Introduction

Critical illness polyneuropathy (CIP) is a disabling neuropathy that occurs in intensive care unit (ICU) subjects. The incidence has been variably reported with a wide range spreading from 45 to 80% according to various studies. Critical illness polyneuropathy and myopathy (CIPNM) is a disabling neuropathy that occurs in intensive care unit (ICU) subjects. It was hypothesized that a low serum level or deficiency of 25(OH)D might be associated with CIPNM. The aim of the present study was to ascertain the 25(OH)D serum level in subjects with CIPNM. Method: Consecutive ICU patients admitted to neuro-rehabilitation were prospectively enrolled. At admission, vitamin D serum levels were measured and EMG examination was performed to ascertain those with CIPNM. 25(OH)D was stratified as sufficient (≥30 ng/mL), insufficient (20-29.9 ng/mL), and deficient (<20 ng/mL). Results: Eighty-four patients (31 F, 53 M; mean age 51.7 ± 12.6) were identified and 63 (21 F, 42 M) enrolled. CIPNM was detected in 38 (9 F, 29 M) patients. A deficient mean serum level of vitamin D was observed in the whole population: 18.1 ± 9.2 ng/mL. No difference of vitamin D serum levels was detected in subjects with and without CIPNM: 17.5 ± 8.4 and 19.0 ± 10.5 ng/mL (p=0.58), respectively. Conclusion: Almost all subjects showed Vitamin D deficiency. No difference was detected between those with and without CIPNM. The condition might represent a secondary phenomenon resulting from the inflammatory process as well as from conditions that could interfere with vitamin D metabolism.

Keywords: Critical Illness Polyneuropathy, Vitamin D, Deficiency, Inflammation

The authors have no conflict of interest. The paper is part of project about the functional recovery of critical illness subjects that was funded by research grant n. RC17O2MF23 from Italian Research Ministry.

Corresponding author: Domenico Intiso MD, Unit of Neuro-Rehabilitation and Rehabilitation Medicine, Hospital IRCCS "Casa Sollievo della Sofferenza", Viale dei Cappuccini, 71013 San Giovanni Rotondo (FG), Italy E-mail: d.intiso@operapadrepio.it • d.intiso@alice.it

Edited by: G. Lyritis
Accepted 21 July 2019
the terms critical illness polyneuropathy and myopathy and polyneuromyopathy (CIPNM) have been proposed. Several risk factors have been reported to favour the development of CIPNM including sepsis, multiple organ failure and longer ICU stay, but the origin of CIPNM remains unknown, and no pharmacological or non-pharmacological treatment has resulted in efficacious prevention of CIPNM occurrence.

The role of vitamin D [25-hydroxyvitamin D (25(OH)D)] in Ca/P balance and pathophysiological mechanisms underlying skeletal system disorders is well-known, but 25(OH)D has a multi-faceted and widespread action in human multi-organ systems. In recent decades, increased attention has been paid to non-skeletal targets such as diabetes, cardiovascular, muscular, and nervous system. Studies have suggested that 25(OH)D may be important for the development of the nervous system, and it may also play a role in neuroimmunology and neuroprotection. Low 25(OH)D serum levels have been associated with risk of multiple sclerosis (MS), Alzheimer’s disease, Parkinson’s disease, stroke, and epilepsy. Furthermore, the relationship between 25(OH)D and other neurological disturbances such as cerebral small vessel disease and spinal cord injury have recently been investigated.

The role of 25(OH)D in acquired peripheral nervous system disorders is unclear. Interestingly, studies have suggested that 25(OH)D deficiency can promote polyneuropathy in diabetic patients and can be associated with immune mediated polyneuropathy.

It has been suggested that CIPNM occurrence might be promote by derangement of hormonal and metabolic alterations such as hyperglycemia, hormone imbalance, hypoalbuminemia, amino acid deficiency and activation of proteolytic pathways that might be related to Vitamin D. On this basis, it was hypothesized that a low serum level or deficiency of 25(OH)D might be associated with CIPNM favouring occurrence, particularly in patients experiencing an ICU stay and suffering from severe critical illness conditions. The aim of the present study was to ascertain the 25(OH)D serum level in subjects coming from ICU with and without CIPNM and if patients with CIPNM showed lower vitamin D serum level than patients without CIPNM.

**Methods and participants**

With approval from the local Ethics Committee (Comitato etico presso IRCCS Casa Sollievo della Sofferenza on 9-18-2016, ICF V.1O_18 ago 16), consecutive subjects admitted to neuro-rehabilitation from the ICU during the period from December 2017 to December 2018 were prospectively enrolled. Patients with a history of polyneuropathy (diabetic polyneuropathy, Guillain Barrè syndrome or chronic inflammatory demyelinating polyneuropathy (CIDP)) or neuro-muscular diseases (myasthenia gravis, polymyositis and amyotrophic lateral sclerosis) were excluded as well as patients with malignancy, impaired renal function (estimated glomerular filtration rate: 30 ml/min) and liver failure. Patients gave informed consent in cases in which they had the capacity. In cases in which the patient lacked the capacity, the patient’s nearest relative or legal representative gave consent for inclusion. All research was performed in accordance with relevant guidelines/regulations. Clinical and neurological evaluations were performed in all subjects at admission. Previous or current 25(OH)D supplementation was recorded as well as supplementation before assessment. All patients underwent an EMG examination to assess the presence of neuromuscular disorders, at admission. All enrolled subjects were divided into two groups, patients with and without CIPNM. To reflect the difficulty in discriminating between myopathic and neuropathic causes of muscle weakness, we decided to use the term critical illness polyneuropathy and myopathy (CIPNM), and differentiation between neuromuscular types was not performed. Furthermore, body mass index (BMI) was calculated in all subjects.

**Vitamin D dosage and blood parameter assessment**

Serum levels of 25(OH)D were analysed using 25-hydroxy chemiluminescent immunoassay (DiaSorin Liaison; Stillwater, MN), which has a 100% cross-reactivity with both metabolites within a week from admission. The serum level of 25(OH)D was stratified as sufficient (≥30 ng/mL [75 nmol/L]), insufficient (20-29.9 ng/mL [50-75 nmol/L]), and deficient (<20 ng/mL [50 nmol/L]) according to the Endocrine Society criteria.

**Electrophysiological evaluation**

Because most of the ICU patients at study entry were poorly collaborative and since CIP and CIM frequently coexist and present overlapping neurological pictures, for the purposes of this study, only conventional electrophysiological examination by an NCS-EMG evaluation (MEDELEC Synergie N2 machine) was used according to a method described elsewhere. All patients underwent conventional orthodromic motor and antidromic sensory nerve conduction studies on eight motor nerves (median, ulnar, common peroneal and tibial nerves, bilaterally) and six sensory nerves (median, ulnar and sural nerves, bilaterally). Muscular activity at rest and, when possible, during contraction was assessed with concentric needle electrodes. Sensory nerve action potential (SNAP), distal motor latencies, F wave, compound muscle action potential (CMAP) and nerve conduction velocities were registered. Abnormal CMAP or SNAP amplitudes were considered significant if they were found in at least two nerves. Spontaneous activity and, when possible, recruitment and interference patterns were detected bilaterally by needle EMG from the deltoid, first dorsal interosseus, tibial anterior and abductor hallucis muscles. CIPNM was defined if electrophysiological results revealed very low amplitudes or absent SNAPs, low amplitudes of CMAPs with normal or mildly reduced conduction velocities, or normal nerve conduction velocity and reduced CMAPs amplitude. In patients who were not collaborative or too weak to exercise,
repetitive stimulation at 3 Hz was performed to exclude myasthenia gravis.

**Statistical analysis**

Patient characteristics were reported as the mean ± standard deviation (SD) and median along with the first-third quartiles (q1-q3) and as frequencies and percentages for continuous and categorical variables, respectively. Comparisons between groups were assessed using Mann-Whitney U (or Kruskal-Wallis) test and Pearson Chi-square test (or Fisher exact test as appropriate) for continuous and categorical variables, respectively. Comparisons between time variables (i.e., days spent in intensive care unit and days between admission and 25(OH)D measure) were assessed using Poisson regression models. A two-sided p-value <0.05 was considered statistically significant. All statistical analyses were performed using SAS Release 9.4 (SAS Institute, Cary, NC, USA).

**Results**

Eighty-four (31 F, 53 M; mean age 51.7±12.6 years) were identified. Of these, 21 subjects were excluded: 9 patients as a result of peripheral nerve diseases (4 subjects with Guillain-Barré syndrome, 2 with CIDP, 3 patients with diabetic polyneuropathy); 5 patients with muscular diseases (3 patients with myasthenia gravis, 2 patients with polymyositis), 4 patients suffering from amyotrophic lateral sclerosis, and 3 subjects as a result of renal failure requiring haemodialysis (Figure 1), and 63 (21 F, 42 M) subjects were enrolled. Clinical characteristics and primary causes of all enrolled patients are reported in table 1. CIPNM was detected in 38 (9 F, 29 M, mean age: 55.3 ± 15.8) (60.3%) patients (Table 1). No difference in body mass index was detected between groups: 24.5 ± 3.5 and 24.3 ± 4.2 (p= 0.912) in subjects with and without CIPNM, respectively. No subjects took vitamin D preparation before hospitalization, and none received vitamin D supplementation before their serum assessment. Eighteen (28.5%) patients: 11 and 7 subjects with and without CIPNM respectively, were treated with antiepileptic agents. Only 3 patients (2 with CIPNM and one without) assumed statins. Deficient mean serum levels of vitamin D were detected in the whole population: 18.1 ± 9.2 ng/mL. Subjects with CIPNM showed lower mean serum levels of vitamin D than those without CIPNM, but the difference was not significant: 17.5 ± 8.4 and 19.0 ± 10.5 ng/mL (p=0.58), respectively (Table 2). No significant variation in seasonal vitamin D assessment was detected (Table 3).

**Discussion**

No difference of vitamin D serum levels was detected in subjects with and without CIPNM, even if a deficiency of
Table 1. Clinical characteristics, primary causes of ICU admission in patients with and without CIPNM.

| Patients | ICU subjects with CIPNM (N = 38) | ICU subjects without CIPNM (N=25) |
|----------|---------------------------------|-----------------------------------|
| Sex | 9 F, 29 M | 12 F, 13 M |
| Mean age ± SD | 55.34 ± 15.89 | 45.96 ± 19.57 |
| Diagnoses (%) | | |
| | CH: n.15 (39.4) | CH: n.8 (32) |
| | Cerebral ischemia: n. 1 (2.6) | Cerebral ischemia: n. 2 (8) |
| | Brain injuries: n. 12 (31.5) | Brain injuries: n.13 (52) |
| | Intracranial meningoias: n. 3 (7.8) | Intracranial meningoias: n. 1 (4) |
| | Cardiac surgery: n. 3 (7.8) - mitral and aortic valve graft; | Cardiac surgery: n. 1 (4) |
| | Respiratory failure: n. 2 (5.2) | |
| Sepsis: 2 (5.2) |
| SAPS II | 42.5±7.6 | 41.8±8.3 |
| ICU stay Mean ± SD | 35.4 ± 18.8 days | 39.9 ± 17.7 days |

Legend: CIPNM = critical illness polyneuromyopathy; ICU= intensive care unit; CH= cerebral hemorrhage; SAPS II = Simplified Acute Physiology Score; percentage is reported in brackets.

Table 2. Clinical characteristics, days spent in ICU, vitamin D serum levels, and seasonal variation of patients with and without CIPNM admitted in neuro-rehabilitation.

| Variable | Category | ICU patients (N=63) | ICU patients without CIPNM (N=25) | ICU patients with CIPNM (N=38) | p-value* |
|----------|----------|---------------------|-----------------------------------|--------------------------------|----------|
| Gender - N(%) | | | | | 0.045 |
| | Females | 21 (33.3) | 12 (48.0) | 9 (23.7) |
| | Males | 42 (66.7) | 13 (52.0) | 29 (76.3) |
| Age (years) | | | | | 0.912 |
| | N obs | 63 | 25 | 38 |
| | Mean±SD | 51.7 ± 17.9 | 46.2 ± 19.8 | 55.3 ± 15.8 |
| | Median (q1-q3) | 54 (40-65) | 47 (25-59) | 57.5 (47-68) |
| | Range (min-max) | 18 - 95 | 18 - 95 | 20 - 80 |
| BMI (kg/m²) | | | | | |
| | N obs | 61 | 24 | 37 |
| | Mean±SD | 24.4 ± 3.8 | 24.3 ± 4.2 | 24.5 ± 3.5 |
| | Median (q1-q3) | 24.4 (22-26.5) | 24.4 (21.2-26.7) | 24.4 (22.6-25.9) |
| | Range (min-max) | 17.2 - 38.6 | 17.4 - 34.2 | 17.2 - 38.6 |
| Days spent in intensive care unit | | | | | 0.006* |
| | N obs | 60 | 23 | 37 |
| | Mean±SD | 37.2 ± 18.4 | 39.9 ± 17.7 | 35.4 ± 18.8 |
| | Median (q1-q3) | 35 (25-44) | 36 (27-57) | 30 (25-41) |
| | Range (min-max) | 9 - 93 | 17 - 88 | 9 - 93 |
| Days between admission and 25(OH)D assessment | | | | | 0.886* |
| | N obs | 63 | 25 | 38 |
| | Mean±SD | 2.6 ± 3.1 | 2.5 ± 2.3 | 2.6 ± 3.6 |
| | Median (q1-q3) | 2 (1-3) | 2 (1-3) | 1 (1-3) |
| | Range (min-max) | 0 - 19 | 0 - 8 | 0 - 19 |
| 25(OH)D level (ng/mL) - N(%) | | | | | 0.843* |
| | N obs | 63 | 25 | 38 |
| | Mean±SD | 18.1 ± 9.2 | 19.0 ± 10.5 | 17.5 ± 8.4 |
| | Median (q1-q3) | 17.4 (12.1-21.3) | 18.8 (12.1-20.8) | 15.7 (12.3-21.3) |
| | Range (min-max) | 4 - 53.6 | 6.5 - 53.6 | 4 - 42.5 |
| | Sufficient (≥30 ng/mL) | 6 (9.5) | 3 (12.0) | 3 (7.9) |
| | Insufficient (20 - 29.9 ng/mL) | 12 (19.0) | 5 (20.0) | 7 (18.4) |
| | Deficient (< 20 ng/mL) | 45 (71.4) | 17 (68.0) | 28 (73.7) |
| Season at which 25(OH)D was assessed - N(%) | | | | | 0.793 |
| | Spring | 15 (23.8) | 5 (20.0) | 10 (26.3) |
| | Summer | 19 (30.2) | 9 (36.0) | 10 (26.3) |
| | Autumn | 14 (22.2) | 6 (24.0) | 8 (21.1) |
| | Winter | 15 (23.8) | 5 (20.0) | 10 (26.3) |

Legend: ICU= intensive care unit; CIPNM= critical illness polyneuromyopathy; SD=standard deviation; *p-values from Mann-Whitney U test or Chi-square test for continuous and categorical variables, respectively; #p-values from Fisher’s exact test; °p-values from Poisson model.
Table 3. Vitamin D serum level and seasonal assessment in all patients admitted to neuro-rehabilitation.

| Variable | Category | Spring (N=15) | Summer (N=19) | Autumn (N=14) | Winter (N=15) | p-value* |
|----------|----------|--------------|---------------|---------------|---------------|----------|
| 25(OH)D level (ng/mL) | N obs | 15 | 19 | 14 | 15 | 0.582 |
|               | Mean±SD | 20.1 ± 10.8 | 18.6 ± 9.2 | 17.9 ± 10.7 | 15.8 ± 5.9 | 0.427 |
|               | Median (q1-q3) | 19.4 (12.6-23.8) | 18.8 (10.9-21.8) | 16.2 (9.1-19.9) | 13.9 (12.3-19.7) | 0.582 |
|               | Range (min-max) | 8.5 - 53.6 | 4 - 42.5 | 6.5 - 41.3 | 6.7 - 31 | 0.582 |
| Sufficient (<30 ng/mL) | 1 (6.7) | 2 (10.5) | 2 (14.3) | 1 (6.7) | 0.582 |
| Insufficient (20 - 29.9 ng/mL) | 4 (26.7) | 6 (31.6) | 1 (7.1) | 1 (6.7) | 0.582 |
| Deficient (≤20 ng/mL) | 10 (66.7) | 11 (57.9) | 11 (78.6) | 13 (86.7) | 0.582 |

Legend: SD=standard deviation; *p-values from Kruskal-Wallis test or Fisher exact test for continuous and categorical variables, respectively.

Vitamin D was observed in both groups. Low or deficient levels of vitamin D have been detected in critically ill patients, and it was suggested that this condition increases the susceptibility for severe infections, longer ICU stays and mortality. In this respect, there are biologically plausible mechanisms by which deficiency might contribute to adverse outcomes, such as immune dysfunction, cardiovascular disease, dysglycaemia, and endothelial and mucosal barrier disruption. However, no relationship was reported with CIPNM, and to the best of our knowledge, this is the first study about a potential relationship between vitamin D deficiency and CIPNM. Our finding supports the fact that a deficient serum level of 25(OH)D can be detected in patients with CIPNM, but given that also patients without CIPNM had vitamin D deficiency, a causal relationship with onset of the disease cannot be supported.

A growing body of evidence suggests that vitamin D plays a pleiotropic effect in the nervous system by regulating brain development, neuroplasticity and function. Its role has been demonstrated in a wide spectrum of neurological disorders that also encompasses degenerative and inflammatory processes. Deficiency or a genetically lowered 25(OH)D level has been strongly associated with increased susceptibility to multiple sclerosis (MS) with a higher risk of disability in the relapsing-remitting MS form and a greater decrease in brain volume and white matter abnormalities in old people. Furthermore, deficiency of the 25(OH)D level has been demonstrated to represent a risk factor of ischaemic stroke as well as a useful prognostic marker that could predict infarct volume, mortality and poor functional outcome in stroke patients. Despite the knowledge that the vitamin D role in CNS is progressively growing, its effect in the peripheral nervous system is still scanty and unclear. The effect of vitamin D in glycemic metabolism and its role as a risk factor in developing type 2 diabetes mellitus has been investigated. It is well-known that diabetes mellitus is one of the main causes of polyneuropathy, and studies have reported that vitamin D deficiency could promote polyneuropathy in diabetic patients. Skalli et al. reported an association between polyneuropathy and vitamin D deficiency in a sample of 111 patients with type 2 diabetes who had a clinically diagnosed polyneuropathy. The finding was confirmed by a recent meta-analysis in which vitamin D deficiency was significantly associated with an increased risk of polyneuropathy in patients with type 2 diabetes. Furthermore, vitamin D deficiency has been detected in subjects with immune-mediate polyneuropathy. In the present study, vitamin D deficiency was detected in both subjects with and without CIPNM. Several reasons could be carried out to explain the finding. This condition might be a consequence of systemic inflammation underlying any pathological process. This hypothesis has been suggested to explain the low level of vitamin D that has been detected in several pathological conditions such as critical illness, obesity, diabetes, cardiovascular diseases, and rheumatic and autoimmune disturbances, in which a common factor is the inflammatory process. On the other hand, normal vitamin D level was detected in non-inflammatory diseases including cognitive dysfunction, muscular disease, non infectious pulmonary disease (chronic obstructive pulmonary disease) and endocrine disorders. Thus, low vitamin D might be considered a secondary phenomenon resulting from the inflammation.

Vitamin D serum levels could be influenced by a number of drugs that can interfere with the vitamin D metabolism including antiepileptic agents, glucocorticoids, anti-estrogens and statins lowering lipids that are commonly used in patients with cardiovascular diseases. In the present study, one third of patients was treated by antiepileptics or statins, but no difference was found between subjects with and without CIPNM in assumption of antiepileptic drugs as well as agents interfering with vitamin D metabolism. Therefore, it is important to consider that this aspect might have a role in the decreased serum levels of vitamin D found in the studied sample.

Given that the majority of ICU showed Vitamin D deficiency, it is conceivable that the finding may reflect a low vitamin D in general population. The estimation of vitamin D status in adult Italian population is lacking and few studies have been carried out in order to evaluate the prevalence of hypovitaminosis D in healthy subjects. A prevalence of circulating 25(OH)D concentration below 25 and 50 nmol/L ranging from 13
to 38.5% has been reported<sup>58-60</sup>, while higher values up to 76% have been observed in elderly women<sup>61</sup>. Among factors that can influence vitamin D level, hospitalization and length of stay should be also considered. Romagnoli et al. observed that the prevalence of hypovitaminosis was 71.4% and 82.3% in subjects with medical condition and subjects engaged in long-term rehabilitation because of various neurological disorders, respectively, during the winter. The prevalence decreased to 29.8 and 57.8%, respectively, in summertime<sup>60</sup>. In the present study, a higher prevalence of hypovitaminosis D was detected, since 90% of all subjects had low vitamin D level. Furthermore, no seasonal variation was observed. However, in comparing the results of mentioned studies, it should be considered that Romagnoli et al. used a different cut off (serum 25(OH)D level below 30 nmol/l) in defining hypovitaminosis. Since vitamin D deficiency is common in critical illness with prevalence between 40-70%<sup>62</sup>, it is not possible exclude that our finding simply reflect this aspect, even if a higher rate was detected in the present study. Furthermore, rehabilitation setting, age and different neurological diseases requiring challenging rehabilitation might explain the finding. Indeed, the majority of enrolled ICU subjects suffered from severe acquired brain injury. This disorder embraces a number of different neurological conditions, including traumatic brain injury, hypoxic brain injury, stroke, and brain tumour that can result in cognitive, physical, emotional, or behavioural impairments<sup>63-64</sup>. In this respect, studies have demonstrated low vitamin D serum levels in subjects suffering from cerebral lesions such as stroke<sup>28-29</sup> or brain injury<sup>65-66</sup>. Reduced exposure to sunlight, urban habitat, urban pollution, clothing habits and seasons may influence vitamin D levels, particularly in hospitalized patients, but data were corrected for the mentioned variables and did not show any differences.

Limitations of the present study are the small sample size and the lack of CIPNM type differentiation: CIM, CIP. Indeed, it is not possible to exclude the fact that low or deficient vitamin D serum levels may be associate or contribute to the development of particular forms of CIPNM. However, almost all ICU subjects with CIPNM had a homogenously low vitamin D serum level; therefore, it is conceivable that all CIPNM subtypes may have a low vitamin D serum level.

Several questions remain unsolved when considering serum level of vitamin D in critical ill patients. Whether vitamin D deficiency is a further component of the inflammatory process or an independent factor affecting the disease course and outcome is unclear. Although there are biologically plausible mechanisms by which vitamin D deficiency produces adverse outcome, no study has demonstrated causative link. Likewise, whether the low vitamin D levels observed are merely a marker of poor general health resulting in limited exposure to sunlight, chronic illness and poor diet or merely due to laboratory techniques remain unsolved. Therefore, designed studies should redefine the values of normality of vitamin D in the critical patient population. Furthermore, well-conducted studies should be planned to investigate vitamin D measurement modalities (optimum range, what level, and assay to use), timing (single or multiple assessments), supplementation (how much, which route, how often and when) and vitamin D effects on outcome.

**Conclusion**

The majority of ICU patients admitted to neuro-rehabilitation showed vitamin D deficiency. No difference of vitamin D serum level was detected in subjects with and without CIPNM. The reasons of this condition remain unclear and might represent a secondary phenomenon resulting from the inflammation that underlies any pathological process as well as from conditions that could interfere with vitamin D metabolism.

**Authors’ contributions**

Domenico Intiso, Andrea Santamato and Michelangelo Bartolo conceived, designed the study and draft the paper; Domenico Intiso and Filomena Di Rienzo performed clinical evaluation, collected and organized the data. Andrea Fontana and Massimiliano Copetti performed statistical analysis. Luigi Amoruso performed electrophysiological exams. All authors read, critically reviewed and approved the final manuscript.

**References**

1. Hough CL, Steinberg KP, Taylor Thompson B, Rubenfeld GD, Hudson LD. Intensive care unit-acquired neuromyopathy and corticosteroids in survivors of persistent ARDS. Intensive Care Med 2009;35:63-68.
2. de Jonghe B, Lacherade JC, Sharshar T, Outin H. Intensive care unit-acquired weakness: risk factors and prevention. Crit Care Med 2009;37:S309-S315.
3. Stevens RD, Dowdy DW, Michaels RK, Mendez-Tellez PA, Pronovost PJ, Needham DM. Neuromuscular dysfunction acquired in critical illness: a systematic review. Intensive Care Med 2007;33:1876-91.
4. Tennila A, Salmi T, Pettila V, Roine RO, Varpula T, Takkunen O. Early signs of critical illness polyneuropathy in ICU patients with systemic inflammatory response syndrome or sepsis. Intensive Care Med 2000;26:1360-63.
5. Druschky A, Herkert M, Radespiel-Troger M, Druschky K, Hund E, Becker CM, Hilz MJ, Erbguth F, Neundörfer B. Critical illness polyneuropathy: clinical findings and cell culture assay of neurotoxicity assessed by a prospective study. Intensive Care Medicine 2001;27:686-693.
6. Latronico N, Feni F, Recupero D, Guarneri B, Tomelleri G, Tonin P, De Maria G, Antonini L, Rizzuto N, Cannidia A. Critical illness myopathy and neuropathy. Lancet 1996;347:1579-1582.
7. Lacomis D. Electrophysiology of neuromuscular disorders in critical illness. Muscle Nerve 2013;47(3):452-63.
8. Bednarik J, Lukas Z, Vondracek P. Critical illness polyneuromyopathy: the electrophysiological components of a complex entity. Intensive Care Medicine
9. Khan J, Harrison TB, Rich MM, Moss M. Early development of critical illness myopathy and neuropathy in patients with severe sepsis. Neurology 2006;67(8):1421-5.

10. Marrero HG, Stålberg EV. Optimizing testing methods and collection of reference data for differentiating critical illness polymyopathy from critical illness myopathies. Muscle Nerve 2016;53(4):555-63.

11. Goodman BP, Boon AJ. Critical Illness Neuromyopathy. Phys Med Rehabil Clin N Am 2008;19:97-110.

12. Visser LH. Critical illness polymyopathy and myopathy: clinical features, risk factors and prognosis. Eur J Neurol 2006;13(11):1203-12.

13. Bednarik J, Vondracek P, Dusek L, Moravcova E, Cundrle I. Risk factors for critical illness polymyopathy. J Neurol 2005;252(3):343-51.

14. Nanas S, Kritikos K, Angelopoulo E, Siafaka A, Tsikrika S, Poriazi M, Kanaloupiti D, Kontogeorgi M, Pratikaki M, Zervakis D, Routsi C, Roussos C. Predisposing factors for critical illness polymyopathy in a multidisciplinary intensive care unit. Acta Neurol Scand 2008;118(3):175-81.

15. Herrmans G, De Jonghe B, Bruyninckx F, Oostevoort P. Intensive care: An overview of the critical illness myopathy and neuropathy. Curr Opin Nephrol Hypertens 2003;12(1):24-30.

16. Shepherd SJ, Newman R, Brett SJ, Griffith DM. Intensive care: An overview of the critical illness myopathy and neuropathy. Curr Opin Nephrol Hypertens 2003;12(1):24-30.

17. Herrmann M, Sullivan DR, Veillard AS, McCorquodale T, Straub IR, Scott R, Laakso M, Topliss D, Jenkins AJ, Blankenberg S, Burton A, Kewan S, Linfoot O. Critical illness polymyopathy. J Neurol Neurosurg Psychiatry 2005;76(4):434-41.

18. Colville ND, Kelly C, Shuttleworth CM. Critical illness myopathy and neuropathy: a review of the literature. J Neurol 2006;253(12):1580-8.

19. Colville ND, Kelly C, Shuttleworth CM. Critical illness myopathy and neuropathy: a review of the literature. J Neurol 2006;253(12):1580-8.

20. Shepherd SJ, Newman R, Brett SJ, Griffith DM. Enhancing Rehabilitation After Critical Illness Programme Study Investigators. Pharmacological Therapy for the Prevention and Treatment of Weakness After Critical Illness: A Systematic Review. Crit Care Med 2016;44(6):1198-205.

21. Herrmann M, Sullivan DR, Veillard AS, McCorquodale T, Straub IR, Scott R, Laakso M, Topliss D, Jenkins AJ, Blankenberg S, Burton A, Kewan S, Linfoot O. Critical illness polymyopathy. J Neurol Neurosurg Psychiatry 2005;76(4):434-41.

22. Colville ND, Kelly C, Shuttleworth CM. Critical illness myopathy and neuropathy: a review of the literature. J Neurol 2006;253(12):1580-8.

23. Mokry LE, Ross S, Ahmad OS, Forgetta V, Smith GD, Goldtmann D, Leong A, Greenwood CM, Thansassoulis G, Richards JB. Correction: Vitamin D and Risk of Multiple Sclerosis: A Mendelian Randomization Study. PLoS Med 2016;13(3):e1001981.

24. Annweiler C, Llewellyn DJ, Beauchet O. Low serum vitamin D concentrations in Alzheimer’s disease: a systematic review and meta-analysis. J Alzheimers Dis 2013;33:659-74.

25. Littlejohns TJ, Henley WE, Lang IA, Annweiler C, Beauchet O, Chaves PH, Fried L, Kestenbaum BR, Kuller LH, Langa KM, Lopez OL, Kos K, Soni M, Llewellyn DJ. Vitamin D and the risk of dementia and Alzheimer disease. Neurology 2014;83:920-8.

26. Evatt ML. Parkinson disease: Low vitamin D and Parkinson disease - a causal conundrum. Nat Rev Neuro 2014;10(1):8-9.

27. Wang L, Evatt ML, Maldonado LG, Perry WR, Ritchie JC, Beecham GW, Martin ER, Haines JL, Pericak-Vance MA, Vance JM, Scott WK. Vitamin D from different sources is inversely associated with Parkinson disease. Mov Disord 2015;30(4):560-6.

28. Turetsky A, Goddeau RP Jr, Henninger N. Low Serum Vitamin D Is Independently Associated with Larger Lesion Volumes after Ischemic Stroke. J Stroke Cerebrovasc Dis 2015;24(7):1555-63.

29. Schneider AL, Lutsey PL, Selvin E, Mosley TH, Sharrett AR, Carson KA, Post WS, Pankow JS, Folsom AR, Gottesman RF, Michos ED (2015). Vitamin D, vitamin D binding protein gene polymorphisms, race and risk of incident stroke: the Atherosclerosis Risk in Communities (ARIC) study. Eur J Neurol 2015;22(8):1220-7.

30. Teagarden DL, Meador KJ, Loring DW. Low vitamin D levels are common in patients with epilepsy. Epilepsy Res 2014;108(8):1352-6.

31. Chung PW, Park KY, Kim JM, Shin DW, Park MS, Chung YJ, Ha SY, Ahn SW, Shin HW, Kim YB, Moon HS. 25-hydroxyvitamin D status is associated with chronic cerebral small vessel disease. Stroke 2015;46(1):248-51.

32. Gueye Y, Marqueste T, Maurel F, Khrestchatisky M, Decherchi P, Feron F. Cholecalciferol (vitamin D₃) improves functional recovery when delivered during the acute phase after a spinal cord trauma. J Steroid Biochem Mol Biol 2015;154:23-31.

33. Putz Z, Martos T, Németh N, Körei AE, Vági OE, Kempler MS, Kempler P. Is there an association between diabetic neuropathy and low vitamin D levels? Curr Diab Rep 2014;14(10):537.

34. Lv WS, Zhao WJ, Gong SL, Fang DD, Wang B, Fu ZJ, Yan SL, Wang YG. Serum 25-hydroxyvitamin D levels and peripheral neuropathy in patients with type 2 diabetes: a systematic review and meta-analysis. J Endocrinol
Invest 2015;38(5):513-8.

35. Elf K, Asmark H, Nygren I, Punja AR. Vitamin D deficiency in patients with primary immune-mediated peripheral neuropathies. J Neurol Sci 2014;345(1-2):184-8.

36. Zhou C, Wu L, Ni F, Ji W, Wu J, Zhang H. Critical illness polyneuropathy and myopathy: a systematic review. Neural Regen Res 2014;9(1):101-10.

37. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM; Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2011;96:1911-1930.

38. Intiso D, Amoruso L, Zarrelli M, Pazienza L, Basciani M, Grimaldi G, Iarossi A, Di Rienzo F. Long-term functional outcome and health status of patients with critical illness polyneuromyopathy. Acta Neurol Scand 2011;123(3):211-9.

39. Lee P, Eisman JA, Center JR. Vitamin D deficiency in critically ill patients. N Engl J Med 2009;360(18):1912-4.

40. Alizadeh N, Khalili H, Mohammad M, Abdollahi A. Serum vitamin D levels at admission predict the length of intensive care unit stay but not in-hospital mortality of critically ill surgical patients. J Res Pharm Pract 2015;4:193-198.

41. de Haan K, Groeneveld AB, de Geus HR, Egal M, Struijs A. Vitamin D deficiency as a risk factor for infection, sepsis and mortality in the critically ill: systematic review and meta-analysis. Crit Care 2014;18(6):660.

42. Lee P, Nair P, Eisman JA, Center JR. Vitamin D deficiency in the intensive care unit: an invisible accomplice to morbidity and mortality? Intensive Care Med 2009;35(12):2028-3.

43. Mpandzou G, Aït Ben Haddou E, Regragui W, Benomar M, Grimaldi G, Iarossi A, Di Rienzo F. Long-term functional outcome and health status of patients with critical illness polyneuromyopathy. Acta Neurol Scand 2011;123(3):211-9.

44. Lee P, Eisman JA, Center JR. Vitamin D deficiency in critically ill patients. N Engl J Med 2009;360(18):1912-4.

45. Annweiler C, Bartha R, Karras SN, Gautier J, Roche F, Thouvenot E, Orsini M, Daures JP, Camu W. Vitamin D is associated with degree of disability in patients with fully ambulatory relapsing-remitting multiple sclerosis. Eur J Neurol 2015;22(3):564-9.

46. Elf K, Asmark H, Nygren I, Punja AR. Vitamin D deficiency in patients with primary immune-mediated peripheral neuropathies. J Neurol Sci 2014;345(1-2):184-8.

47. Zhou C, Wu L, Ni F, Ji W, Wu J, Zhang H. Critical illness polyneuropathy and myopathy: a systematic review. Neural Regen Res 2014;9(1):101-10.

48. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM; Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2011;96:1911-1930.

49. Zhang B, Wang Y, Zhong Y, Liao S, Lu Z. Serum 25-hydroxyvitamin D deficiency predicts poor outcome among acute ischemic stroke patients without hypertension. Neurochem Int 2018;118:91-95.

50. Santos RKF, Brandão-Lima PN, Tete RMDD, Freire ARS, Pires LV. Vitamin D ratio and glycaemic control in individuals with type 2 diabetes mellitus: A systematic review. Diabetes Metab Res Rev 2018;34(3).

51. Issa CM. Vitamin D and Type 2 Diabetes Mellitus. Adv Exp Med Biol 2017;996:193-205.

52. Wu F, Juonala M, Pitkänen N, Jula A, Lehtimäki T, Sabin MA, Pakkala K, Nutri-Kähönen N, Kähönen M, Laitinen T, Viikari JSA, Magnussen CG, Raitakari OT. Both youth and long-term vitamin D status is associated with risk of type 2 diabetes mellitus in adulthood: a cohort study. Ann Med 2018;50(1):74-82.

53. Skalli S, Muller M, Pradines S, Halimi S, Wion-Bardot N. Vitamin D deficiency and peripheral diabetic neuropathy. Eur J Intern Med 2012;23(2):e67-8.

54. Kruit A, Zanen P. The association between vitamin D and C-reactive protein levels in patients with inflammatory and non-inflammatory diseases. Clin Biochem 2016;49(7-8):534-7.

55. Gröber U, Kisters K. Influence of drugs on vitamin D and calcium metabolism. Dermatoendocrinol 2012;4(2):158-66.

56. Trehan N, Afonso L, Levine DL, Levy PD. Vitamin D Deficiency, Supplementation, and Cardiovascular Health. Crit Pathw Cardiol 2017;16(3):109-118.

57. Pennisi M, Di Bartolo G, Malaquarnera G, Bella R, Lanza G, Malaquarnera M. Vitamin D Serum Levels in Patients with Statin-Induced Musculoskeletal Pain. Dis Markers 2019;2019:3549402.

58. Manios Y, Moschonis G, Lambrinou CP, Tsoutsouloupoulou K, Binou P, Karachaliou A, Breidenassel C, Gonzalez-Gross M, Kiely M, Cashman KD. A systematic review of vitamin D status in southern European countries. Eur J Nutr 2018;57(6):2001-2036.

59. Pettica P, Bevilacqua M, Vago T, Norbiato G. High prevalence of hypovitaminosis D among free-living postmenopausal women referred to an osteoporosis outpatient clinic in northern Italy for initial screening. Osteoporos Int 1999;9(3):226-9.

60. Romagnoli E, Caravela P, Scarnecchia L, Martinez P, Minisola S. Hypovitaminosis D in an Italian population of healthy subjects and hospitalized patients. Br J Nutr 1999;81(2):133-7.

61. Isaa A, Giorgino R, Rini GB, Bevilacqua M, Maugeri D, Adami S. Prevalence of hypovitaminosis D in elderly women in Italy: clinical consequences and risk factors. Osteoporos Int 2003;14(7):577-82.

62. Amrein K, Papinutti A, Mathew E, Vila G, Parekh D. Vitamin D and critical illness: what endocrinology can learn from intensive care and vice versa. Endocr Connect 2018;7(12):R304-R315.

63. Zampolini M, Corea F, Avesani R, Boldrini P, De Tanti C. Intiso et al.: Vitamin D serum level in subjects with critical illness polyneuropathy and myopathy
A, Di Stefano MG, Formisano R, Lamberti G, Lombardi F, Mazzucchi A, et al. Rehabilitation of acquired brain injuries: a multicentric prospective survey. Eur J Phys Rehabil Med 2013;49(3):365-72.

64. Laver K, Lannin NA, Bragge P, Hunter P, Holland AE, Tavender E, O’Connor D, Khan F, Teasell R, Gruen R. Organising health care services for people with an acquired brain injury: an overview of systematic reviews and randomised controlled trials. BMC Health Serv Res 2014;14:397.

65. Toman E, Bishop JR, Davies DJ, Su Z, Criseno S, Mason A, Toogood AA, Belli A. Vitamin D Deficiency in Traumatic Brain Injury and Its Relationship with Severity of Injury and Quality of Life: A Prospective, Observational Study. J Neurotrauma 2017;34(7):1448-1456.

66. Intiso D, Fontana A, Copetti M, Di Rienzo F. Serum vitamin D deficiency in subjects with severe acquired brain injury and relationship with functional severity. Brain Inj 2018;32(13-14):1817-1823.