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Research Article

# Adequacy and Importance of Dietary Antioxidants in Traumatic Brain Injury Patients

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## ABSTRACT

**Objective:** To evaluate dietary adequacy of patients presenting for evaluation at an outpatient Traumatic brain injury (TBI) clinic.

**Research Design and Method:** We identified 6 key dietary antioxidants with defined dietary intake reference ranges that are considered important for brain health. Adult patients completed the 24-hour recall-face-to-face interview to calculate estimated nutrient intake. Nutrients were assessed individually and were also summarized into a summary score of intakes. Individual nutrients, summary nutrient intake, were compared with recommended dietary requirement (RDA) to assess the adequacy, body mass index was calculated, and medical records were abstracted for diagnoses of TBI.

**Results:** A total of 71 TBI patients were complete the study, the majority were young age between 18-30 years, half of patients were classified as mild TBI while 12.7% and 40.8% were classified as moderate and severe TBI respectively based on Glasgow Coma Scale (GCS). Motor vehicle accidents were the most common cause of TBI followed by falls from height. One fourth of patients were underweight, while (47.9%) were normal weight and 24% were overweight and/or obese. Most of patients (72%) were current smokers; no patient met the RDAs for all six dietary antioxidants. Eighteen patients only (25%) fulfilled the requirements for 4 or more nutrients, while 53 patients fulfilled 6 or fewer requirements. The overall daily intake of dietary antioxidants was significantly lower than the RDA.

**Discussion:** The importance of micronutrients is often neglected. Diets failing to meet RDAs for important brain nutrients were common in an outpatient TBI clinic, with the worst mean scores of intakes for those patients compared with the estimated average requirements. Multidimensional treatment plans, perhaps incorporating some of the described nutritional adjuvants, will thus merit more investigations from both the bench and the bedside to elucidate effective strategies to best treat TBI patients.

**Keywords:** Traumatic brain injury; Nutrition; Diet; Vitamins; Antioxidants

## INTRODUCTION

Supportive nutrition is considered a critical part of treating patients with acute severe traumatic brain injury (TBI), but there is little research on the role of nutrition in different forms of TBI and there is no specific standard of nutritional care for TBI patients after discharge from the hospital.

TBI is a major public health concern, more than 10 million people worldwide each year are affected by traumatic brain injury (TBI), representing 30% to 40% of all injury-related

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mortalities and disabilities among all age groups, with enormous social and economic impacts [1,2]. The incidence of patients suffering from TBI-related disabilities is 2-3-times higher than those with neurological disabilities from Alzheimer's disease or cerebrovascular disorders have been expected by epidemiological previsions until 2030.

TBI still represents a major global health burden and public health challenge among all ages in all countries regardless of the patient's income level, despite recent advances in trauma research and the ongoing efforts of collaborative multidisciplinary studies to tackle this problem and improve patients' outcomes. The incidence of TBI is estimated to be 939 in 100,000 worldwide with the major causes being falls, vehicle accidents, wars, and sports [3-6]. The mortality rate of TBI worldwide is estimated to be between 7% and 23% with 90% of TBI-related deaths occurring in developing countries [7,8]. Additionally, TBI imposes an economic burden on societies where its annual global cost reaches 400 billion dollars [9].

The energy associated with an external mechanical force, because cerebral tissue to absorbed part of it results with TBI. This amount of energy causes the derangement of a myriad of biochemical, metabolic, and molecular functions, deeply affecting brain cell homeostasis and leading to temporary or permanent impairment of consciousness, neurocognitive deficits, neuromotor disabilities, or psychological disturbances [10,11]. These disturbances in TBI depend on the severity of the impact. The most commonly used system and scale to assess the severity of TBI is the Glasgow Coma Scale (GCS) which classifies TBI into mild (GCS range 13-15), moderate (GCS range 9-12) and severe (GCS range 3-8). The GCS is obtained by scoring specific clinical assessments, including eye opening, motor and verbal responses [12]. Cerebral cells and blood vessels damage occurred during primary TBI injury. A cascade of biochemical and molecular mechanisms triggered by the primary insult are refer to secondary TBI injury which start immediately after impact, last for hours, days, or weeks depending on the injury severity, and may culminate in cerebral cell death with a loss of neuronal functions. Imbalance of ionic homeostasis, release of excitatory neurotransmitters (glutamate, aspartate), glucose dysmetabolism with mitochondrial dysfunction, and free radical overproduction are the main characteristics of secondary insult. The activation of different molecular pathways and inflammatory cascades, leading to cellular apoptosis and damage of the BBB permeability are the final consequences of TBI [13].

Triggering molecular damaging processes (lipid peroxidation, DNA damage, protein oxidation) and in exacerbating glutamate excitotoxicity, mitochondrial dysfunction, ionic dysregulation, and activation of cellular proteases are well documented as a result of reactive oxygen species (ROS) and free radicals formation in brain tissue following TBI [14-16]. After TBI one of the main processes activated is glutamate release, that causes an influx of $Ca^{2+}$ into neuronal cells via activation of NMDA receptors and leads to an "early" calcium dysregulation [17,18]. This negatively impacts the main mitochondrial function, leading to energy imbalance and contributing to increased ROS production with documented post-traumatic membrane lipid peroxidation [19-22]. A state where oxygen levels along with oxygen-derived free radicals overwhelm the scavenging antioxidant system is referred to oxidative stress. These include agents like hydrogen peroxide ($H_2O_2$), superoxide anions ($O_2^-$), hydroxyl ($OH^-$), and peroxyl ($ROO^-$) radicals [23].

Excitotoxicity occurs once injury-induced, as a result excess of $Ca^{2+}$ promotes the production of ROS as well as nitric oxide (NO) where protective mechanisms such as antioxidants fail to control these radicals, leading to oxidative stress [24]. Alteration of various macromolecules including DNA, proteins, and lipids which eventually impairs various cellular processes occurred because of free radical concentration increased [25]. The macromolecules alterations reversibility predisposes individuals to a wide range of disorders including neurodegenerative diseases [26,27].

High oxidative metabolic activity, relatively low antioxidant capacity, and low repair mechanisms leads to brain tissue damage due to oxidative stress [28,29]. In TBI, ROS can be produced via the arachidonic acid (AA) cascade activity, mitochondrial leakage, catecholamine oxidation, and by neutrophils [30,31]. In addition, NADPH oxidases (Nox) are a family of membrane enzymes that reduce oxygen into ROS. Nox play a major role in the pathophysiology of the nervous system and they have a crucial contribution in the development of secondary injury after TBI. It was shown that the activity of Nox is elevated 1 h after TBI and is set in action by microglia and that the inhibition of Nox can attenuate the secondary injury post TBI [31,32]. Hence, Nox inhibition can also act as a therapeutic target [32]. No treatment has been effective in eradicating the consequences of injury up to date. Focusing on alleviating the impact of secondary injury and managing its biochemical contributors is the main aim of all therapies. With a growing body of evidence on the role of oxidative stress in TBI, antioxidants are being considered as potential therapeutics [20,21,33,34].

System reinforcement could play a key role in the management. This reinforcement appears as a safe, low-cost, and multifunctional novel therapeutic approach in TBI patients. Antioxidant therapies are effective over a long period of time, allowing for suitable use in clinical settings. Due to the encouraging preclinical results and the antioxidant drug profiles, acute antioxidant reinforcement is emerging as a highly cost-effective alternative for neuroprotection in TBI patients [35]. Major changes in nutritional status have been observed after TBI in the clinic. The combination of alterations in blood flow, excitotoxicity, free radical damage and altered global and regional metabolic rates has been identified as a major contributor to secondary damage from brain injury [36]. This metabolic crisis in the early stages of TBI can be detrimental to outcomes, recent studies have shown that supplementing basic nutrition can significantly improve functional outcomes in patients [37,38]. Based on the Brain Trauma Foundation guidelines for hospital management of TBI, minimal standards for nutritional supplementation were included, suggesting that patients be placed on full nutritional replacement within 72 hours [39].

Currently, there is no neuroprotective agent, which demonstrated improved neurological outcomes in a large phase

III clinical trial. The potential use of unconventional treatments, such as antioxidant defense, of note is that standard nutritional replacement is typically formulated to contain mainly macronutrients: carbohydrates, fats, and proteins, with no vitamins or other minerals. Deficiencies in nutrition may further exacerbate TBI symptoms and the depletion of bioactive vitamins, minerals and other compounds may make it difficult for the body to process other pharmaceutical compounds, a phenomenon observed in experimental brain injury [40,41].

As nutritionally based therapies supplement basic biological function and have therapeutic action in the injured brain, these therapies may eventually represent an important component of combination therapies. In this paper, we provide an overview of the overlooked area of nutritional antioxidants adequacy in TBI patients. However, in recent years, many vitamins, minerals, and essential nutrients have risen to prominence as potential primary therapeutics and have generated increasing interest [42,43]. Nutraceutical therapies may provide an excellent avenue of treatment for many patients with brain injury. However, they are considerably understudied relative to other pharmacotherapies. The nutritional antioxidants discussed below represent a wide array of therapeutic mechanisms which offer many opportunities for complementary or even synergistic mechanisms with other pharmaceuticals, below we highlight the most findings from the experimental brain injury and their actual intake of these nutrients in Khoula hospital (National Trauma Center)-Muscat/Sultanate of Oman. Vitamins are nutrients that are required for normal physiological functioning; many play crucial roles within the brain in a variety of processes. Recent research has begun to examine how they are involved in dysfunction of the nervous system, from chronic disease to acute insults. The vitamins reviewed below were selected based on existing evidence showing benefits in the treatment of neural insults. Most of the vitamins have been explored with regards to experimental brain injury. The specific nutrients responsible for this effect remain elusive, but antioxidant vitamins, such as vitamin E, carotene, and vitamin C, which are free radical scavengers, may be major contributing factors to this phenomenon. Patient intake of the below dietary antioxidants have been directly assessed in post TBI patients, and adequacy was assessed by comparing the actual daily intake with the required dietary allowances (RDA) guidelines.

Vitamin C (ascorbic acid, ascorbate) is a potent water-soluble antioxidant in humans. It inhibits peroxidation of membrane phospholipids and acts as a scavenger of free radicals [44]. It also behaves as an enzyme modulator, causing the up-regulation of endothelial NOS (eNOS) and down-regulation of NADPH oxidase. A sorbate can protect neurons from NMDA-induced excitotoxicity and to prevent lipid peroxidation induced by various oxidizing agents, especially in combination with α-tocopherol because of its antioxidant and pharmacodynamics properties. Ascorbic acid is widely recognized as one of the most important endogenous free radical scavengers [45]. It has also been suggested to have a neuroprotective role in reducing damage from excitotoxicity [46]. As part of the general metabolic dysfunction in TBI, tissue levels of ascorbic acid have been shown to be severely reduced immediately and do not return to normal until 72 hours post-injury [47,48]. Another important role of vitamin C is the regeneration of vitamin E [49]. Brain concentration of vitamin C is 10-fold higher than its plasma levels [50,51]. This may indicate its potential role as a cerebro-protective agent. Additionally, reduced vitamin C levels have been reported in aged animals as a potential mechanism for increased injury [52]. Vitamin C involvement in patients with severe TBI and the radiologic diagnosis of diffuse axonal injury clinically was trialed. A significant earlier stabilization of the perilesional edema compared with the placebo group after received a total dose of 32 g of intravenous vitamin C during the first 7 days after TBI, with a maximum single dose of 10 g on the first day and absence of many parameters of clinical importance and monitoring techniques may make the interpretation of these results challenging, although encouraging results regarding the use of vitamin C in humans [35].

Vitamin E is a fat-soluble vitamin known to be one of the most potent antioxidants. It breaks the propagation of the free radical chain reaction in the lipids of biological membranes. Vitamin E deficiency in humans is caused by either fat malabsorption or genetic abnormalities, leading to peripheral neuropathy and ataxia [53]. Low levels of antioxidants such as vitamin E, ascorbic acid, and reduced glutathione (GSH) could lead to tissue peroxidation disability in rats. Vitamin E deficiency also influences the activities of SOD, catalase, and glutathione peroxidase [54]. The consumption of vitamin E beyond the requirement levels cited in the Dietary Reference Intakes (DRIs) has been studied extensively from 1990 through 2010. Early observational studies and animal studies suggested that vitamin E antioxidant properties would protect the body against devastating chronic diseases having oxidative stress as part of their pathobiology, such as cardiovascular diseases and cancer [55]. On the other hand, Vitamin E, mainly alpha tocopherol, is the major peroxyl radical scavenger in biological lipid phases such as cell membranes, and its antioxidant mechanism is related to the inhibition of lipid peroxidation and NADPH oxidase. One clinical trial of vitamin E has been performed in patients with severe TBI and the radiologic diagnosis of diffuse axonal injury for 7 days, patients received vitamin E at 400 IU/day intramuscularly, which resulted in improved clinical outcome and reduced mortality at discharge. Despite promising results, clinical trials using vitamins C and E, isolated or in combination, are needed to change current therapeutic measures in patients suffering TBI [35].

The requirement for the essential nutrient vitamin D can be met by a combination of de novo synthesis and intake, either from dietary sources or supplements. Plant sources derived vitamin D is D2, while D3 is the form derived from the intake of animal-based foods. Vitamin D3 also can be synthesized from cholesterol by exposure of the skin to ultraviolet light. Both forms of vitamin D act as prohormones. Modified first by the liver enzyme 25-hydroxylase, vitamin D is then transported to the kidney microsomes where it is converted to the active hormonal form known as 1,25-dihydroxyvitamin D, or calcitriol.

In addition to the role of vitamin D in calcium absorption, serum calcium balance, and bone metabolism, it recently has appreciate an essential role in the brain and central nervous system (CNS), the enzyme 1 alpha-hydroxylase, that expressed by

the human brain is responsible for the hydroxylation of 25-hydroxyvitamin D to its active, hormonal form, 1,25-dihydroxyvitamin D: as well as the nuclear receptor for vitamin D. The current Recommended Dietary Allowance (RDA) for vitamin D is 600 International Units (IU) per day for both male and female adults up to the age of 70 [56]. At age 70, the RDA increases to 800 IU. There are several considerations to consider when applying these recommendations to others at risk for traumatic brain injury (TBI). It is not known whether the dietary vitamin D requirement for optimal brain function under normal or injured conditions should be different. Median estimates of vitamin D intake from foods are below the Estimated Average Requirements (EARs) of 400 IU recently established by the IOM. However, vitamin D also is synthesized in the skin, and therefore vitamin D status is not accurately reflected exclusively by dietary intake. Using National Health and Nutrition Examination Survey (NHANES) data from 2000 to 2006, levels of 25-hydroxyvitamin D in serum, a depiction of total vitamin D exposure, were above 50 nmol/mL, the level identified as meeting the needs of most of the population. There have been no clinical trials to address the possibility that vitamin D supplementation may promote resilience to subsequent TBI. However, human data (in elderly populations) does indicate that failure to maintain adequate vitamin D nutriture is associated with diminished neurocognitive health. For example, plasma 25-hydroxy vitamin D concentrations of less than 20 ng/mL in individuals 65-99 years of age were associated with increased prevalence of dementia, and concentrations below 10 ng/mL were associated with increased cranial indicators (detected via magnetic resonance imaging [MRI]) of cerebrovascular disease such as white matter hyperintensity volume and large vessel infarcts [57].

Thiamin (vitamin B1) is a water-soluble vitamin found in many food products including meat, legumes, sunflower seeds, vegetables, and whole or enriched grain products. In animal products, >95% of thiamin is found in its phosphorylated and biologically active form, thiamin pyrophosphate (TPP) (also known as thiamin diphosphate [TDP]), while it exists in its free form in plants sources. The essential roles of thiamin in the body consequences of Thiamin Deficiency (TD), and treatment strategies for at-risk patients should be aware by the nutrition and metabolic support professional. In the body, Thiamin plays both coenzyme and non-coenzyme roles. Untreated TD Impaired oxidative and energy metabolism, serious and potentially irreversible neurological damage or death can occur. Moreover, thiamin facilitates neurotransmission, probably by potentiation of the release of the neurotransmitter's acetylcholine, dopamine, and norepinephrine. A finding of an increased brain inflammation, as evidenced by increased proinflammatory cytokines, chemokines, interferons, and interferon-inducible proteins, as well as up-regulated inflammatory gene expression have been reported in TD patients as well, oxidative stress, glutamate-mediated excitotoxicity, and inflammation which are the brain pathophysiology were associated with TD.

Niacin (vitamin B3), a soluble B group vitamin which has been shown to be neuroprotective in rodent models of cerebral ischemia. A reduction in the size of the infarction when administered up to 2 h with B3 has been shown following induction of permanent focal cerebral ischemia in rats [58]. It has been shown that a dose of 500 mg/kg of B3 provided the greatest reduction in the size of the infarct, although, other doses reduced the size of the infarct to a lesser extent [59]. As well, Administration of B3 after transient focal cerebral ischemia has been shown to reduce the size of the infarct and improve neurological outcome [60].

### Dietary requirement

The dietary reference intakes for dietary antioxidants of most age groups are listed as the recommended dietary allowance (RDA). According to the Institute of Medicine, "the RDA is the average daily dietary intake level; sufficient to meet the nutrient requirements of nearly all (97%-98%) healthy individuals in a group and is calculated from an Estimated Average Requirement (EAR)."

## METHODS

The Institutional Review Board of sultan Qaboos university and khoula hospital (National Trauma Center)-in Muscat/Sultanate of Oman approved the research plan (MERC/11/03) and these analyses using the criteria described by Bourre [61,62]. Regarding macronutrient and micronutrient intake and the brain, we identified micronutrients important to optimal brain function, we focused on measuring the estimated nutrient intake of dietary antioxidants with RDA and patients' written informed consent was obtained.

Seventy-one adult outpatients aged 18-65 years; males referred to the polytrauma clinic were invited to participate in the study. All patients had a history of a documented medically confirmed TBI; blast injury; or a head injury involving a fall, bullet wound, vehicular accident, or other type of head injury and subsequent, ongoing neurobehavioral symptoms.

The exclusion criterion included: psychiatric or neurological history other than those resulting from a TBI, non-Omani patients and those who were known to have cognitive impairments that would preclude completion of the protracted assessment or age younger than 18 years.

### Demographic and anthropometric measurements

Demographic information including age, education level, marital and smoking status were collected using a structured questionnaire. Age was divided into two groups: 18-30 years and 31-65 years. Weight was measured in kilogram to the nearest 0.1 kg using a digital weighing scale (Seca 208, Vogal and Halke, Germany). Height was measured to the nearest 0.5 cm by using a stadiometer protocol adapted from Lohman et al. with a vertical measuring scale fixed to a metal bar connected to weighing scale [63]. Body Weight change was calculated as: (current BW in kilograms ideal BW in kilograms)/ideal BW × 100. as "height=85.10+1.73 × knee height-0.11 × age" for males, "height=91.45+1.53 × knee height-0 For patients who were unable to stand, height was estimated by using knee height equation.16 × age" for females, and by ulna length for males, height (cm)=4.605U+1.308A+28.003, and for females, height

(cm)=4.459U+1.315A+31.485, and by demi span for Males: height (cm)=(1.40 × demi-span in cm)+57.8 and for Females: height (cm)=(1.35 × demi-span in cm)+60.0 [64-66]. The mean height of the three measurements was considered in calculations. Body Mass Index (BMI) was calculated as wt. (kg)/ht.($m^2$), and the cutoff points of the world health organization were used [67]. Glasgow Coma Scale (GCS) is a neurological scale which aims to give a reliable and objective way of recording the conscious state of a person for initial as well as subsequent assessment. GCS is, a valid, reliable, and highly objective instrument used all over the world in multi clinical settings, conditions, especially in the emergencies' situations. GCS is considered the gold standard instrument for health care providers, including nurses to assess the level of consciousness [68]. Traumatic brain injury was classified into three categories based on Glasgow Coma Scale (GCS): mild if GCS scores ≥ 13, moderate If GCS between (9-12), and severe head injury if GCS score ≤ 8 [69].

### Food intake

Patient's dietary intake was assessed from daily food intake only (no supplementation) by using the 24 hour recall, through face-to-face interview with each patient [70]. Household utensils with the different portion size of common foods were used to assist the patients to report the accurate amount of food consumed, and the results were used to generate estimated nutrient intake for each respondent. Cut-off nutrient values were based on age and gender specific estimated average requirements (EARs) and the RDAs in the DRIs from the Food and Nutrition Board [71]. EAR is considered the micronutrient intake that would meet the needs for half of the population, while RDA is the intake level that would meet the needs of ~ 98% of the population. Dietary antioxidants adequacies were assessed by comparing the actual intake with the recommended daily allowance (RDA), after analysis of daily food intake using electronic program [72,73]. Based on World Health Organization categories, body mass index (BMI) was divided into four groups: underweight (<18.5 kg/$m^2$), normal (18-24.9 kg/$m^2$), overweight (25-29.9 kg/$m^2$) and obese (≥ 30 kg/$m^2$) [74]. No other behavior or mood assessments were carried out. We did not assess any laboratory tests as part of the study. The aims of this study were: (1) To identify data from TBI patients on the consumption of vitamins, and dietary antioxidants reported to be important for optimal brain function (2) To assess the adequacy of dietary antioxidants in patients presenting for an evaluation of possible TBI in providing those nutrients. Our hypothesis was that many of the patients presenting for evaluation for possible TBI are consuming diets that are not meeting the recommended dietary allowances (RDAs) for micronutrients considered helpful for optimal brain physiology.

## RESULTS

### Demographic and clinical characteristics

Demographic and clinical characteristics were obtained for all 71 patients with nutrient intake values, patients age ranging from 18 to 65 years and a mean age of 27.3 years (SE:1.4) fulfilled the eligibility criteria of enrollment in the study. All patients were males, most of them (75%) were young age between 18-30 years, 46.5% of subjects were classified as mild TBI while 12.7% and 40.8% were classified as moderate and severe TBI respectively based on Glasgow Coma Scale (GCS). Motor vehicle accidents were the most common cause of TBI (91.7%), followed by falls from height (8.3%). One fourth of patients were underweight BMI<18.5 (kg/$m^2$), while (47.9%) were normal weight BMI 18.5-24.9 (kg/$m^2$), 16.9% were overweight BMI 25-29.9 (kg/$m^2$) and 7.1% were obese BMI ≥ 30 (kg/$m^2$). Fifty-one (72%) patients were current smokers Table 1.

| Characteristics | n | % |
|---|---|---|
| Age | | |
| 18-30 years | 53 | 75 |
| 31-65 years | 18 | 25 |
| Body Mass Index (kg/$m^2$) | | |
| Underweight BMI ≤ 18.5 (kg/$m^2$) | 20 | 28.1 |
| Normal weight BMI 18.5-24.9 (kg/$m^2$) | 34 | 47.9 |
| Overweight BMI 25-29.9 (kg/$m^2$) | 12 | 16.9 |
| Obese BMI ≥ 30 (kg/$m^2$) | 5 | 7.1 |
| The severity of Trauma (Glasgow Coma Scale) GCS | | |
| Mild (GCS ≥ 13) | 33 | 46.5 |
| Moderate (GCS 9-12) | 29 | 12.7 |
| Severe (GCS ≤ 8) | 9 | 40.8 |
| TBI Cause | | |
| Vehicle accident | 65 | 91.5 |
| Fall from height | 6 | 8.5 |
| Current smoker | | |
| Yes | 51 | 71 |
| No | 20 | 29 |

**Table 1:** Demographic and Anthropometric Characteristics of TBI Patients.

### Dietary antioxidants intake

Seventy-one patients were complete the 24-hour dietary recall interview, and the results were used to generate estimated nutrient intake for each patient. Cut-off nutrient values were based on age and gender-specific estimated average requirements

(EARs) and the RDAs in the DRIs from the Food and Nutrition Board [75]. RDA is the intake level that would meet the needs of ~ 98% of the population. The study findings showed that no patient met the RDAs for all six dietary antioxidants. Eighteen patients only (25%) fulfilled the requirements for 4 or more nutrients, while 53 patients fulfilled 6 or fewer requirements. The overall daily intake of vitamin C was (76 mg), vitamin D (3.7 mg), and vitamin E (4 mg) were significantly lower than the RDA ($p<0.0001$, 0.0002 and 0.0001) respectively Figure 1 (A, B, C). Thiamin (B1), Niacin (B3) and Choline overall daily intake (0.8 mg) and (12 mg) and (420 mg) respectively were significantly lower than the RDA ($P<0.02$, 0.02 and 0.0001) Figure 1 (D, E, F).

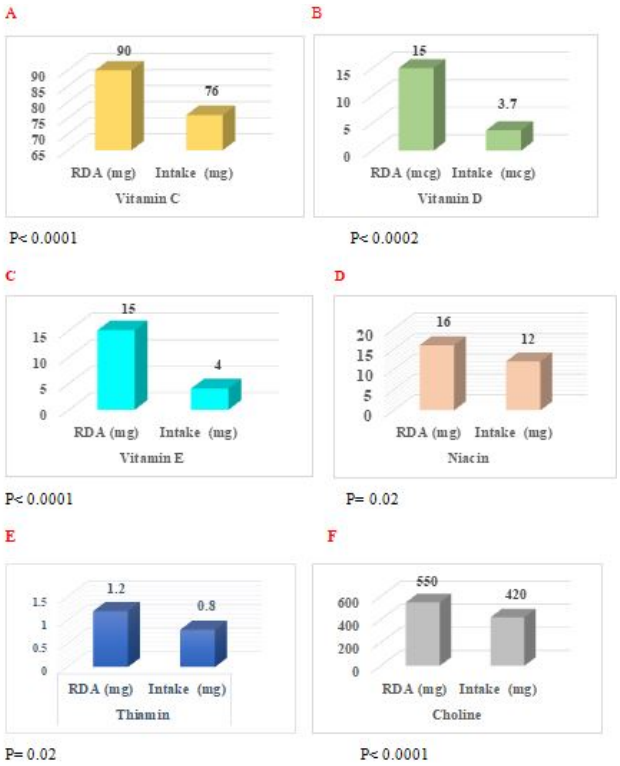


**Figure 1:** Adequacy of dietary antioxidants intake compared with RDA.

## DISCUSSION

Reactive oxygen and nitrogen species (ROS/RNS) play an integral role in brain injury and posttraumatic neuronal degeneration [76,77]. Endogenous protective mechanisms such as glutathione (GSH) and superoxide dismutase (SOD) may become overwhelmed by increased production of free radicals in the setting of acute traumatic stress, another important factor in posttraumatic neuronal degeneration is lipid peroxidation mediated by oxygen radical species [76,77]. In addition to disrupting the membrane phospholipid architecture, lipid peroxidation contributes to the formation of cytotoxic aldehyde containing by products that bind to and impair the function of cellular proteins [78]. The oxidation of DNA and proteins then may trigger programmed cell death. This process is exacerbated during the reperfusion phase of injury, resulting in additional microvascular damage and neuronal cell death. Oxidative stress has been implicated as a central pathogenic mechanism in traumatic brain injury (TBI) because the brain is especially vulnerable to such stress, compared to other tissues [79,80]. Many of the harmful biological events associated with TBI such as DNA damage, brain-derived neurotrophic factor (BDNF) dysfunction, and disruption of the membrane phospholipid architecture, and has therefore been suggested as a principal culprit in both acute and long-term events of TBI may cause by overproduction of reactive oxygen species (ROS) [81,82].

Antioxidant supplementation probability to reduce the risk of developing other forms of trauma (e.g., stroke and epilepsy) or protect against developing adverse health outcomes after injury have investigated through several clinical trials. It has nevertheless become clear that oxidative stress after TBI triggers many of its outcomes, and antioxidant compounds should be considered to ameliorate these outcomes. AS mammals are unable to perform their synthesis of low molecular weight antioxidants, they depend on regular intake with diet to have adequate circulating and tissue concentrations of antioxidants [83]. In the case of increased ROS and RNS formation, the quality of food consumed and/or supplementation of adjuvants and nutraceuticals is of fundamental importance to provide significant protection [84,85]. Despite of the link between oxidative/nitrosative damage and TBI is evident, as well as continuous growth of studies, reporting either preclinical or clinical data, using supplementation with natural or synthetic low molecular weight antioxidants, that have appeared in the literature in the last decades as potentially useful treatments in TBI, still the awareness that deficiency in antioxidant-rich foods in the daily diet may further exacerbate TBI symptoms still highly plausible [86-88].

Ascorbic Acid (AA) is one of the most abundant water-soluble antioxidants within mammalian tissues, acting as a reducing factor in several enzymatic reactions [89]. Being a powerful reducing agent, it quickly reacts, with a wide range of ROS and RNS, including peroxyl nitrite and hydroxyl radicals. As the body cannot be synthesize AA, it depends on vitamin C-rich food ingestion to satisfy its needs [90]. Although AA is one of the most studied free radical scavengers and is particularly abundant in the brain, only one preclinical and one clinical study have examined the effects of AA in TBI, even though it has been shown that the level of AA in the cerebral tissue decreases rapidly following experimental TBI [91,92]. Its depletion is strictly dependent on the severity of the injury, remaining well below control values even longer after severe TBI and returning to pre-impact concentrations after 72 h in mildly injured animals [93,94]. Our study found that the overall daily intake of vitamin C was (76 mg), significantly lower than RDA $p<0.0001$, which may aggravate post-TBI symptoms, the finding of this study is in consistent with others in literature [95,96], who indicated that AA, even if administered alone, reduced mortality rate, decreased cerebral tissue and circulating levels of malondialdehyde (MDA), restored brain values of AA, and stimulated tissue superoxide dismutase levels In a model of closed-head TBI. Beneficial effects of high dosage of this antioxidant were observed in AA-treated patients who showed decreased progression of perilesional edema on CT scan in a double blind controlled clinical trial of 100 TBI patients [97]. Our findings showed that intake of vitamin E (Tocopherols) (4

mg) were significantly lower than the RDA, (P<0.0001) which may complicate post-TBI symptom this finding is matching with other studies in literature.

Tocopherols are a family of fat-soluble compounds, having a remarkable antioxidant capacity. Tocopherol administered early post-injury is beneficial to decrease tissue damage associated with TBI and may reduce ROS-mediated tissue damage and promote cerebral tissue regeneration following TBI [98,99]. Improvement of neurocognitive tasks and motor function were reported after administration of tocopherol-succinate suggesting that this type of infusion might be effective in the clinical setting to decrease TBI-associated damage [100]. TBI-increased oxidative damage to proteins, the decrease in SOD and BDNF caused by TBI, and improved TBI-associated motor function impairments. The authors' conclusions were that dietary-tocopherol supplementation could decrease the damaging effects of mild TBI on synaptic plasticity and cognitive functions [101]. The overall daily intake of vitamin D (3.7 mg) was significantly lower than the RDA (p<0.0001). Vitamin D is a fat-soluble serco steroid is another hormonal factor that could influence recovery after TBI. Recovery after TBI may impair because of neuro inflammation and may be a linking mechanism for the beneficial effects of vitamin D in rat models of TBI [102-104]. This study showed inadequate intake of vitamin D compared with RDA, this finding is consistent with the observation of Daradkeh et al. who reported 23.8% of patients being vitamin D deficient, and a further 66.7% were insufficient Post-TBI [104]. These finding was inconsistent what has been reported by Lowrance et al. and Cordain L et al. [105,106].

Choline is an essential nutrient available from a wide variety of nutritional sources. It is an important molecule involved in synthesis of structural cell membrane phospholipids, other signaling molecules, and is also a precursor for acetylcholine [107]. As such, it is postulated that dietary choline supplementation may minimize cognitive deficit, reduce brain inflammation, and protect the penumbra. Our findings showed that choline dietary intake was significantly lower than RDA (P<0.0001) which may lead to aggravates and delay post-TBI complications. This finding is supported by the findings of others; dietary choline supplementation was shown to significantly reduce brain injury induced spatial learning deficits in a rat model. Additionally, the choline-supplemented diet helped reduce brain inflammation and spared cortical tissue [108]. Our finding showed overall daily intake (12 mg) of niacin (B3) was significantly lower than the RDA (P<0.02), this finding inconsistent with other findings. Vitamin B3 (nicotinamide) is one very interesting compound has been shown to be neuroprotective in rodent models of cerebral ischemia. Reduce the size of the infarction when administered up to 2 h following induction of permanent focal cerebral ischemia in rats has been shown [109]. Significantly reduced infarct size in different strains of rats and improve neurological outcome [110-112]. Significantly improved performance and motor performance was reported after a single dose of B3 administration following ischemia within 7 days, while improved behavioral performance has also been shown after multiple doses of B3 administered following ischemia [113]. Given the recent evidence that B3 administration following experimental ischemia has a beneficial effect it is reasonable to assume that B3 may also be therapeutic following TBI. Adequate dietary intake of thiamin (B1) is very necessary because thiamine reserves are depleted as early as 20 days of inadequate oral intake. Thiamine contributes to wound healing by functioning in antibody and leukocyte cell formation and collagen synthesis. Thus, maintaining thiamine levels is important for patients with traumatic and other surgical wounds. Our finding showed overall daily intake (0.8 mg) of thiamin (B1), was significantly lower than the RDA (P<0.02), this finding inconsistent with other findings in literature. The practical use of micronutrient supplementation in nutrition therapy in general has been recently reviewed [114]. The specific role of thiamine (vitamin B1) in nutrition therapy in certain disease states particularly traumatic brain injuries is important for fundamental biological processes and enzymatic reactions, and deficiencies may lead to disastrous consequences [115,116]. The importance of micronutrients is often neglected. The attitude that "one size fits all" is not applicable to vitamin and trace element supplementation. A statistically significant biochemical thiamin deficiency was noted in healthy patients who sustained significant trauma with Injury Severity Score ≥ 12 requiring admission to the ICU. There is some suggestion that thiamine administration may play a role in recovery from trauma [117].

## CONCLUSION

TBI represents a heterogeneous pathophysiological process that is clearly a challenge to manage. Multiple clinical studies of nutritional strategies have not defined a specific pathway that can serve as a sole, standalone target in TBI nutritional therapy. Multidimensional treatment plans, perhaps incorporating some of the described nutritional adjuvants, will thus merit more investigations from both the bench and the bedside to elucidate effective strategies to best treat TBI patients. Unfortunately, many strategies that are promising in the lab or in animal models have not borne fruit in clinical trials to date.

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