Original Research Paper

Volume - 15 | Issue - 08 | August - 2025 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Clinical Laboratory

POLYAMINES AND DIETARY AMINO ACID RESTRICTION: IMPACT IN CANCER PREVENTION OR TREATMENT

Eliseo Ruiz Bedolla Clinical Laboratory. Hospital Infantil de México "Federico Gómez" México cíty.

Israel Parra Ortega Clinical Laboratory. Hospital Infantil de México "Federico Gómez" México city.

ABSTRACT Polyamines are molecules synthesized by amino acid decarboxylation and play an important role in several physiological and biochemical processes of living organisms. The dietary intake of polyamines revealed that its intake showed an alternative by maintaining the health and controlling various diseases and can be used for the treatment of various health disorders. Polyamines production begins with the intake of amino acids (arginine, lysine and methionine) through food. The controlled diet of polyamines can also reduce the growth of tumor cells in cancer patients. Glycine, glutamine and aspartate serve as carbon and nitrogen donors for purine biosynthesis. Arginine and methionine produce polyamines that alter gene expression by modulating global chromatin structure and cancer cell proliferation. Amino acid-degrading enzymes such as arginine and asparagine have been shown to exert antitumor effects in preclinical and clinical setting. Use of amino acids that restrict the synthesis of polyamines mainly, it is full therapeutic potential in the fight against cancer. The principal focus of this review is the specific relationship between polyamines, amino acids and cancer metabolism.

KEYWORDS : polyamines, amino acids metabolism, cancer prevention. treatment

INTRODUCTION

Polyamines are found in all living, organisms. Polyamines are formed by the decarboxylation of amino acids and they facilitate cell growth and development. Polyamines are the integrated part of the cellular and genetic metabolism and help in transcription, translation, signaling, and post- translational modifications. The levels of polyamines decline with age in humans, which is associated with different health disorders. Recent studies have shed light on the important role of amino acids in cancer metabolism. Amino acids are involved in pathways that feed cancer cells and provide building blocks for cancer cell growth; some such as glutamate, branched chain amino acids and threonine fuel the TCA cycle intermediates, resulting in the release of ATP and also nucleotides require amino acids as nitrogen/or one-carbon donors for their biosynthesis. Some drugs targeting amino acid metabolism have been applied in a clinical setting and highlight the therapeutic potential of this mode of inhibition.

Increased polyamine synthesis and inflammation have long been associated with intraepithelial neoplasia., which are risk factors for cancer development in humans. Inflammation plays an essential role in the initiation and progression of many types of human epithelial cancers (1). Chronic inflammation leads to activation of macrophages and other inflammatory cells that generate increased amounts of growth factors and cytokines, as well as reactive oxygen and nitrogen species that may cause DNA damage. Polyamine catabolism occurs through of three enzymes that acetylates providing acetylated polyamines as substrates for further back-conversion to spermidine or putrescine. Importantly, the oxidization reactions of both result ion, the generation of the toxic product, hydrogen peroxide. This H2O2, a reactive oxygen species (ROS), has been shown to play an essential role in the DNA damage associated changes observed following elevated levels of polyamine. Polyamine metabolism is an integral component of the mechanism of carcinogenesis in epithelial tissues. Causes of inflammation that have been linked to cancer include bacterial and viral infection; **Helycobacter pylori** for gastric adenocarcinoma; hepatitis B and hepatitis C for hepatocellular carcinoma and human papillomavirus for penile cancers or noninfective physical and/or chemical irritants. Increased polyamine synthesis has been detected as a product of inflammation and elevated intracellular polyamine pools are frequently observed in actively proliferating cells, including tumor cells (2).

POLYAMINES

These compounds have protonated amino groups at physiological pH levels, allowing them to interact with negatively charged macromolecules, thereby involving them in a variety of cellular processes, including chromatin organization, gene regulation, cellular proliferation and differentiation, cell death and immune system function (3). Extracellular polyamines originate from the diet, microbiota and sloughed or damaged cells. Most luminal polyamines passively diffuse into the circulation through the proximal portion of the small intestine, while some are actively transported into intestinal epithelial cells, where they may be interconverted via the polyamine metabolic enzymes or excreted as acetylated polyamines.

Polyamines play a pivotal role in cell signaling, DNA binding, transcription, RNA splicing and functioning of cytoskeletons and eukaryotic translation. Cancer cells require sustained, elevated intracellular polyamine pools to maintain continual proliferation. The key enzymes in biosynthesis of polyamines are ornithine decarboxylase (ODC), which produce putrescine and S-adenosyl-methionine decarboxylase which is involved in spermidine and spermine synthesis. An important intermediate required for the synthesis of spermidine and spermine is derived from S-adenosylmethionine (SAM) (4).

L-arginine is a precursor of the polyamines. These compound bind to the clefts of DNA double strand. It has also been observed electrostatic bond to the sugar-phosphate skeleton without altering the structure of DNA; on the contrary, they stabilize the double chain; spermine participates in the regulation of protein binding to RNA and interaction with DNA to protect it from denaturation and ionizing agents such as radiation from sunlight. They also regulate the methylation of histones which is one of the main means of epigenetic control (5).

There are three ways to maintain the polyamine pool in the body: intestinal microorganisms, *de novo* biosynthesis (endogenous), and supply through diet (exogenous). The exogenous diet provides the maximum quantity of polyamines more than the process of endogenous biosynthesis. Various food items contain the required amounts of polyamines,1.e. plant-derived foods have mostly putrescine and spermidine, and meat products mainly contain spermine (6).

Polyamines control the expression and stability of p53, a nuclear phosphate protein, which regulates different genes associated with the growth and death of the cell (7). In the mammalian gut, the enzyme arginase first decomposes the amino acid arginine to produce ornithine. The accumulated ornithine is then decarboxylated by the action of the ornithine decarboxylase (ODC) enzyme to produce the polyamine putrescine. (Figure 1). Meanwhile, methionine is transformed to S- adenosylmethionine which after various process is converted to spermidine. Structural analogs of ornithine, α-mehyl ornithine and difluoromethyl ornithine (DFMO) are the most used competitive inhibitors. Blockade of polyamine synthesis slows down cellular growth and proliferation of malignant tissues (8).

Nutritional Roles Of Polyamines In Health Maintenance And Disease Prevention

In the prostate, studies had been observed widespread asymptomatic prostatitis arising from a multitude of stimuli, including microbial infection and dietary components. In putrescine and spermidine levels in the prostate. Inhibition of polyamine synthesis by DFMO showed marked reduction in weight and volume of the prostate as well as metastasis (9).

Plant and animal derived foods are significant sources of polyamines.

Spermidine and putrescine are generally most abundant in plant-based foods and cheeses, while levels of spermine tend to be highest in fresh meat, including red meat, pork and poultry meat. Dietary polyamines are fully absorbed in the proximal portion of the small intestine and have been detected unmodified in the inferior vena cava and portal vein (10).

The decreased level of dietary polyamines and intestinal decontamination were found beneficial for the controlling the pain in the patients of prostate cancer. Other studies, the hypoplasia of colonic mucosa and small intestine was significantly achieved when a polyamine-deficient diet was given for a long time period; This suggested that the dietary polyamines level might be a strategy to prevent colon cancer chemotherapy. The dietary putrescine decreased the activity of sulindac for suppressing oncogenesis of the intestine in a mouse model, which suggested that the dietary polyamines level might be a strategy to prevent colon cancer chemotherapy. Suppression of arginine intake reduces NO production resulting in apoptotic cell death in breast cancer cells (11).

In colon cancer tissue, the activities of polyamine-synthesizing enzymes and polyamine content are increased 10 to 15 folds in comparison to normal colonic epithelium, and polyamines therefore have been considered even as specific markers for neoplastic proliferation in the colon. Derivatives of spermidine and spermine, acetylated at the N1 position by acetyltransferase, have been shown to accumulate in neoplastic but not normal tissues during carcinogenesis in the rat model and in human cancer, reflecting high levels of these amines in neoplasia (12).

Agmatine induces the production of insulin, adrenaline and noradrenaline. Its presence in humans is primarily due to diet. Red wine, beer and sake contains significant amounts of polyamines, primarily putrescine, spermidine and spermine. Furthermore, toxic levels of polyamines have been reported in sausages, which may represent a potential health risk.

AMINO AC IDS

While glucose is a renowned energy source for cancer growth, amino acids are also important fuels supporting cancer development. Glutamine, for example, is largely anaplerotic and provides both amine groups to support the TCA cycle**.** In addition to glutamine, other as branched-chain amino acids (BCAAs; valine, leucine and isoleucine) are alternative sources of organic molecules that can also fuel the TCA cycle. Glycine, glutamine and aspartate serve as carbon and nitrogen donors for purine biosynthesis. Additional sources of carbon for nucleobases as a form of formate include glycine, serine and methionine, which provide one-carbon units through the methionine-folate cycle Arginine derived polyamines alter gene expression by modulating global chromatin structure and cancer cell proliferation (19).

Arginine a semi-essential amino acid is indispensable for cell proliferation and survival. Arginine is derived from dietary protein intakes, body protein breakdown (approximately 80%), or endogenous *de novo* arginine production in the kidneys (10 to 15% of the total arginine production). Dietary glutamine plays an important role in this process, as 90% of circulating citrulline arises from glutamine. Intestine derived citrulline is released into the circulation and taken up primarily by the kidney for arginine synthesis. The arginine deprivation-mediated immunosuppressive tumor micro-enviroment (TME) mainly focuses on two enzymes, Arginine depletion may be the best choice for those with low levels of enzyme arginine-succinate synthetase (ASS1) and ornitintranscarbamilase (OTC), while ARG inhibitors may be suitable for those receiving immunotherapies (14). Bacteria produce endotoxins such as lipopolysaccharide (LPS) that activate iNOS in macrophages. The NO produced binds to the iron in numerous enzymes thar contain the metal in their active sites (15).

Asparagine is classified as a nonessential amino acid, but it is essential for leukemia and lymphoma owing to low expression or lack of asparagine synthetase in these cancer cells. Asparagine deprivation with asparaginase can degrade asparagine to aspartic which is the cornerstone of treatment protocols for acute lymphocytic leukemia and has been used for remission induction and intensification treatment for decades. In short. amino acid metabolism characteristics present both challenges and opportunities for the development of treatments for leukemia and lymphoma (16).

Cysteine metabolism is vital for leukemia stem cells (LSC) maintenance; depletion of cysteine only induces the death of acute myelocytic leukemia stem and progenitor cells. Upon cysteine depletion glutathione synthesis is impaired, leading to reduced glutathione action of succinate dehydrogenase.

Glutamine. Glutamine, vital for the body´s functions, is pivotal in cancer metabolism as it influences tumor growth. Recent studies have shed light on the effects of glutamine on the epigenetic regulation of cancer cells and the enhancement of anti-cancer immune functions, providing valuable insights for potential therapeutic advancements. Due to its implication in various cellular processes, ranging from energy production to nucleotide biosynthesis, glutamine has been of growing interest in cancer biology research (17). Like glucose, glutamine can be degraded to lactate and produce the nicotinamide adenine dinucleotide phosphate (NADPH) as a by-product of this flux via malic enzyme, contributing to fatty acid synthesis. Glutamine has important physiological functions, mainly serving as a precursor in the synthesis of other amino acids and glucose for energy, also is an arginine precursor, and precursor of NAD and glutathione (18).

Glycine. Glycine restriction alone didn´t have the same detrimental effect on cancer cells as serine starvation, which might be explained by the inter-conversion between serine and glycine in one- carbon metabolism by serine hydroxymethyl transferase, especially the mitochondrial glycine synthesis enzyme.

Leucine is an essential amino acid. Leucine is not only necessary for protein synthesis; also acts as a signaling molecule activating mechanistic target of rapamycin (mTOR). Leucine is one of branched chain amino acids (BCAAs), which are not first catabolized in the liver due to the low activity of BCAA aminotransferase; therefore, leucine increases rapidly in circulation after meal. Although leucine is the highest enrichment amino acid in proteins; leucine deprivation showed modest effects on human breast cancer cells (19).**Lysine**. Lysine is a particularly important essential amino acid; interesting, although the abundance of lysine in human proteome ranked third after leucine and valine. Lysine is very important for cell functions and cell growth might be particularly vulnerable for lysine restriction. Indeed, lysine deprivation could completely block the proliferation of either p53-competent or p53-deficient cancer cells (20). Importantly, kwashiorkor is a severe protein malnutrition disease of childhood associated with lysine deficiency in normal corn diet. Normal corn has low levels of lysine and tryptophan, which lead to the imbalance of amino acids and malnutrition. Five cases of kwashiorkor were reported; all cases had a history of lacking breast-feeding, and were only fed with the food prepared from normal corn; it took at least 4 months for the development of the kwashiorkor disease in those children. Lysine is an important amino acid, its concentration in proteins and their modification play indispensable roles in homeostasis, proliferation, differentiation and diseases including malnutrition and cancer (21).

Serine Is a nonessential amino acid; its metabolism is altered and enhanced in cancer cells. When there is a deficiency of the amino acid serine; glycine; serine and folic acid should be administered. Serine deficiency occurs due to a deficiency of one of the enzymes involved in its synthesis; mainly 3-phosphoglycerate dehydrogenase, which is the most serious defect. Serine starvation induced stress and promoted p53-independent and p53-dependent metabolic remodeling in cancer cells. Under the starvation of serine, the upregulation or enhancement of the *de novo* serine synthesis pathway and oxidative phosphorylation were independent of p53, while the inhibition of nucleotide synthesis was dependent of p53-p21 activation so that the limited amount of *de novo* serine was shunted to glutathione production for the survival of cancer cells. Therefore, serine starvation might have a potential role in the treatment of p-53-deficient tumors (22).

Methionine. Methionine is essential for the initiation of protein synthesis. Serine acts as one-carbon donor and tetrahydrofolate (THF) serve as one-carbon receptor in the folate cycle. In the methionine synthase reaction, vitamin B12 act as essential cofactor. Methionine is an amino acid important for cancer growth and metabolism. A growing body of evidence indicates that methionine restriction inhibits cancer cell growth and may enhance the efficacy of chemotherapeutic agents. Our understanding of cancer´s unique programming has led to the definition of the six hallmarks of cancer. These characteristics include cancer cell ability to: 1) maintain proliferative signaling, 2) bypass growth suppressors, 3) resist apoptosis, 4) enable replicative immortality, 5) induce angiogenesis and 6) initiate invasion and

metastasis. Traditional chemotherapy treatment for cancer based on its ability to inhibit rapidly dividing cancer cells. While this treatment has increased the lifespan of many patients, the toxic effects on normal cells have detrimental health consequences.

The dependence of many tumor cells on an exogenous source of methionine; makes dietary methionine restriction (MR) and exciting potential tool in the treatment of cancer. Proliferation and growth of several types of cancer cells, are inhibited by MR, while normal cells are unaffected by limiting methionine as long as homocysteine is present (23). Malignant cells lack the enzyme required to recycle homocysteine therefore giving methionine restriction the capacity to alter cancer cells while maintaining normal, healthy cells.

Prostate cancer is the second leading cause of cancer death among adult men in the USA and current treatment options include hormonal therapy to reduce testosterone levels, radiationtherapy or surgical procedures. Dietary MR inhibits prostate cancer development especially in the anterior and dorsal lobes of the prostate, where the most severe lesions are found. The cells of the prostate produce high levels of polyamines and inhibition of polyamine synthesis is effective at suppressing tumor growthy in prostate cancer. Given the dependence of polyamine synthesis on methionine, the polyamine biosynthetic pathway may be a primary target of MR in prevention and/or treatment of prostate cancer. Methionine restriction has been shown to induce apoptosis in the human prostate cancer cell lines.

Breast cancer is the second most common form of cancer diagnosed in women. Depending on the type of breast cancer, treatment options include surgery to remove the cancer or the entire breast, chemotherapy, hormone therapy, radiation therapy and in some cases, targeted therapy drugs or immunotherapy. Breast cancer cells are hormone receptor positive if they express either (or both) of the estrogen and/or progesterone receptors and are considered HER-2 positive if the breast cancer cells overexpress the protein, HER-2 (human epidermal growth factor receptor 2). If the cells meet none of these criteria, it is triple negative breast cancer (TNBC). TNBC makes up about 16% of all breast cancer diagnoses. TNBC has fewer treatment options than other forms of breast cancer due to the lack of a response to hormone therapy and drugs that target HER-2. Methionine restriction may provide a way to enhance efficacy of potential treatment options for TNBC.

Colorectal cancer. The relationship between methionine restriction and colon cancer has been established in tumor prevention and treatment in animal and cell culture models. Importantly, MR also enhanced efficacy of 5-fluorouracil, a chemotherapeutic drug with great efficacy against colorectal cancer (23).

Tyrosine. Is transported into catecholamine-secreting neurons and adrenal medullary cromaffin cells where catecholamine synthesis takes place. The first step in the process requires tetrahydropteridine (BH4) as cofactor. The product of the tyrosine hydroxylase reaction is 3,4-dihydrophenylamine (L- DOPAO; more commonly just (DOPA). The enzyme DOPA decarboxylase converts DOPA to dopamine. Protein tyrosine kinases, especially receptor tyrosine kinases, have dominated the cancer therapeutic sphere as proteins that can be inhibited at selectively target cancer (22).

Tyrosine kinase inhibitors (TKIs) are a form of targeted therapy used to treat certain types of cancer. TKIs block the action of tyrosine kinase enzymes in cells, which may stop cancer cells from growing and multiplying. TKIs work by disrupting the signaling pathways that tyrosine kinases use to control cell growth as cel signaling, cell growth and division. TKIs are used to treat many types of cancer, including gastrointestinal stromal tumors; kidney cancer, chronic lymphocytic leukemia, chronic myeloid leukemia, HER2-positive breast cancer, brain-metastatic breast cancer (22).

Tryptophan. Tryptophan is an interesting and unique amino acid, which is the least used; this cannot be synthesized in vivo and must be acquired from foods. Immune system could induce tryptophan degradation to inhibit the growth of certain cancer cells catabolizing activity of indolamine 2,3- dioxygenase (IDO). The clinical trials at IDO inhibitors showed limitations and off-target effects due to the multifaceted tryptophan metabolism.

Therapeutic Applications From Amino Acid Metabolism

Most cancer studies have been carried out from a genetic point of view and little importance has been given to biochemical alterations. The metastatic potential of cancer cells is coordinated through cell-cell adhesion, cell matrix adhesion protrusion and contraction all of which require proper cytoskeleton regulation. Therefore, inhibiting the formation of the cytoskeleton is a promising strategy for the treatment of cancer metastasis. Lysine deprivation could completely block the proliferation of either p53-competent or p53-deficient cancer cells (24). Malnutrition can impair tolerance to chemotherapy and decreased response to treatment, leading to severe toxic side effects, decreased quality of life and ultimately shorter survival. Chemotherapy is the first therapeutic option for acute lymphocytic leukemia patients. In several studies were found that body composition changes only occurred during induction chemotherapy with an average weight-loss of 4.28%. Studies have shown that both cancer and its treatment exacerbate muscle loss and that patients suffer continuous muscle mass loss during treatments.

Glutamine, arginine and tryptophan are critical for the occurrence and development of leukemia and lymphoma, as well as immune regulation in the TME (24). Although glutamine is a nonessential amino acid, this is the most abundant in the human bloodstream and serves as an alternative energy source when glucose metabolism is blocked. Glutamine acts as a nitrogen donor for the *de novo* biosynthesis of both purines and pyrimidines and is a precursor for other amino acids such as proline, aspartate, serine and alanine (16).

The discovery of amino acids in plants, has been reported from a wide variety of plants; these are called non-protein amino acids (NPAAs). Some of them are similar to some of the 20 protein amino acids and are known as analogs; which can be incorporated into animal and human proteins. L- canavanine and sulforaphane are below mentioned (25).

SULFORAPHANE

Sulforaphane a natural compound derived from broccoli, has been proved to exhibit chemoprotective effects for various types of cancer, including prostatic cancer, lung cancer, leukemia, pancreatic cancer and colon cancer. Sulforaphane (SFN) has many properties such as anti- inflammatory, anticancer, cardioprotective, antioxidative, DNA protective and antimicrobial properties. The most important property is its potential against cancer. By inhibiting cancer cell proliferation, arresting the cell cycle and enhancing the process of apoptosis. Sulforaphane stall the activity of the enzyme histone deacetylase in cancerous cells.

Breast cancer metastasis is the main cause of cancer death in women. Proteomic analysis shown that SFN affected the formation of cytoskeleton. SFN inhibit the formation of actin stress fibers, thereby inhibiting breast cancer cell metastasis (26). Inhibitory effects of SFN have been shown in vitro treatment of HMEC-1 cells with SFN significantly decreased the formation of new microcapillaries., also inhibited lung metastasis of melanoma cells and oral carcinoma cells (27).

Broccoli sprouts are the chief source of sulforaphane and are 20 to 50 times richer than mature broccoli as they contain 1,153 mg/100g whereas mature broccoli is 44-171 mg/100g. Combination of sulforaphane and fluorouracil is more effective in enhancing the process of apoptosis than Polyamines and amino acids Ruiz fluorouracil alone. Several studies had showed that in combination with other agents is more effective, in cancer prevention compared to a single treatment. A study showed that sulforaphane, significantly reduced the progression of prostate cancer and disease severity after the broccoli soup.

Another study was observed that sulforaphane is highly effective in reducing serum prostate-specific antigen (PSA) levels. SFN exhibits notable anti-proliferative and pro-apoptotic properties on cancers such as prostate cancer, lung cancer, and osteosarcoma. SFN also suppresses histone deacetylase activity and increases acetylation of histones H3 and H4 (28).

For prostate cancer trials have used 60 mg/day for six months, while breast cancer studies have administered doses of 50-100 mg/day over 2 to 4 weeks. Numerous studies proved that sulforaphane can be used at various doses and in combination with other compounds without showing toxicity (29).

CANAVANINE

L-Canavanine is an analogue of arginine and acts as an antimetabolite

in many biological systems. - L-Canavanine is incorporated into proteins in competition with arginine because the tRNA is unable to differentiate between arginine and canavanine. Canavanine is an amino acid that is not part of animal proteins, but because of its structural similarity to arginine it takes its place and therefore affects the metabolism of arginine (30). The toxicity of canavanine is due to the fact that it inhibits protein synthesis and it has also been observed that the enzyme arginyl-RNA-synthetase facilitates the incorporation of canavanine into nascent peptides chains. Canavanine is incorporated into the nucleus of cell and into the cytoplasm it also interferes with the helix of DNA and RNA in formation L- Canavanine is an inhibitor of DNA and RNA synthesis; the inhibition is rapid causing structural and functional aberrations of the proteins involved in DNA replication. When 20 mg/hour of canavanine are administered for 24 hours, it inhibits 86% of DNA synthesis in mouse (31). L-canavanine is known to possess cytotoxicity to tumor cells in culture and experimental tumors in vivo. In this way shown that apoptotic cell death is associated with antitumor activity of l-canavanine against human acute leukemia (32). During apoptosis, a distinctive series of morphological changes occurs, which involves cell shrinkage, loss of cell-cell adhesion, membrane blebbing and chromatin condensation.

Glioblastomas are the most frequent and aggressive form of primary brain tumors with no efficient cure. Arginine deprivation was evaluated in vitro on a glioblastoma based on canavanine. The treatment profoundly affected cell viability, morphology, motility and adhesion, destabilizing the cytoskeleton and mitochondrial network; and induced apoptotic cell death. Importantly, the effects were selective toward glioblastoma cells, as they were not pronounced for primary rat glial cells. It has been observed that numerous cancers are defective in arginine biosynthesis and some of they become hypersensitive to the deprivation of this amino acid. Canavanine across the brain-blood barrier; it is transported by the same carriers as arginine thus increasing the feasibility of a potential prospective therapy. Furthermore, the number of death cells was noticeably increased after 48h of treatment with 100 µmol canavanine (33). It was observed that 12.6% of all arginine sites were occupied by canavanine after culturing cells in media with 50umol canavanine for 48h (34).

Dietary strategies for cancer therapy.

The World Cancer Research Fund estimates that 30% - 40% of cancer can be prevented by healthy dietary regimens improved physical activity and maintenance of appropriate body weight. Prostate cancer studies and breast cancer have shown results when certain life style factors are associated with the progression of malignancy.

The efficacy of cancer treatment is determined by its interaction with biochemical pathways. When choosing a nutrition plan, it is important to consider factors such as the type of cancer, current treatment, age, sex, lifestyle and any known genetic mutations. From the standpoint of energy expenditure and anabolism for cell growth; amino acid restriction might be an effective metabolic intervention for cancer since the energy expenditure (ATP) of amino acid metabolism is up to 58% for protein and nucleotide syntheses. Lysine rather than leucine is likely the amino acid which deprivation cell proliferation is the most sensible to at cell and disease levels, the magnitude of lysine value was demonstrated by that lysine restriction completely blocked the proliferation of cancer cells, and that lysine deficiency caused human childhood malnutrition disease-kwashiorkor. Therefore, restriction of lysine might have a potential as a practically available dietary strategy for cancer therapy. Several studies have shown that just reducing methionine by 30 – 40% can benefits reducing their meat will lower methionine significantly. Foods amino acid composition can be found on the website of the Food and Agriculture Organization (FAO) of the United Nations, including amino acid content of foods and biological data on proteins.

Cancer cells have higher nutrient demands than normal non-malignant cells due to their accelerated metabolic and proliferation rates. Some of them become auxotrophic for arginine and depend on the exogenous supply of this amino acid. By now, the therapeutic potential of arginine deprivation has been established in clinical trials for melanomas and hepatocellular carcinomas trials and other ASS1-deficient malignances are underway e.g. leukemia, lymphoma, prostate cancer and others. Canavanine treatment upon arginine deprivation, is not toxic for normal colon epithelium (35).

Dietary intake of polyamines showed an alternative path for the treatments of various health disorders. Therefore, the optimized dietary methods can be applied along with clinical applications against fatal diseases for maintaining good health. When choosing a nutrition plan, it is important to consider factors such as the type of cancer recurrent treatment, age, sex, lifestyle and any known genetic mutations.

It is recommended to use amino acids that restrict the synthesis of polyamines mainly; when eliminating some foods that contain methionine and polyamines the patient recovers faster; also, it is recommended to eat vegetables that contain analogous amino acids such as broccoli and cabbage that contains sulforaphane. Lentils and great beans that contain canavanine which affects cellular metabolism. In conclusion, amino acid restriction could be a common and effective metabolic intervention for cancer since the amino acid metabolism could use up to 58% of the total ATP for protein synthesis and RNA/DNA synthesis. In this way, the side effects are reduced because the doses of chemotherapy drug can be reduced because in this way cell division decreases and apoptosis increases at lower doses and the patients recovers faster.

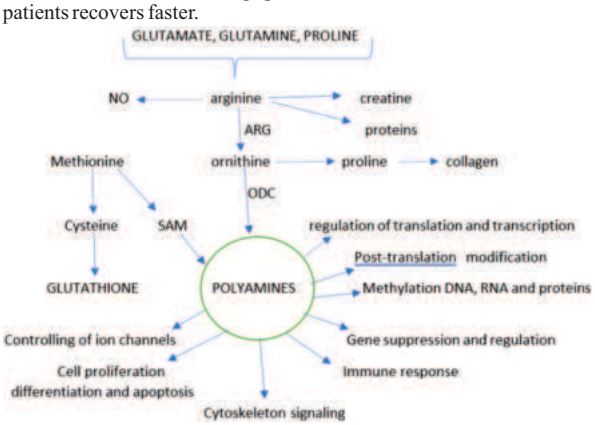

Figure 1. Synthesis and biological functions related to polyamines.

ODC- ornithine decarboxylase, SAM- S-adenosyl methionine ARG- arginase, NO- nitric oxide

REFERENCES

1.- Babbar N, Gerner EW. Targeting polyamines and inflammation for cancer prevention. Recent Results Cancer Res. 2011; 188: 49-64.
2.- Chakradar V, Rammath L. Polyamines: potential anti-inflammatory agents and their possible mechanism of action. Indian J Pharmacol. 2008; 40: 121-125
3.- Alok SN, Tarafdar S, Agarwal S, Tarafdar A, Sharma S. Polyamines: Functions, metabolism and role in human disease management. Med Sci. 2021; 9(2): 44; doi. 10.3390/medsc9020044.
4.- Nicoletta RM, Cervelli M. Polyamine metabolism and functions: Key roles in cellular health and disease. Biomolecules. 2024; 14: 1570; doi.org10.3390/biom14121570
5.- Mahaligan SS, Pandiyan P. Polyamines: Key players in immune metabolism and immune regulation. J cell Immunol. 2024; 6: 196-208
6.- Holbert EC, Cullen TM, Casero AR Jr, Murray ST. Polyamines in cancer: integrating organismal metabolism and antitumor immunity. Nat Rev Cancer. 2022; 22: 467-480
7.- Sun JX, Man N. An Y, Numer DS, Wang L. The role of histone acetyltransferase in normal and malignant hematopoiesis. Front Oncol. 2015: doi:10.3389/fonc.2015. 00108.
8.- Liu He, Liu Ye, Xiao Z, <wang X, Ni Q, et al. Anti-tumor potential of polyamines in cancer. Acta Bioch Bioph Sinica. 2025, doi:.org/10.3724/abbs.2025030
9.- Cheu Y, Leon LRA; Abdel SAH, Vykon Kal J. C-MYG-driven polyamine metabolism in ovarian cancer: From pathogenesis to early detection and therapy. Cancers. 2023; 15:623. Doi: 10.33%/cancers 15030623.
10.- Hernando RO. Rubio RMC. Nutricion y cancer. Nutr Hosp. 2015; 32 (Supl-1): 67-72
11.- Yi MC, Ling FY, Abu LA, Yang X, et al. Dietary polyamines intake and risk of colorectal cancer: A case control study. Nutrients; 2020; 12: 13575. Doi: 10.3390/nu12113575.
12.- Nowotarski ES, Woster MP, Casero Jr AR. Polyamines and cancer: implications for chemoprevention and chemotherapy. Expert Rev Mol Med. 2013; 15e3. doi: 10.1017/erm.2913.3
13.- Lieu LE, Nouven T, Rhyne S, Kim j. Amino acids in cancer. Exp Mol Med. 2020; 52: 15-30
14.- Sheng-Kang J. Dietary restriction of amino acids for cancer therapy. Nut Metab. 2020: 17: 20-41.
15.- Lin CC, Chieh HS, Ann KD, YY, Jien KH. Arginine signaling and cancer metabolism. Cancers. 2021; 13: 3541. Doi: 10.3390/cancers 13143541
16.- Gilinsky AM, Polityko KY, Markel lA, Latysheva VT, et al Norvaline reduces blood pressure and induces diuresis in rats with inherited stress-induced arterial hypertension. Bio Med R Inter. 2020. Doi.org.10.1155/2020/4935386
17.- Gandara MJA, Lares AI, Reyes EEA, et al. L-asparaginasa en el tratamiento de la leucemia linfoblástica aguda, sus efectos adversos y oportunidades en la optimización del tratamiento. Rev Hematol Mex. 2023; 24: 145-162.
18.- RC, Hamilton RJ, Martindale GR, Sarav M, Et al. Acquired amino acid deficiencies: A focus on arginine and glutamine. Nutrition Clin Pract. 2017; 32: 30-47
19.- Uranaka H, Akinsola R, Billet S, Pandol JS, et al. Glutamine supplementation as an anticancer strategy: A potential therapeutic alternative to the convention. Cancers; 2024 16(5): 1057, doi: 10.3390/cancers 16051057.
20.- Liao P, Chang N, Xu B, Qiu Y. et al. Amino acid metabolism: challenges and opportunities for the therapeutic treatment of leukemia and lymphoma. Immunol cell biol. 2022; 100: 507-528
21.- Gray A, Dang NB, Moore BT, Clemensressman P. A review of nutrition and dietary interventions in oncology. Sage Open Med. 2020; 8, doi: 10,1177/20503120926877.

22.- Sivaganesh V, Scandon Ch, Iskander A, et al. Protein tyrosine phosphatases: mechanisms in cancer. Int J Mol Sci. 2021; 22: doi: 10.3390/ijms222312865.
23.- Wanders D, Hobson K Ji X. Methionine restriction and cancer biology. Nutrients. 2020; 12: 684-693
24.- Jones LC, Stevens MB, DÁlessandro A, Reisz AJ, Hill CR et al. Inhibition of amino acid metabolism selectively targets human leukemia stem cells. Cancer Cells. 2018: 34: 724-740
25.- Nunn BP, Bell AE, Watson AA, Nash JR. Toxicity of non-protein amino acids to humans and domestic animals. Nat Product Commun. 2010; 5: 485-504
26.- Bayat MR, Baluch N, Homayouni ST, Morgatskaya E, et al. The role of sulforaphane in cancer chemoprevention and health benefits a mini-review. J Cell Commun Signal. 2017; 12: 91-101.
27.- Mohammad DS, Rahimzadeh P, Farahani N. Sulforaphane in alternative cancer chemotherapy: From carcinogenesis suppression to drug resistance reversal. Results Chem. 2025 Doi.org/10.1016/j.rechem.2025.102059
28.- Vanduchova A, Ansenbacher P, Anzenbacherova E. Isothiocyanate from broccoli, sulforaphane and its properties. J Med Food. 2019; 22: doi.org/10.1089/jmf,2018.0024
29.- Asif AM, Khan N, Kaleen N, Ahmad W, et al. Anticancer properties of sulforaphane: current insights at the molecular level. Front Oncol. 2023; 13: doi: 10,3389/fonc,1168321
30.- Staszek P, Weston LA, Clacka K.et al. L-canavanine: How does a simple non-protein amino acid inhibit cellular function in a diverse living system?. Phytochem Rev. 2017; 16 (5). DOI:10.1007/s11101-017-9536-y
31.- Bence AK, Worthen DR, Adams VR, Crooks PA. The antiproliferative and immunotoxic effects of L-canavanine and L-canaline. Anti-cancer drugs. 2002. 13:313-320
32.- Lopez MB, Gutierrez RM, Ruiz BE. Evaluación del amino acido L-canavanina como tratamiento coadyuvante en leucemias agudas linfoblásticas. Rev Hematol Mex. 2015; 16: 3-8
33.- Kurlishchuk Y, Vinnytska B, Grosse GP, et al. Co-application of canavanine and irradiation uncouples anticancer potential of arginine deprivation from citrulline availability. Oncotarget, 2016; 7: 73292-73308.
34.- Thomas DA, Rosenthal GA. Metabolism of L(guanidinoxi-^{14}C) canavanine in the rat. Toxicol Appl Pharmacol. 1987; 91: 406-414
35.- Karatsal O, Shlaha P, Jensen ON, Stasyk O, Redowicz MJ. Combinatory treatment of canavanine and arginine deprivation efficiently targets human glioblastoma cells via pleiotropic mechanism. Cells, 2020; doi:10.3390/cells 9102217.