Vitamin B1 given at low dose is contraindicated in cancer because it increases neoplastic cell proliferation. In high dose it activates the pyruvate dehydrogenase complex and decreases the cellular proliferation.

José de Felippe Junior

Vitamin B1, thiamine, combines with phosphorus to form the coenzyme pyrophosphate of thiamine or thiamine diphosphate. It is required in the oxidative de-carboxylation of pyruvate to form acetyl-CoA that enters the Krebs cycle, in the activation of Krebs cycle ketoglutarate dehydrogenase and acts as a cofactor of the enzyme transketolase, for ribose synthesis.

Thiamine increases both the synthesis and activity of transketolase, the enzyme that enters into the generation of ribose, the master-beam purine and pyrimidine molecule required for the synthesis of RNA and DNA, elements without which there is no cellular proliferation (Cascante-2000, Comin-Anduix, 2001).

In patients with cancer vitamin B1 deficiency is common and doctors do not hesitate to prescribe it. However, the deficiency is generally caused not by the decrease in intake but by the excess consumption that occurs in the intense cellular proliferation. Thiamine is a proliferative incentive.

Since Basu’s work in 1976, it has been known that cancer patients are deficient in vitamin B1 because developing tumors remove all available thiamine from the bloodstream. This explains why patients with rapidly developing hematological cancers show signs and symptoms of thiamine deficiency, such as muscle weakness, gastrointestinal problems, respiratory problems and cardiovascular problems, including high-throughput heart failure – beriberi (Van Zaanen-1992). In these cases, the priority allows the use of the mitotic vitamin.

Tumor cells use the oxidative pathway of glucose-6-phosphate dehydrogenase (G6PD) to produce ribose, but the main route of ribose synthesis for the formation of nucleic acids, key pieces of cell replication, is the non-oxidative pathway of transketolase (Horecker-1958, Katz-1967, Boros-1967, Macallan-1998).

Transketolase and its thiamine cofactor are crucial for the development of the Ehrlich tumor (Cascante-2000). Thus, modulation of the transketolase, which controls the flow of substrates through the non-oxidative branch of the pentoses cycle, could be useful in the control of cancer.

Transketolase stimulants, such as dietary thiamine, maintain tumor cell proliferative survival and unfortunately, cancer patients continue to ingest this vitamin, in the view of their physicians who are unaware of these effects. According to Boros, thiamine is a supplement frequently administered by physicians to cancer patients, as a prophylactic nutritional deficiency (Boros-1998).

Reactions of pentoses cycle in tumor cell: NADPH and ribose

The classic function of the pentoses cycle in mammals is the production of NADPH through a flow of carbons from 6-carbene (hexoses) to 5-carbene (pentoses) sugars. Pentoses are then recycled back to glycolysis in non-oxidative reactions of the pentose cycle by the enzymes: transketolase, transaldolase, aldolase, and isomerases.
Chesney in 1999 showed in eight different types of tumors that the non-oxidative reactions of the pentose cycle play a central role in cell proliferation due to the production of 5-phosphoribosyl-1-pyrophosphate.

Another work that shows the importance of transketolase is that of Boros in 1997, where it reveals that oxythyamine, a noncompetitive inhibitor of transketolase, causes cell proliferation and ribose synthesis to stop in vitro and in vivo. In 1999, Rais shows that oxythyamine induces drastic cell cycle arrest in the G0-G1 phase in mouse Ehrlich’s tumor.

**Nucleic acid synthesis pathways in tumor cells**

Two enzymes that regulate the oxidative pathway of the pentoses cycle are glucokinase (enzyme of the first anaerobic glycolysis reaction) and glucose-6-phosphate dehydrogenase (the enzyme of the first reaction of the pentoses cycle). The enzyme that regulates the non-oxidative pathway is transketolase (the enzyme limiting the main reaction).

The other enzymes, transaldolase, epimerases and isomerases, are of little importance.

The strong controlling action of transketolase on the proliferation of the Ehrlich tumor makes the non-oxidative pathway of the pentoses cycle a new therapeutic target in cancer: inhibit ribose synthesis (Cascante-1999). Since G6PD does not have much importance in ribose formation, G6PD inhibitors like dehydroepiandrosterone present only mild efficacy in ribose synthesis (Boros-1997).

The role of transketolase is strictly dependent on the presence of thiamine and the presence of this vitamin puts the cancer patient at a great disadvantage. Thus, thiamine that promotes both the transketolase synthesis and its activity increase is contraindicated in patients with cancer. If there is a 100% increase in transketolase activity, the rate of ribose synthesis and tumor proliferation increase by almost 60% each.

In mice, administration of thiamine at the 25-fold dose of RDA stimulates tumor growth by 164% compared to the control that did not receive vitamin B1 (Comin-Anduix – 2001).

Studies using carbon isotope-labeled glucose in various types of experimental tumors, both in vivo (Yoshida tumor) and in vitro (HeLa, Mia and Hep G2), demonstrate without a shadow of a doubt that it is the non-oxidative part of the pentose cycle which performs the major function of nucleic acid synthesis (Horecker-1958, Katz-1967, Boros-1967, Macal lan-1998). More than 70% of the ribose of these tumors are derived from the non-oxidative pathway of the pentose cycle, that is to say, they depend on the transketolase and only 10 to 15% are derived from G6PD, oxidative route of the pentose cycle.

In human H411 lung epithelial carcinoma, 99% of ribose synthesis was shown to be from the transketolase pathway (Boros-2000).

The intense use of ribose for the synthesis of purine nucleotides has been demonstrated in the four types of leukemia: acute lymphoid leukemia, chronic lymphocytic leukemia, acute myeloid leukemia and chronic myeloid leukemia (Becher-1978). Such findings were also confirmed in human cells of the colorectal tumor (Butler-1998).

Oxythyamine, a noncompetitive and irreversible transketolase inhibitor, decreases levels of DNA and RNA from Ehrlich tumor cells and reduces the ribose fraction of nucleic acids in human pancreatic adenocarcinoma cells. Both changes are followed by a large decrease in cell proliferation due to cell cycle arrest in G1 phase. There are no signs of toxicity or tumor cell damage caused by oxythyamine, it simply occurs halting from mitosis followed by apoptosis. Any cancerous or normal cell when it ceases reproduction lives a certain time and then is eliminated by apoptosis.

Vitamin B1 increases the proliferation of human endometrial cells (La Selva-1996), neuroblastoma cells (Bettendorff -1996) and liver tumor cells (Lee-1998).

**Thiamine antagonists**

Natural compounds that degrade thiamine:

a) Thiaminase I – fish

b) Thiaminase II – intestinal bacteria and polyhydroxyphenols such as: caffeic acid, chlorogenic acid, black/mate teas, Brussels sprouts and purple cabbage

They are foods rich in thiaminase: raw fish, fermented raw fish, roasted insects (Africa and Asia), wheat bark, trout liver, Bethel or bete nut, sarmental and aromatic plant of the Piperaceae family – Piper chavica betel -, native of India whose red walnut is used in dyeing and is widely used by the Indian people to chew, and the edible mollusk: scallop or scallop shell or scallop of St. James. The fishes richer in thiaminase are bordalo (dace) and Baltic herring.

The herbal medicine, Equisetum arvense, is rich in thiaminase, the antibiotic metronidazole converts to an analog of thiamine that is an antagonist of vitamin B1 and there are thiaminase producing bacteria: Bacillus thaminoliticus, Clostridium sporogenes, and other bacteria that can infect man and produce acute picture of beriberi. Anaphe venata Butler larvae (Lepidoptera)
and Anodonta cygnea mollusc produce many cases of acute beriberi in Asia. Another element rich in thiaminase is the mushroom Lentinus edodes (Berg).

New studies show cancer treatment efficacy with high dose thiamine

New studies show the benefits of thiamine in the treatment of cancer when in pharmacological doses: it increases the activity of pyruvate dehydrogenase and increases the efficacy of mitochondrial oxidative phosphorylation

High dose thiamin causes activation of the PDH complex in two ways: it inhibits pyruvate dehydrogenase kinase (Hanberry-2014) and activates pyruvate dehydrogenase phosphatase- (Parkhomenko-1987).

In 2014, Hanberry has brought new impetus to understanding the role of vitamin B1 in cancer. It has been shown that at low doses, thiamine increases neoplastic proliferation and in high doses decreases proliferation: bell-shape effect. In an elegant way the author has shown that thiamine in pharmacological doses activates pyruvate dehydrogenase (PDH), similarly to sodium dichloroacetate, i.e., inhibiting pyruvate dehydrogenase kinase (PDK).

Cancer cells have the ability to phosphorylate pyruvate dehydrogenase kinase, increase its activity and inhibit PDH, which closes the doors of oxidative phosphorylation, which allows the full action of anaerobic glycolysis and consequent tumor proliferation. Inhibition of PDK by sodium dichloroacetate (DCA) increases the activity of PDH which increases ATPS generation via mitochondrial, which decreases anaerobic glycolysis and suppresses the growth of many types of cancer.

It has recently been shown that thiamine coenzyme, thiamine pyrophosphate, reduces phosphorylation of PDK, which activates PDH-complex and opens the doors to oxidative phosphorylation. The problem lies in finding out what the high dose of thiamin is effective in reducing cell proliferation in humans.

In vitro, both thiamine and DCA reduce glucose uptake, lactate production and mitochondrial membrane potential in SK-N-BE and Panc-1 cell lines, neuroblastoma and pancreatic cancer. Dichloroacetate or high doses of thiamine do not increase the generation of free radicals, while increasing the activity of caspase-3, which facilitates apoptosis. It was concluded that high doses of thiamine in vitro reduces the proliferation of cancer cells by a mechanism similar to that described by sodium dichloroacetate.

In 2014, Gevorkyan showed efficacy of vitamin B1 derivative, hydroxyethyl thiamine diphosphate, in the murine Ehrlich tumor, in vivo, by decreasing the tumor volume by 73% in 45 days. Anatomopathological study revealed necrotic areas, inflammatory infiltration, central necrosis with adjacent infiltration of mononuclear and polynucleated neutrophils, mast cells and lymphoid follicular hyperplasia.

It has been shown by authors from the Soviet Union, in mitochondria isolated from rat liver, that thiamine diphosphate causes pronounced activation of PDH-phosphatase and inhibition of PDK, which activates the PDH complex. Thiamine triphosphate competitively inhibits PDH-phosphatase and inhibits PDK and in turn activates PDH-complex (Parkhomenko, 1987).

Finally in 2018 came another confirmation of the beneficial role of vitamin B1 in cancer. In high concentration reduces the proliferation of MCF-7 human breast cancer by 63%. There is an increase in pyruvate dehydrogenase (PDH) activity followed by increased oxidative phosphorylation, along with inhibition of the Embden-Meyerhof cycle (Liu-2018).

If we were to use it in a clinic, we would prefer thiamine diphosphate.

Foods rich in Thiamin (Vitamin B1 in mg)

<table>
<thead>
<tr>
<th>Food (100 grams)</th>
<th>mg of vit. B1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beer yeast</td>
<td>13.3 (1 teaspoon)</td>
</tr>
<tr>
<td>Rice Bran</td>
<td>3.0 (2 tablespoons)</td>
</tr>
<tr>
<td>Dry barley</td>
<td>2.7 (1 tablespoon)</td>
</tr>
<tr>
<td>Sunflower seed dry</td>
<td>2.6 (2 tablespoons)</td>
</tr>
<tr>
<td>Wheat germ</td>
<td>1.7 (3 tablespoons)</td>
</tr>
<tr>
<td>Flaked oats</td>
<td>1.3 (1 tablespoon)</td>
</tr>
<tr>
<td>Cooked pine nuts</td>
<td>1.3 (1 cup)</td>
</tr>
<tr>
<td>Brazilian nut</td>
<td>1.0 (30g)</td>
</tr>
<tr>
<td>Dried sesame seed</td>
<td>0.75 (2 tablespoons)</td>
</tr>
<tr>
<td>Almond</td>
<td>0.6 (30g)</td>
</tr>
<tr>
<td>Granola</td>
<td>0.6 (2 tablespoons)</td>
</tr>
<tr>
<td>Buckwheat flour</td>
<td>0.6 (2 tablespoons)</td>
</tr>
<tr>
<td>Integral soy flour</td>
<td>0.5 (2 tablespoons)</td>
</tr>
<tr>
<td>Hazelnut</td>
<td>0.5 (30g)</td>
</tr>
<tr>
<td>Pistachio roasted</td>
<td>0.5 (30g)</td>
</tr>
<tr>
<td>Whole wheat flour</td>
<td>0.45 (2 tablespoons)</td>
</tr>
<tr>
<td>Rye bread</td>
<td>0.41 1 slice</td>
</tr>
<tr>
<td>Quinoa</td>
<td>0.36 (1 tablespoon)</td>
</tr>
<tr>
<td>Chickpeas</td>
<td>0.31 (1 shell)</td>
</tr>
<tr>
<td>Green corn</td>
<td>0.25 (1 ear)</td>
</tr>
<tr>
<td>Almond</td>
<td>0.24 (1 serving)</td>
</tr>
<tr>
<td>Beans</td>
<td>0.22 (1 shell)</td>
</tr>
<tr>
<td>Brown rice</td>
<td>0.1 (½ cup)</td>
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</tbody>
</table>
The daily recommendation of dietary vitamin B1 intake, according to the National Academy of Sciences in the United States is 1.2mg for adult men and 1.1mg for adult women. Such doses in cancer increase mitotic velocity. Dose of 300mg/day decreases neoplastic proliferation by activating the pyruvate dehydrogenase complex.

**Conclusion**

The dose of thiamine required only to correct deficiency, i.e., low doses, is already sufficient to stimulate tumor growth. However, we can use it in high doses and still along with other pyruvate dehydrogenase-activating nutrients, such as lipoic acid, ursolic acid, DCA and nicotinamide. As we have seen, PDH activates oxidative phosphorylation, which inhibits anaerobic glycolysis causing a decrease in mitotic proliferation.

I have never seen in clinical practice, doctors or nutritionists worry about vitamin B1 in cancer. We have the most modern drugs, the most sophisticated devices, but we do not follow the correct prescriptions for thiamine. It seems that doctors in general do not respect biochemistry and physiology.

More dedicated and human medical teachers teach us that: "First, the doctor should not cause harm."

**Strategic plan**

1. Supplementing 300mg a day of thiamine plus intake of foods rich in vitamin B1.
2. Do not make thiamine intravenously. In the book of Medical Clinic Farreras – 1966 is written: never administer vitamin B1 intravenously.

*It is never too late to learn. Popular saying that served as a lesson to JFJ*

**References**

1. Abstracts and papers in full on site: www.medicinabiomolecular.com.br
Cancer cells exhibit aberrant glucose metabolism characterized by aerobic glycolysis, a phenomenon known as Warburg effect. Accelerated glucose uptake and glycolysis are main characteristics of cancer cells that allow them for intensive growth and proliferation. Accumulating evidence suggests that O-GlcNAc transferase (OGT), an enzyme responsible for modification of proteins with N-acetylglucosamine, may act as a nutrient sensor that links hexosamine biosynthesis pathway to oncogenic signaling and regulation of factors involved in glucose and lipid metabolism. Recent studies suggest that metab Ki-67, a cell proliferation-associated marker (and probably the only one with an expression pattern under a level of cell cycle regulation) (Scholzen and Gerdes, 2000), has been described as one of the most promising biomarkers of PCa. Cell-based therapies have shown promising outcomes; use of Platelets Rich Plasma (PRP) has overcome the hitches associated with rejections, has exhibited enhanced wound closure, and is economic.

Cancer is a complex cellular disease that is characterized by uncontrolled cell proliferation followed by invasion to the adjoining parts of the body, spread to other organs, and resistance to cell death (Hanahan & Weinberg, 2000). Isocitrate dehydrogenase reaction, alpha-ketoglutarate dehydrogenase complex, malate dehydrogenase (also pyruvate to acetyl-CoA). What step in the CAC produces FADH2? Succinate dehydrogenase. What steps in the CAC produce CO2? Isocitrate DH and alpha-ketoglutarate DH (also pyruvate to acetyl-CoA). A phospho-site at or near the substrate binding site will likely decrease the binding of isocitrate due to electrostatic repulsion and steric effects. When the O2 supply from blood fails to meet the demand of O2-consuming cells, oxygen deprivation (hypoxia) occurs. This is common in muscle under strenuous exercise. It has been recognized for over 100 years that O2-deprived cells show increased conversion of glucose to lactate (the Pasteur effect).