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DIETARY POLYAMINES AND DISEASES: REDUCING POLYAMINE INTAKE CAN BE BENEFICIAL IN CANCER TREATMENT

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ABSTRACT

Polyamines are most abundant polycationic natural amines and involved in several physiological processes. They can be supplied by the endogenous synthesis inside the cell or by the intake from exogenous sources. The polyamine content of cells is regulated by biosynthesis, degradation, uptake and excretion. The benefits of dietary polyamines can be changed; they may be harmful, neutral or beneficial. For example, increasing the amount of dietary polyamines is suggested during rapid growth, such as during the neonatal period, wound healing and after surgery. However, in cancer patients, reducing polyamine dietary intake has been shown to be beneficial on the quality of life. This review aimed to evaluate the effect of dietary polyamines in health and disease.

Keywords: Dietary polyamines, Nutrition, Human health, Disease.

Contribution/ Originality

This study contributes in the existing literature by providing a detailed information on the importance of dietary polyamines in health and diseases. This study also highlights the beneficial impact of low polyamine diet on cancer treatment, and helps to increase awareness of daily polyamine intake regarding individual requirements.

1. INTRODUCTION

Since their discovery, the cellular functions of the physiological polyamines (putrescine, spermidine, and spermine) have been the focus of many studies. The naturally occurred polyamines are derived from ornithine; putrescine (tetramethylenediamine), spermidine (aminopropyl-tetramethylenediamine) and spermine (diaminopropyl-tetramethylenediamine). They are most abundant polycationic natural amines, distributed widely in biological material and are protonated with four (spermine), three (spermidine) and two (putrescine) positive charges at intracellular pH. Therefore, they tend to bind anionic cellular components such as nucleic acids,

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membrane phospholipids and enzymes [1]. The polyamines spermine, spermidine and putrescine are naturally present in all cells and their cellular functions are widening starting from DNA stabilization and regulation of gene expression to ion channel function and, particularly, cell proliferation. They play an essential role in rapidly dividing cells such as in the immune system and digestive tract as well as involved in carcinogenesis.

The body pool of polyamines is maintained by three sources; endogenous or *de novo* biosynthesis, intestinal microorganisms, and exogenous supply through the diet. As a result, the intracellular polyamine content is the consequence of the simultaneous regulation of their synthesis, catabolism and transport [2]. The external dietary source provides a larger quantity of polyamines than the endogenous biosynthesis. Therefore the nutritional polyamines may be important for metabolism in terms of the results for human health.

2. DIETARY POLYAMINES

Food is an important source of dietary polyamines. The polyamine content of foods is extremely wide ranging from a few nanomoles to a few micromoles per gram. Seasonal variations, their origins, planting-husbandry methods, soil character, climate, process of foods, stock conditions cooking-preparing styles, and analysis methods are effective on polyamine concentrations in foods [3-7]. Up to date, the amount of food polyamines was listed on a number of studies [8-28]. In general, meat is rich in spermine, plant based foods contain mostly putrescine and spermidine, dairy products include mainly putrescine and spermidine, and among them, cheeses have higher polyamine values depending on fermentation conditions.

Dietary polyamines are one of the major sources for body pool. In the intestinal lumen, they are absorbed quickly and distributed to all organs and tissues as shown in radiolabelling studies in rats [28]. Continuous intake of polyamine-rich food gradually increases blood polyamine levels. The normal adult diet provides a daily supply of several micromoles of polyamines. The estimated values for the daily polyamine intake in different studies vary between 250 to 700 μmol. The mean dietary intake of polyamines has been estimated in several studies [19, 29-32]. However, the optimum dietary intake of polyamines has not been identified yet. In Europe, a higher intake of total polyamines (700 μmol/day) was reported in the Mediterranean regions compared to UK and northern Europe (350–500 μmol/day) [10]. Although the values differ from each other, the percentage distribution of daily polyamine intake resulted in the level of each polyamine having a similar pattern in different populations; from the highest to the lowest, contribution rose from putrescine, spermidine and spermine [30-32].

3. POLYAMINES IN DISEASES

3.1. Dietary Polyamines in Health and Diseases

Dietary polyamines are a part of polyamine body pool. Thus, diet can have a role on regulation of polyamine biosynthesis. Any distortion of polyamine metabolism results in various

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pathological conditions including cancer [33, 34], inflammation [35], stroke [36, 37], renal failure [38] and diabetes [39]. The differences in the dietary food polyamines have been demonstrated to associate with the incidence of chronic diseases [40].

There are several studies to report that dietary polyamines promote carcinogenesis in animal and human [41-44]. There is a close relation between polyamine catabolism and tumor development [41]. Increased amounts of polyamines in the urine of human cancer patients were first reported by Rusel [45]. Polyamines were identified as participating in almost all stages of tumorigenesis. Enhanced levels of polyamines and polyamine biosynthetic enzymes, ornithine decarboxylase and S-adenosylmethionine decarboxylase are often associated with hyper-proliferation and cancer. The activities of ornithine decarboxylase and S-adenosylmethionine *decarboxylase* and then polyamines increased in rapidly growing cells and tumor cells [46]. Therefore polyamines can be used as a target for potential chemotherapeutic agents [47]. Polyamines are useful indicators of the eficacy of chemotherapy [48]. Prostate cancer is linked to chronic or recurrent inflammation [49]. In particular, the initiation of prostate carcinomas appears to be associated with inflammation followed by a hyper proliferative state [50]. Battaglia, et al. [47], suggested that polyamine catabolism represents a promising target for chemoprevention or chemotherapy [47].

Polyamines exert a suppressor effect on pulmonary immunologic and intestinal immunoallergic responses and are involved in differentiation of immune cells and in regulation of inflammatory reactions. Furthermore, inflammation is involved in all stages of carcinogenesis. Inflammatory bowel disease, such as ulcerative colitis and Crohn's disease is a longstanding inflammatory disease of intestine with increased risk for colorectal cancer [51]. Polyamines, with anti-inflammatory properties, have roles on inhibiting age-associated chronic diseases and prolong longevity [52]. Strong anti-inflammotory function of polyamines causes inhibition of chronic inflammation, which is one of the main symptoms of geriatric diseases. Intracellular production of polyamines and their concentrations in tissue and organs decrease with aging [20, 53]. Therefore, intake of exogenous polyamines may be beneficial in the treatment of some geriatric diseases. Dietary polyamines have been reported to be beneficial for aging and their levels decline continuously with age. Polyamine supplementation increases life span in various living organisms including mammals. Spermidine is a new longevity drug that can increase life span in yeast, nematodes and flies, possibly through an effect on the regulation of gene expression [54]. The age-related beneficial effects of spermidine demonstrated to improve locomotor performance in aged flies [55]. In human, Binh et al, indicated a close positive correlation between increased polyamine intake and increased components of healthy dietary pattern for the food polyamines that are abundant in the Mediterranean diet in prolonging life [56]. Specifically spermidine supplementation has been found to improve arterial aging, promising nutraceutical treatment for arterial aging and prevention of age-associated CVD [57].

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The importance of polyamines in the maintenance of intestinal function is well-documented [58-60]. Polyamines are shown to play an important role in the regulation of gastrointestinal mucosal growth and healing after injury under physiological and various pathological conditions. Polyamine levels generally increase with inflammation. The intestinal mucosa is able to repair itself by restitution or replacement of lost cells by cell division. Polyamines are essential for these repair processes. Polyamines have been also involved in inflammatory responses. Lagishetty and Naik reported that exogenous polyamines administered by subcutaneous route exhibited anti-inflammatory activity in acute and chronic inflammation [61]. Kibe et al reported that oral intake of arginine, one of the polyamine precursor, with the probiotics increased the concentration of putrescine in the colon and of spermidine and spermine in the blood via upregulation of polyamines produced by intestinal microbiota and this caused senescence delay in mice [62]. Polyamines play a crucial role in the intestinal permeability which is related to Crohn's disease, ulcerative colitis and Celiac disease. Intestinal ephitelium is impermeable to macromolecules, but gliadin in celiac disease patients in physiological conditions. Their positive charges allow polyamines to form bridges between distant negative charges, resulting in unique effects on permeability. Gluten-induced damage on epithelial mucosa can be prevented by cellular polyamines via maintaining epithelial integrity [63, 64]. Moreover, gluten free diet has been shown to improve the condition of some people with psoriasis indicating the gastrointestinal tract might be involved [65]. Broshtilovo reported that a comparison of non-lesional skin and psoriatic lesions in psoriatic patients demonstrated two-time higher levels of the most essential biogenic polyamines compared to healthy controls. The highest concentration belonged to spermine that may prove the crucial role of adenosine methionine decarboxylase in the polyamine metabolism changes in psoriasis [66].

Glycation plays an important role in the genesis of diabetic complications. Spermine and spermidine have been shown to display a significant antiglycation effect at physiological concentration suggesting the role for polyamines in diabetes [67]. Many of the secondary complications of diabetes result from protein glycation and oxidation mediated by agents and processes against which carnosine may protect [68, 69]. Additionally there are a number of observations which suggest an inverse relationship between diabetes and carnosine.

Polyamines have been implicated in the pathogenesis of ischemic brain damage. For example, polyamine biosynthesis increased after the onset of cerebral ischemia through an induction of ornithine decarboxylase, a key enzyme in the polyamine biosynthetic pathway. Makletsova, et al. [70] proposed a mechanism of carnosine influence on polyamine metabolism indicating that the addition of carnosine to the treatment protocol for chronic brain ischemia promoted the normalization of the content of putrescine and spermine which is accompanied by improvement in cognitive functions of the brain. Polyamines play an important role in brain development, mature brain function and also in neurodegenerative conditions. Endogenous polyamine levels are altered in dementing illnesses such as Alzheimer disease and Down syndrome [71]. An inherited human

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disease, Snyder-Robinson syndrome, an X-linked mental-retardation and developmental disease is caused by an alteration in the *SpmS* gene that encodes spermine synthase [72, 73].

Polyamines putrescine, spermidine and spermine play a role in cell growth and proliferation in human cell. However, their participation during wound healing has also been of great interest. This can be important for post-operation patients [74]. Arginine has been shown to enhance wound strength and collagen deposition in artificial incisional wounds in rodents and humans. A role for dietary intervention in the form of arginine supplementation has been proposed to normalize or enhance wound healing in humans [75].

Polyamines are also important in diseases such as pancreatitis. Among organs, pancreas has the highest levels of spermidine in mammals. Acute induction of spermidine/spermine N^1-acetyltransferase, the key regulatory enzyme for polyamine catabolism, leads to pancreatic inflammation, suggesting that sufficient pools of higher polyamine levels are essential to maintain pancreatic integrity [76].

3.2. Reduced Polyamine Diet in Favor of Cancer Patients

Several studies are subject to reduced polyamine diet in favor of cancer patients. However, reductions in blood polyamine concentration were not achieved only by restricting oral polyamine intake since exogenous polyamines can be supplied by foods and intestinal microbiata. Therefore, it should be noted that decrease in blood polyamine levels achieved both by restricting food polyamines and by eliminating intestinal microbiota beside of inhibiting metabolic enzymes [77].

A polyamine-free diet has been shown to increase the efficiency of difluoromethyl ornithine, a chemotherapeutic agent that inhibits ornithine decarboxylase, in animal model of cancer indicating that inhibition of polyamine uptake via the polyamine transporter [33, 78]. A polyamine blocker therapy applied to explore the role of tumor-associated polyamines as immunosuppressive metabolites in oncogenesis and tumor progression and resulted that the applied therapy did not only block tumor growth but also promoted anticancer immune responses [79]. In prostate cancer patients it was shown that the reduction of dietary polyamine intake and partial intestinal decontamination was beneficial for patient quality of life and pain control [80].

In a study to assess the tolerance and side effects of polyamine-free oral nutritional supplement (2500-fold reduction of daily dietary polyamine intake) combined with intermittent gut decontamination in a Phase I trial was safe, well tolerated with no major toxicity and had beneficial effects on the quality of life and control pain [81]. Polyamine-deficient diet seems to be effective as a pain relief treatment for both chronic and acute pain [82, 83]. A synthetic polyamine-deficient diet showed a significant general analgesic effect for the treatment of inflammatory pain [84]. Oxaliplatin is used for the treatment of advanced colorectal cancer but also caused painful peripheral neuropathies. Ferrier at al. reported that polyamine deficient diet could represent a promising and valuable nutritional therapy to prevent oxaliplatin-induced acute pain hypersensitivity [85]. In addition, long term feeding of polyamine deficient diets resulted in

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a significant hypoplasia of small intestinal and colonic mucosa. Virtually, dietary luminal polyamines are important local factors for growth and the development of small intestinal and colonic mucosa [86]. Rats fed a polyamine-deficient chow survived longer an infection by *Trypanosoma brucei brucei* and were found less anemic [87]. From the interaction between dietary polyamines and treatment with a combination of difluoromethyl ornithine and sulindac on adenoma recurrence study it was suggested that controlling exogenous polyamines could be an adjunctive strategy to therapeutic prevention using polyamine-inhibitory agents [88]. Moreover, dietary putrescine reduced the ability of sulindac to suppress intestinal tumorigenesis in the mouse model suggesting that reducing polyamine metabolism and dietary polyamine levels might enhance strategies for colon cancer chemoprevention [42]. Consuming low polyamine diet and reducing bacterial gut production improved performance status and pain control in hormone refractory prostate cancer patients [80, 89]. The association between high dietary polyamine intake and risk of colorectal adenoma was provided in literature [90, 91].

4. CONCLUSION

Although there are enormous number of studies and reviews reporting the relation between polyamines and diseases, the role and depth effect of exogenous polyamines is not sufficiently clear. An increase of polyamine level has been reported in cell growth and proliferation, tumor cells as well as polyamine intake from foods and gut microbiata. However, the contribution of exogenous polyamines to the level of cellular polyamines is not certain. What is clear from publishes is that the concentration of polyamines rises following food intake. Therewithal, epidemiological studies show the close positive or negative correlation between increased polyamine intake and diseases. Their benefits can be changed depending on the specific polyamine and disease; they may be harmful, neutral or beneficial. Due to the dietary polyamines seem to be having both adverse and beneficial effects on human health it seems that a reliable polyamine database from foods and the surveys on daily intake of society will provide enormous information to direct people for proper daily polyamine diet. On the other hand, it is necessary to take into consideration the amount of dietary intake for each food item to arrange high or low polyamine diet, however data on the amount of polyamines in foods are not accurately established.

Considering health and wellness benefits, dietary polyamines seem to be important in human health and diseases, therefore daily dietary intake of polyamines should be carefully evaluated depending on individual requirement.

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