Biomedical Importance of Thiamin and Impact on Mitochondrial Machinery

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Abstract

Essential micronutrients are primary metabolites that the human body needs for reproduction, growth and survival. These include minerals and vitamins, but not essential fatty acids nor essential amino acids. They are called essential because they cannot be synthesized *de novo* in the human body neither partially nor completely. These nutrients have huge biological significance in that they are often found together with certain enzymes in complexes that are directly involved in vital metabolic pathways. Among these pathways are glycolysis, Krebs' cycle, oxidative phosphorylation and the pentose phosphate pathway. Thiamin (also called Thiamine, aneurine or vitamin B1) is one of these essential water-soluble micronutrients that functions as a coenzyme, or prosthetic group, to activate many apoenzymes that are involved in core metabolic processes, without which humans cannot survive. It thus functions as a helper molecule that aids an enzyme in catalyzing a chemical reaction. Deficiency of thiamin can cause many diseases and predispose us to many others indirectly by affecting the function of metabolic pathways, which in-turn disturbs mitochondrial function. Individuals with alcoholism in Western society and pregnant women of the developing world are most prone to this deficiency type of malnutrition. Geriatric and antenatal health care providers must be made aware of the incidence of such a deficiency state. In addition, audiences targeted for this mini review are the following: undergraduates of medicine, pharmacy and nursing, junior doctors of emergency and outpatient units, and doctors and nurses in geriatric units and obstetric hospitals.

Keywords: *Micronutrient; Metabolism; Holoenzyme; Cofactor; Krebs Cycle; Antioxidants*

Abbreviations

TMP: Thiamin Monophosphate; TPP (TDP): Thiamin Pyrophosphate (Thiamin Diphosphate); TTP: Thiamin Triphosphate; ATDP: Adenosine Thiamin Diphosphate; ATTP: Adenosine Thiamin Triphosphate; PPP: Pentose Phosphate Pathway

Introduction

Prelude: Food is the commodity consumed by humans to provide nutritional support to our bodies. The main sources are plants, animals and fish. These contain macronutrients such as carbohydrates, fats and proteins.

Regarding a nutrient, it can be defined as any substance used by an organism necessary for reproduction, growth and survival. Humans need in addition a class of materials known as micronutrients. These are usually so-called essential because they cannot be synthesized in the human body *de novo,* neither partially nor completely.

Essential micronutrients do not include essential fatty acids nor essential amino acids, since these two categories are needed in much larger amounts. In other words they are not considered as being "micro" nutrients. In general the total human needs for micronutrients is less than 100 mg/day. These include 13 elements and vitamins. Minerals are available in the sea and soil and reach the human body via plants and fish/animal products, or via fortification of the diet with different nutrients such as table-salts (iodine, potassium) and processed food. Vitamins get access to the human body by similar means to those of minerals. Micronutrients (both vitamins and minerals) are classified as primary metabolites for humans because life would not be possible without them. Micronutrients have different vital biological functions in the human body, among these, they function as cofactors in many proteins (enzymes) that are key-points in major metabolic pathways in the body, such as glycolysis (Emden-Meyerhof-Parnas pathway), citric acid cycle (Szent Györgyi-Krebs cycle) and pentose phosphate pathway (PPP). The two first metabolic pathways are heavily involved in ATP synthesis, and the latter (PPP) is pivotal regarding the enforcement of the antioxidant system of the human body.

Thiamin, properties, metabolism and biological significance

As stated earlier, thiamin functions biologically as a cofactor for enzymes that are crucial in the above-mentioned metabolic pathways.

Enzymes

They are the catalysts of biological systems. These protein molecules possess specificity in their catalytic action (s). Almost all types of cellular biochemical reactions cannot occur without the catalytic power of these molecular systems, because many of these reactions are thermodynamically unfavorable. Enzymes render these unfavorable reactions favorable. Biological catalysts increase the speed of reactions by a factor of almost 10^6. Many catalysts hydrolyze ATP molecules in order to accomplish these reactions. Enzymes are indeed proteins, and the statement that reads: "protein is the material of life" is an undoubted fact.

Cofactors: Are of two main types, these are: 1) Metals, as is the case with metalloenzymes or 2) Vitamin derived metabolites. Metal ions are needed by metalloenzymes, and those (cofactors) which originate from vitamins are complementary parts of certain apoenzymes. An apoenzyme with its cofactor forms an integrated protein known as a holoenzyme. Cofactors derived from vitamins are best known as prosthetic groups, because these remain associated with the mother enzyme (apoenzyme). Water-soluble vitamins such as thiamin and pyridoxal are among the well-known essential metabolites that give rise to many of these prosthetic groups.

Thiamin: Many scientists have indeed contributed to the elucidation of the significance of thiamin in humans. The first observation was by Kanehiro a general surgeon in the Japanese navy in 1884 when he rejected the notion that beriberi was of infectious origin. He ordered that barley, meat, milk and bread was to be added to white rice which was the main diet of soldiers for whom he was responsible for their health and sanitary conditions. By this means he was able to eliminate beriberi during a 9 month sea voyage. In 1901 the associate "G. Grijns to Eijkman C" interpreted the correct relation between polished rice and beriberi. Eijkman eventually was awarded the Nobel Prize for Physiology or Medicine because of his observations that finally resulted in the discovery of thiamin. Its structure was determined in 1934 by the American chemist Robert R. Williams.

Dietary sources of thiamin: It is found in foodstuffs such as whole grain, legumes, brown rice, cauliflower, kale, potatoes, oranges, dairy products, eggs, red meat, liver and nuts, all of which are good sources of thiamin. Some processed foods such as breakfast cereals (that contain brans of different grains) are also among the richest sources of thiamin.

Dietary thiamin can be degraded by a variety of means and thus loses its biological value. Sulfites for example added to processed food as a preservative, attack thiamin at the methylene bridge cleaving the pyrimidine ring of the molecule from the thiazole ring [1]. For chem-

ical structures see figure 1. Under acidic conditions, the degradation rate of thiamin is highest. Interestingly, raw marine products such as fish and shellfish contain thermolabile thiaminases. These enzymes hydrolyze thiamin, and thus act in an antagonistic manner to the action of thiamin [2]. Sulfites of any dietary source antagonize the absorption of thiamin from the human GIT. Those that originate from plants are heat-stable, and occur as hydroxy phenols, examples are caffeic acid, chlorogenic acid and tannic acid. These xenobiotics oxidize the thiazole ring, thus they impede thiamin absorption. Certain flavonoids such as rutin and quercetin also exhibit similar actions [1].
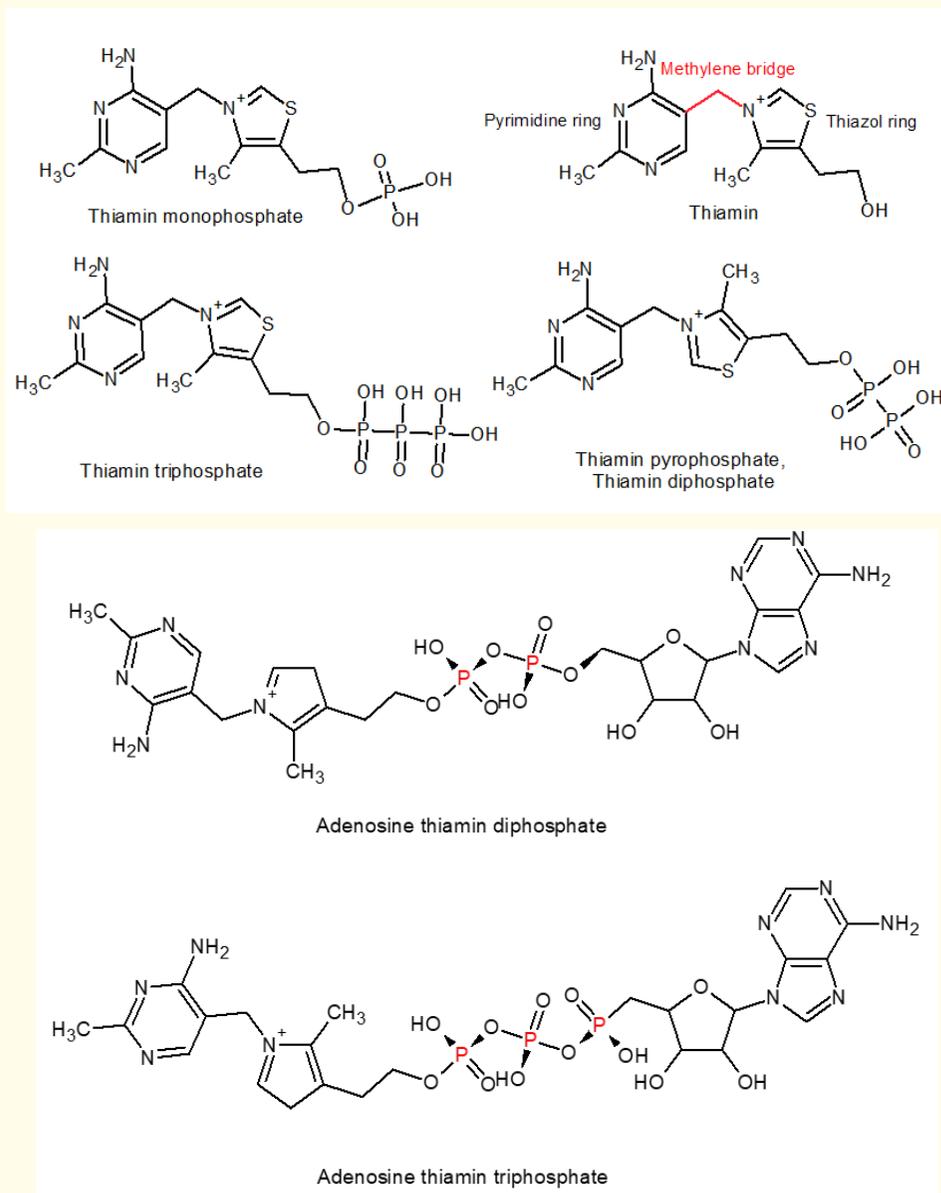

Figure 1: *Chemical structures of thiamin and phosphate derivatives.*

Dietary recommendations: Are somewhat different in Europe compared to those in the USA.

European Food Safety Authority (EFSA), applies Population Reference Intake (PRI) instead of the American Recommended Daily Allowance (RDA). EFSA recommends 0.1 mg per megajoule of energy consumed by all age groups above 7 months. According to this system, the upper tolerable limit is not determined. For dietary recommendations according to the American system see table 1 [3].

Age group	RDA* (mg/day)	Upper tolerable intake level
Infants 0 - 6 months	0.2◊	^ND
Infant 6 - 12 months	0.3◊	
1 - 3 years	0.5	
4 - 8 years	0.6	
9 - 13 years	0.9	
Females 14 - 18 years	1.0	
Males > 14 years	1.2	
Females > 19 years	1.1	
Lactating and pregnant ladies (14 - 50) years	1.4	
◊ Adequate intake for infants as an RDA has not been established yet.		
* RDA: Recommended Daily Allowance.		
^ND: Not Determined.		

Table 1: *Recommended daily allowances of thiamin in the USA.*
Data adapted from [3] in the bibliography.

Metabolism of thiamin: This water-soluble essential metabolite has first to be released from the foodstuff a human consumes. This step occurs in the upper GIT (duodenum) by the catalytic actions of two enzymes, phosphatase and pyrophosphatase. The next step is absorption that occurs mainly in the jejunum. At high concentrations absorption occurs by passive diffusion. At lower concentrations absorption takes place by active transport (a carrier-mediated process), mainly in the jejunum and ileum. Absorption is impeded by alcohol intake and/or folate deficiency. Folate is another subtype of the vitamin B-complex family, in which thiamin is a distinct subtype. The amount absorbed declines when the body has a sufficient store of this essential micronutrient.

After the first pass, and via the portal system, it reaches the liver where it first binds to albumin, thus most of this metabolite is protein bound. In a hormone-regulated process, it is believed that thiamin is then transferred, and binds to a carrier protein, called thiamin-binding protein. This step is important for tissue distribution of this primary metabolite. It is worthy to mention that this process has not yet been confirmed in humans [1]. In humans about 90% of total thiamin is deposited in erythrocytes. The uptake of this vitamin by the erythrocytes and other tissues of the human body, especially brain and heart, is mediated by both passive and active processes. When thiamin is to be internalized by different cells it is phosphorylated and then binds to albumin again. This is the case for almost 80% of intracellular thiamin. Uptake and release seem to be mediated via certain transporter proteins that are dependent on Na$^+$-dependent ATPase and a membranal proton gradient. In the human body most of the thiamin is stored in skeletal muscle, heart, brain, liver, and kidneys, this makes about 25 - 30 mg. Thiamin monophosphate (TMP) and unphosphorylated thiamin (free thiamin) are present in plasma, cerebrospinal fluid and in the milk of lactating women. It is therefore presumed that it exists in all extracellular fluids. This is attributed to fact that these two classes of thiamin, namely TMP and free thiamin, possess the ability to cross cell membranes despite the knowledge

that they are water soluble molecules. Divalent electrolytes such as Ca^{++} and Mg^{++} influence the distribution of thiamin in the human body [4]. An excess of thiamin and its carboxylic metabolites, being water soluble biomolecules is excreted mainly via urine [5].

Thiamin deficiency: Was best recognized because of "beriberi". This morbidity has been virtually abolished from the Western world, but can be seen sporadically especially in chronic alcoholics, older lonely adults, persons with AIDS, diabetics and those that have had bariatric surgery [6]. High doses of furosemide (a diuretic) used to treat certain complications in heart failure, have also been blamed to be an additional predisposing factor to thiamin deficiency. In poor societies of the developing world it can also be seen in adults. This occurs in two major forms, conventionally named as wet and dry beriberi. The wet subtype affects the cardiovascular system, manifested as tachycardia, dyspnea or peripheral edema (swelling of the legs). The dry subtype affects the nervous system, in a syndrome characterized as paresthesia and numbness in extremities, inability to move the legs, confusion, loss of appetite and constipation. In babies the clinical picture is exhibited as loss of appetite (resulting in a failure to thrive), vomiting, cardiomegaly, dysrhythmia, and lactic acidosis. In adults, advanced states of deficiency can cause Wernicke -Korsakoff syndrome [7], optic neuropathy and other rare deficiency syndromes such as central pontine myelinolysis, African ataxia and Leigh's disease [8].

Pregnancy *per se*, especially when associated with excessive vomiting, a condition known as hyperemesis gravidarum, is another risk factor of thiamin deficiency [9,10]. For this group of pregnant women, as antenatal care of pregnant women and their forthcoming babies, prenatal thiamin supplementation should be a mandatory measure, especially in poor countries of the third world. Pregnant and lactating females require more thiamin than other groups of the population, see table 1. The significance of thiamin is clearly manifested in the 3rd trimester, because thiamin preferentially diffuses from maternal blood to the placenta and thereby to the fetus. During breastfeeding, lactating women lose their thiamin via delivered milk [11]. The reference range of 20 - 50 ng/mL is accepted as normal although there is controversy surrounding this theme [12].

Biologic functions of thiamin: This is an essential (primary) metabolite that must be obtained via dietary sources. Its deficiency causes syndromes, some of which have already been mentioned above. Thiamin is well tolerated, and non-toxic when ingested [13]. Since it is a water-soluble micronutrient, in theory it should not cause hypervitaminosis when more than needed is deposited in the body, simply because the excess should be excreted in the urine as carboxylic metabolites. Indeed, some adverse effects have been documented for this metabolite, especially when administered parenterally, these include: impaired coordination, allergic reactions, nausea and lethargy [14]. The biological significance of this essential micronutrient is that it is a cofactor for core enzymes in the most important metabolic processes occurring in human cells. Its phosphate derivatives are involved in many cellular activities. The best known of these is thiamin pyrophosphate (TPP), which is a coenzyme in catabolism of sugars and amino acids. This is a universal metabolite used by all organisms, being synthesized in significant amounts in plants. Animals (ruminants) must get this from their diet (plants), and humans get it both from animal and plant sources. As already mentioned humans cannot synthesize this primary metabolite, therefore it is an essential micronutrient. Certain organisms, however, can indeed synthesize thiamin *de novo,* such as bacteria and fungi.

Thiamin has 5 natural phosphate-derived metabolites. These are: thiamin monophosphate (TMP), thiamin pyrophosphate (TPP), thiamin triphosphate (TTP), adenosine thiamin triphosphate (ATTP) and adenosine thiamin diphosphate (ATDP). It is worthy to note that thiamin pyrophosphate is sometimes called thiamin diphosphate (TDP). Chemical structures of thiamin phosphate derivatives are shown in figure 1. These phosphorylated metabolites demonstrate the significance of glycolysis, Krebs cycle and thus oxidative phosphorylation, which in turn reflects the importance of ATP and its biosynthesis. ATP is the universal energy currency of biological systems including the cells of human beings. Apart from the catalytic function of TPP (TDP) as coenzyme for certain enzymes, thiamin and its derivatives exhibit other non-catalytic actions when associated with other proteins [15], this is known as protein-protein interactions. This illustrates the wide spectrum function of thiamin in biological systems in general.

Thiamin pyrophosphate (TPP): Also known as thiamin diphosphate and thiamin cocarboxylase, is the biologically active phosphate derivative of thiamin. Interestingly the physiological role of the monophosphate form even today is unknown. TPP is synthesized by the reaction between thiamin and a molecule of ATP, where an ATP molecule is hydrolyzed by thiamin diphosphokinase (EC 2.7.6.2). TPP is a biochemical motif, because it is a coenzyme (prosthetic group) in many apoenzymes. These holoenzymes (apo + prosthetic group) generally catalyze the transfer of 2-carbon units and their subsequent conjugation with coenzyme A, that is dehydrogenation of 2 molecules of α-keto acid. TPP as a coenzyme (cofactor) is found in many enzyme species where these catalyze reactions of core metabolic pathways in the human body. Examples of such enzymes are pyruvate dehydrogenase, α-ketoglutarate dehydrogenase and transketolase. The significance of these three enzymes is that they play major roles in carbohydrate metabolism (producing the major fuel for ATP synthesis) in addition to their pivotal roles in scavenging what is known as reactive oxygen species (ROS) or the free radicals. The most important of these enzymes are:

- **Transketolase:** Is a major player in the pentose phosphate pathway (PPP), where pentose sugars are biosynthesized. These include ribose and deoxyribose. In association with phosphate groups these form the backbone of RNA and DNA macromolecules, and in addition many other vital metabolites in human cells such as ATP, NADH, FAD and coenzyme A. This cycle is also important for biosynthesis of the phosphorylated form of reduced NADH, namely NADPH through an intricate series of biochemical reactions. The oxidized form of NADPH, $NADP^+$, is a cofactor of many enzymes used in a series of anabolic reactions, such as the Calvin cycle, and lipid and nucleic acid synthesis, where NADPH is mandatory. The significance of this antioxidizing metabolite is demonstrated by the fact that it is used by all forms of cellular life [16]. Defect in transketolase activity because of thiamin deficiency has a considerable impact on the diabetic syndrome [17]. In addition to that mentioned so far as regards transketolase, the metabolic significance of this enzyme is that it connects the PPP to glycolysis by feeding the excess of phosphorylated sugar molecules into the glycolytic pathway. As mentioned earlier under this subtopic, transketolase is necessary for the production of NADPH. This antioxidant metabolite is engaged in biosynthesis of fatty acids, both in liver and the mammary glands and also for the synthesis of steroids by the liver and suprarenal glands. Bear in mind that thiamin diphosphate (TDP), together with calcium, is an essential cofactor in the action of this enzyme.

  The mitochondrion is an organelle that has many biological functions, in addition to fatty acid metabolism (β-oxidation), it is devoted to the biosynthesis of energy currency, namely ATP. This property is governed by virtue of the presence of two important key enzymes namely, pyruvate dehydrogenase (PDH) and the α-ketoglutarate dehydrogenase complex (α-KGDH).

- **Pyruvate dehydrogenase (PDH):** This again is a major player in carbohydrate metabolism. This is attributed to the fact that it links glycolysis to the citric acid cycle (TCA cycle). Not only this but it also plays an important role in synthesis of acetylcholine, a neurotransmitter at the neuromuscular synaptic junction. PDH is also involved in synthesis of the myelin sheet that protects and isolates the axons of neurons in the nervous system.

- **Alpha (α)-ketoglutarate dehydrogenase:** This enzyme is biologically important, because it is a rate-limiting protein of the citric acid cycle, in other words it is the check point of this vital metabolic pathway. Anaplerotic reactions can replenish the cycle at this juncture by synthesizing α-ketoglutarate from transamination of glutamate, and/or through action of glutamate dehydrogenase on glutamate.

Discussion

In eukaryotic cells the citric acid cycle occurs explicitly in the matrix of mitochondria, a double membraned organelle. Poly unsaturated fatty acids (PUFAs) and cardiolipin are also important constituents of phosphoglycerides that form the leaflets of mitochondrial mem-

branes [18,19]. Intact and integrated membranes, especially the inner ones, are studded with proteins such as electron carriers, proton pumps, and different membranal shuttle proteins, all of which are pivotal for progression and completion of oxidative phosphorylation. About 26 of the net total of 30 molecules of ATP are formed from oxidation of each glucose molecule in this intricate biochemical pathway [20]. The significance of thiamin is not only limited to mitochondrial membranal development and integrity, but also to the proper functioning of synaptosomal membranes. Synapses are the points where two neurons adjunct each other leaving a space in-between of about 20 nm (0.02μ), this is known as the synaptic cleft or synaptic gap. In these membranal clefts, neurotransmitter is exocytosed from the membrane of the afferent synaptic neuron to attach the receptors of the corresponding membrane of the efferent neuron in order to fire an impulse signal and thus initiate neuronal transmission [21]. Thiamin deficiency has been blamed as being one of the important causative factors behind improper development of the fetal brain that this can cause sudden infant death syndrome (SIDS) [4]. This illustrates the significance of this essential micronutrient as a prenatal supplement to the diet of pregnant women in order to assure that their forthcoming babies have a healthy and soundly developed brain. It is worthy of mention that thiamin *per se* is a treatment for certain ailments such as maple syrup urine disease [22,23] and Leigh disease [24]. Thiamin is a member of a distinct category of water-soluble essential micronutrients known as the B-vitamins or vitamin B-complex. These micronutrients have almost the same dietary sources, and, therefore, when one of these is deficient the clinician should expect deficiency with regard to other members of this vitamin complex. This might be one of the reasons behind why these subgroup metabolites are available as vitamin B-complex tablets for therapeutic use. These subgroups (members of the B-complex) indeed cannot be called vitamers or isomers (as, for example, is the case with vitamin A isomers). This is because here, with regard to vitamin B subgroups, these are structurally not analogues, because they exhibit no similarity in biological functions nor in their chemical structures, apart from the fact that they are all water-soluble compounds. Thiamin alone (i.e. not in combination with other B-vitamins) is also available for oral use as tablets, and also in ampules for parenteral use (intramuscular and intravenous) where urgent therapy is mandatory such as in cases of complications associated with alcoholism. It is also important to mention that lipid-soluble derivatives of this essential micronutrient are available, such as benfotiamine, to improve the bioavailability this vitamin. Preparations of thiamin are generally well tolerated, anaphylaxis and other allergic adverse effects may be encountered when the agent is administered repeatedly after parenteral use.

Mitochondria: From the Greek, meaning grain-like thread, represent the powerhouse of eukaryotic cells, with some exceptions in humans such as mature red blood corpuscles (RBC). This is probably also the case in a few other unicellular organisms e.g. protozoa (flagellates). A mitochondrion is a double membraned organelle. There is a huge variation in size, number and structure in different cell types which generally have an area of 0.75 - 3 μm^2. This variation is dependent on the metabolic activity of the cells in which they are found [25,26]. Hepatocytes, platelets, neurons and myocytes (of cardiac and skeletal musculature) possess a large number of these organelles. They are also found in considerable abundance in neuronal synaptic clefts and neuromuscular junctions. Human RBCs produce ATP via glycolysis, an anaerobic pathway that occurs exclusively in cytoplasm, thus they do not possess mitochondria. In other words these cells rely entirely on glucose as a fuel for biosynthesis of the ATP molecules they require. By the virtue that these cells contain hemoglobin, they function as vehicles to transport O_2 from the lungs to other cells of the body, and thus explaining why these cells do not exhibit a wide metabolic panorama. Some biologists believe that these well-organized (delicately compartmentalized) organelles indeed were originally minute bacteria that gained access into other cells and accommodated their survival within these host cells in a symbiotic manner [20]. Similar to their bacterial ancestors, a mitochondrion has its own independent genome which is substantially similar to that of bacteria. Mitochondrial proteins are directly transcribed from the genome, where the types synthesized are dependent on the actual tissues and cell types these organelles are found in. For example, in human cardiomyocytes almost 615 distinct protein types have been identified encoded by the mitochondrial genome [27]. Properly functioning mitochondria is a prerequisite for normal cell activity and survival. Dysfunctional mitochondria can predispose and/or cause a dozen or so disabilities and ailments, taken together these are known as mitochondrial diseases. Thiamin deficiency, or a defect in its metabolism, affects mitochondrial function via improper functioning of enzymes engaged in the machinery of metabolism. And this in-turn affects almost all bodily systems, simply because mitochondria are so centrally engaged in

the most vital metabolic pathways in cells of the human body. Mitochondrial dysfunction can cause a wide spectrum of syndromes that affect neurologic function (cognitive disability, Alzheimer's dementia [28], Huntington's and Parkinson's diseases), autonomic dysfunction, muscular problems (weakness, loss of muscle coordination, chronic fatigue syndrome, poor growth, sarcopenia, aging and senescence), sensory defects (visual and auditory), and cardiorespiratory disorders. Mitochondrial dysfunction has also been blamed to be involved in pathophysiology of many acquired conditions such as cancer, diabetes type II and many mental diseases such as: schizophrenia, bipolar affective disorders, major depressive disorder and anxiety neurosis [29-40]. As for diabetes mellitus, it is considered a situation where both thiamin and energy deficiency states exist. This being attributed to limited synthesis of the phosphate derivative of thiamin, namely thiamin pyrophosphate (TPP). Evidence from recent research has shown that therapeutic administration of this water-soluble micronutrient or a fat-soluble variant e.g. benfotiamine, has a beneficial outcome in diabetic individuals. Therefore, administration of dietary supplement preparations that contain TPP is recommended in this patient group as a strategic measure to avoid complications of long-standing diabetes, such as neuropathy and nephropathy. These are the two most devastating complications of diabetes that result as sequelae of microangiopathy [41]. It is believed that these positive effects are resultant of activation of pentose phosphate pathway enzymes (transketolase and/or pyruvate dehydrogenase complex) in mitochondria. Most of the complications that are encountered in diabetes are attributed to defects in blood circulation at arteriolar and/or capillary levels. Endothelial cells are mirror-like smooth epithelial cells that are in contact with the blood running through these very small vessels. These cells synthesize nitric oxide (NO), important for viability and functionality, namely because NO is a vasodilator and has an important role in oxygenation of mitochondria within these cells. Thus, these short-lived free radicals are necessary for the proper functioning of mitochondria. Recent data has suggested that mitochondrial activity is a key regulator of NO synthesis. In diabetic patients a deficiency in NO has been reported, a fact that necessitates administration of supplementary thiamin to these individuals. As of today, apart from a few case reports, no solid evidence exists from documented research proves that thiamin deficiency *per se* can cause all the above-mentioned ailments [12,42]. On the contrary thiamin deficiency can occur as a complication of such diseases [43,44], probably because of isolation, ignorance and loneliness that these individuals experience. It is now generally accepted that the assertion that reads "properly functioning mitochondria is pivotal for balanced carbohydrate metabolism, which is in turn a must for mental and physical wellbeing of humans [45,46]" is indeed correct. To sustain good health physiologically functioning mitochondria must have their core enzymatic processes running properly and smoothly. This demands normal and stable levels of thiamin in our bodies. Thiamin deposits in the adult human body (20 - 30 mg) are sufficient for 14 - 18 days [47,48]. This amount needs to be replenished regularly via uptake from a healthy diet. It is therefore necessary to consume a variety of food items that contain this essential micronutrient (and others) in order to maintain a sound and healthy body, both physically and mentally. One must also bear in mind that the opposite can be manifested in e.g. schizophrenic patients, who can develop Wernicke's encephalopathy because of thiamin deficiency that results in a reduction in the quality of life. A phenomenon that makes the clinical picture more complicated [49].

Conclusion

Thiamin is an essential micronutrient that cannot be synthesized in the human body, and therefore must be obtained via the diet. Its importance, first and foremost, is to maintain high-level activity of enzymes involved in functional control of core metabolic pathways such as glycolysis, lipid and amino acid metabolism that mainly occur in mitochondria. It might be difficult to diagnose subtle cases of thiamin deficiency because this, in its early stages, might give an ambiguous clinical picture that can mimic other common non-pathognomonic symptoms such as lethargy, laziness and apathy, and thus may mislead even expert clinicians. Deficiency of this micronutrient is seen commonly among aged alcoholics who live isolated in a life motif mainly encountered in the developed world. Deficiency of this vitamin can also be encountered in pregnant women of the third world, for different reasons. Infants of these women are also liable to be affected by the consequences of such a deficiency. A fact that elucidates the importance of proper antenatal, perinatal and postnatal care these women deserve. In alcoholics, the deficiency is much easier to treat in its early stages than neglected chronic advanced cases of brain

damage (dementia) and Korsakoff's psychosis, especially in elder individuals. Mitochondrial dysfunction attributed to thiamin deficiency worsens the process of brain aging and increases the risk of developing Alzheimer's later in life. The optimal medical intervention to treat advanced cases of thiamin deficiency is parenteral administration of the vitamin in appropriate doses. The consumption of a variety of foods, both from animal and plant sources, can ensure that deficiency will not develop in vulnerable groups of individuals.

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