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DIAGNOSTIC SIGNIFICANCE OF SERUM CONCENTRATIONS OF OSTEOPROTEGERIN AND PROINFLAMMATORY CYTOKINE IL-1ß IN CHILDREN WITH AUTOIMMUNE THYROID DISEASE

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INTRODUCTION

Chronic autoimmune thyroiditis (cAIT) and **Graves' disease (GD)** are the **most common autoimmune disorders in children**.
cAIT leads to **hypothyroidism** in most cases due to T cell-mediated cytotoxicity. In contrast, **GD** and its thyrotropin receptor stimulatory autoantibodies generates **hyperthyroidism.**
Osteoprotegerin (OPG) is a soluble glycoprotein that belongs to the **tumor necrosis factor TNF receptor superfamily (TNFR)** and plays an important role in **bone homeostasis** and in **vasculature.** It acts as a **decoy soluble receptor** for the receptor activator of nuclear factor kB ligand **(RANKL) inhibiting osteoclastogenesis.**
OPG is also a **decoy receptor** for the TNF-related apoptosis induced ligand **(TRAIL)**. Thus, OPG acts as a **potential counter-regulatory and anti-apoptotic factor**.

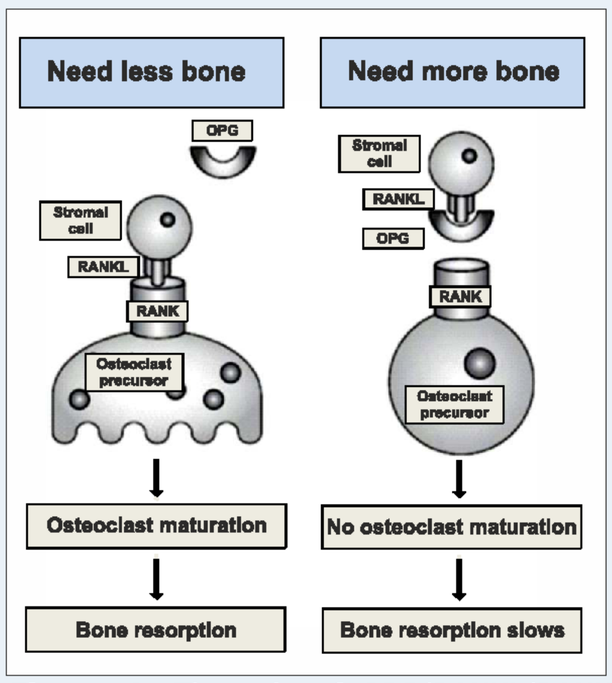

Figure 1. *The role of OPG/RANKL/RANK pathway in bone homeostasis (addapted from Raggi P et al. (2007); Nat Clin Pract Cardiovasc Med 4: 26–33)*

IL-1ß is an **important mediator** of the **inflamatory response** and is involved in a **variety of cellular activities**, including **cell proliferation, differentiation** and **apoptosis**.

AIM OF THE STUDY

The aim of this study was to **determine the relationship between the concentration of proinflamatory cytokines IL-1ß and OPG** with immune thyroid factors in the **serum of children with autoimmune thyroid disease (AITD).**

MATERIAL AND METHODS

1. Studied groups and analyzed markers: 64 children, 3 subgroups: 22 children with hypoT, 22 children with hyperT (newly diagnosed patients) and 20 healthy subjects as an euthyroid control.
Summary of the groups and **descriptive statistics** are presented in **Table 1.:**

	Hypothyroidism (hypoT) mean ± SD median (IQR)	Hyperthyroidism (hyperT) mean ± SD median (IQR)	Control group mean ± SD median (IQR)	Significance of differences
n	n=22	n=22	n=20	
sex	18 girls / 4 boys	16 girls / 6 boys	11 girls / 9 boys	ns
Age [years]	11.39 ± 2.68	14.75 (7.09)	11.57 ± 4.86	ns
BMI [kg/m2]	18.69 (5.45)	18.25 ± 3.42	18.17 ± 3.50	ns
BMI-SDS	0.3 (2.04)	-0.38 ±1.05	-0.55 (1.29)	ns
Cole Index	1.05 ± 0.22	0.95 ± 0.13	0.9 ± 70.14	ns
TSH [0.5-5.0 µIU/mL]	37.34 (17.69) ↑	0 (0.01) ↓	2.42 (1.52)	p<0.001 (K-W) (s***)
fT4 [0.7-1.85 ng/dL]	0.54 ± 0.31 ↓	4.24 ± 1.06 ↑	1.03 ± 0.12	p<0.001 (ANOVA) (s***)
fT3 [1.7-3.5 pg/mL]	2.10 ± 0.97	19.01 ± 5.30 ↑	2.70 ± 0.56	p<0.001 (ANOVA) (s***)
ATG [<60 IU/mL]	124 (589) ↑	101 (552) ↑	20 (4.5)	p<0.001 (K-W) (s***)
ATPO [<60 IU/mL]	3000 (111) ↑	3000 (1536) ↑	10 (29)	p<0.001 (K-W) (s***)
TRAb [<1 IU/L]	0.7 ± 0.3	16.75 (24.6) ↑	0.5 ± 0.3	p<0.001 (K-W) (s***)
IL-1β [pg/mL]	2.58 ± 1.8 2.16 (0.87)	1.45 ± 0.67 1.39 (1.27)	1.48 ± 0.7 1.88 (1.04)	p=0.002 (K-W) (s**)
OPG [pmol/l]	3.79 ± 1.28 3.77 (1.79)	4.48 ± 2.01 4.68 (2.86)	3.02 ± 1.17 3.00 (1.98)	p=0,013 (ANOVA) (s*)

Table 1. *Descriptive statistics and significance of diffrences - hyperT, hypoT and control group (ANOVA - analysis of variance, K-W - Kruskal-Wallis non-parametric test)*

2. Inclusion criteria: clinical, hormonal and autoimmune: TRAb+ in GD: ATPO+/ ATG+ in cAIT.
3. Methods: thyroid **hormones** - **MEIA** tests (Abbott, AxSym); **OPG and IL-1ß** - **ELISA** tests (Biomedica and BenderMedSystem, Vienna, Austria), antibodies **TRAb / ATG / ATPO – RIA** tests (Brahms, Berlin, Germany).
4. Serum concentrations OPG and IL-1ß in groups of patients with hypo-and hyperthyroidism (vs control) were evaluated at the onset of disease (before treatment introduction).
5. Statistical analysis was carried out in SPSS 17.0 for Windows (SPSS, Chicago, IL). Shapiro–Wilk normality test, ANOVA (Newman–Keuls post-test; N-K), nonparametric Kruskal–Wallis (K-W) (Dunn's post-test) and Spearman's rank correlation were used.

RESULTS

1. IL-1ß concentrations were **significantly higher** in **cAIT** (median; IQR: 2.16 pg/ml; 0.87) vs **control** (1.88 pg/ml; 1.04; p<0.05) and in **cAIT** vs **GD** (1.39 pg/ml; 1.27; p<0.01)(K-W p=0.002) **(Fig. 1).**

2. OPG concentrations were **significantly higher** in **children** with **GD**: (mean±SD: 4.48±2.01 pmol/L; ANOVA p=0.013; N-K p<0.01) compared to control group (3.02±1.17 pmol/L); whereas **no significant difference** between **children** with **cAIT** (3.79±1.28 pmol/L) vs **control** group (N-K p>0.05) and **cAIT** vs **GD** (N-K p>0.05) **was observed (Fig. 2)**
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3. In **cAIT** significant **positive correlation** between **IL-1ß** and **OPG** was identified (r=0.44; p<0.05) **(Fig. 3).**

4. In **GD, significant positive correlation** between **IL-1ß** and **ATPO** was identified (r=0.47; p<0.05) **(Fig. 4).**

5. ROC curve analysis enables **determination** of **usefulness** of **monitoring cytokine concentrations** in order to **discriminate** children with **autoimmune thyroid disease** from **healthy** children:

a) IL-1ß discriminated **healthy** and **autoimmune-hypothyroid (cAIT)** children with **low sensitivity** of **59.1%**, but **high specificity** of **95%** (AUC=0.77; p=0.003). Concentrations of this marker **increase** in **hypothyroidism (Fig. 5)**

b) Morevoer, ROC curve of **IL-1ß** showed **good efficacy** to discriminate between **cAIT** and **GD** children with **sensitivity** of **72.7%** and specificity of **86.4%** (AUC=0.773; p=0.002) **(Fig. 6)**

c) ROC curve of **OPG** indicates **good efficacy** to **discriminate** groups of **hyperthyroid (GD)** and **healthy children** (AUC=0.716; p=0.017) with **low sensitivity (54.5%)** but **high specificity (95%).** Concentrations of this marker **increase** in **hyperthyroidism (Fig. 7).**

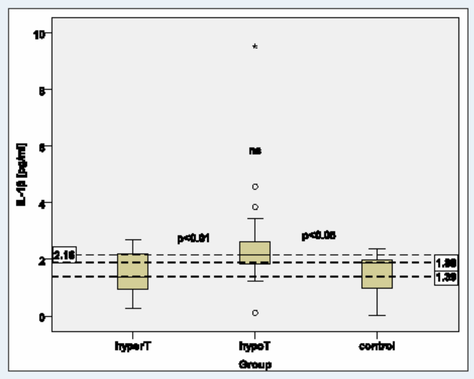

Figure 1. *Boxplot of IL-1ß: hypoT vs control p<0.05; hyperT vs hypoT p<0.01; hyperT vs control ns*

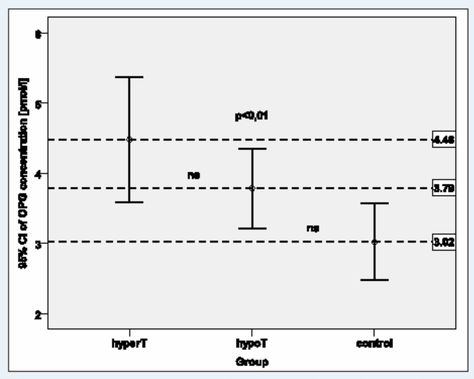

Figure 2. *Scatterplot of OPG: hyperT vs control p<0.01; hyperT vs hypoT ns; hypoT vs control ns*

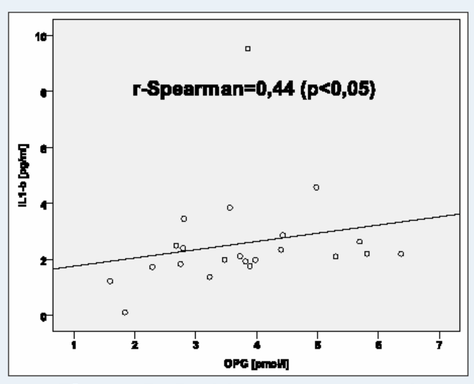

Figure 3. *Positive nonparametric correlation in cAIT: IL-1ß and OPG*

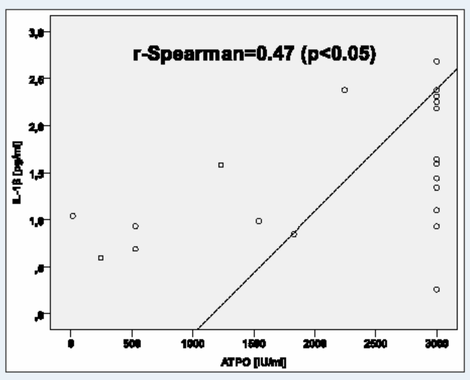

Figure 4. *Positive nonparametric correlation in GD: IL-1ß and ATPO*

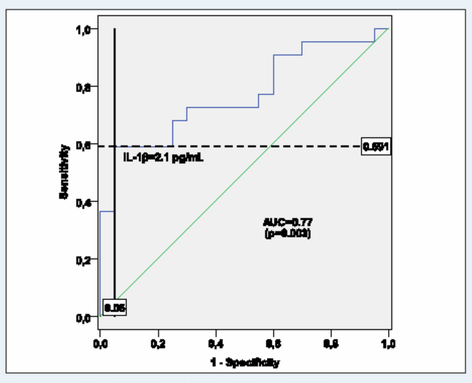

Figure 5. *ROC of IL-1ß: cAIT versus control group (AUC=0.77, p=0.003, cut-off=2.1 pg/ml; sens.: 59.1%, spec.: 95%)*

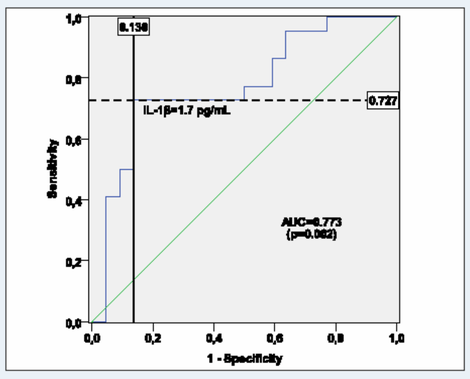

Figure 6. *ROC of IL-1ß: cAIT versus GD (AUC=0.773, p=0.002, cut-off=1.7 pg/ml, sens.: 72.7%, spec.: 86.4%)*

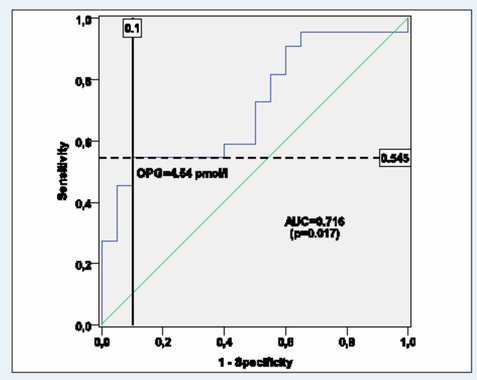

Figure 7. *ROC of OPG: GD versus control group (AUC=0.716, p=0.017, cut-off=4.54 pmol/l; sens.: 54.5%, spec.: 95%)*

CONCLUSION

We suggest that OPG may serve as a marker of hyperthyroidism (GD) and IL-1ß as a marker of hypothyroidism (cAIT) in children with autoimmune thyroid disease (AITD).

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There was no conflict of interest related to this study.

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