Gianferante L (1996) A double-blind, prospective, randomized study of glutamine-enriched compared with standard peptide-based feeding in critically ill patients. American Journal of Clinical Nutrition 64, 615-621.

36. Griffiths R, The evidence for glutamine use in the critically-ill Proceedings of the Nutrition Society (2001), 60, 403-410

37. Yoshida S., Kaibara A., Yamsaki K., Ishibashi N., Noake T. & Kakegawa T. (1995) Effect of glutamine supplementation on protein metabolism and glutathione in tumor-bearing rats. J. Parenter. Enteral Nutr. 19:492-497

38. Myers CE: Prostate Forum, March 2000;Vol 5, No 34.

39. Medina M. A., Sánchez-Jiménez F., Quesada A. R., Márquez J. & Núñez de Castro I. (1988b) Effect of palmitate, acetate and glucose in glutamine metabolism in Ehrlich ascites tumor cells. Biochimie 70:833-834.

40. Bruce N. Ames Supplements and Tuning Up Metabolism J. Nutr. 134:3164S-3168S, November 2004

41. Andrew G. Renwick Establishing the Upper End of the Range of Adequate and Safe Intakes for Amino Acids: A Toxicologist's Viewpoint J. Nutr. 134:1617S-1624S, June 2004

42. Philip Newsholme Why Is L-Glutamine Metabolism Important to Cells of the Immune System in Health, Postinjury, Surgery or Infection? Journal of Nutrition. 2001;131:2515S-2522S.)

43. Marco Castagneto The Relationship between Plasma Taurine and Other Amino Acid Levels in Human Sepsis Journal of Nutrition. 2000;130:2222-2227.)

44. Grimble R. F. Nutritional antioxidants and the modulation of inflammation: theory and practice. New Horizons 1994;2:175-185

45. Hashiguchi Y., Fukushima R., Saito H., Naka S., Inaba T., Lin M. T., Muto T. Interleukin-1 and tumor necrosis factor alter plasma concentration and interorgan fluxes of taurine in dogs. Shock 1997;7:147-153

46. Malmezat T., Breuillé D., Pouyet C., Patureau Mirand P., Obled C. Metabolism of cysteine is modified during the acute phase of sepsis in rats. J. Nutr. 1998;128:97-10

47. Peter J. Reeds and Peter J. Garlick Protein and Amino Acid Requirements and the Composition of Complementary Foods J. Nutr. 133:2953S-2961S, September 2003

48. Reeds, P. J. & Jahoor, F. (2001) The amino acid requirements of disease. Clin. Nutr. 20(Suppl 1):15-22.

49. Breuille, D. & Obled, C. (2000) Cysteine and glutathione in catabolic states. Furst, P Young, V. R. eds. Protein, Peptides and Amino Acids in Enteral Nutrition 2000:173-198 S. Karger AG Basel, Switzerland .

50. Institute of Medicine (2002) Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients) 2002 National Academy Press Washington, D.C.

51. G. Harvey Anderson, Sandy N. Tecimer, Deepa Shah, and Tasleem A. Zafar Protein Source, Quantity, and Time of Consumption Determine the Effect of Proteins on Short-Term Food Intake in Young Men J. Nutr. 2004 134: 3011-3015.

52. D. Joe Millward Human Amino Acid Requirements The Journal of Nutrition Vol. 127 No. 9 September 1997, pp. 1842-1846

53. Peter Fürst and Peter Stehle What Are the Essential Elements Needed for the Determination of Amino Acid Requirements in Humans? J. Nutr. 134:1558S-1565S, June 2004

54. Huxtable, R. I. (1992) Physiological actions of taurine. Physiol. Rev. 72: 101–163

55. Wang, J. H., Redmond, H. P., Watson, R. W., Condron, C. & Bouchier-Hayes, D. (1996) The beneficial effect of taurine on the prevention of human endothelial cell death. Shock 6: 331–338

56. Desai, T. I. C., Maliakkal, J., Kinzie, J. L., Ehrinprels, M. N., Luk, G. D. & Ceijka, J. (1992) Taurine deficiency after intensive chemotherapy and/or radiation. Am. J. Clin. Nutr. 55: 708–711

57. TK Desai, J Maliakkal, JL Kinzie, MN Ehrinpreis, GD Luk and J Cejka Taurine deficiency after intensive chemotherapy and/or radiation American Journal of Clinical Nutrition, Vol 55, 708-711, Copyright © 1992 by The American Society for Clinical Nutrition, Inc

58. Bode, B. P. & Souba, W. W. (1994) Modulation of cellular proliferation alters glutamine transport and metabolism in human hepatoma cells. Ann. Surg. 220: 411–424

59. Peter B. Soeters, Marcel C. G. van de Poll, Wim G. van Gemert and Cornelis H. C. Dejong Amino Acid Adequacy in Pathophysiological States J. Nutr. 134:1575S-1582S, June 2004

60. Guoyao Wu, Yun-Zhong Fang, Sheng Yang, Joanne R. Lupton and Nancy D. Turner Glutathione Metabolism and Its Implications for Health J. Nutr. 134:489-492, March 2004

61. Kent K.D.; Harper W.J.; Bomser J.A.1 Effect of whey protein isolate on intracellular glutathione and oxidant-induced cell death in human prostate epithelial cells Toxicology in Vitro, Volume 17, Number 1, February 2003, pp. 27-33(7)

62. Okada, S., Clinical application of amino acid preparation for nonspecific prostatitis. Hinyokika Kiyo, 1985 Jan. 31(1): p. 179

63. Cuervo Blanco, E., Clinical study of a phytosterol extract of Prunus arborea and 3 amino acids: glycine, alanine and glutamic acid. Arch Esp Urol, 1978 Jan-Feb. 31(1): p. 97.

64. Renard, P., et al., Improvement of motility and fertilization potential of postthaw human sperm using glutamine. Cryobiology, 1996. 33(3): p. 311-9.

65. Ries LAG, Eisner MP, Kosary CL et al. SEER Cancer Statistics Review, 1975 -2002, National Cancer Institute. Based on Nov 2004 SEER data submission, posted to SEER web site 2005.

66. Etminan M, FitzGerald JM, Gleave M, Chambers K., Intake of Selenium in the Prevention of Prostate Cancer: a Systematic Review and Meta-analysis. Cancer Causes and Control. 2005 Nov;16(9):1125-31

67. Concato Dr. John, Prostate-specific antigen (PSA) testing. Jan. 9 Archives of Internal Medicine.

68. OAM. Office of alternative medicine workshop on the collection of clinical research relevant to alternative medicine and cancer. Bethesda: Office of Alternative Medicine, 1994.
O'Leary A: Stress, emotion and human immune function. Psychological Bulletin 1990; 108(3): 363-77

69. Libbey R. Policy on research ethics within Immune System Management Inc. according to Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, Internal Document (2005)

70. Shapira E, Blitzer MG, Miller JB, et al., Biochemical genetics; a laboratory manual. Oxford, UK, Oxford University Press, 1989: 94-5

71. Lamm D, Schenkman E, Superficial Bladder Cancer Therapy, J Urol, Vol 151, 1994

72. Rao AR et al., Jpn J Ca Res., Vol 81, p1239, Dec 1990

73. Anderson, H. L., Cho, E. S. & Wixom, R. K. (1986) Effects of long-term, low histidine diet on men. In: Histidine III (Fürst, P. & Kluthe, R., eds.), p. 2. Wiss. Verlagsgesellschaft, Stuttgart, Germany.