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Relevance of serum sclerostin concentrations in critically ill patients

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ABSTRACT

Purpose: Sclerostin is a negative regulator of bone metabolism and associated with chronic morbidities. We investigated circulating sclerostin in critically ill patients.
Methods: A total of 264 patients (170 with sepsis) were studied prospectively upon admission to the medical intensive care unit (ICU) and on day 7. Patients' survival was followed for up to 3 years.
Results: Sclerostin serum levels were significantly elevated in critically ill patients at ICU admission compared with 99 healthy controls. Unlike in healthy controls, sclerostin did not depend on sex or age of ICU patients. Sclerostin was associated with disease severity, independent of the presence of sepsis. Sclerostin levels increased during the first week of treatment at the ICU but were not a predictor of mortality. Sclerostin was elevated in patients with preexisting chronic kidney disease or liver cirrhosis, but was not related to diabetes, obesity, or cardiovascular disease. Circulating sclerostin in ICU patients correlated with biomarkers reflecting renal, hepatic and cardiac dysfunction, and biomarkers reflecting bone metabolism.
Conclusion: Serum sclerostin concentrations are significantly elevated in critically ill patients, linked to renal or hepatic organ failure, and associated with bone resorption markers, supporting its value as a potential tool for the assessment of ICU-related metabolic bone disease.

1. Introduction

Metabolic bone disease in the intensive care unit (ICU) is considered as a potentially devastating consequence of critical illness. Routinely used laboratory parameters related to bone metabolism such as calcium, phosphate, alkaline phosphatase, or parathyroid hormone have limited value in the ICU setting due to confounding influences by organ dysfunction, comorbidities, and therapeutic measures [1]. Sclerostin has emerged as a key negative regulator of bone metabolism [2]. It is an inhibitor of the anabolic Wnt/β-catenin signaling pathway that is specifically produced by osteocytes [3]. Sclerostin decreases bone formation by repressing osteoblast differentiation and proliferation [3]. The ability to measure sclerostin levels in the blood has led to the further investigation of circulating sclerostin as a biomarker of bone metabolism [4]. Several independent clinical studies have suggested associations between sclerostin levels and bone mineral density changes, fracture risk, responses to hyperparathyreoidism, or bisphosphonate therapy as well as vascular calcification [2,4-6].

These clinical associations imply that serum sclerostin measurements could be useful in predicting patient-specific outcomes. This has been exemplarily demonstrated in hemodialysis patients. However, these studies yielded conflicting results. In 2 large cohorts of hemodialysis patients from the Netherlands (n = 673) as well as from Belgium (n = 100), high serum sclerostin was identified as a prognostic indicator for improved cardiovascular and all-cause survival [7,8]. On the other hand, a study from Brazil comprising n = 99 hemodialysis patients reported that the long-term mortality (10-year observation period) was significantly increased in patients with high sclerostin levels [9]. High sclerostin have also been reported in patients with advanced liver disease [10], type 2 diabetes [11], obesity [12], and cardiovascular diseases [6], indicating that sclerostin has implications in various types of chronic diseases.

The regulation of sclerostin in conditions of critical illness is currently unknown. We therefore assessed serum sclerostin levels in a large cohort of 264 critically ill patients at a medical ICU at the time of admission as well as after the first week of ICU treatment. We herein demonstrate that sclerostin levels are significantly increased in critically

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ill patients compared with controls, and we identified important clinical parameters influencing circulating sclerostin.

2. Materials and methods

2.1. Study design and patient characteristics

We conducted a single-center prospective observational trial at the Medical ICU at the University Hospital Aachen, Germany. We included consecutively all patients on admission to the ICU. Patients for postinterventional ICU observation after elective procedures were excluded from this study [13]. We obtained written informed consent from the patient, his or her spouse, or the appointed legal guardian. The study protocol was approved by the local ethics committee (ethics committee of the University Hospital Aachen, RWTH-University, Aachen, Germany).

Sepsis was defined following the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [14]; all other patients were categorized as nonsepsis patients. The *mortality* during the ICU treatment was defined as "ICU mortality." Furthermore, the patient's outcome was followed for approximately 2 years by contacting the patients, patients' relatives, and/or general practitioner, resulting in assessment of an "overall mortality" rate [15]. The Charlson Comorbidity Index (CCI) was retrospectively assessed [16].

Healthy blood donors with normal blood counts, normal liver enzymes, and negative serology for viral hepatitis and HIV served as controls [17].

2.2. Sclerostin measurements

At the time point of admission to the ICU as well as in the morning of day 7 after admission, blood samples were collected, centrifuged, and frozen at −80°C until analysis. To exclude potential effects of treatment measures on sclerostin levels, the blood samples at admission were obtained before therapeutic interventions at the ICU [17]. Sclerostin serum concentrations were analyzed using a commercial enzyme immunoassay (Biomedica Medizinprodukte GmbH, Vienna, Austria). The intra-assay coefficient of variation was 4% to 6%, and the interassay coefficient of variation was 5% to 7%. Sclerostin measurements were performed by a scientist, who was fully blinded to any clinical or other laboratory data of the patients or controls.

2.3. Statistical analysis

Clinical and experimental data from this study are presented as median and range due to the skewed distribution of most of the parameters. Mann-Whitney *U* test was used to determine differences between 2 groups. Box plot graphics were calculated to display the median, quartiles, range, and extreme values. Box-and-whisker plot reaches from the minimum to the maximum value excluding outside and far-out values which are displayed as separate points. An outside value (indicated by an open circle) was defined as a value that is smaller than the lower quartile minus 1.5 times the interquartile range, or larger than the upper quartile plus 1.5 times the interquartile range. A far-out value was defined as a value that is smaller than the lower quartile minus 3 times the interquartile range, or larger than the upper quartile plus 3 times the interquartile range [13]. Importantly, all values, including "outliers," have been included for statistical analyses. Correlations between parameters were analyzed by Spearman rank correlation. Throughout this study, *P* values less than .05 were considered statistically significant. The prognostic value of sclerostin was tested by Cox regression analysis. All statistical analyses were performed with SPSS (SPSS, Chicago, Ill).

3. Results

3.1. Sclerostin serum levels are significantly up-regulated in critically ill patients and is related to disease severity

We measured sclerostin serum concentrations in a large cohort of medical ICU patients at admission (=before therapeutic interventions) and on day 7 (Table 1). We enrolled 264 patients (158 men, 106 women with a median age of 63 years; range, 18-90 years) who were admitted to the General Internal Medicine ICU at the RWTH-University Hospital Aachen, Germany (Table 1). As a control population, we analyzed 99 healthy blood donors (66 men, 33 women; median age, 32 years; range 18-67 years). Sclerostin serum levels were significantly higher in ICU patients (n = 264; median, 33.6 pmol/L; range, 5.1-239.3 pmol/L) as compared with healthy controls (n = 99; median, 30.4 pmol/L; range, 10-84.1 pmol/L; $P = .018$; Fig. 1A). In our healthy control cohort, serum sclerostin levels correlated with age ($r = 0.201$, $P = .047$), and sclerostin was higher in male than in female individuals (median, 32.5 pmol/L vs 24.6 pmol/L; $P = .006$), in line with the literature [18]. No significant association between serum sclerostin and sex or age was found in critically ill patients (detailed data not shown).

Table 1
Baseline patient characteristics and sclerostin serum measurements

Parameter	All patients	Nonsepsis	Sepsis
No.	264	94	170
Sex (male:female)	158:106	57:37	101:69
Age (y), median (range)	63 (18-90)	60.5 (18-85)	64 (20-90)
APACHE II score, median (range)	17 (2-43)	14.5* (2-33)	19* (3-43)
ICU days, median (range)	8 (1-137)	6* (1-45)	10* (1-137)
Death during ICU, n (%)	65 (24.6)	16 (17)*	49 (28.8)*
Death during follow-up (total), n (%)	125 (47.3)	32 (34)*	93 (54.7)*
Mechanical ventilation, n (%)	180 (68.2)	57 (60.6)*	123 (72.4)*
Preexisting diabetes, n (%)	80 (30.3)	30 (31.9)	50 (29.4)
Preexisting cirrhosis, n (%)	25 (9.5)	18 (19.1)*	7 (4.1)*
BMI (m^2/kg), median (range)	26 (15.9-86.5)	26 (15.9-53.3)	26 (17.1-86.5)
WBC ($\times 10^3$/μL), median (range)	12.7 (0-149)	11.7* (1.8-29.6)	13.2* (0-149)
CRP (mg/dL), median (range)	97.5 (5-230)	17* (5-230)	161.5* (5-230)
Procalcitonin (μg/L), median (range)	0.9 (0.03-248)	0.2* (0.03-100)	3.1* (0.1-248)
Creatinine (mg/dL), median (range)	1.33 (0.1-21.6)	1.0* (0.2-15)	1.6* (0.1-21.6)
INR, median (range)	1.18 (0.9-13)	1.18 (0.9-6.73)	1.17 (0.92-13)
Sclerostin day 1 (pmol/L), median (range)	33.6 (5.1-239.3)	33.4 (10-208)	33.6 (5.1-239.3)
Sclerostin week 1 (pmol/L), median (range)	45.4 (0.5-169.7)	36.9 (8.5-148.6)	47.3 (0.5-169.7)

For quantitative variables, median and range (in parenthesis) are given.
BMI indicates body mass index; WBC, white blood cell count; CRP, C-reactive protein; INR, international normalized ratio.
* $P < .05$ for the difference between sepsis and non-sepsis patients (*U* test for quantitative and chi-square test for qualitative variables).