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# Role of Nutritional Factors, Mitochondrial Dysfunction, Altered Body Composition and Various Biological Factors in Chronic Fatigue Syndrome

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***Authors' contributions***

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## ABSTRACT

Fatigue is a prevalent complaint among individuals, characterized by a decline in energy levels, mental and physical fatigue, reduced stamina, and longer recovery time following exertion. While the root cause of tiredness remains unclear, it is typically associated with illness. Although tiredness

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is not exclusively linked to a particular condition, mitochondrial malfunction is a common contributor to exhaustion, indicating that mitochondrial dysfunction may be a biological factor that causes fatigue. Additionally, factors such as mitochondrial energy metabolism, immunological response, and genetics can also play a role. However, the absence of a standard methodology for assessing fatigue and a limited understanding of its pathophysiology pose challenges for diagnosing fatigue in clinical settings but a detailed studies suggests a number of marginal nutritional deficiencies may have etiologic relevance. Throughout life, significant changes in body composition occur, with the most notable being a decrease in lean body mass and an increase in body fat as we age. These changes have a profound impact on the development of frailty in older adults. Frailty is a complex condition that reduces patient's homoeostatic reserves, making them more susceptible to shocks.
In this review, we present an overview on the mechanisms that may mediate fatigue levels, with a special focus on nutritional and vitamin supplement.

*Keywords: Chronic fatigue syndrome (CFS); inflammation; oxidative stress; nutritional supplements.*

## 1. INTRODUCTION

Vitamin B group plays a crucial role in maintaining optimal body energy levels, supporting brain function, and regulating cell metabolism [1].

However, deficiencies in this essential nutrient can result from several factors, including an imbalanced diet, unregulated use of fertilizer in agriculture, excessive alcohol consumption, certain medications, and gut malabsorption conditions [2]. The other supplements that play a critical synergistic role with vitamin B group are ginseng, taurine, and guarana, which may work together to provide additional benefits. For instance, the caffeine in guarana may enhance the cognitive benefits of ginseng, while the taurine may help reduce the negative side effects of caffeine, such as anxiety and increase heart rate."

The symptoms of vitamin B deficiency can vary, ranging from paresthesias and peripheral neuropathy to psychosis, heart attack, stroke and diabetes mellitus over time if left untreated. Given the vital role of this nutrient in the body, it is essential to consider both the nutritional aspect of our food and the need for pharmaceutical supplementation of vitamin B to adequately support body function on a daily basis. Despite its prevalence and significant impact on individuals, fatigue is often overlooked as a symptom. It is a syndrome characterized by a decrease in physical and/or mental resources, resulting in weariness and reduced ability to perform daily tasks [3,4].

Fatigue can range from a general feeling of lethargy to a specific burning muscle sensation caused by excessive effort. Somnolence is the most common sign of cerebral fatigue [5]. "Fatigue has several definitions and operationalizations, with interchangeable names such as tiredness, exhaustion, fatigability, low vitality, anergia, weakness, and lassitude [6,7].

It is associated with poor physical performance and diet containing essential minerals, vitamins and is a significant predictor of negative outcomes in general population as well as older individuals, including hospitalizations, increased use of healthcare services, disability, and death [8-10]. It is a common symptom in many conditions, including cancer, neurological disorders, rheumatologic disease, and heart failure. For many elderly adults, Fatigue is difficult to explain or trace to a specific condition [11,12]. It may be a restricted homeostatic reaction to a disproportionate stressor and is vastly underappreciated as a symptom in both clinical and research settings due to the absence of a gold standard for measuring it. Nutritional status and vitamin supplementation are important mediators of fatigue suppression, as exhaustion may mimic the depletion of metabolic reserves and if untreated may have deleterious impact on individual's health and quality of life.

## 2. VITAMIN B IN ENERGY PRODUCTION

Vitamin B3 also known as niacin referred as nicotinamide which is a precursor for NAD as well as nicotinamide adenine dinucleotide phosphate. During glucose breakdown, electrons are removed by $NAD^+$ and converted to NADH molecule. NAD is also required in numerous metabolic cycles for energy generation such as tricarboxylic acid cycle. Finally, NADH generated through metabolism, transported to electron transport chain, where NADH is oxidized and donates its electron to initiated transport across the chain in order to phosphorylate ADP to ATP as a principal energy source in the body [13].

Pyridoxine (vitamin B6) refers to a group that includes pyridoxine, pyridoxal and pyridoxamine, and their respective phosphorylated forms. The metabolically active forms act as cofactors of enzymes involved in amino acid metabolism, one-carbon reactions, glycogenolysis and gluconeogenesis, heme synthesis, and niacin formation from tryptophan, as well as in lipid metabolism and hormone action [14]. Pyridoxal phosphate (PLP) is a cofactor for glycogen phosphorylase, which releases glucose-1-phosphate from glycogen and provides additional glucose when needed, such as in exercising muscle (not shown on figure) [14].

Pantothenic acid (vitamin B5) is fundamentally important precursor for synthesis of coenzyme-A that contributes to normal mental performance and a reduction in tiredness and fatigue. Vitamin B5 also contributes to the normal synthesis and metabolism of steroid hormones and some neurotransmitters. It is involved in breakdown of fat and carbohydrate for energy, it essential in biosynthesis of red blood cells as well as stress-related hormones produced in adrenal glands. Pantothenic acid also has potential antioxidant effects that reduce low grade inflammation which can be present in early stage of diseases.

Vitamin B12 is required for conversion of homocysteine to methionine amino acid by methylation process. The extent of homocysteine elevation was inversely proportional to the level of vitamin B12 in the CFS, thereby suggesting that vitamin B12 deficiency in the CFS caused a reduction in the remethylation of homocysteine by methionine synthase and methylcobalamin. In some study, it has been found some improvement of symptoms in some individuals who had CFS and who were given repeated high dose treatment with methyl vitamin B12 [15, 16].

## 3. GINSENG, GUARANA, TAURINE, AND CAFFEINE

Caffeine is a well-known stimulant that affects numerous neurotransmitter and endocrine signaling pathways. Taurine is a sulfur-containing amino acid with antioxidant properties [17] that is abundant in the developing brain, as well as in the adult hippocampus [18], cerebellum [19], and hypothalamus. Numerous studies investigated a Powerful Combination for Energy and Health. When it comes to boosting energy levels and promoting overall health, many people turn to supplements such as ginseng, guarana, taurine, and caffeine. These supplements are popular for their potential to provide mental and physical benefits, and when taken together, they may work synergistically to provide even greater benefits [20].

Ginseng is a root of a plant that has been used for centuries in traditional medicine and is believed to have cognitive and physical benefits. It has been suggested that ginseng may improve mental performance, boost energy levels, and reduce stress and fatigue. Several studies have shown that ginseng can improve cognitive function, including memory, attention, and reaction times [21,22].

It may also help to reduce oxidative stress and inflammation in the body, which can contribute to chronic diseases such as heart disease and cancer. Guarana is a plant that is native to the Amazon basin and is known for its caffeine content. Guarana contains more caffeine than coffee beans, making it a popular ingredient in energy drinks and supplements. In addition to providing a natural source of energy, guarana has been suggested to improve cognitive function and reduce fatigue [23,24].

Some studies have also shown that guarana may have antioxidant and anti-inflammatory properties, although more research is needed [25,26]. Taurine is an amino acid that is commonly found in energy drinks and supplements. It has been suggested that taurine may help to reduce muscle damage, improve exercise performance, and enhance mental focus. Taurine has also been shown to have antioxidant and anti-inflammatory properties, which may help to protect against chronic diseases such as heart disease and diabetes [27-29]. Caffeine is a stimulant that is found in many beverages and supplements. It is known for its ability to increase alertness and improve mental and physical performance. Caffeine has also been suggested to have potential health benefits, such as reducing the risk of certain types of cancer and improving cognitive function in older adults [30,31].

When taken together, ginseng, guarana, taurine, and caffeine may work synergistically to provide additional benefits. For example, the caffeine in guarana may enhance the cognitive benefits of ginseng, while the taurine may help to reduce the negative side effects of caffeine, such as anxiety.

In conclusion, ginseng, guarana, taurine, and caffeine are popular dietary supplements that have been used for their potential health benefits. When taken together, they may work synergistically to provide even greater benefits for energy and overall health. This article provides an overview of fatigue trends and emphasizes the role of diet and supplements in altering fatigue levels in older individuals as well as general population.

## 4. BIOLOGICAL CONTRIBUTION

Weakness is a complex and multi-faceted symptom. The underlying mechanisms that contribute to fatigue are not fully understood, but they may involve a variety of biological factors that can aid in understanding the phenomenon. Changes in heart function, chronic inflammation, alterations in skeletal muscle, nutritional deficiencies, and sleep disturbances are all potential contributors to fatigue [4,5]. The intricate interplay of these biological factors may help to explain the complexity of fatigue and its varied presentation in different individuals.

Fatigue is associated with overall cardiovascular function [32] and a reduce aerobic threshold [33,34]. Pain may contribute to fatigue by increasing heart rate, blood pressure, respiratory rate, muscular tension, and oxygen consumption [35]. Additionally, sleep disturbances (both subjective and quantitative) are common in the older population and may contribute to the onset of fatigue. Individuals who sleep for shorter periods of time often experience more fatigue than those who sleep for longer periods [36].

It is not surprising that older adults who report sleep problems experience more fatigue than others [37]. Lack of sleep has also been associated with metabolic changes. Experimentally induced sleep deprivation in healthy individuals has been shown to increase cortisol levels and calorie intake, while decreasing glucose resistance and leptin levels [38,39]. Distinguishing between drowsiness and fatigue can be challenging. Both drowsiness and fatigue can lead to a decrease in quality work performance or an increase in calorie consumption as individuals try to boost their energy levels [40]. Changes in body composition and eating habits are also factors that may contribute to fatigue. Alterations in sleep, mood, and skeletal muscle function can all contribute to fatigue and its underlying conditions.

## 5. LIFE STYLE MODIFICATIONS

Many changes accompany advancing age, including physiological, psychosocial, and neurological changes, which may lead to decreased appetite and affect the amount and quality of food consumed [41]. This condition has been described as "anorexia of aging," a syndrome that can cause malnutrition and weight loss in older adults [42,43].

The underlying causes of anorexia of aging are complex and may involve a combination of factors, including changes in taste and smell, reduced gastrointestinal motility, altered hormonal regulation, and social and psychological factors [44]. The consequences of anorexia of aging can be serious and may include increased frailty, functional decline, and mortality. Therefore, it is crucial to identify and address anorexia of aging in older adults to prevent adverse outcomes and improve overall health and well-being.

Undernutrition can lead to weight loss and nutritional deficiencies, which can result in fatigue through the "lack of energy" concept [45]. When protein and energy intakes are insufficient to meet the body's needs, body reserves are catabolized to provide energy, leading to muscle fatigue and loss of both fat and muscle mass, which can result in fatigue or lethargy [45,46]. Poor nutritional status is also associated with decreased physical performance, which can further exacerbate fatigue [45]. Therefore, addressing undernutrition and ensuring adequate nutrient intake is essential for preventing and managing fatigue. The other nutritional factor that requires special investigation is nutritional value of food. Since the advancement in agriculture lead to usage of numerous fertilizers over time, hence it induced a great impact on quality and nutritional value of ingredient used in food preparation. There appears to be a bidirectional association between malnutrition and fatigue. While undernourished individuals are more likely to experience fatigue, individuals experiencing fatigue may also be at risk of undernutrition due to a lack of energy to prepare meals or consume sufficient nutrients. This can create a vicious cycle where fatigue leads to undernutrition, which in turn exacerbates fatigue. Therefore, addressing both fatigue and undernutrition is essential to break this cycle and improve overall health and well-being in individuals at risk [44].

Persistent low-grade inflammation, a symptom of the aging process, is considered one of the main causes of anorexia in older adults. This phenomenon, known as "inflamm-aging," is characterized by increased circulating concentrations of cytokines such as interleukin

(IL) 1, IL-6, and tumor necrosis factor alpha (TNF-α) [44,47], which are responsible for a decrease in food intake, altered metabolism (i.e., increased resting energy expenditure), and increased muscle catabolism. These effects can ultimately lead to malnutrition and an increased risk of illness in older adults. Addressing the underlying inflammation in older adults may be an important strategy for preventing and managing anorexia and its associated consequences [48]. Furthermore, Micronutrient deficiencies can also contribute to oxidative stress and perpetuate a chronic cycle of inflammation. In addition, chronic low-grade inflammation has been implicated in mediating many chronic conditions characterized by the presence of fatigue. These conditions include autoimmune diseases, neurodegenerative disorders, and some types of cancer. Therefore, addressing micronutrient deficiencies and reducing inflammation through dietary interventions may be crucial for preventing and managing fatigue and associated chronic diseases [49].

Excessive food consumption, leading to weight gain, can also contribute to fatigue. Overeating, especially increased fat consumption, has been linked to altered sleep patterns (i.e., daytime drowsiness, poor nocturnal sleep quality, and sleep apnea), resulting in fatigue [50-53]. Additionally, a high-carbohydrate meal, especially one high in simple sugars, may disrupt sleep patterns and lead to emotional fatigue symptoms [51,54,55]. Therefore, maintaining a balanced and healthy diet is crucial for preventing fatigue and promoting overall health and well-being. Consuming high-fat and sugar foods can lead to increases in blood levels of glucose, insulin, leptin, cholecystokinin (CCK), peptide YY, and enterostatin, all of which have somnogenic effects [56].

Cholecystokinin is the hormone secreted after taking high fat and meals as a satiety hormone that has direct impact on the quality of sleep and therefore it has strong influences on fatigue. On the other hand, dietary modification by decreasing the intake of fat and sugar could be beneficial in reducing fatigue [51,55]. Additionally, maintaining a balanced and healthy diet that includes sources of protein, fiber, and complex carbohydrates can help regulate blood sugar levels and promote sustained energy throughout the day [57,58]. Long-term high-fat consumption can lead to elevated levels of leptin, an obesity hormone, and decreased levels of ghrelin, a hormone that modulates arousal and attention through orexin. Overproduction of leptin can induce the release of pro-inflammatory cytokines and has also been linked to frailty [58]. Therefore, poor dietary habits, irritability, and sleep disturbances may all play a significant role in the complex etiology of fatigue. Addressing these factors through dietary interventions, improving sleep hygiene, and managing stress may be important strategies for preventing and managing fatigue [59-61].

## 6. ALTERATION IN BODY COMPOSITION

As previously mentioned, changes in food intake during aging can have an impact on nutritional status, which can in turn lead to changes in body composition [62]. With advancing age, fat mass tends to increase while muscle mass declines, resulting in a decrease in resting metabolic rate (RMR) [63]. This decrease in RMR can contribute to fatigue and reduced physical activity, which can further exacerbate the loss of muscle mass and increase the risk of malnutrition. Therefore, maintaining a healthy and balanced diet, with adequate protein intake, is important for preserving muscle mass and preventing age-related declines in RMR and physical function. Additionally, regular exercise can help to maintain muscle mass and improve overall health and well-being in older adults [64].

Despite the higher risk of malnutrition in older adults, there has been an increase in the prevalence of overweight and obesity in this population in recent years. This is a concerning issue as obesity has been linked to higher levels of fatigue [65-67]. Fatigue in obese adults may be mediated by systemic inflammation, which is a hallmark of obesity. Adipose tissue releases pro-inflammatory cytokines, which can contribute to chronic low-grade inflammation and fatigue. Additionally, excess body weight can lead to physical inactivity, which can further exacerbate fatigue and other health issues. Therefore, managing weight and reducing inflammation through dietary interventions and regular exercise may be important strategies for preventing and managing fatigue in obese older adults [68].

Individuals with higher levels of adiposity have been found to have higher levels of C-reactive protein, TNF-α, IL-6, leptin, and resistin, all of which are markers of inflammation [69,70]. Obesity has also been linked to sleep disturbances, and vice versa. Sleep disruptions can lead to metabolic changes such as lower glucose tolerance and insulin sensitivity, as well as endocrine changes such as lower leptin levels, higher evening cortisol levels, higher ghrelin levels, and increased hunger and appetite, all of which can promote obesity [71]. Therefore, addressing both obesity and sleep disturbances through lifestyle interventions may be important for preventing and managing fatigue and associated health issues. This may include dietary modifications, regular exercise, and optimizing sleep hygiene [72].

Obesity is associated with metabolic changes such as insulin resistance and impaired glucose tolerance, as well as endocrine changes such as elevated cortisol levels but increased leptin and decreased ghrelin levels, in the same domains as sleep disorders [73]. Interestingly, sleep disturbances may also be caused by elevated levels of pro-inflammatory cytokines, and obesity may cause sleep difficulties by increasing pro-inflammatory cytokines, resulting in fatigue. Obesity appears to be consistently related to changes in both qualitative and quantitative sleep dimensions, including decreased sleep quality, shorter sleep duration, and increased sleep-disordered breathing. Therefore, addressing both obesity and sleep disturbances through lifestyle modifications may be important for preventing and managing fatigue and associated health issues [74,75]. This may include dietary changes, regular physical activity, and optimizing sleep hygiene.

Obesity has been identified as a major risk factor for obstructive sleep apnea in several studies. Additionally, obese individuals often report daily drowsiness and fatigue. Obesity may be considered a "chronobiological disorder" that affects fatigue levels, based on the relationship between sleep changes, adiposity, and metabolic issues. Another interesting issue is that obesity is commonly associated with fatigue-related symptoms such as depression and discomfort [75]. Moreover, in addition to hindering physical activity, excess body weight may also impair the ability to perform various daily tasks, leading to increased fatigability. Therefore, managing weight and addressing sleep disturbances through lifestyle modifications such as diet, exercise, and sleep hygiene may be important for preventing and managing fatigue and associated health issues in obese individuals [76]. Physical activity levels tend to decline with age, and insufficient physical exercise has been linked to fatigue. Recent data suggests that physical activity may help to reduce fatigue; however, older adults with increasing levels of fatigue, particularly those who are weak and/or obese, may lack the energy required for exercise and may further decrease their levels of physical activity. In fact, deconditioned older adults often have difficulty performing even ordinary daily tasks. Therefore, addressing fatigue in older adults may require a multidisciplinary approach that includes not only dietary interventions and optimizing sleep hygiene but also tailored exercise programs that are appropriate for their level of physical function and mobility. This may include resistance training, balance exercises, and aerobic activity, with adjustments made based on individual needs and abilities. Gradual increases in physical activity levels may help to improve energy levels and reduce fatigue over time.

## 7. UNDERNUTRITION

Poor dietary status is another issue that may contribute to fatigue. As mentioned earlier, fatigue can mimic the exhaustion of an undernourished individual's metabolic reserves, which is a signal issued by the organism in response to a significant decline in its reserves. In fact, fatigue is a common symptom of various micronutrient deficiencies [77]. Additionally, it has been suggested that fatigue may be caused by the link between dysphagia (difficulty swallowing) and malnutrition, as inadequate nutrient intake can contribute to fatigue and other health issues [78]. Therefore, maintaining a healthy and balanced diet that includes a variety of nutrient-dense foods may be important for preventing and managing fatigue. It may also be helpful to consult a healthcare professional or registered dietitian to identify and address any nutrient deficiencies or other dietary issues that may be contributing to fatigue [79,80].

Dysphagia and masticatory issues can be debilitating disorders that contribute to fatigue in older adults as well as general population. Eating a sufficient amount of food can be challenging for dysphagic individuals who require more time to eat, making meals a stressful and exhausting experience. Moreover, alterations in masticatory function, such as tooth loss, can result in the selection of soft and easy-to-chew meals due to muscle weariness, which may have a negative impact on nutritional status. In fact, chewing difficulties and tooth loss have been linked to malnutrition and fatigue in the elderly.

Fatigue can also be considered an energy balance problem, as it is often reported as a feeling of reduced energy. Resting metabolic rate (RMR) accounts for the majority of energy used during the day (60-70%). As previously mentioned, aging is associated with metabolic changes, and RMR decreases in older adults, mainly due to changes in body composition. In addition to these alterations, several comorbidities can affect cellular balance and activate processes that require additional energy [81]. For example, thyroid diseases, which are common in older adults, can affect RMR and frequently result in fatigue. The hypothalamic-pituitary-thyroid axis controls physiological energy needs via thyroid hormones, which are related to body weight and energy expenditure. Hyperthyroidism is characterized by a hypermetabolic state marked by higher RMR, weight loss, lower cholesterol levels, and increased lipolysis and gluconeogenesis. Hypothyroidism, on the other hand, is characterized by hypo-metabolism with decreased RMR, weight gain, elevated cholesterol levels, and decreased lipolysis and gluconeogenesis. These findings provide a solid foundation for a potential link between bodily changes, metabolic alterations, and fatigue symptoms [82-84].

## 8. MITOCHONDRIAL DYSFUNCTION AND FATIGUE

Sarcopenia, the age-related decline in muscle mass and function, is thought to be driven by multiple processes, with mitochondrial dysfunction in skeletal muscle cells playing a key role [85,86]. Mitochondrial damage is associated with the aging process and may contribute to the development of age-related diseases. Mitochondria are crucial for bioenergetics, particularly in high-energy-demanding tissues like muscle [87]. Additionally, mitochondria are a primary source of reactive oxygen species (ROS) in the cell. ROS play a role in cellular signaling and survival under normal conditions [88].

High levels of ROS can cause damage to intracellular macromolecules, such as proteins, lipids, and nucleic acids [85]. Mitochondria are the primary source of energy generation through the oxidative phosphorylation process, which utilizes nutrients to produce ATP. Mitochondrial dysfunction can lead to energy deficiency, resulting in reduced stamina and fatigue. Additionally, mitochondrial dysfunction and oxidative stress have been linked to inflammation [86,89,90]. Pro-inflammatory mediators can impact mitochondrial energy metabolism and function, promoting inflammation through the production of oxidants and the release of damage-associated molecular patterns (DAMPs) [89,90]. Interestingly, fatigue is a common symptom in various disease states characterized by both inflammation and mitochondrial dysfunction [91]. However, due to its complexity, fatigue cannot be fully explained by a single illness or process. Nevertheless, the significant role of mitochondrial activity in many age-related metabolic processes may support the involvement of these organelles in the development of fatigue. In other words, fatigue may be a multifaceted clinical symptom of mitochondrial dysfunction can also lead to increased anaerobic metabolism and the generation of lactic acid, which can contribute to muscle fatigue. Therefore, mitochondrial impairments may provide insight into the relationship between aging, muscle loss, and fatigue, as mitochondria play a vital role in energy and ROS production [85,92].

## 9. NUTRITIONAL INTERVENTIONS

As noted earlier, fatigue can be felt at the muscle level. Therefore, dietary interventions aimed at preventing muscle deterioration may be beneficial in managing fatigue. Research suggests that older adults require more protein to maintain muscle mass compared to younger individuals [93]. In fact, both the European Society for Clinical Nutrition and Metabolism (ESPEN) [94] and the PROT-AGE research group [93] have agreed that the current recommended dietary allowance (RDA) for protein (0.8 g/kg body weight/day) is inadequate for older adults.

Increasing protein intake may help to prevent muscle loss and promote muscle regeneration, which may improve energy levels and reduce fatigue. Additionally, adequate protein intake is essential for maintaining other physiological functions, such as immune function and wound healing. It is important to note that dietary protein intake alone may not be sufficient to prevent or manage fatigue in older adults. A comprehensive approach that includes tailored exercise programs, optimizing sleep hygiene, and addressing any underlying medical conditions is likely necessary to effectively manage fatigue in this population. To preserve muscle mass, it is recommended to increase daily protein intake to 1-1.2 g/kg body weight/day and up to 1.5 g/kg body weight/day in the presence of acute or chronic illnesses [93,94]. Moreover, the per-meal anabolic threshold of protein intake appears to be higher in older adults than in young adults, suggesting that older adults may need to consume at least 25 to 30 g of protein per meal, which should include approximately 2.5 to 2.8 g of leucine [93].

In addition to the quantity of protein, the source of protein is also important. Plant-based proteins are thought to have fewer anabolic effects than animal proteins, in part due to their low content of essential amino acids and leucine [93,95]. Therefore, older adults may benefit from consuming a variety of high-quality protein sources, including animal-based proteins like meat, poultry, fish, and dairy products, as well as plant-based proteins like soy, legumes, and nuts.

It is worth noting that dietary protein intake should be considered in the context of an individual's overall dietary pattern and health status. Older adults should aim to consume a balanced diet that includes a variety of nutrient-dense foods, in addition to meeting their protein needs. Consulting a registered dietitian or healthcare provider can help individuals develop a personalized nutrition plan that meets their unique needs and goals. It has been suggested that combining plant-based and animal protein sources can provide adequate protein intake [95]. Additionally, research suggests that rapidly digestible proteins may induce muscle protein synthesis more effectively, although this needs to be confirmed in larger studies [93]. Certain proteins can be converted into short-chain fatty acids (such as propionate, butyrate, and acetate), which can be utilized by muscle cells for energy production [96-99]. Short-chain fatty acids also possess anti-inflammatory properties and can enhance muscle anabolism [100-103]. Therefore, it would be interesting to investigate whether protein supplementation can have a beneficial effect on fatigue symptoms.

Most of the evidence linking dietary factors to fatigue comes from studies on chronic fatigue syndrome (CFS). Deficiencies in certain dietary components (such as vitamin C, B vitamins, salt, magnesium, zinc, folic acid, L-carnitine, L-tryptophan, essential fatty acids, and coenzyme Q10) have been observed in patients with CFS [104]. However, many of the dietary deficiencies that may contribute to CFS are also commonly observed in older adults. Therefore, dietary interventions aimed at managing CFS may have a positive impact on older adults experiencing fatigue. It is important to note that fatigue, while often unexplained, can also be a symptom of an underlying medical condition. Therefore, any intervention for fatigue should involve a comprehensive approach. Nutritional therapies for older adults should be individualized to their specific needs, taking into account factors such as nutritional status, physical activity level, and medical history [105].

Certain food components have been shown to be effective against fatigue symptoms. For instance, acetyl L-carnitine has been demonstrated to alleviate both mental and physical fatigue in older adults, while vitamin D insufficiency has been associated with both mental and physical fatigue [106]. Given the link between fatigue, inflammation, and oxidative stress, antioxidant supplementation has been proposed as a potential method for reducing fatigue. Nicotinamide adenine dinucleotide and coenzyme Q10 have been shown to improve fatigue in individuals with CFS, and animal studies have also demonstrated that antioxidants can reduce fatigue [107,108]. However, evidence in humans is still limited [109].

In summary, managing fatigue requires a comprehensive approach that addresses the underlying cause(s) of fatigue, optimizes nutrition, promotes physical activity, and manages any underlying medical conditions. Further research is needed to determine the effectiveness of specific dietary interventions and antioxidant supplementation in reducing fatigue in target population.

## 10. CONCLUSION

There is a strong interplay between cellular energy production, vitamins, and other energy supplementation in humans, with significant implications for physical and mental performance, as well as cognitive and psychological functions. Two of the most energy-demanding organs in the human body are skeletal muscle and the brain. The role of vitamins, minerals, and other supportive supplements such as ginseng, guarana, taurine, and caffeine cannot be underestimated in this complex relationship. These micronutrients exhibit a close synergistic effect at every step of energy production in metabolism, and any deficiency in these nutrients can lead to general fatigue.

While energy production is crucial, both muscles and the brain require additional energy to function optimally. Hemoglobin, found in red blood cells, plays a vital role in delivering oxygen to these organs. The synthesis of hemoglobin, known as erythropoiesis, occurs in the bone marrow through an energetically demanding process that relies on the presence of vitamins and minerals. Inadequate levels of these micronutrients can impair erythropoiesis, leading to decreased oxygen-carrying capacity and reduced performance in both physical and mental activities.

Moreover, vitamins and minerals are also involved in the development and maintenance of neurotransmitters, which are essential for proper neuronal and cellular functions in the brain. Neurotransmitters facilitate communication between brain cells and play a significant role in various cognitive processes, including memory, learning, attention, and mood regulation. Deficiencies in these micronutrients can disrupt neurotransmitter synthesis and function, impacting cognitive abilities and contributing to cognitive impairments.

For instance, vitamin B12 is essential for the synthesis of myelin, a protective sheath that covers nerve fibers. Myelin enables efficient transmission of nerve signals and supports overall neuronal integrity. Inadequate vitamin B12 levels can result in demyelination, leading to impaired neural communication and potential cognitive decline.

Similarly, vitamin D, often referred to as the sunshine vitamin, is crucial for brain health. It modulates the expression of genes involved in neurotransmitter synthesis and promotes the production of neurotrophic factors, which support neuronal growth, survival, and plasticity. Vitamin D deficiency has been associated with an increased risk of cognitive impairment, depression, and other mental health issues.

Minerals such as iron, zinc, and magnesium are also vital for energy production and brain function. Iron is a key component of hemoglobin and plays a crucial role in oxygen transport. Inadequate iron levels can lead to anemia, characterized by fatigue, weakness, and impaired cognitive function. Zinc is involved in numerous enzymatic reactions in the brain, including those related to neurotransmitter synthesis and modulation. Zinc deficiency has been linked to cognitive deficits and mood disorders. Magnesium, on the other hand, supports neuronal excitability regulation, synaptic plasticity, and energy metabolism in the brain. Insufficient magnesium intake has been associated with increased risk of cognitive decline, anxiety, and depression.

In conclusion, the interplay between cellular energy production, vitamins, minerals, and other supportive supplements is essential for optimal physical and mental performance, as well as cognitive and psychological functions. Deficiencies in these micronutrients can disrupt energy production pathways, impair neurotransmitter synthesis, and compromise the overall functioning of skeletal muscle and the brain. Adequate intake of vitamins and minerals, along with a well-balanced diet and lifestyle, is crucial for maintaining optimal energy levels and supporting cognitive health.

## CONSENT AND ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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