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Bone markers during acute burn care: Relevance to clinical practice?

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ARTICLE INFO

Article history:
Accepted 20 July 2016

Keywords:
Burns
Bone markers
Bone turnover

ABSTRACT

Objective: Bone changes are increasingly described after burn. How bone markers could help to detect early bone changes or to screen burn patients at higher risk of demineralization is still not made clear. We performed an observational study assessing the changes in serum bone markers after moderate burn.

Methods: Adults admitted in the first 24 h following burn extended on >10% body surface area were included. Serum levels of collagen type 1 cross-linked C-telopeptide (CTX), tartrate-resistant acid phosphatase 5b (TRAP), type 1 procollagen N-terminal (P1NP) and bone alkaline phosphatase (b-ALP) were measured at admission and every week during the first month. Data are expressed as median [min-max].

Results: Bone markers were measured in 20 patients: 18 men, 2 women (including one post-menopausal). Age was 46 [19–86] years old, burn surface area reached 15 [7–85] %. Twelve patients completed the study. All biomarkers mainly remained into normal ranges during evolution. A huge variability was observed regarding biomarkers evolution. Patient's evolution was not linear and could fluctuate from a decrease to an increase of blood concentrations. There was not necessarily a consistency between the two formation or the two resorption markers. Variations observed between two consecutive measurements were lesser than the accepted critical difference in almost one third of the cases.

Conclusions: Considering available data, role and interest of bone markers in management of burn related bone disease remain unclear.

1. Introduction

Burn patients are at risk for bone disease following injury. This is thought to be due to different factors, commonly co-existing after burn: prolonged and sustained inflammation or neuro-endocrine response, immobilization and vitamin D deficiency [1].

A reduced bone turnover and a demineralization have been reported in the burn literature for more than two decades [2].

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http://dx.doi.org/10.1016/j.burns.2016.07.020

These data concern both adults and children. In burn children, these changes had even been associated with an increased risk of bone fractures during the first years following injury [3,4]. In burn adults, such outcome evaluation is currently lacking.

Alterations in some bone markers have been described in a few publications. However, the results were not always consistent, mostly due to differences in the studied population or in the measured bone markers [3,6,7]. A recent study reported changes in a panel of bone turnover markers and regulators of bone metabolism in severe burned males during both early and late phase after injury [8]. These changes seemed to be the expression of an altered bone quality, characterize by a precocious appearance. Yet, from a pragmatic and clinical point of view, choice and use of bone markers to detect early bone changes or to screen burn patients at higher risk of demineralization is still not well defined.

Published data about bone health after burn mainly focused on patients suffering from severe burn. Recently, animal data suggest that non-severe burn can also lead to bone changes as soon as the first month following injury [5]. These findings are disturbing, as the mean BSA of patients admitted in burn centers in Europe has decreased over the past decades, to reach 11–24% [9]. In this context, the present observational study assessed the changes in four serum bone markers in non-severe burned adults during the first month following injury. The objective of the study was to determine the clinical value of the mainly used bone biomarkers in a quite broad spectrum of burn patients.

2. Materials and methods

This cohort study was conducted from March 2012 to January 2013 in a 6-bed burn unit after approval by the local Ethics Committee of our University Hospital (Ref B707201213417, 6th March 2012). Informed consent was obtained from the patients or their relatives prior to enrolment.

Caucasian patients over 18 years, with a burn surface area (BSA) greater than 10% and admitted within the first 24 h following injury were included. Pregnancy, renal or liver failure, prior vitamin D substitution were considered exclusion criteria. They benefited from local standard monitoring and care procedures in term of fluid resuscitation, nutrition and surgery. They daily received vitamin D3 (cholecalciferol, VD3) from oral nutrition (Fresubin 2kcal®, Fresenius-Kabi, Germany, Resource 2.0 fibres®, Nestlé, Switzerland), enteral nutrition (Fresubin HP Energy®, Fresenius-Kabi, Germany) and multivitamin complex supplementation (Supradyn Energy®, Bayer, Germany or Cernevit®, Baxter, USA), reaching a daily dose of 600–800 UI.

For each patient, assessment of global bone health at admission was performed using the FRAX tool (Fracture Risk Assessment tool) (https://www.shef.ac.uk/FRAX/tool.aspx?country=18). The University of Sheffield, in association with the World Health Organization, developed this instrument. FRAX uses validated clinical risk factor to provide a prediction of individual's risk of fracture in the next 10 years. The risk is expressed in percentages.

Blood samples were collected in all patients at admission (D0) and then in the early morning of the 7th, 14th, 21st and 28th day of in-hospital follow-up. Blood was then centrifugated (3500 rpm, 15 min, 4 °C) and supernatant was finally frozen and stored at −80 °C.

Serum collagen type 1 cross-linked C-telopeptide (CTX), serum type 1 procollagen N-terminal (P1NP) and serum bone alkaline phosphatase (b-ALP) were assayed using chemoluminiscence (iSYS automate, IDS, Boldon, UK). CTX concentration <695 ng/l and b-ALP concentration <21 μg/l were considered normal. Normal range for P1NP was 7.5–95.4 ng/ml with changes according to age and gender [10]. Serum tartrate-resistant acid phosphatase 5b (TRAP) was measured using ELISA (IDS, Boldon, UK): NR was 1.5–4.7 U/l. CTX and TRAP are bone resorption markers while P1NP and b-ALP are bone formation markers.

Intra-individual coefficient of variation (CV_i) for the used bone markers was collected via the website https://www.westgard.com/biodatabase1.htm, excepting for TRAP [11]. CV_i is essential to calculate the critical difference (CD), which is the value above (or under) which a variation between two consecutive biological measurements may be considered as biologically significant, with a probability of 95%. CD depends also on the analytical coefficient of variation (CV_a) of the parameter and can be calculated according the following formula: $CD = 2^{1/2} \times 1.96 \times (CV_a^2 + CV_i^2)^{1/2}$ [12]. In daily practice, since CV_a is much lower than CV_i, CD is usually estimated as $3\times$ CV_i.

Serum level of 25OH-D and 3rd generation PTH were determined with Liaison® (DiaSorin, Stillwater, MN, USA). The normal ranges were respectively 30–100 ng/ml and 4–26 pg/ml. 1,25$(OH)_2$-D was assayed with iSYS® automate (IDS, Boldon, UK): normal range was <85 pg/ml. Serum levels of albumin (ALB) was assayed using spectrophotometry (Cobas automate, Roche, Mannheim, Germany): NR was 38–49 g/l. Levels of calcium (Ca), phosphate (P) and creatinine were assayed with Cobas automate (Roche, Mannheim, Germany): NR were respectively 2.15–2.6 mmol/l, 0.74–1.51 mmol/l and 7.2–11.8 mg/l. Serum total calcium (Ca Tot) level was corrected for albumin level according to the following formula: Corr Ca Tot (mml/l) = serum Ca Tot − 0.025 (serum albumin − 40).

Statistical analysis was performed using Graphpad Prism (version 6.0 for Mac OSX, Graphpad Inc., San Diego, CA, USA). Data were tested for normality using the Shapiro-Wilk test. Results are expressed as medians and ranges (min-max). Unpaired data were compared using Mann and Whitney test. Paired data were analyzed using Wilcoxon test or Friedman test with multiple comparisons, as required. Correlation between bone markers and baseline data were assessed using nonparametric Spearman test. A p value <0.05 was considered to be statistically significant.

3. Results

Biological data were measured in 20 patients: 18 men, 2 women (including a post-menopausal). Median age was 46 [19–86] years old. Definitive median BSA, as evaluated by a senior intensivist, reached 15 [7–85] %. Frequency distribution

Please cite this article in press as: Rousseau A-F, et al. Bone markers during acute burn care: Relevance to clinical practice? Burns (2016), http://dx.doi.org/10.1016/j.burns.2016.07.020