Mechanism of bone disease in Prader-Willi syndrome

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BACKGROUND

Low bone mineral density (BMD) is found in up to 50% of adolescents and adults with Prader-Willi syndrome (PWS). High fracture risk has been described in adult PWS patients. This bone fragility could be due to inadequate gonadal hormones levels during pubertal development, and to relative growth hormone insufficiency during childhood and adolescence. However, the mechanism/s of low BMD in PWS have not been clarified.

OBJECTIVE AND HYPOTHESES

We aimed; 1. to study the osteoclastogenic potential of peripheral blood mononuclear cells (PBMCs) of PWS subjects and controls; 2. to evaluate the alteration of RANKL/OPG axis.

METHODS

PBMCs of 26 PWS patients and 26 age and sex-matched controls were cultured in presence/absence of M-CSF and RANKL. Mature multinucleated osteoclasts (OCs) were identified as TRAP+ cells. RANKL and OPG levels were measured in the sera. RANKL expression was also evaluated by flow cytometry. Bone status was assessed by DXA.

RESULTS

BMD in PWS patients and in controls

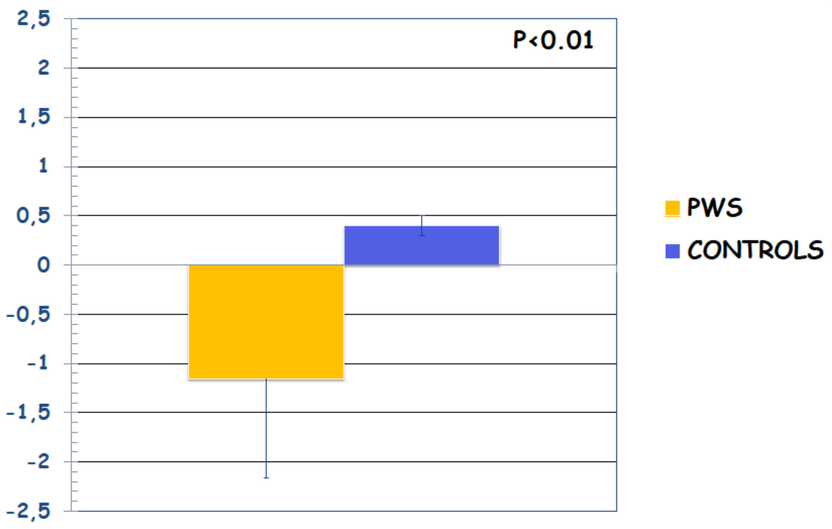

Figure 1. PWS patients showed a lower BMD than controls

Spontaneous OC formation in PWS patients

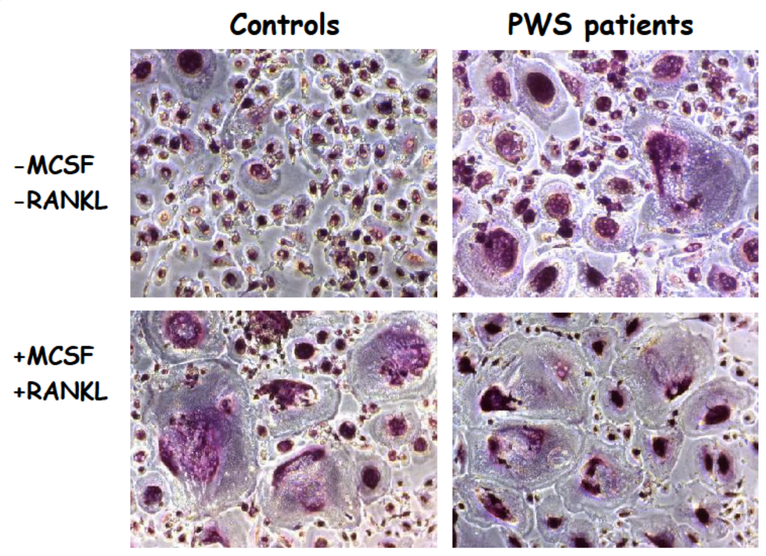

Figure 2. OCs obtained from unfractionated PBMCs of PWS patients and controls without or with MCSF and RANKL

RANKL expression in the lymphomonocyte fraction of controls and PWS patients

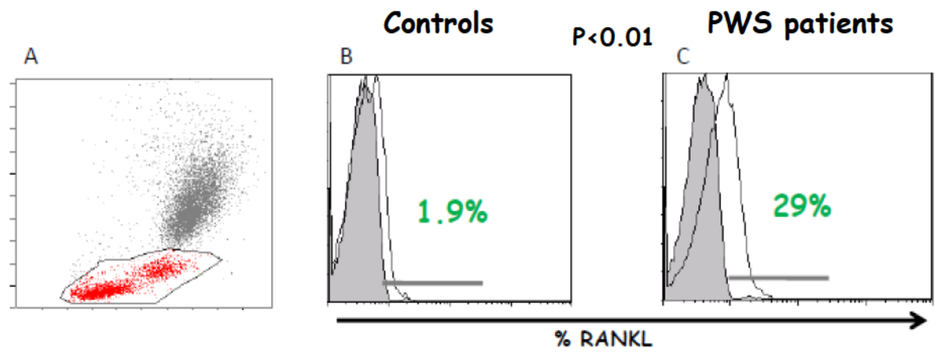

Figure 3. RANKL expression in the lymphomonocyte fraction (highlighted in A) of peripheral blood samples from a representative control (B) and PWS patient (C)

RANKL and OPG serum levels in controls and in PWS patients

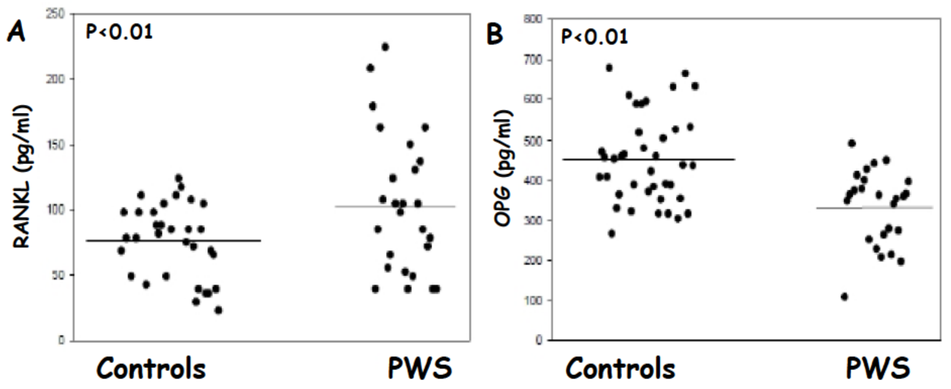

Figure 4. (A) Significant higher RANKL and (B) lower OPG levels were found in PWS patients than controls

BMD Z-score was between <-1 and <-2 in 30% of PWS patients, and < -2.5 in 20% of them (Fig. 1). A high number of multinucleated TRAP+ OCs were identified in the unstimulated PBMC cultures of PWS patients, while few OCs appeared in cultures of controls (OC number/well 60 ± 5 vs 10 ± 4, $p<0.01$). In the stimulated cultures the same OC number was obsreved in patients and controls (fig. 2). Flow cytometry on lymphomonocyte circulating fraction of PWS patients showed higher levels of RANKL than controls (32% ± 5 vs 5% ± 2, $p<0.01$) (fig. 3). Significant higher RANKL and lower OPG levels were found in PWS patients than controls ($p<0.01$) (fig. 4).

CONCLUSIONS

We demonstrated a high osteoclastogenic potential of PBMCs of PWS patients, which could be due to increased RANKL/OPG ratio. This condition could contribute to bone disease affecting PWS patients.

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