Analysis of the Receptor Activator of NF-κB Ligand/Osteoprotegerin (RANKL/OPG) ratio as potential biomarker for infection-related bone destruction in pyogenic vertebral osteomyelitis

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INTRODUCTION:

Circulating soluble Receptor Activator of NF-κB Ligand (sRANKL) and soluble Osteoprotegerin (sOPG) serum levels have been suggested as biomarkers for different aspects of bone diseases. We aimed to characterize the relation between the local mRNA RANKL/OPG ratio and the amount of vertebral bone loss in patients with vertebral osteomyelitis (VO). Secondly, to evaluate the sRANKL/sOPG ratio as a potential surrogate marker for bone loss in patient serum.

METHODS:

Subsequent adult patients with VO were prospectively included and followed up for at least 12 weeks (Figure 1). Demographic information, treatment details, microbiological findings, and serum parameters (C-reactive protein (CRP) and white blood cell count (WBC)) were documented. Serum samples were taken at the time-point of initial diagnosis of VO (t0), one week after diagnosis (t1), and at the time point of surgery (if, applicable, ts). ELISA was used to determine serum levels of free sRANKL and sOPG. Bone samples from infected vertebral bodies were collected from surgically treated patients and the mRNA expression levels of RANKL and OPG were determined by RT-qPCR. The initial vertebral bone loss was quantified with 3D volumetric segmentation (Figure 2) based on the initial CT scan (t0) using a previously established calculation method.

RESULTS:

Included patients (68.1±12.6 years; 63.6% male, 36.4% female) suffering from cervical (18.2%), thoracic (45.5%), and lumbar (36.4%) VO. In 45.5% of cases, a pathogen was identified. In 54.5% of cases, surgery was conducted, and bone samples were collected. The mean CRP concentration at t0 was 70.4±48.5 mg/dL and decreased to 52.4±40.9 mg/dL (t1) and the mean WBC decreased from 9.0±2.0 cells/nL (t0) to 7.3±2.9 cells/nL (t1).

The mean free sRANKL concentration at t0 was 0.9±0.5 pg/mL and decreased to 0.8±0.4 pg/mL at t1 (p=0.316). The mean free sOPG concentration at t0 was 707.7±252.0 pg/mL and increased to 752.7±354.4 at t1 (p=0.389). This calculates to a mean free sRANKL/sOPG ratio at t0 of 1.54E-03±1.05E-03 which decreased until t1 to 1.48E-03±1.10E-03 (p=0.457).

The mean calculated bone loss was 26.8±13.1% (7.8 – 50.9%; Table 1). We identified a strong and statistically significant correlation between the height of the local mRNA RANKL/OPG ratio (ts) and the amount of bone loss (r=0.983, p<0.001). There was a small and not significant correlation between the free sRANKL/sOPG ratio (t0) and the amount of bone loss (r=0.133; p=0.820). Lastly, there was a moderate correlation between the sRANKL/sOPG and local RANKL/OPG ratio without reaching statistical significance (r=0.371; p=0.526).

DISCUSSION AND CONCLUSION:

VO was linked to significant initial vertebral bone mass loss, with the local mRNA RANKL/OPG ratio closely associated with bone loss extent, unlike the free sRANKL/sOPG ratio.

The significant correlation between the local mRNA RANKL/OPG ratio and vertebral bone loss in VO supports previous findings by our study group (Lang et al. ECM; 2021), which highlight the local RANKL/OPG ratio characterizes VO. Liò et al. demonstrated how osteomyelitisn disrupts RANK/RANKL/OPG signaling, leading to severe bone loss (Liò et al. BMC Bioinformatics; 2012). A study on rheumatoid arthritis demonstrate that targeting the RANKL/OPG pathway via TNF-α inhibitors can reduce bone resorption, suggesting potential therapeutic strategies for VO (Jura-Półtorak et al. JCM; 2021).

However, the current study's limitations, including the small sample size and lack of control groups, necessitate further research to validate these findings. Larger, controlled studies are essential to confirm the therapeutic potential of RANKL/OPG modulation in VO and to establish standardized treatment protocols. This approach could significantly improve patient outcomes by providing a targeted method to protect against bone degradation in VO, ultimately enhancing the quality of life for affected individuals.

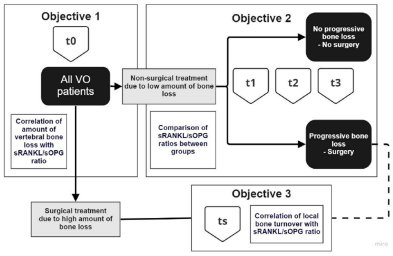
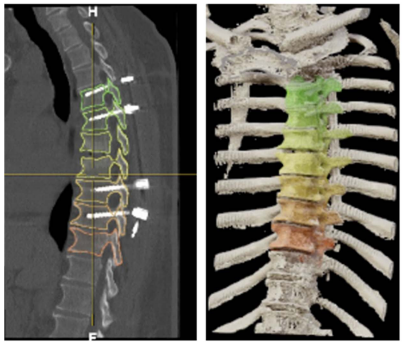


Figure 2: Segmentation of 3D Volumetric images of vertebral bodies



Patient	Calculated bone loss
I-1	-8.6%
I-2	-30.4%
I-3	-22.8%
I-4	-7.8%
I-6	-26.9%
I-8	-33.4%
I-9	-28.7%
I-10	-32.0%
I-11	-50.9%
Mean	**-26.8%**
SD	**13.1%**
Max	**-50.9%**
Min	**-7.8%**