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The Role of Micronutrients in Modulating Biochemical Pathways and Their Impact on Metabolic Health

Naif Abdullah Saad Binquryan[1], Mohammad Salem Mubark Almaqattar[1], Khaleel Abdulrahman Abdullah Alshamasi[1], Ahmad Hassan Yahya Homadi[1], Mansour Saeed Ahmad Alahmari[1], Meshary Saleh Mohammed Algharib[1], Thamer Sulaiman Hizab Algofiliy[1], Waleed Abdulrahman Mohamed Alfadhe[1]l, Muqbil Hamoud Muqbil Alotaibi[1], Ali Abdullah Ali Al-Hobaish[1], Yasser Ali Abdulrahman Almotawa[1], Sultan Omar Abdulaziz Alsubael[1], Abdulrhman Mohamed Abdullah Albarrak[2]

1 Hospital in Riyadh region, Ministry of Health, Saudi Arabia

2 King Saud Medical City in Riyadh, Ministry of Health, Saudi Arabia

Abstract

Background: The physiological mechanisms underlying energy production and fatigue are complex, involving biochemical pathways that rely heavily on vitamins and minerals. These micronutrients play crucial roles in cellular energy production, oxidative stress regulation, and neurotransmission, all of which are vital for maintaining physical and mental performance. Deficiencies in these micronutrients can lead to increased fatigue and diminished metabolic health.

Aim: This article explores the role of vitamins and minerals in modulating biochemical pathways that influence energy metabolism and metabolic health. It emphasizes the importance of these micronutrients in cellular functions, particularly in energy production, oxygen transport, and oxidative stress regulation, and examines the consequences of inadequate micronutrient status on physical fatigue.

Methods: A comprehensive review of clinical studies and biochemical literature was conducted to analyze the impact of various vitamins and minerals, such as B vitamins, iron, magnesium, and vitamin C, on cellular energy production and physical fatigue. The mechanisms of micronutrient action, including their roles in oxidative phosphorylation, oxygen transport, and neurochemical synthesis, were evaluated.

Results: Vitamins and minerals, including B vitamins, iron, magnesium, and vitamin C, play pivotal roles in cellular energy production through processes like oxidative phosphorylation and oxygen transport. Deficiencies in these nutrients result in fatigue, impaired physical performance, and diminished energy levels. For instance, inadequate iron levels impair oxygen transport, while magnesium deficiencies affect muscle function and endurance. Clinical studies confirm that supplementing these micronutrients improves energy levels and reduces fatigue, particularly in individuals with deficiencies.

Conclusion: Micronutrients are essential for maintaining optimal metabolic health and energy production. Their roles in oxidative stress regulation, oxygen transport, and neurotransmitter synthesis are critical for sustaining physical and mental performance. Addressing deficiencies through supplementation can significantly alleviate fatigue and improve overall health outcomes. However, more research is needed to establish optimal supplementation guidelines and the long-term effects of micronutrient interventions on fatigue.

Keywords: micronutrients, energy metabolism, fatigue, vitamins, minerals, oxidative stress, metabolic health, iron, magnesium, vitamin C

1. Introduction

More than a century ago, it was determined that vitamins and minerals were essential to human health. Recommendations for dietary consumption are made to guarantee that most people get amounts that satisfy their physiological needs [1]. The relationship between biochemical and physiological processes, as well as the impact on clinical outcomes, has been extensively studied for specific vitamins and minerals. For example, vitamin A is a part of the retina's rhodopsin pigment, which is necessary for vision and blindness prevention. The exact function of micronutrients in cellular and molecular interactions that result in physiological and functional effects, however, is frequently still poorly understood. Claims on how vitamins and minerals affect psychological, cognitive, and fatigue processes are allowed in many nations [2]. However, rather than being supported by reliable, empirical physiological evidence, the scientific basis for these statements is frequently based on theoretical biochemical ideas and clinical observations during overt inadequacies. Clinical inadequacies of this kind are uncommon, especially in developed countries. On the other hand, subclinical deficiencies or inadequate intakes—sometimes referred to as "insufficiencies"—occur frequently around the world, with differences based on age and nation [3,4]. Enough vitamins and minerals are often provided by a varied, well-balanced diet full of nutrient-dense foods including fruits, vegetables, and dairy products. However, there is strong evidence that food availability or choices frequently hinder such diets, resulting in a sizable population in both developed and emerging countries not fulfilling their ideal dietary requirements. For instance, 55% of Turkish adults, both male and female, have thiamine (vitamin B1) intakes below the estimated average requirement (EAR) [6], while 68% of Mexican women have folate (vitamin B9) intakes below the EAR [5]. Many people still do not meet the EAR, or Adequate Intake, levels, even though the majority of Americans consume enough of most nutrients to avoid clinical symptoms [7]. Supplementing with vitamins and

*Corresponding author e-mail: nbnquryan@moh.gov.sa (Naif Abdullah Saad Binquryan)

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minerals may help meet dietary needs in certain situations. A greater sense of well-being, less physical and mental exhaustion, and increases in psychological and cognitive abilities are also regularly mentioned as reasons for supplement use, and this is often cited as the main one [8,9].

This narrative review aims to assess the scientific data pertaining to the impact of several vitamins and minerals on psychological and cognitive processes, as well as health outcomes associated with exhaustion. Three minerals (iron, magnesium, and zinc) and nine vitamins (B1, B2, B3, B5, B6, B9, B8, B12, and C) have been selected because of the approved health benefits of these nutrients in Europe. The first part of the examination will examine how energy is conceptualized and how it relates to both mental and physical exhaustion and performance. The biochemical/physiological viewpoint as well as the perceptual and psychological expressions of energy will be briefly discussed in this section. Following that, the review will include a thorough and current examination of the data relating these micronutrients to cognitive processes, physical and mental exhaustion, and biochemical pathways, when available. Human research, particularly those involving healthy populations and those with inadequate nutrient consumption or status, will be prioritized. Observed signs of deficits or sub deficiencies in human populations will serve as the basis for the review of cognitive functions and weariness.

Energy and Fatigue: Subjective Perceptions with an Underlying Physiological Foundation

Diverse Interpretations of 'Energy' and 'Fatigue'

According to nutritional science, food is the only source of energy that maintains the body's structural and biochemical integrity. For the general public, energy is frequently linked to feelings of health, vigor, and stamina, which allow people to carry out their regular social, intellectual, and physical activities. Conversely, the subjective feeling of low vitality or lowered energy is commonly used to characterize weariness [10]. Fatigue, vitality, and energy are all related ideas; the latter is the negative extreme of a continuum, while the first two are frequently viewed as the positive ends. They may, nevertheless, also be regarded as separate psychological phenomena [11]. There are several mental and physical components that can be used to characterize these ideas. Energy and vitality, for instance, can include mental toughness, emotional health, perceived levels of fatigue, and persistence, while fatigue can be characterized by physical exhaustion or difficulty doing tasks [12]. There are mental and physical components to fatigue as well. Physical exhaustion is more closely linked to the body's depletion of energy, whereas mental fatigue impacts cognitive and emotional processes. Poor or insufficient sleep was the main cause of exhaustion in a study of 24 healthy people between the ages of 24 and 72 [13]. Personal and environmental stresses, such as noise and family concerns, also had a role. In more than half of the subjects, physical weariness was linked to decreased strength and endurance. Furthermore, 75% of the individuals noticed mood swings and a lack of motivation, while 50% reported feeling less energetic and having trouble focusing. Reduced exercise levels were associated with both physical and mental weariness, according to a comparable assessment carried out in Sweden [14].

Fatigue, Energy Deficits, and Diminished Performance

Despite being subjective reports, the results of the surveys listed above are consistent with objective evaluations of how fatigue affects mood, physical performance, and cognitive function. However, it is difficult to precisely characterize and measure the impact of tiredness on human performance because of the lack of specific language and proven experimental models [15]. Several studies have demonstrated that physical exertion-induced weariness impairs athletic performance. For instance, after a 25-minute fatiguing exercise session, cross-country skiers performed worse in double poling than after a 25-minute rest period [16]. Ballet dancers also showed decreased control over their movements when they were tired, which increased their risk of injury [17]. Furthermore, poor performance has been connected to mental exhaustion. Prior to playing table tennis, players who completed a 90-minute cognitive assignment showed reduced ball speed and accuracy [18]. Cognitive performance deteriorates as a result of fatigue brought on by extended work environments, such as long shifts or stressful situations. Specifically, radiologists' diagnostic accuracy was negatively impacted by exhaustion from overnight hospital shifts, as evidenced by a 34% increase in the time needed to diagnose fractures [19]. Road traffic accidents, particularly those involving automobile drivers [20] and railroad workers [21], are also significantly influenced by fatigue. Furthermore, research suggests that children who are tired perform worse academically [22, 23, 24].

Physiological Mechanisms Behind Physical and Mental Fatigue

The feeling of "energy depletion," which is objectively related to inadequate energy availability (calories), is a basic characteristic of weariness. When the energy supply cannot keep up with the demands of the muscles and brain, respectively, weariness sets in. The largest energy expenditures at rest are made by the heart and kidneys (around 440 kcal/kg), followed by the brain (240 kcal/kg) and the liver (200 kcal/kg). Skeletal muscle, on the other hand, only uses roughly 13 kcal/kg. Nonetheless, even at rest, the brain (1.33 kg) and muscle (26.3 kg) are among the most metabolically active tissues when taking into account the typical adult body weight [25]. Muscles require more energy during physical activity, especially when exercising for longer periods of time and with greater intensity. Despite significant variations in demand, muscles adjust to these changes and maintain a comparatively constant energy supply. Given this flexibility, it is likely that muscle exhaustion results from restrictions in energy-generating processes, which in turn limit the pace at which energy is expended and, hence, performance [26]. According to recent studies, metabolic issues affecting a limited subset of fast-fatiguing muscle fibers—where ATP levels fall below 30% of resting concentrations—may be the cause of muscle weariness. Performance is greatly influenced by these fibers, which are in charge of quick motions and high power production; their depletion results in both decreased performance and physical exhaustion [27].

Despite making up only 2% of the total weight, the adult human brain uses 20% of the body's energy, mostly from glucose, which powers neurotransmission. Compared to non-primate vertebrates, which devote approximately 2-8% of their basal metabolism to the brain, the energy demand

of the brain is more than doubled. The human brain's larger growth and neuronal density are probably related to this higher energy demand [28]. Neuronal function, especially synaptic transmission—which entails transforming electrical signals into chemical messages (neurotransmitters)—uses the majority of this energy.

To maintain resting potential and control neurotransmitter production and processing inside synapses, this mechanism needs a lot of ATP [29]. The brain has limited energy stores and is dependent on the constant flow of glucose and other energy substrates from the blood-brain barrier, in contrast to skeletal muscles, which store energy in the form of glycogen. Glucose is the brain's main energy source under normal circumstances. The brain can, however, use lactate, ketones, and medium-chain triglycerides as alternate energy sources when glucose levels are low [30]. The brain's constant metabolic activity, which continues even while you sleep, is another characteristic that sets it apart. This baseline activity is only marginally increased (less than 5%) by mental work. Additionally, during the shift from sleep to awake and in response to changes in sensory or motor cues, neuronal activity and energy use vary. Neuronal communication is also significantly altered during memory formation and synaptic plasticity. This process is controlled by 'neurometabolic coupling,' which modifies cerebral blood flow and local energy supply in response to changes in neuronal activity [31].

Fatigue Resulting from Impaired Oxygen Supply to Muscles and the Brain

Both brain and muscle tissues are highly dependent on oxygen. The brain consumes about 3.5 mL of oxygen per minute per 100 g of tissue, which accounts for roughly 20% of the body's total oxygen demand. Any reduction in oxygen supply can adversely affect brain function, with chronic hypoxia leading to cognitive impairments [33]. Muscles, at rest, consume around 1 mL of oxygen per minute per 100 g of tissue, but during exercise, oxygen consumption can increase up to 50 times in contracting muscles, enhancing performance [34][35]. In conditions such as anemia, where hemoglobin levels are low, the impaired oxygen transport affects not only cognitive and physical performance but also contributes to the sensation of fatigue [35][36][37]. Moreover, prolonged mental exertion can result in a measurable decrease in circulating glucose and oxygen levels [38][39][40][41]. Fatigue is considered a prominent symptom of anemia, regardless of the underlying cause of reduced hemoglobin levels [42].

Vitamins and Minerals in Cellular Energy Production

Overview of Cellular Energy Production

In humans, macronutrients from the diet provide the necessary fuel to sustain the body’s biochemical and structural integrity, facilitate physical activity, and support new tissue formation [43]. The digestion of food by enzymes breaks down carbohydrates into monosaccharides, fats into fatty acids, and proteins into amino acids. These components enter cells, where they undergo oxidation, first in the cytosol and later in the mitochondria. This energy production process occurs in three main stages, ultimately yielding adenosine triphosphate (ATP), which serves as the cell’s primary energy source. Acetyl-CoA, an activated carrier molecule, is derived from pyruvate (which is produced from glucose via glycolysis), fatty acids through beta-oxidation, and some amino acids (which are primarily reserved for protein synthesis) [44].

Citric Acid Cycle: Within the mitochondria, acetyl-CoA combines with oxaloacetate, a four-carbon molecule, forming citric acid, which is then gradually oxidized across eight reactions. This oxidation generates energy stored in three molecules of nicotinamide adenine dinucleotide (NADH) and one molecule of reduced flavin adenine dinucleotide (FADH2), both of which are essential electron carriers [44].

Oxidative Phosphorylation: The inner mitochondrial membrane contains an electron transport chain composed of five protein complexes. Three of these complexes (I, III, and IV) pump protons (H+) to establish a proton gradient, which facilitates ATP production at complex V [44]. NADH and FADH2 transfer electrons to the transport chain, losing energy as they move through it. This energy is used to phosphorylate adenosine diphosphate (ADP) into ATP. The low-energy electrons are then combined with oxygen and protons from the surrounding solution to form water [44].

Approximately one billion ATP molecules exist in solution within a typical cell at any given time, with ATP turnover occurring every one to two minutes in most cells [44]. This highly efficient system relies on the energy derived from macronutrients, as well as the vitamins and minerals essential for extracting energy from these nutrients.

B Vitamins in Cellular Energy Production

All B vitamins, except folate, participate in one or more stages of the cellular energy production system (**Figure 1**). Adequate levels of each B vitamin are necessary for the system’s proper function, as a deficiency in any one can hinder energy production, potentially leading to severe metabolic and health issues.

- **Vitamin B1** exists as free thiamine and its phosphorylated forms, including thiamine pyrophosphate (TPP). TPP plays a crucial role in dehydrogenase reactions that decarboxylate pyruvate and branched-chain amino acids to form acetyl-CoA [45][46]. Within the citric acid cycle, TPP also supports the conversion of alpha-ketoglutarate to succinyl-CoA [45].
- **Vitamin B2** (riboflavin) forms part of the coenzymes flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN), which act as proton carriers in redox reactions critical to the metabolism of carbohydrates, fats, and proteins [47]. FAD is involved in acetyl-CoA production from fatty acids, glucose, and branched amino acids [45]. Additionally, FAD contributes to the citric acid cycle, where it helps convert succinyl-CoA into succinate and aids electron transport during oxidative phosphorylation [44].
- **Vitamin B3** (niacin) is a precursor to NAD, which plays a pivotal role in the electron transport chain by accepting electrons from glucose-derived carbons during glycolysis, as well as in the citric acid cycle and mitochondrial oxidative phosphorylation [45].
- **Vitamin B5** (pantothenic acid) is a precursor for coenzyme A, essential for the formation of acetyl-CoA and succinyl-CoA, both crucial intermediates in the citric acid cycle [44].
- **Vitamin B6** (pyridoxine) exists as pyridoxal phosphate (PLP), a cofactor for enzymes involved in amino acid metabolism, glycogenolysis, gluconeogenesis, and niacin formation, as well as lipid metabolism [48].

- **Vitamin B8** (biotin) is a cofactor for carboxylases involved in fatty acid synthesis, amino acid catabolism, and gluconeogenesis, essential for energy production [49][50].
- **Vitamin B12** (cobalamin) participates in the conversion of methylmalonyl-CoA to succinyl-CoA during the oxidation of odd-chain fatty acids and the catabolism of ketogenic amino acids [51].

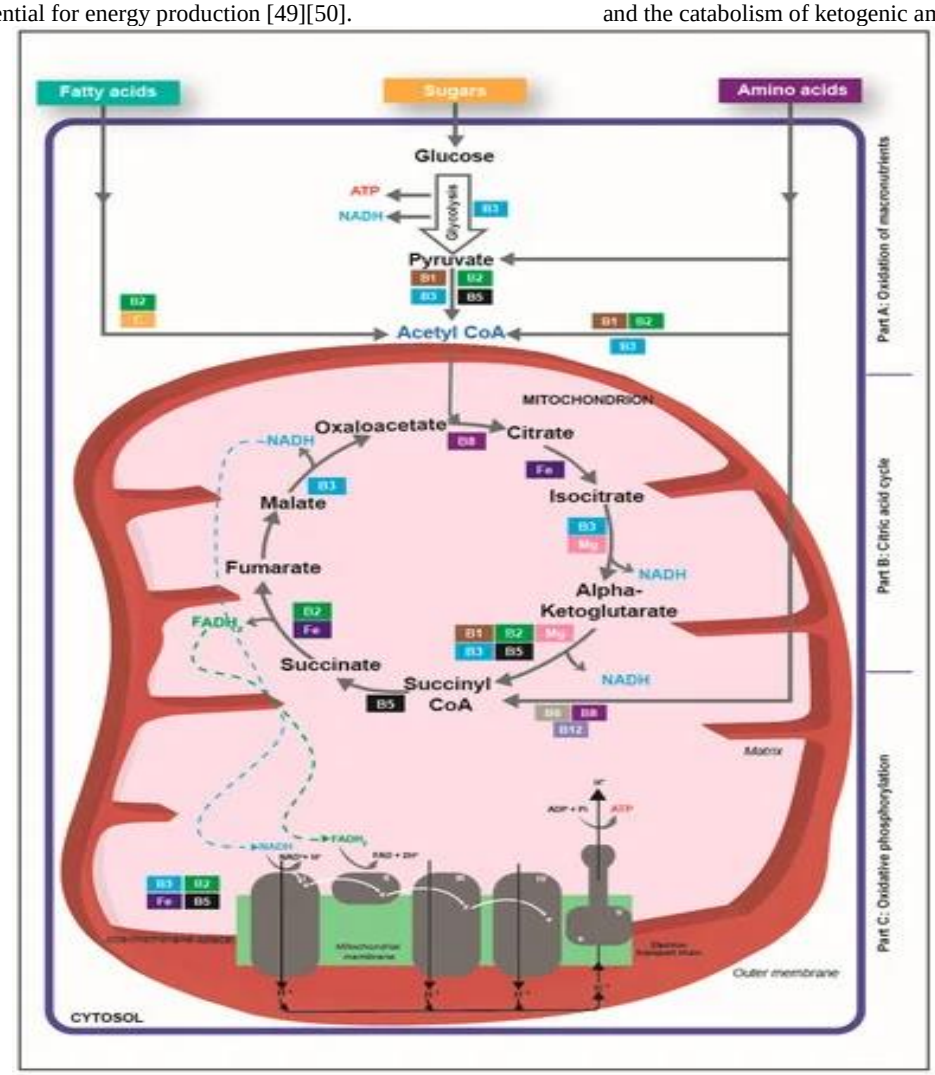

Figure 1: An overview of the role of vitamins and minerals in key cellular energy production pathways.

Other Nutrients Involved in Energy Metabolism

- **Vitamin C** is critical for the synthesis of carnitine, a cofactor required for transporting long-chain fatty acids into mitochondria for beta-oxidation, thus playing a role in energy production [52][53].
- **Iron** is integral to heme-containing cytochromes, which are essential for electron transport in the mitochondria during ATP synthesis [54].
- **Magnesium** is crucial for ATP production and utilization, binding to ATP to form a biologically active complex necessary for various enzyme activities in glycolysis and the citric acid cycle [55][56][57].

Vitamins and Minerals Play a Crucial Role in Regulating Oxygen in the Body

Iron and Vitamins B6, B9, and B12 in Oxygen Transport

Around two-thirds of the body's iron is located within hemoglobin, a heme-containing protein found predominantly in red blood cells. Heme iron exists in its ferrous form (Fe^{2+}), which allows it to reversibly bind oxygen. A single hemoglobin molecule can carry up to four oxygen molecules, enabling blood to transport oxygen 50–70 times more efficiently than plasma alone. Hemoglobin's essential function stems from iron's ability to rapidly bind oxygen during its brief contact with the lungs and release it as required while circulating through tissues [54]. Similarly, myoglobin, another heme protein, facilitates oxygen transport and short-term storage in muscle cells, ensuring that oxygen supply matches the high demand of active muscles. A deficiency in iron, leading to iron-deficiency anemia, reduces the oxygen-carrying capacity of blood, negatively affecting endurance and energy efficiency [54].

Anemia can also arise from nutrient deficiencies other than iron, with evidence indicating that inadequate levels of B vitamins—specifically B6, B9, and B12—can contribute to anemia. The metabolic and functional pathways of vitamins B9 and B12, and to a lesser degree B6, are interdependent (**Figure 2**). The folate cycle, which is crucial for generating the active form of vitamin B9, relies on vitamin B12. In its methylcobalamin form,

vitamin B12 is vital for the enzyme methionine synthase, which facilitates the methylation of tetrahydrofolate and the conversion of homocysteine to methionine [51]. Vitamin B6 also participates in homocysteine metabolism through the transsulfuration pathway, converting homocysteine to cysteine with the help of vitamin B6-dependent enzymes. A deficiency in vitamins B9, B12, or B6 can cause a buildup of homocysteine [59]. Vitamin B6 is essential for oxygen transport because pyridoxal 5'-phosphate (PLP), the active form of B6, acts as a cofactor for alpha-amino levulinate synthase, an enzyme involved in the synthesis of hemoglobin's porphyrin ring. A chronic B6 deficiency may result in microcytic anemia, characterized by low hemoglobin levels in erythrocytes [48]. Folate (vitamin B9) functions as a cofactor or co-substrate in numerous one-carbon transfer reactions essential for amino acid metabolism and nucleic acid synthesis [60]. Disruption in DNA synthesis impairs red blood cell production, which depends on cell replication. A folate deficiency leads to megaloblastic anemia, characterized by a low red blood cell count and the accumulation of large, immature red blood cell precursors (megaloblasts) in the bone marrow, reducing the blood's oxygen-carrying capacity [61]. Given the interdependence of folate and cobalamin (vitamin B12) metabolism (**Figure 2**), cobalamin deficiency frequently presents as megaloblastic anemia, affecting 70–80% of cases. A deficiency in vitamin B12 impairs DNA synthesis by inhibiting folate activation, thereby reducing red blood cell production and impairing oxygen delivery [62].

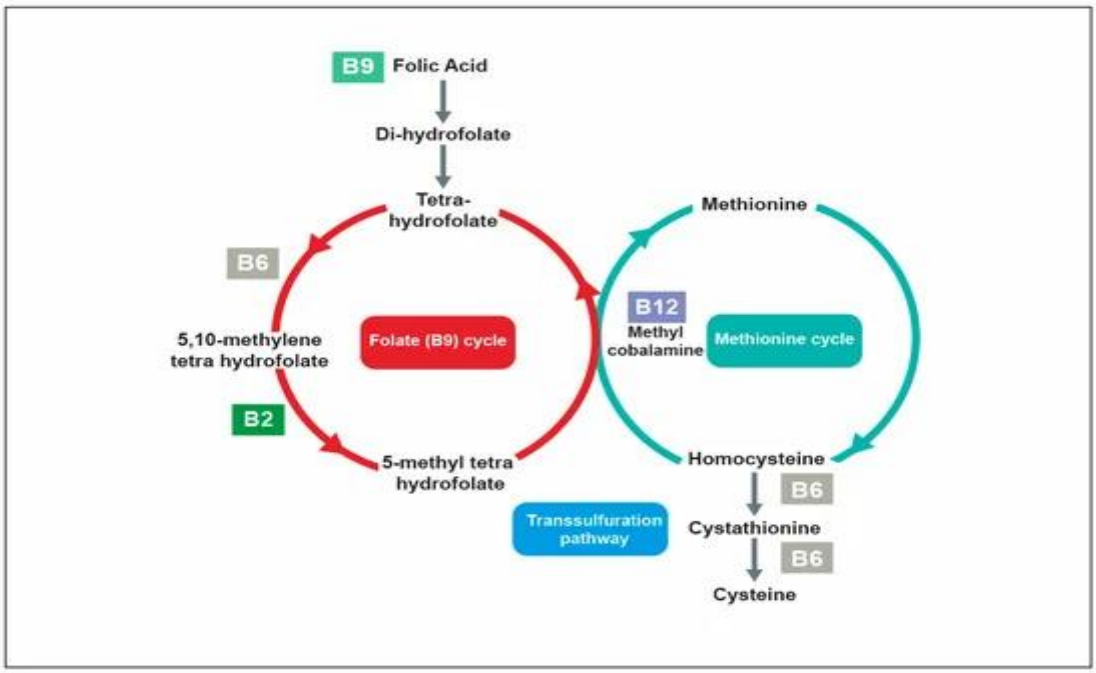

Figure 2: The metabolic and functional interactions between vitamins B9, B12, and B6.

The Role of Riboflavin, Vitamin C, Iron, Magnesium, and Zinc in Oxidative Stress

Brain and muscle cells, which require oxygen for aerobic metabolism, are also highly susceptible to oxidative damage due to the reactivity of oxygen free radicals [63]. This is especially relevant in tissues like the brain and muscles, which consume large amounts of oxygen. To combat this, the body has developed an antioxidant defense system, in which specific vitamins and minerals play significant roles. Riboflavin (vitamin B2) is crucial in protecting against lipid peroxides by participating in the glutathione (GSH) redox cycle. GSH, a potent antioxidant, contains a thiol group that donates electrons. After GSH is oxidized, it is regenerated by the FAD-containing enzyme GSH-reductase, enabling it to continue combating free radicals. Riboflavin deficiency reduces glucose-6-phosphate dehydrogenase activity, which is involved in the GSH cycle [64].

Vitamin C, in the forms of ascorbic acid and L-dehydroascorbic acid, is a potent antioxidant due to its electron-donating properties. Ascorbic acid scavenges reactive oxygen species (ROS) and singlet oxygen, offering significant antioxidant protection in tissues exposed to free radicals [52,53]. Deficiency in vitamin C in the brain may lead to oxidative stress and neurodegeneration, due to the brain's high oxygen consumption [65]. Vitamin E plays a crucial role in halting lipid oxidation, particularly in neuronal membranes. It neutralizes free radicals but is itself oxidized in the process, a function that can be replenished by vitamin C in oxidative-reductive reactions [67]. Although magnesium is not strictly an antioxidant, magnesium deficiency is associated with increased oxidative stress. Inflammation related to low magnesium levels promotes free radical production in phagocytes and neutrophils, contributing to endothelial dysfunction [68]. Preclinical studies also suggest that magnesium deficiency increases nitric oxide production, which, in excess, may lead to the formation of ROS such as hydrogen peroxide [71]. Zinc exhibits antioxidative properties by inhibiting oxidation of macromolecules like proteins and nucleic acids. Zinc activates the expression of metallothionein and catalase, both of which neutralize ROS. As a cofactor of superoxide dismutase, zinc helps convert superoxide anions into hydrogen peroxide, which is further metabolized by catalase [72,73]. Zinc's anti-inflammatory role modulates the nuclear factor-κB pathway, indirectly influencing immune and inflammatory responses [74]. While iron is essential for oxygen transport, excess iron can be toxic, generating free radicals through the Fenton reaction, where iron reacts with hydrogen peroxide to produce hydroxyl radicals, potentially leading to cell damage [54]. In the brain, iron-induced oxidative stress may contribute to

neurodegenerative diseases [75,76]. However, in normal physiological conditions, iron metabolism is tightly regulated to prevent overload. Free iron, the most reactive form, is absent from the body in physiological states as iron is bound to transferrin, ferritin, and various iron-binding proteins, minimizing the potential for free iron to catalyze the Fenton reaction [77,78]. Vitamins and minerals are essential for brain cell structure and function, not only meeting the brain's high energy demands but also playing a crucial role in the formation and maintenance of brain structures and enabling intercellular connections. This is important for healthy individuals of all ages [79] but is particularly critical during infancy and early childhood when brain development is occurring [80], and during aging when significant structural and functional changes in the brain take place [81].

Vitamins and Minerals in Neuronal Structures:

- **Thiamine (Vitamin B1)** plays a role in synapse formation, axon growth, myelin production, and the development of a functional neuroglia. It also helps stabilize the membranes of newly formed neuronal cells during embryogenesis and may regulate apoptosis, potentially through thiamine-binding sites found on biological membranes [82].
- **Pantothenic Acid (Vitamin B5)** is an essential precursor for the synthesis of acetyl-CoA, which is involved in protein acetylation. This process is crucial for the regulation and function of proteins, and it is particularly significant in nervous system structures [83]. Protein acetylation is vital for neuronal development [84].
- **Folate (Vitamin B9)** contributes to cerebral methylation and is essential for maintaining the integrity of neuronal and glial membrane lipids, impacting broader brain functions such as mood, irritability, and sleep [85,86].
- **Vitamin C (Ascorbate)** influences neurotransmitter receptors and brain cell structures, including glutamatergic and dopaminergic neurons, and is involved in the synthesis of glial cells and myelin [65,87].
- **Iron** is necessary for neuronal differentiation and proliferation. Iron deficiency impairs neural processes such as myelination, dendritic arborization, and neural plasticity [88].
- **Zinc** is vital for the formation and migration of neurons and for the development of neuronal synapses [89].

The Role of Vitamins in Neurotransmitter Synthesis:

- **Thiamine (Vitamin B1)** is needed for the synthesis of fatty acids, steroids, nucleic acids, and aromatic amino acids, which serve as precursors to neurotransmitters like acetylcholine, glutamate, and gamma-aminobutyric acid [90].
- **Pantothenic Acid (Vitamin B5)** is crucial for synthesizing acetylcholine, as evidenced by studies where pantothenic acid depletion due to chronic alcohol exposure led to decreased acetylcholine synthesis in the brain [91].
- **Vitamin B6** is essential for the synthesis of neurotransmitters such as serotonin from tryptophan and dopamine from phenylalanine, through the action of the aromatic L-amino acid decarboxylase, which requires pyridoxal phosphate (PLP) as a cofactor [92].
- **Folate (Vitamin B9)** influences cerebral methylation and the metabolism of neurotransmitters like serotonin and dopamine, which are involved in mood regulation. Folate helps maintain adequate levels of tetrahydropterin, a critical cofactor for the synthesis of serotonin and catecholamines [85,93].
- **Vitamin B6, B9, and B12** interact to ensure proper methionine provision, which is necessary for the synthesis of S-adenosyl-L-methionine, a key methyl donor in neurotransmitter and protein synthesis [94].
- **Vitamin C** acts as a cofactor for enzymes involved in the synthesis of catecholamines (noradrenaline and adrenaline) and neuropeptides [65].

The Role of Vitamins and Minerals in Neurotransmission:

- **Niacin (Vitamin B3)**, through NAD, regulates intracellular calcium release, which is integral to nucleotide metabolism and energy status, both of which are crucial for calcium signaling in neurons and brain function [95].
- **Pantothenic Acid (Vitamin B5)** is involved in the palmitoylation of neuronal proteins, which is essential for neurotransmitter release and synaptic communication [83].
- **Iron** plays a role in synaptic function, with iron deficiency shown to alter neural circuitry and neurotransmitter systems. It also modulates calcium signaling, which is essential for synaptic plasticity [88,96].
- **Magnesium** is essential for the active transport of potassium and calcium across cell membranes, contributing to neuromuscular coordination and optimal nerve transmission. It also protects against excessive excitation that could lead to cell death by interacting with the aspartate receptor [97].
- **Zinc** is involved in regulating synaptic excitability in certain neurons and modulates neurotransmission via both glutamate and gamma-aminobutyric acid. While it is essential for neuronal function, excessive zinc can be neurotoxic, although neurons possess mechanisms to maintain zinc homeostasis and prevent toxicity [89].

Clinical Evidence of the Role of Vitamins and Minerals in Physical Fatigue

When vitamins and minerals are provided in sufficient amounts, their biochemical properties support normal physiological functions. However, deficiencies below the required levels can result in clinical symptoms. Increasingly, it is recognized that suboptimal nutrient statuses—often termed 'inadequate' or 'marginal deficiencies'—can lead to functional deficits or increased risk of various pathologies. Both clinical and subclinical deficiencies can be managed through nutrient supplementation [98].

Impact of Inadequate Vitamin and Mineral Status on Physical Fatigue

Severe deficiencies in most vitamins and minerals are linked to physical fatigue, with such symptoms also emerging in marginal deficiencies, although they often go unnoticed due to their nonspecific nature.

Inadequate Status of Individual B Vitamins and Physical Fatigue

- Thiamine (Vitamin B1) deficiency leads to beriberi, which affects various organs, including the muscular and peripheral nervous systems. Symptoms include fatigue, ataxia (muscle weakness in the limbs), muscle pain, and dyspnoea with exertion [99].
- Riboflavin (Vitamin B2) deficiency is typically accompanied by other nutrient deficiencies, making its symptoms hard to isolate. Anemia, which is related to fatigue, has been associated with insufficient riboflavin intake. For instance, in a cohort of 1,253 Chinese adults, over 97% had inadequate riboflavin intake at baseline, correlating with an increased risk of anemia at follow-up [100]. High rates of riboflavin insufficiency have also been found in women from Canada and Malaysia, indicating a greater risk of fatigue-related anemia [101].
- Niacin (Vitamin B3) deficiency can lead to nonspecific symptoms like weakness, loss of appetite, fatigue, and apathy [102].
- Pantothenic Acid (Vitamin B5) deficiency, induced experimentally, caused fatigue, insomnia, and headaches in subjects. After supplementation with pantothenic acid, symptoms improved or disappeared [103]. A case of lethargy linked to anemia and weight loss also showed dramatic improvement with pantothenic acid supplementation [104].
- Pyridoxine (Vitamin B6) deficiency is typically marked by microcytic anemia, leading to symptoms like weakness, tiredness, and fatigue [105]. A study showed that iron supplementation was ineffective in treating anemia in pregnant women with vitamin B6 deficiency, suggesting the critical role of B6 in anemia recovery [106].
- Folate (Vitamin B9) deficiency can cause megaloblastic anemia, which presents with symptoms such as fatigue, headache, and shortness of breath. Fatigue typically becomes apparent at later stages of anemia, especially in the elderly [108].
- Cobalamin (Vitamin B12) deficiency results in decreased energy and exercise tolerance, along with fatigue and shortness of breath. These symptoms resolve with vitamin B12 supplementation [109].

Inadequate Vitamin C Status and Physical Fatigue

Before scurvy symptoms (caused by severe vitamin C deficiency) appear, moderate deficiency can lead to fatigue, irritability, and muscle pain. A study evaluating plasma vitamin C levels in the general UK population found a correlation between low vitamin C levels and poorer physical functional health. Among over 15,000 men and women aged 40-79, those in the lowest quartile of vitamin C had significantly worse self-reported physical health, vitality, and pain scores compared to those in the highest quartile. The results were more consistent for participants not taking vitamin C supplements, supporting previous findings that higher intake of fruits and vegetables (major sources of vitamin C) is linked to better physical health outcomes [110, 111].

Consequences of Inadequate Iron and Magnesium Status on Physical Fatigue

Iron and magnesium deficiencies have significant effects on physical fatigue, particularly in terms of muscle function, energy metabolism, and exercise performance.

- **Iron Deficiency and Fatigue**: Iron is crucial for oxygen transport and enzyme activity. Iron deficiency, even in the absence of anemia, can lead to fatigue, reduced physical performance, and impaired aerobic capacity (VO2max). Clinical studies show that anemia due to iron deficiency, characterized by hemoglobin levels below 120 g/L in women and 130 g/L in men, significantly reduces exercise capacity and work efficiency. Supplementing with iron restores hemoglobin levels and can reverse these impairments, improving energy levels and physical performanceiency and Fatigue**: Magnesium plays a vital role in muscle contraction, nerve transmission, and energy metabolism. Deficiency in magnesium can lead to symptoms like muscle cramps, weakness, fatigue, and loss of appetite. Studies indicate that magnesium deficiency impairs muscle performance and endurance. Athletes, for instance, have shown better strength and performance when magnesium levels are adequate. Magnesium also impacts cardiorespiratory functions, with higher magnesium intake associated with lower oxygen needs and improved exercise performance .

Effects of Suprals on Physical Fatigue

The role of supplementation with specific vitamins and minerals, particularly B vitamins, vitamin C, and magnesium, in alleviating physical fatigue has been explored in various studies [112].

- **B Vitamins and Fatigue**:
  - **Thiamine (B1)**: High-dose thiamine supplementation (100 mg/day) in athletes reduced fatigue and increased blood thiamine levels .
  - **Riboflavin (B2)**: Riboflavin supplementation to improved anemia and reduced fatigue. Studies in young women showed that riboflavin supplementation improved hemoglobin levels and reduced muscle soreness and fatigue in ultramarathon runners .
  - **Pantothenic Acid (B5)**: Though animal studies suggest cid in reducing muscular fatigue, human studies have been inconclusive .
  - **Folate (B9)**: Folate supplementation has been shown to reduce fatigue in children, highlighting its role in maintaining energy levels in certain conditions .
- **Vitamin C and Fatigue**:
  - Vitamin C supplementation has been shown to reduce perceived moderate exercise. Studies involving doses of 500 mg to 10 g of vitamin C daily have demonstrated improvements in fatigue ratings and general well-being. This may be due to vitamin C's role in enhancing iron absorption and oxygen delivery, as well as its

antioxidant properties that prevent oxidative damage to red blood cells .

Overall, adequate levels of iron, magnesium, and certain vitamins are essential for maintaining physicaparticularly physically active individuals. Supplementation, when necessary, can be beneficial in restoring optimal levels and alleviating fatigue, though appropriate dosages and long-term effects require further research.

Conclusion:

This review highlights the critical role of micronutrients in regulating biochemical pathways involved in energy metabolism and metabolic health. Vitamins and minerals, such as B vitamins, iron, magnesium, and vitamin C, are essential for cellular energy production, oxygen transport, and the management of oxidative stress. The cellular processes of oxidative phosphorylation, which generate ATP for energy, are heavily reliant on these nutrients. Iron, for instance, is pivotal in oxygen transport through hemoglobin, while magnesium supports muscle function and endurance, and vitamin C aids in iron absorption and protects against oxidative damage. Inadequate micronutrient status, particularly deficiencies in iron, magnesium, and B vitamins, leads to impaired energy production, increased oxidative stress, and heightened fatigue. These deficiencies are commonly linked to physical and mental fatigue, reduced endurance, and diminished performance, particularly in individuals under physical stress or in clinical populations. Clinical evidence supports the efficacy of micronutrient supplementation in alleviating fatigue and improving overall metabolic health. For instance, iron supplementation can restore hemoglobin levels and enhance oxygen transport, while magnesium and vitamin C supplementation can improve muscle function and energy levels. The findings of this review suggest that maintaining optimal micronutrient levels is vital for sustaining energy levels, improving physical performance, and preventing fatigue. Micronutrient supplementation should be considered in individuals at risk of deficiencies, particularly in those with low intake or higher metabolic demands, such as athletes or individuals with chronic diseases. However, more research is needed to determine the precise dosages, combinations, and long-term effects of micronutrient supplementation in combating fatigue and improving metabolic health. Ultimately, a balanced diet rich in essential vitamins and minerals, along with targeted supplementation when necessary, can significantly enhance energy metabolism, reduce fatigue, and improve overall well-being. Further studies should aim to explore the synergistic effects of micronutrient combinations and their potential for supporting optimal metabolic and physical health.

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