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Assaultive Role of Thiamine in coalition with Selenium in treatment of liver cancer

Alisha Rawat*, Meenakshi Sajwan[1], Yamini Chandola[2] Nidhi Gaur[3]

[1]Himgiri Zee University, Dehradun, Uttarakhand, India. bisht84meenakshi@gmail.com

[2]Himgiri Zee University, Dehradun, Uttarakhand, India. yamichandolasemwal10@gmail.com

[3]Himgiri Zee University, Dehradun, Uttarakhand, India. nidhigaur1418@gmail.com

*Correspondence to Author
Dr. Alisha Rawat
Associate Professor
GRD (PG) IMT.
Dehradun, Uttarakhand
Pin code: 248001
India
alishanegi7115@gmail.com

Abstract: Alarming rate of up thrust in incidences of liver cancer, holding second position worldwide had revolved the interest of many research scholars in finding more eminent ways in treatment of liver cancer. Despite acknowledging the fact that first line of treatment involves all surgical methods, additional use of therapeutic regime has always been the focus to prolong the survival rate in cancerous patients. Role of Selenium and augmentation of its effects through implementing thiamine both at supranutritional levels may prove to be a new therapeutic approach in treatment of liver cancer.

Keywords: liver cancer, nutritional resources, Thiamine, Selenium, improved prognosis.

Introduction:

Pernicious effects on patients with hepatocellular carcinoma and increasing frequency across the board had made it a serious concern globally (1). The majority of Hepatocellular carcinoma cases are due to chronic viral B and C hepatitis infections. Men have an incidence of 11.5 per 100,000 compared to 3.9 in women. Hepatocellular carcinoma death rates have also increased by 2.8% for males and 3.4% for females, per year (2). In recent years new surveillance strategies in patients at a higher risk of HCC have led to the diagnosis of the disease at much earlier stages. Patients in early stages have a much higher chance of curative response with different treatment options (3, 4). More clinical trials evaluating new therapies and multimodal regimens are necessary to help clinicians, design better treatment algorithms and improve outcomes (5). This insight has paved the way of finding more progressive therapeutic strategies producing less side effects in cost effective manner, had taken our attention of using nutrients at supranutritional levels to provide symptomatic relief along with supportive care for various hepatocellular cancer sufferers.

Selenium as a potential antineoplastic agent

The inherent quality of selenium can be the stepping stone to generate selenium based front line chemotherapeutic drug against ever evolving disease landscape of cancer. Not only as a therapeutic agent, but also in supportive care this essential micronutrient may be a good supplement to balance redox homeostasis and boost up patients immunity. (6) Supranutritional dietary level of Se ensures proper antioxidant and anticancer defence and as a result, normal functioning of immune and nervous systems. (7) Trace amounts of Se are required for maintaining optimal health as Se is a component of the selenoproteins (mostly in the form of amino acid selenocysteine) that participate in a wide range of cellular physiological processes. These processes includes (8), redox homeostasis (9, 10), inflammatory and immunological responses (11), carbohydrate metabolism (9), cardiovascular (10) and reproductive (11, 12) health, and brain function maintenance (13–15).

Possible mechanics of selenium as anticancer agent

Five hypothesis soo far seems to be possible to account for selenium's chemo preventative activity although none have been conclusively shown to be the sentinel effector. Most accepted hypotheses posptulating to account for selenium's anti-carcinogenic properties include; Selenium's antioxidant role as a component of the glutathione peroxidase enzymes (16) , Selenium's enhancement of immunity (17), Selenium's effect on the metabolism of carcinogens (18), Selenium's interactions that affect protein synthesis and the cycle of cell division (19), and the formation of anti-cancer selenium metabolites (20).

1) Glutathione Peroxidases an important selenium constituent:

Numerous research data have stated about the antioxidant property of selenium compounds comprising glutathione peroxidases act as potential cancer inhibitor along with healing effect on various heart disease and viral infections owing to the antioxidant role of the enzymes (21).
Glutathione peroxidase along with phospholipid hydroperoxidase (22) and thioredoxin reductase (23) contribute to major antioxidant effect of dietary selenium compounds. As free radicals accounts for greater possibility of inducing or promoting cancer and hence antioxidant capacity of selenium can serve the role (24). Selenium with its different classes of cytosolic glutathione peroxidase has been found to significantly reduce protein damage to cells or organelles along with preventing effect on DNA damage through free radicals (16). Henceforth it can be stated that the dietary selenium over supranutritional levels can improve the prognosis in cancer sufferers.

2) Selenium in relation to Immune responses.

Researches has frequently been justifying the positive involvement of selenium in producing various immune responses. Various experimental data gives the evident proofs on role of selenium as dietary selenite (17) to produce antibodies against various antigen antibody reactions (25). T cells and NK cells were found to significantly respond and enhance their activity in influence of selenium derivatives. (26, 27). Numerous animal studies have extrapolated the elevated responses of immune system along with stimulating interleukins and various T- cells genes in presence of selenium compounds (28).

Selenium effect on carcinogens metabolism

Other possibility making selenium a potential anticarcinogenic agent is its effect on metabolic by products of carcinogenic agents. Selenium introduced through diet or through metabolism of its in human system is been found to interact with various toxic carcinogenic metabolites thereby rendering them inactive or hindering their binding to various DNA molecules [18]; DMBB and aflatoxin (29) are example of such derivatives which were rendered non carcinogenic by the effect of selenium compounds. Selenium moiety has also been found to noticeably alter liver profile, hydroxylating enzymes, cytochrome P450 thereby modify the chemical structure of carcinogens and making them expelled from the system and preventing DNA damage triggered by them (30).

4) Reparative changes in Cell Cycle and Protein Synthesis

In vitro cell culture studies have revealed many selenium compounds to convincingly show substantial effects on cell viability, cell cycle and protein synthesis thereby maintaining the integrity of DNA (18, 31). Selenite at low doses has also shown results reducing GSH: GSSG ratio through oxidation of Glutathione; thereby arresting cell cycle in cancerous cells at G_1, G_2 and S phase of cell division and protein synthesis (32). Selenium oxidise the thiol (SH) group of various metabolic enzymes in cancer cells; arginase, urease, thioredoxin reductase (33), protein kinase C (34) thereby inhibiting cancer cells reproducibility rendering apoptosis o cancerous cells (35). Many other selenium derivatives like selenium glutathione (36), methyl selesinic acid (37, 38) and methyl selenocysteine (38) all have shown their alternative effects on cell cycle, protein formation and synthesis. Changes in redox status of cells rules out to be one of the major mechanics involved in it.

5) Formation of nontoxic Selenium's carcinostatic metabolites

Last most powerful hypothesis states about the possibility of formation of dietary selenium into the system contributing to selenium's carcinostatic property [40]. Consumption of selenium in diet has shown to break up into metabolites such as hydrogen selenide (H_2Se) in reduced state which in turn gets attached to carcinogenic elements in the cells rendering them non- toxic or carcinostatic [41].

Possibilities of using Thiamine as anticancer agent:

Vitamins have always been considered as one of the key ingredient involved in treatment regimen of various cancers, hence introducing vitamins supplement in cancer prognosis have marked some improvement in such patients. Thiamine has always shown noticeable coalition in cancer sufferers; low level of thiamine has always been reported in various serum samples of study models. Enormous hypothesis have been into studies syndicating the involvement of thiamine in cancer status of varied groups of clinical subjects. Some of them under consideration involves, Solute carrier transporters (SLC 19) gene, Transketolase (TKT) enzymes, P53 factor, ADP ribose polymerase 1 gene, reduced forms of NADP.

Other components of cell such as matrix metalloproteinases, Prostaglandins, cyclooxygenase -2, Reactive oxygen species and Nitric oxide synthase are also markedly effected by presence of supplemented thiamine. Beside the fact that thiamine deficiency has always been observed in cancer patients. Its clear role and involvement has always been debatable, apart from diverse research data [42, 43].

Factors showing association of thiamine with cancer

The solute carrier (SLC) transport protein.

SLC comes from the transporter protein class have different isoforms binding different substrate with different sites of protein (44). Their essential role showing their involvement in thiamine metabolism comes up with their prototype genes SLC19 A2 and SLC 19 A3 showing its role in folate homeostasis and thiamine transport in the body (45, 46). Inclusion of SLC19A3 gene in regulating thiamine exogenously and its frequent overexpression in varied cell lines have also been a justification towards collation of thiamine in various cancers(47); such as gastric cancers cells(47), breast cancer (48,49) along with inhibiting resistance to apoptosis in different types of tumor.(49). Henceforth SLC19 genes expression is also considered as a biomarker in various forms of tumor diagnosis (50). SlC19A2 and its other polymorphic forms are also been shown to be part of active transport of mono and pyrophosphate derivatives of thiamine molecules (51, 52).

Transketolase

Participation of thiamine has been seen in various coenzymes such as transketolase, pyruvate dehydrogenase (PDH) and αketoglutarate dehydrogenase complexes, all involved in intracellular metabolism of glucose. Thiamine has acted as a cofactor for different forms of metabolic and energy releasing reactions intracellularly. Deficiency of thiamine is recorded to effect underexpression of mRNA genes locus for transketolase and PDH enzymes (53) synthesis. Blood levels of cancer patients have always been examined with reduced concentration of thiamine and thiamine diphosphate (TDP) to approximately 20-45% of their

normal levels (54). TKT enzyme and its subtypes like TKT L-1expression has been reported for various forms of cancer (55) and affecting one of the mostly used pentose phosphate pathway(PPP) which is being rigorously exploited by cancer cells, precisely non oxidative phase of PPP (56) which ultimately leads to poor prognosis of cancer subjects (57). Increase TKT L-1 levels have been identified for various types of cancers; thyroid cancer (68, 69), nasopharyngeal cancer (58, 59), colorectal cancer (60) and many more under study. Hence these data gives us an overview of thiamine and its significant role in cancer.

Transcription factor p53

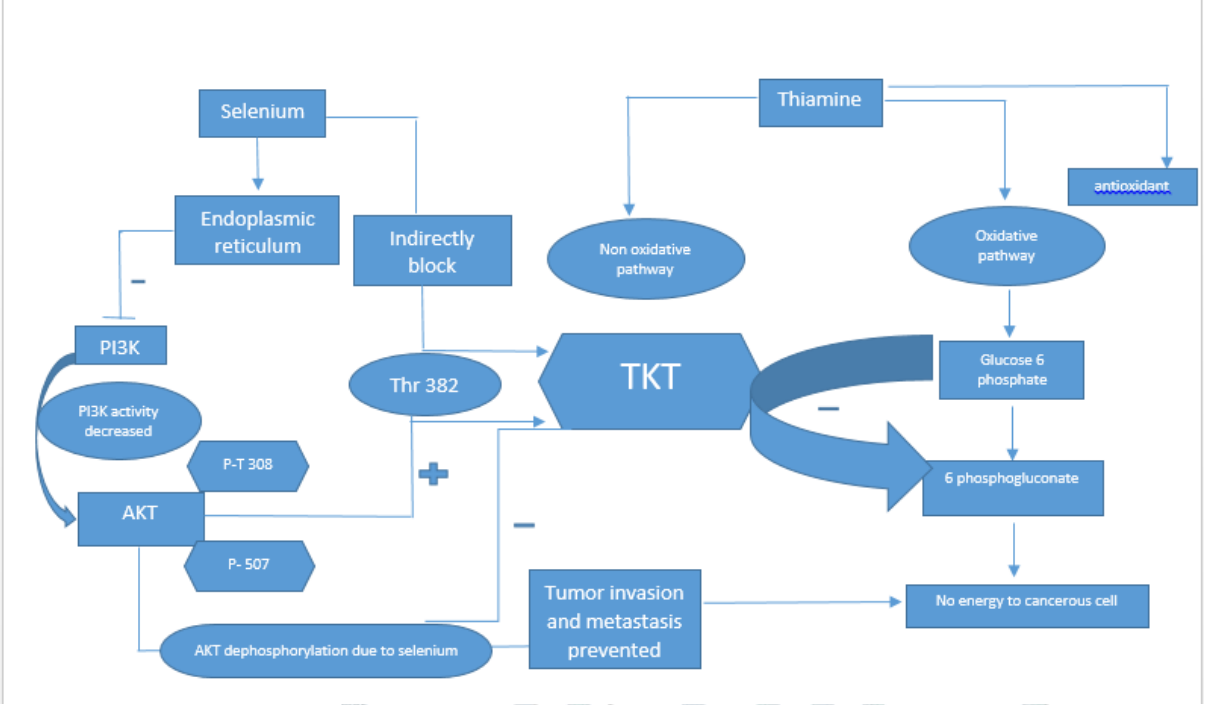
Transcription factor p53 hold one of the important activator's place in regulation of cell cycle, its arrest and various stages of apoptosis. Its considerable association also determines the shelf life of surviving cells with the extent of DNA damage if any. Various oncogenetically activated cancer cells have been seen to be remarkably obstructed by p53 genes and its prototype transcription factors as an immune response of the body. Genetic makeup of p53 genes and its polymorphic forms are dramatically been altered in varius types of cancer (61) such as breast cancer, cervical cancer (62) to name some. Thiamine transporters SLC19A2, TDP all are involved in regulating intracellular binding of p53 (63), henceforth managing p53 activity and DNA Damage in cancer cells (64).

Poly (ADP-ribose) polymerase-1 (PARP-1)

PARP 1 plays an instrumental role in context of both cell survival and cell death. PARP 1 gene comes into action when activated by breakage in DNA strands. PARP 1 is a nuclear protein whose deficiency sensitize the cells to various carcinogens such as ionizing radiations, alkylating agents (65). PARP 1 deficient mice have been reported to develop mammary and liver tumor more reluctantly as compared to normal control groups (66, 67). Dietary thiamine and its analogs have been seen to provide cytoprotective effects on various cell culture models such as cardiomyocytes (68) by strikingly hindering PARP division and DNA putrification (69, 70). Another thiamine analogy adenosine thiamine triphosphate (ATTP) have also been reported to retard and obstruct PARP1 activity in mouse models of isolated brain, heart, skeletal muscle, liver and kidney (71). Adding to this facts have been stated demonstrating NADPH oxidase (NOX) complexes involvement in various physiological functioning and cellular signalling process leading to generation of free radical species (72) which are crucially being altered in thiamine deficient diet (73). All these data provides us an opinion of considering thiamine as a cancer protective agent by its regulatory effects on NADPH- cytochrome c activity.

Possible Mechanism behind fruitful results of Selenium and Thiamine combination

As per the Statistical data obtained from the research work proposed by our researchers (74). Have depicted significant restoration of various liver profile markers along with remarkable effects on histology and alfa feto protein. All these reports have made us conclude on a possible mechanics behind combined use of selenium and thiamine in coliation as supportive therapy for its antineoplastic effects with marked improvement in liver prognosis. The potent results of Selenium and Thiamine coalition may be due to down regulated Akt phosphorylation by selenium by decreasing phosphatidylinositol 3-kinase (PI3K) activity (75). Akt pathway is also very much essential for activating TKT from Thr382 site of amino acid (76) which is then introduced into PPP, blocking this activity through selenium compounds make the use of thiamine doses fully available as nutrient in free form for normal functioning of cellular processes along with its antioxidant activity (77). The mechanism postulated for selenium and thiamine combination is depicted in underdrawn figure.



Possible mechanics behind potent effect of selenium and thiamine a combined regimen for cancer.

Conflict of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. This work is self-funded and is granted by no such organization.

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