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Vitamin D Insufficiency in Post-Traumatic Brain Injury Patients from the State of Qatar

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ABSTRACT

Background: Vitamin D insufficiency has been shown to be prevalent in modern society. It has been associated with worsening outcomes in critically ill patients. However, its effect on critically injured trauma patients is unknown. We hypothesize that Vitamin D insufficiency is an independent risk factor for increased in-hospital mortality in critically injured trauma patients (CITPs) requiring admission to the intensive care unit (ICU). **Methods:** This cross-section study includes 21 trauma brain patients transferred from ICU at Hamad general hospital to the rehabilitation unit at Rumailah hospital in the state of Qatar between August 2014 and June 2015, and 21 control healthy adults. Serum vitamin D3 levels were measured upon rehabilitation unit admission. Patients were stratified into sufficient group (≥ 27 ng/ml), insufficient group (14 - 26 ng/ml) and severely insufficient (< 14 ng/ml) group. The secondary measure was the prevalence of vitamin D insufficiency/deficiency. Vitamin D dietary intake was assessed using 24-recall and analyzed by an electronic software program (Super tracker). Adequacy/inadequacy was assessed by comparing the actual intake with the Recommended Dietary Allowance (RDA). **Results:** In total, 23.8% of patients had vitamin D deficiency and an additional 66.7% were insufficient with only 9.5 % being normal Figure1. Patients with vitamin D deficiency were significantly younger than depleted group ($P < 0.05$). Patients with vitamin D insufficiency also had a higher BMI compared with patients in the other two groups. Insufficient intake of vitamin D (82.7%) after TBI was significantly greater than would be expected in the controls (4.7%) ($P< 0.05$), as well as it was significantly lower than RDA. **Conclusion:** Insufficient vitamin D dietary intake combined with low 25-hydroxy-Vitamin D3 levels may be an independent risk factor for worse clinical outcomes, increased length of stay and affect patient quality of life. For optimal brain function, a plentiful supply of vitamins, minerals, antioxidants, and fatty acids are required by using food plans and targeted supplementation.

INTRODUCTION

Traumatic Brain Injury (TBI) can be defined as a disruption in the normal function of the brain caused by a blow or jolt to the head or a penetrating head injury [1]. TBI is a major public health concern; as many as 1.7 million Americans suffer TBIs every year. The leading causes of TBI related to deaths, hospitalizations, and emergency department visits are falls, motor vehicle accidents, and assaults [2]. Around 5.3 million Individuals are suffering from TBI related problems in the USA [3]; the similar high rate has been noted in other developed countries. In emerging economies such as that country in the Arabian, Gulf TBI is common due to high number of road traffic accident due to increased motorization. Therefore, in the regions, there are urgent needs to quantify the sequel as well to contemplate remedial intervention among the victims of TBI. An estimated 43% of those who suffer TBI will develop a long-term disability as a result [2].

Long-term disability post-TBI is a major cause of neuropsychiatric and cognitive impairments, including problems with memory and executive function, mood, sleep disturbance, and lethargy. High rates of deaths and disability are caused by Traumatic brain injury (TBI), annually 50,000TBI-related deaths and 235,000 TBI- related hospitalizations [4]. Recovery after TBI varies markedly between patients. Pituitary hormones deficiencies especially growth hormone after TBI because of neuroendocrine dysfunction may contribute to persistent symptoms, it was reported that 5–20% of TBI patients having hypothalamic-pituitary dysfunction [5]. Vitamin D is a fat-soluble Serco steroid essential for musculoskeletal health that is primarily synthesized in the skin upon sun exposure is another hormonal factor that could influence recovery after TBI. Recovery after TBI may impair as a result of neuroinflammation [6] and may be a linking mechanism for the beneficial effects of vitamin D in rat models of TBI. [7, 8].

More time spent indoors after TBI because of hospitalization, impaired social functioning, and absence from work may increase the prevalence of vitamin D deficiency. Many systemic conditions, such as obesity, cardiovascular and neurodegenerative diseases [9, 10] have been associated with Vitamin D deficiency. Depression [11, 12] was linked with vitamin D status, as well as vitamin D status has been linked with impaired cognitive function [13-16]. The human brain is widely distributed with vitamin D receptors and the vitamin D - activating the enzyme, 1-alpha-hydroxylase [17], so vitamin D status may play a role in the development or exacerbation of cognitive and psychiatric problems after TBI, affecting recovery and quality

of life. The major circulating and best form of vitamin D assessment with a long half-life of 2–3 weeks is 25-hydroxycholecalciferol, 25(OH)D3 [18]. Neuroprotective properties in multiple models of acquired brain injury including traumatic, ischemic, excitotoxic, degenerative and autoimmune have been demonstrated with vitamin D supplementation [7-10, 19-28].

Furthermore, influence response to brain injury, with deficient endogenous vitamin D was established as a risk factor for cardiovascular disease, stroke and autoimmune central nervous system (CNS) disease [29-31]. Neuronal injury and recovery from TBI have also been associated with Vitamin D supplementation and vitamin D deficiency [7, 8, 10, 19, 26]. However, the role of vitamin D following TBI was combined with progesterone (PROG) in all studies [8, 10, 26]. The neuroprotective role of vitamin D monotherapy in TBI has been studied in isolation. In vitro [7, 32] studies showed that vitamin D status can influence behavioral recovery, including memory, and neuropathology after TBI. Nutritional interventions are promising treatment adjuncts given their documented benefits [32-35] because of low cost, ease of accessibility and favorable safety profiles [6]. A better understating of the dietary requirements of an individual recovering from a TBI and identifying nutritional agents that can improve post-concussion recovery could complement and potentiate current management strategies. To date, the evidence to support specific nutritional therapies following head injury and concussion is limited [33–35]. However, there is the dearth of published clinical data on the prevalence of vitamin D deficiency in patients after TBI or its association with poorer clinical outcomes.

Peripheral calcium homeostasis is predominantly associated with Vitamin D [36]; however, the broader physiological role for vitamin D including immune modulation [37], neurological and muscular function [38] and cell-cycle control has been recently evidenced [39]. The main source of circulating, most biologically active metabolite of vitamin D (VDH; 1, 25-dihydroxyvitamin D3; 1,25OHD; ‘calcitriol’) is derived from Ultra Violet light exposure [40].

Moreover, vitamin D has a pivotal role in brain development, health, and function, as well as it has a significant retroactive which exerts its endocrinological influence through a nuclear vitamin D receptor (VDR) [41, 42] which produced by two - steps of hydroxylation reaction. These reactions involving 25-hydroxylase and 1-α- hydroxylase, primarily located in the liver and kidney, respectively [43]. A healthy young adult with a light skin tone requires 4 minutes

of UVB exposure to 25% of their body (arms and legs), whereas an older adult or darker skin toned individual would require 18 minutes to obtain 1000 IU of vitamin D3 [44-46]. Therefore, the purpose of this cross-sectional study was to determine the prevalence of vitamin D deficiency and insufficiency post-TBI and to assess the adequacy of vitamin D intake among traumatic brain injury patient in Qatar.

METHODS

This study was conducted in a rehabilitation ward at Rumailah Hospital, Hamad Medical Corporation - Doha - Qatar from August 2014 to June 2015. Twenty-five post-traumatic brain injury patients, aged 18 – 65 years, males, free of any chronic diseases and 21 healthy participants as control were recruited from the community. Cognitive assessment for all patients was conducted using the Montreal Cognitive Assessment (MOCA) [47]. Four patients were excluded from the study due to incomplete nutritional assessment or refused to continue.

Demographic Characteristics

Demographic information, including age, sex, and education level, marital and smoking status were collected using a structured questionnaire. Anthropometric data: Weight, height, and body mass index (BMI) were measured, height was estimated by using knee height, ulna length and demi-span equations as detailed elsewhere for patients who were unable to stand [48-52].

Energy (Kcal), carbohydrate (gm), protein (gm), fat (gm) and fiber (gm) intakes were assessed by using the 24 – hour recall method [53] through face–to–face interview with each patient. Household utensils with the different portion size of common foods were used to assist the patients to report the accurate amount of food consumed. Macro and micronutrients were analyzed electronically using electronic program (super - tracker) [54]. Vitamin D adequacy was calculated as the ratio of actual intake to the Recommended Daily Allowances (RDA) [55]. Vitamin D status was stratified into categories based on the Imperial College Healthcare NHS Trust (ICHNT) ICHNT guidelines: normal >70 nmol/l (>28.0 ng/ml), insufficient 40–70 nmol/l (16.0–28.0 ng/ml) and deficient <40 nmol/l (<16.0 ng/ml) [56].

Nutritional Status and TBI Severity

"Malnutrition Universal Screening Tool" (MUST) [57] was used to assess the nutritional status of all subjects and it was classified as: no risk, moderate risk and high risk of malnutrition when MUST score was 0, 1 and ≥ 2 respectively. The severity of TBI was classified into mild, moderate, and severe based on Glasgow Coma Scale (GCS) when it ≥13, 9 -12 and ≤ 8 respectively [58].

Ethical Approval

The written informed consent was obtained from each participant. The study was approved by Ethical Committee of Medical Research Center - Hamad Medical Corporation - Qatar.

Statistical Analysis

Graph Pad Prism (version 6.0) was used for statistical analysis. Means and standard deviations (using t-tests for two means, one way ANOVA was used to compare between groups), two-sided statistical significance was set at $\alpha \leq 0.05$ and Proportions were compared by using chi-square test.

RESULTS

Patient Demographics and Clinical Characteristics

Half of the patients (52.4%) and (42.8%) of controls were aged between 29-38 years. Based on GCS 23.8% of patients were classified as mild TBI while 28.6% and 47.6% were classified as moderate and severe respectively. Motor vehicle accidents were the most common cause of TBI (52.4%), followed by falls from height (47.6%). Approximately 38.1% of patients were smokers, compared with (23.8%) of control. The majority of both patients and controls were married and with primary education level. 23.8% of TBI patients were underweight and 9.5% were overweight and the rest were in normal range Table 1.

Table 1. Demographic Characteristics of TBI Patients and Controls

Variable	TBI		Control	
	(n)	(%)	(n)	(%)
Education Level				
Primary	12	57.1	14	66.7
Secondary	3	14.3	2	9.5
High	6	28.6	5	23.8
Body mass index				
Underweight	5	23.8	----	-----
Normal	14	66.7	4	19.0
Overweight	2	9.5	13	67.0
Obese			4	19.0
Marital status				
Married	12	57.1	15	71.4
Single	9	42.9	6	28.6
Smoking status				
Yes	8	38.1	5	23.8
No	13	61.9	16	76.2

A previously validated Vitamin D3 deficiency scale to define Vitamin D3 insufficiency was used in this study Table 2.

Table 2 Vitamin D3 Deficiency Scale

Vitamin D Severity Scale	Lower limit	Upper limit	% Distribution
Deficient	4 ng/ml	≤ 13 ng/ml	23.8%
Insufficient	14 ng/ml	26 ng/ml	66.7%
Sufficient	≥ 24 ng/ml	≤ 100 ng/ml	9.5%

In total, 23.8% of patients had vitamin D deficiency and an additional 66.7% were insufficient with only 9.5 % being normal Figure1. Patients with vitamin D deficiency were significantly younger than depleted group ($P < 0.05$). Patients with vitamin D insufficiency also had a higher BMI compared with patients in the other two groups. Insufficient intake of vitamin D (82.7%) after TBI was significantly greater than would be expected in the controls (4.7%) ($P< 0.05$), as well as it was significantly lower than RDA.

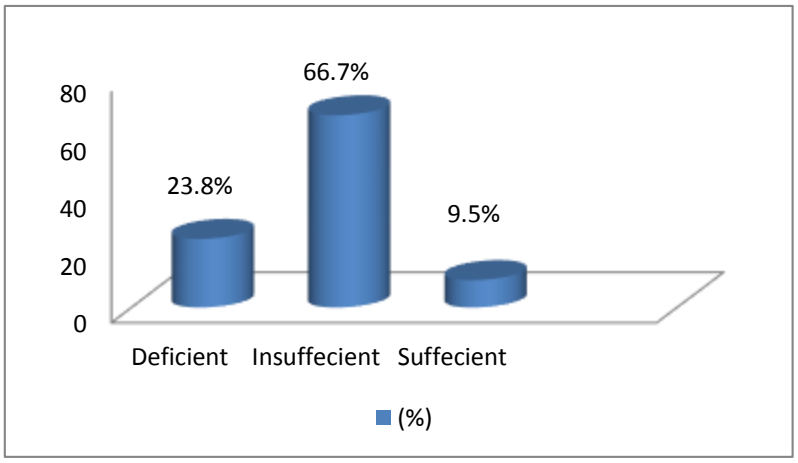

Figure 1. Serum Vitamin D Status *in Traumatic Brain Injury Patients*

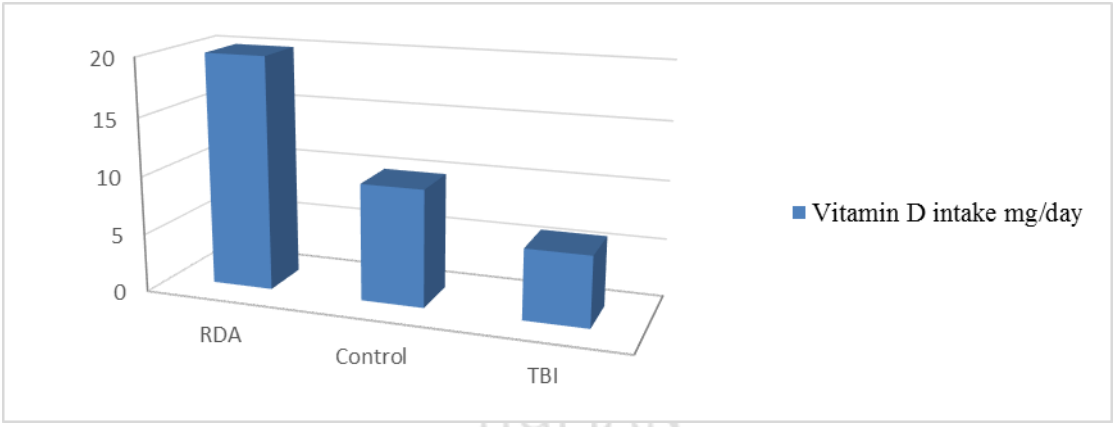

Figure 2. Inadequacy Vitamin D Intake of TBI Compared with Control & RDA

*P< 0.004 TBI and RDA **P< 0.002 TBI and control

DISCUSSION

The important relationship between diet nutrient density and health status is well known. The nutritional needs of the brain at both macro- and micro-levels have been discussed by many authors, ample levels of vitamins, minerals, antioxidants, and essential fatty acids that supplied by nutrient-dense diets were stressing by such authors [59-61]. Brain tissue recovery and function are with high response to critically important methylation pathways at the mitochondrial level caused by methyltetrahydrofolate, and methylcobalamin [62, 63]. This study has found that vitamin D deficiency is common in patients after TBI with 23.8 % of patients being vitamin D deficient, and a further 66.7

% were insufficient, with overall 90.5 % having low concentrations. These findings were similar to what has been reported by (Lowrance, 2016 [64]. Based on vitamin D dietary intake our findings showed that (82.7%) were insufficient intake post-TBI compared with (4.7%) in controls. These findings are consistent with the observation that diets of many Americans fail to meet the RDA for most of the water- and fat-soluble vitamins and minerals [65].

The majority of TBI and nutrition studies are focused on acute severe brain injury; while in an outpatient setting, few studies that assess the nutritional status of central nervous system injury. Vitamins, minerals, and essential fatty acids intake were failed to meet the RDA of spinal cord injured patients [66–69]. Bioactive Vitamin D3 is a powerful modulator of the immune response [70-74] and it **is** one of the major regulatory hormones of the entire immune system [75]. Therefore, in the setting of critical illness after severe trauma it is plausible that the insufficient Vitamin D3 state may contribute with an increased risk of severe sepsis and sepsis-related complications, Systemic Inflammatory Response Syndrome (SIRS), and invasive infections [75- 77]. Augment the innate immune response have been shown when Sufficient Vitamin D3 levels reached [72-74, 78, 79]. On the other hand, sufficient level of vitamin D3, which is typically above 30 ng/ml, helps to turn off the humoral and cell-mediated immune responses, [80]. Theoretically, this could have contributed to decreased mortality rate with adequate baseline vitamin D3 levels by abating the septic response.

Lacking in multiple micronutrients that considered important for optimal brain health including vitamin D was noticed for many patients who nutritionally assessed in this study. Usually, patients with the lowest overall nutrient intake, consuming less vitamin D than the RDA standard. Higher baseline 25-hydroxy-Vitamin D3 levels of critically injured or ill trauma patients has been better immunologic protection and ability to recover from additional inflammatory insults and acquired infections than in the insufficient group. These findings are also supported by the findings that all of the patients that died (93.3%) had a Vitamin D level ≤ 28 ng/ml and were in the insufficient or insufficient Vitamin D category [81].

CONCLUSION

The nutritional status of TBI outpatients and the importance of nutritional intervention were highlighted by our study. Based on our findings greater attention to the nutritional status and assessment of TBI patients in the outpatient setting have been underscoring. Similar to other studies, we conclude that insufficient vitamin D dietary intake combined with low 25-hydroxy-Vitamin D3 levels may be an independent risk factor for worse clinical outcomes, increased the length of stay and affect patient quality of life. For optimal brain function, a plentiful supply of vitamins, minerals, antioxidants, and fatty acids are required by using food plans and targeted supplementation.

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