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Vitamin D status after a high dose of cholecalciferol in healthy and burn subjects

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ABSTRACT

Background: Burn patients are at risk of vitamin D (VD) deficiency and may benefit from its pleiotropic effects as soon as acute phase. Aim of this observational study was to assess effects of a cholecalciferol (VD3) bolus on VD status in adult burn patients (Group B, GB) after admission, compared to healthy subjects (Group H, GH).

Methods: Both groups received an oral dose of 100,000 IU VD3. Blood samples were collected before (D0) and 7 days (D7) after bolus to measure 25OH-D, $1,25(OH)_2$-D, parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23). Albumin (ALB) and VD binding protein (DBP) were measured and used to calculate free 25OH-D level. Data were expressed as median (min–max) or proportions.

Results: A total of 49 subjects were included: 29 in GH and 20 in GB. At D0, prevalence of VD deficiency was higher in GB: 25OH-D was 21.5 (10.1–46.3) ng/ml in GH vs 11 (1.8–31.4) ng/ml in GB. DBP and ALB were lower in GB. At D7, DBP was stable in both groups while ALB decreased in GB. 25OH-D increased by 66.6 (13.5–260.3)% in GH. In GB, changes in 25OH-D extended from −36.7% to 333.3% with a median increase of 33.1%. Similar changes were observed in each group for free 25OH-D. High FGF23 levels were observed in GB.

Conclusions: This study highlighted the differences in VD status and in response to a high dose VD3 in burn patients when compared to healthy patients. Pitfalls in VD status assessment are numerous during acute burn care: 25OH-D measurement needs cautious interpretation and interest of free 25OH-D is still questionable. They should not prevent burn patients to receive VD supplements during acute care. Higher doses than general recommendations should probably be considered.

1. Introduction

Vitamin D has recognized effects on mineral metabolism and is now known to have a number of pleiotropic effects, especially on immune system, muscle function or regulation of cell proliferation and differentiation [1,2].

Burn patients, particularly those with large burn surface area, are clearly at risk of vitamin D deficiency. From a theoretical point of view, several factors may be implicated.

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Deficiency may occur during acute phase due to prolonged hospital stay, and nutrition deficiency or vitamin D renal wasting secondary to reduced transport proteins [3]. During the chronic phase following burn, the risk of hypovitaminosis D continues. Wound dressings, pressure garments and use of sunscreens limit the impact of sun radiations. Moreover, biosynthetic function of the skin is known to be impaired after burn, in both burn scar and adjacent normal skin [4]. Furthermore, metabolism of vitamin D may be impaired by post-burn abnormalities in the calcium (Ca)–parathyroid hormone (PTH) axis as systemic inflammatory response induces an up-regulation of the parathyroid gland calcium-sensing receptor [5,6]. Subsequent reduction of the set-point for suppression of circulating PTH by blood calcium leads in turn to inappropriately low levels of circulating PTH and decreased action of 1-alpha hydroxylase in the kidney [7].

Vitamin D deficiency has been associated with a wide range of adverse health outcomes including muscle weakness, infectious diseases and mortality in the general population but also in critically ill patients [1,8].

Vitamin D deficiency diagnosis is a subject of debate. Deficiency is defined as serum 25OH-D levels < 20 ng/ml according to the Institute of Medicine [9]. However, this definition could better fit for healthy people [10]. According to the Endocrine Society, serum 25OH-D should reach at least 30 ng/ml to ensure vitamin D sufficiency [11]. However, minimal thresholds may differ whether one is interested in bone effects or other systemic effects. For those later effects, such as muscle effects, cut-off values are not known precisely. Moreover, during acute illness, diagnosis of vitamin D deficiency is thought to be hazardous due to fluid shifts, fluctuations of binding proteins (mainly albumin, ALB, and vitamin D binding protein, DBP) or assays' limitations [12].

Data about vitamin D deficiency, from diagnosis to prevention and treatment, are scarce in burn patients [13]. Most studies are focused on burn children and, to the best of our knowledge, only two papers reported interventional results in adults: one during acute care [14] and one during sequelar phase [15]. Even if a lot of questions remain unsolved regarding burn related hypovitaminosis D, there is a solid rationale to supplement burn patients with vitamin D as soon as acute phase [1]. Recently, it has been demonstrated that dietary reference intakes of cholecalciferol were unable to increase 25(OH)-D levels in these patients [14]. However, there are no formal protocol for treatment of vitamin D deficiency in healthy people and even less in burn patients. To initiate investigations, we decided to follow doses suggested by some experts [16] and to evaluate effect of 100,000 IU cholecalciferol on vitamin D status (vitamin D metabolites and regulators) in adult burn patients during acute phase. Results were compared to those obtained in healthy adults receiving the same supplementation.

2. Method

This study was conducted in 2013 and 2014 after approval by the local Ethics Committee of the University Hospital of Liège (ref 2013/44). The study was registered in the EudraCT database under reference 2013-000306-31. Informed consent was obtained from the patients or their relatives prior to enrolment. Healthy Caucasian workers were recruited among members of our lab during winter (Group H). Adult burn patients admitted within the first 24 h after injury were recruited at the discretion of admission and regardless of season (Group B). Inclusion criteria were: age over 18 years, Caucasian ethnic profile and burn surface area (BSA) greater than 10%. For both groups of subjects, pregnancy, renal or liver failure and prior vitamin D substitution were considered exclusion criteria. Burn patients were included just after admission in the Burn Centre.

Study medication consisted in 1 ml ampoules containing each an oily solution of 25,000 IU cholecalciferol (D-Cure®, SMB Laboratories, Belgium). All subjects received a bolus of 100,000 IU cholecalciferol. Medication was given orally in Group H. In Group B, route of administration depended on burn severity and patient condition: either orally or by nasogastric tube placed for clinical use. Cholecalciferol was administered during the first 12 h after admission.

During all the duration of the protocol, healthy subjects were asked to avoid solarium. Nutrition was not controlled in this group. Burn patients benefited from local standard monitoring and care procedures. Nutrition was prescribed according to recent recommendations [17]. Depending on burn severity and clinical status, oral or enteral feeding was prescribed according to Toronto formula. Daily protein intake was prescribed to obtain 1.5–2 g protein/kg/d. Daily vitamin D intakes associated with oral (hospital made menu) feeding associated to oral nutritional supplements (Fresubin® 2 kcal, Fresenius-Kabi, Germany or Resource® 2.0 fibres, Nestle, Switzerland) reached at least 400 IU D3. Enteral nutrition (Fresubin® HP Energy, Fresenius-Kabi, Germany) daily supplied about 600 IU D3. Diet was daily supplemented with one dose of multivitamin preparation, either per os if BSA $\leq 20\%$ (Supradyn® Energy, Bayer, Germany) or intravenously if BSA $> 21\%$ (Cernevit®, Baxter, USA). One tablet of Supradyn® Energy contains 200 IU D3 and one vial of Cernevit® contains 220 IU D3. These regimens do not impact on 25OH-D levels during acute phase as previously demonstrated [14].

In both groups, blood samples were collected at baseline before cholecalciferol administration (D0) and after 7 days (D7) to assess vitamin D status and regulation factors of vitamin D metabolism. Blood was drawn into serum gel tubes and EDTA tubes (Venosafe Plastic Tubes, Terumo, Haasrode, Belgium), before being centrifugated (3500 rpm, 15 min, 4 °C). Supernatant was finally frozen at −80 °C until later analysis.

Serum level of 25OH-D was measured with the MassChrom 25-OH-Vitamin D3/D2 LC-MS/MS kit including 3-epi-25-OH-Vitamin D3 upgrade (Gräfelfing, Germany) on the AB SCIEX QTRAP® 5500 system (AB SCIEX, Framingham, MA, USA). This LC–MS/MS is traceable to the National Institute of Standards and Technology reference material (NIST) SRM 2972 and the ID-LC-MS/MS 25OH-D Reference Method Procedure [18]. The normal ranges for 25OH-D were 30–80 ng/ml. In our lab, the coefficient of variation (CV) of the 25OH-D assay was $< 2\%$ for LC–MS/MS. Serum level of ALB was assayed using spectrophotometry (Cobas® automate, Roche, Mannheim, Germany): normal ranges 38–49 g/l. DBP concentration was determined using ELISA (R&D Systems, Minneapolis, MN, USA): normal

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