

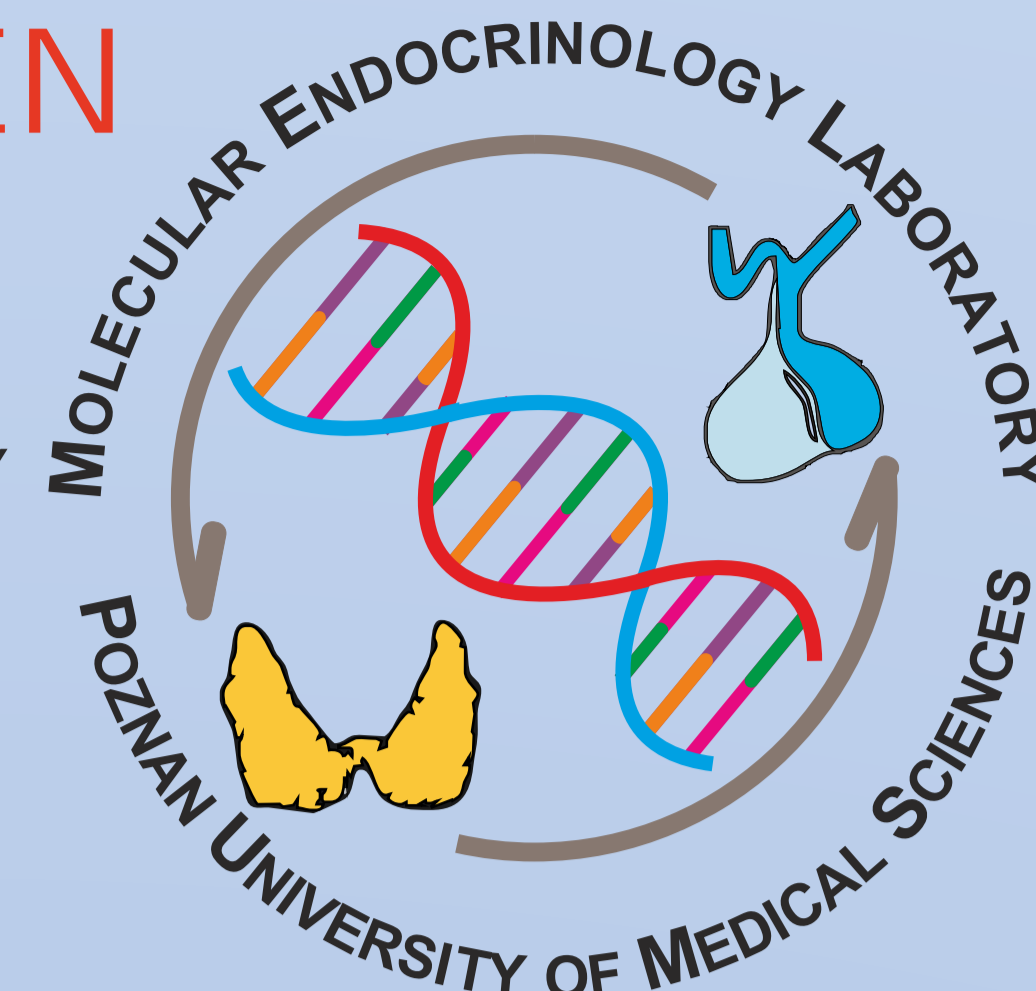
# EVALUATION OF SERUM CYTOKINES IL-6 AND OSTEOPROTEGERIN (OPG) MEASUREMENTS IN THE DIAGNOSIS OF CHRONIC AUTOIMMUNE THYROIDITIS AND GRAVES' DISEASE IN CHILDREN

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## INTRODUCTION

Chronic autoimmune thyroiditis (cAIT) and Graves' disease (GD) are the most common autoimmune disorders in children.

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 κB 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.

Proinflammatory cytokine IL-6 has been associated with the induction of inflammation and autoimmunity. IL-6 is released by fibroblasts, T-cells, endothelial cells and monocytes. It is a pleiotropic cytokine exerting multiple biologic activities on different types of target cells including induction of B-cell differentiation, activation of T-cells, induction of acute phase proteins, stimulation of hemopoietic precursor cell growth and differentiation, pyrogenic action as well as inhibition of cell growth and apoptosis.

## AIM OF THE STUDY

The aim of the study was to determine concentrations of IL-6 and OPG in autoimmune thyroid disease (AITD) in children.

## 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/m <sup>2</sup> ]	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 ± 0.14	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-6 [pg/mL]	2.09 ± 2.13 1.60 (0.07)	1.96 ± 1.76 1.60 (0.04)	1.40 ± 0.53 1.56 (0.37)	ns
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 differences - hyperT, hypoT and control group (ANOVA - analysis of variance, K-W - Kruskal-Wallis non-parametric test)

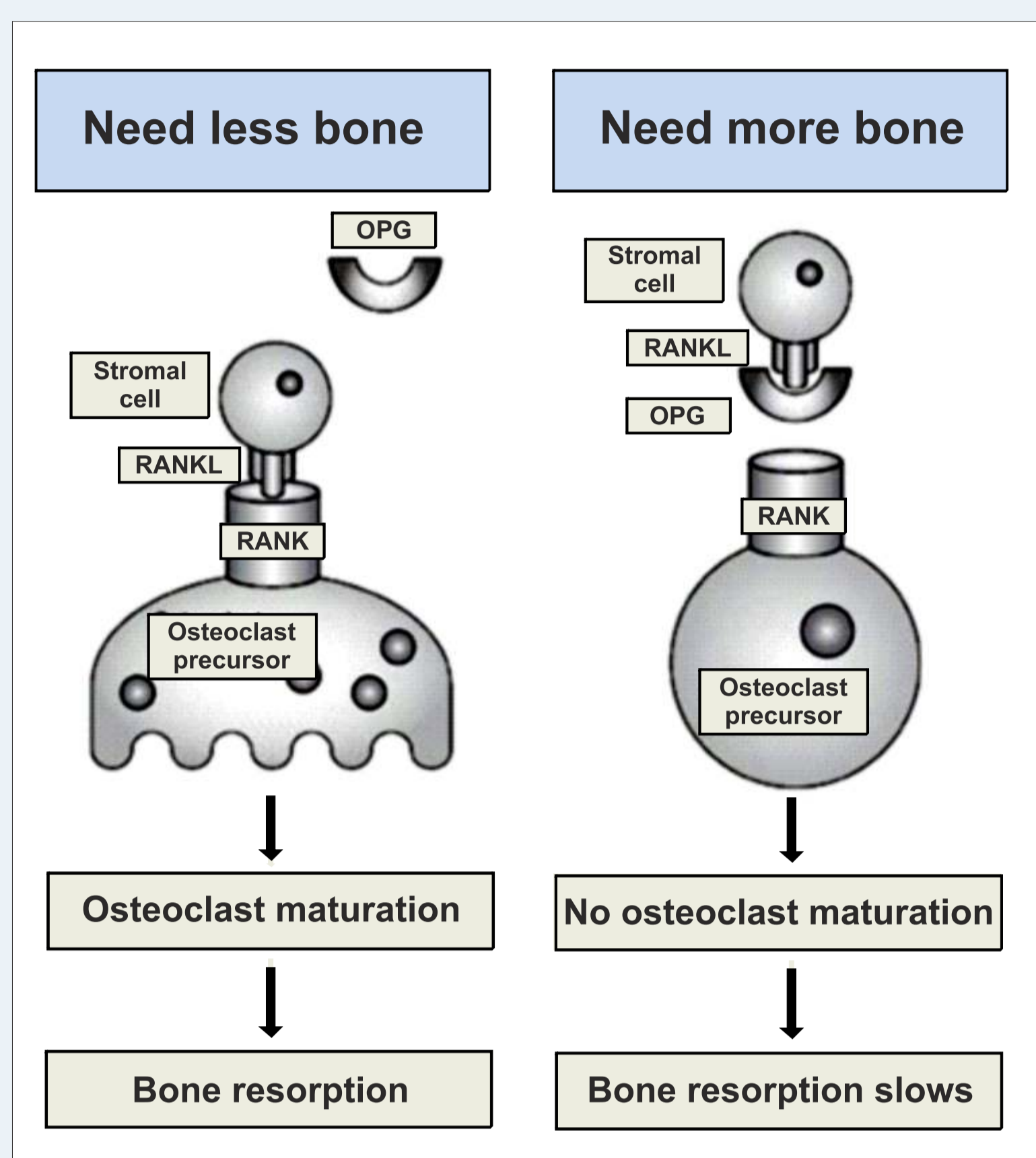


Figure 1. The role of OPG/RANKL/RANK pathway in bone homeostasis (adapted from Raggi P et al. (2007); Nat Clin Pract Cardiovasc Med 4: 26–33)

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-6 - ELISA tests (Biomedica and BenderMedSystem, Vienna, Austria), antibodies TRAb/ATG/ATPO - RIA tests (Brahms, Berlin, Germany).

4. Serum concentrations of IL-6 and OPG 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), nonparametric Kruskal-Wallis (Dunn's post-test) and Spearman's rank correlation were used.

## RESULTS

1. No significant difference was observed between IL-6 serum concentrations in studied groups (p=0.48; Kruskal-Wallis test).

2. OPG concentrations were significantly higher (ANOVA p=0.013; Newman-Keuls p<0.01) in children with GD: (mean ± SD: 4.48 ± 2.01 pmol/L) 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 (Newman-Keuls p>0.05) and cAIT vs GD (Newman-Keuls p>0.05) was observed. (Fig. 1)

3. In children with hyperthyroidism we identified significant positive correlation between OPG and IL-6 (r=0.51; p<0.05). (Fig. 2.)

4. ROC curve indicates good efficacy of OPG to discriminate groups of hyperthyroid and healthy children (AUC=0.716; p=0.017) at cut-off point of 4.54 pmol/L with low sensitivity (54.5%) but high specificity (95%). (Fig. 3.)

5. In these groups of children (hyperT vs control) AUC of IL-6 based on ROC curve did not differ significantly from 0.5 (p=0.435).

## CONCLUSION

Based on performed study we suggest that OPG may be considered as a marker of hyperthyroidism in children with GD.

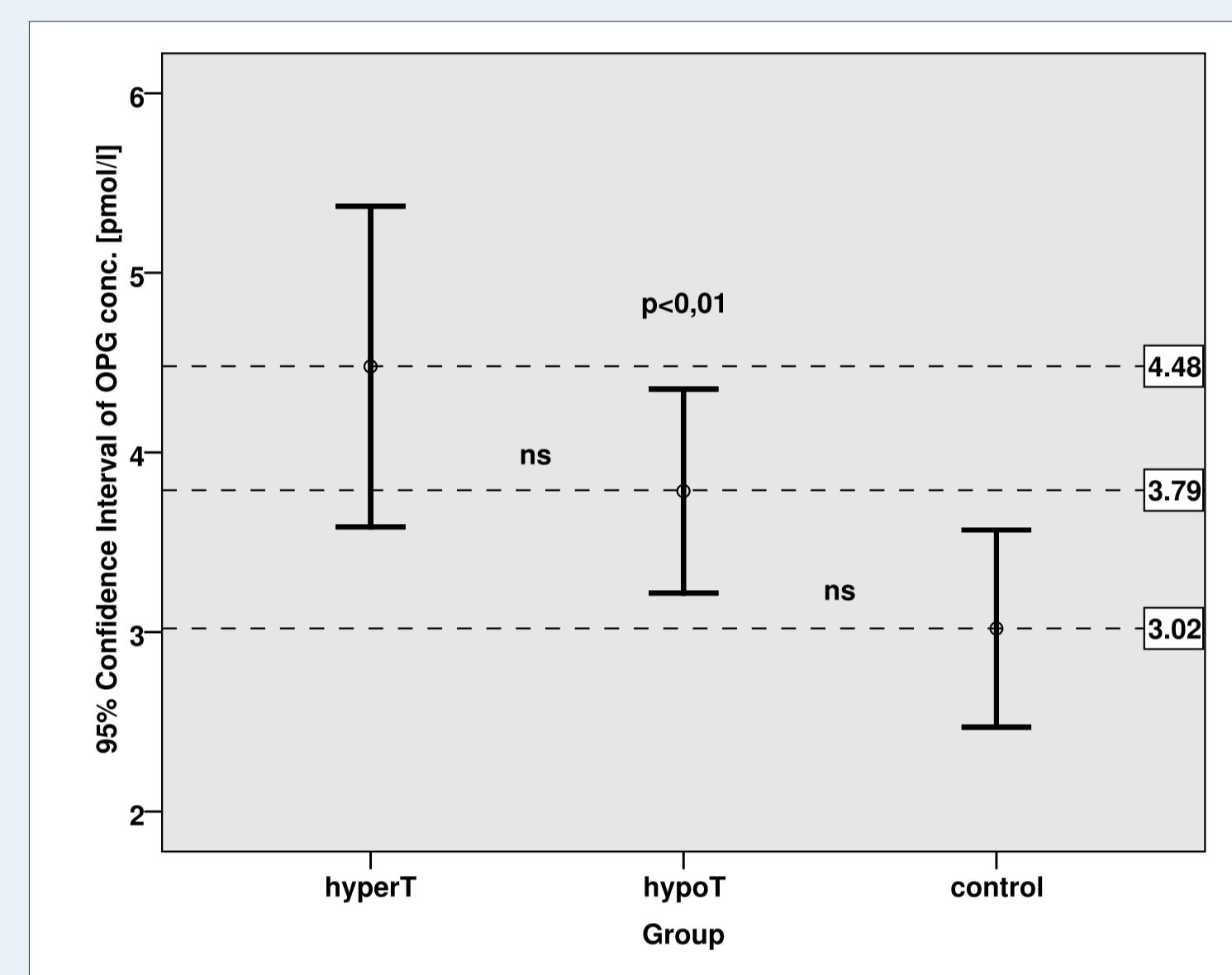


Figure 1. Scatterplot (95% confidence intervals) of OPG concentration in studied groups: hyperT vs control p<0.05

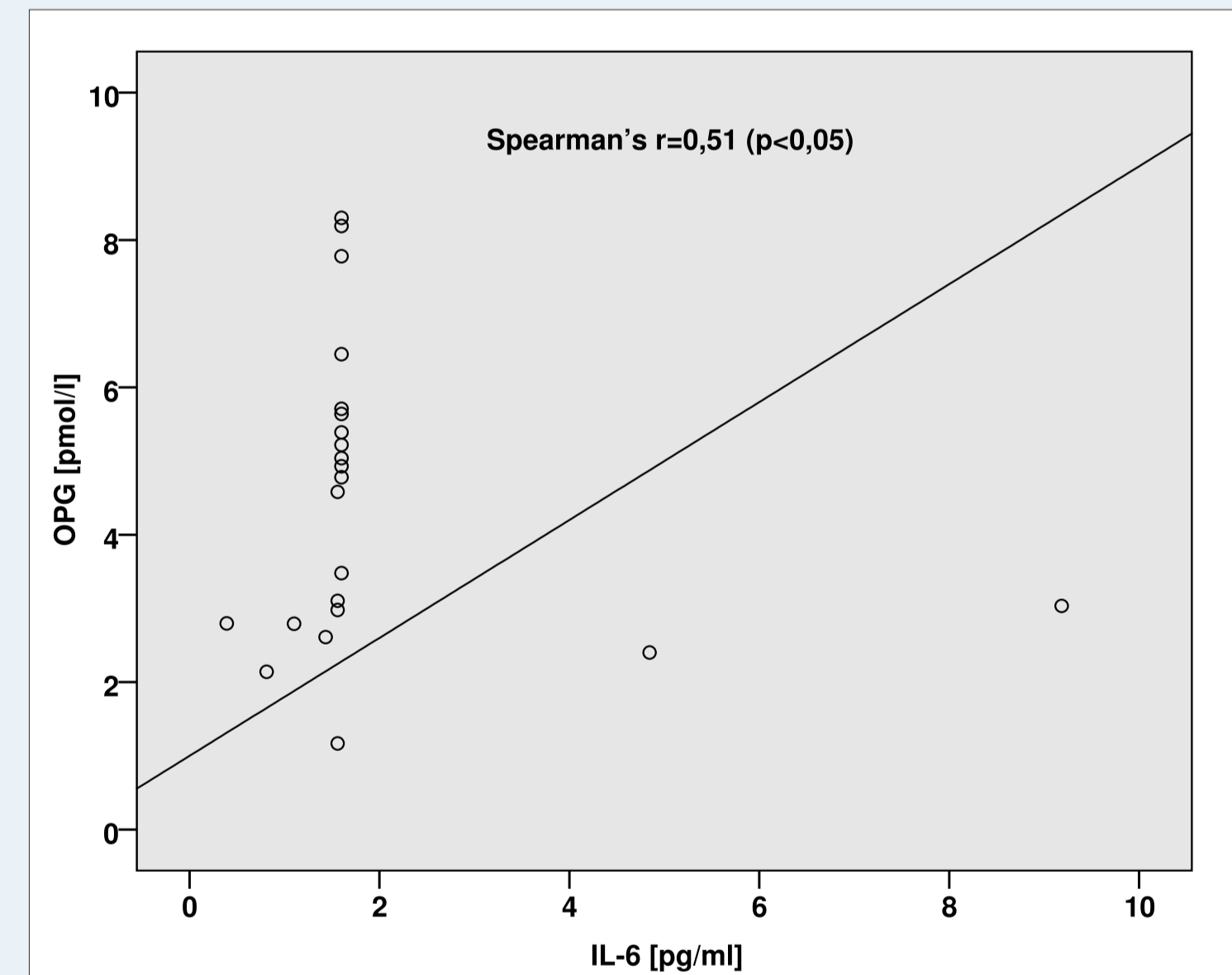


Figure 2. Positive nonparametric correlation in GD: IL-6 and OPG (p<0.05)

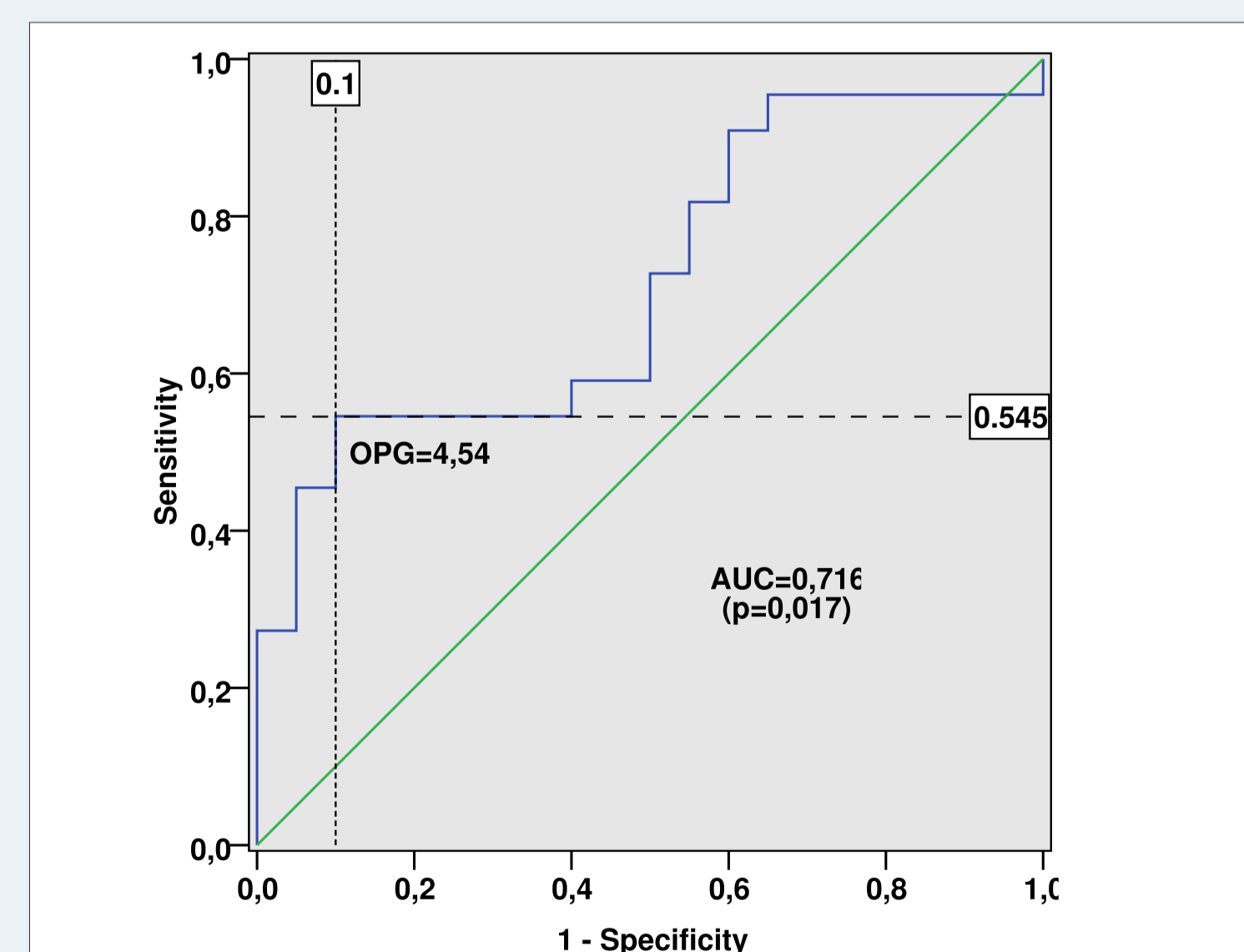


Figure 3. ROC of OPG: GD vs control (AUC=0.716, p=0.017, cut-off=4.54 pmol/L, sens.: 54.5%, spec.: 95%)



There was no conflict of interest related to this study.  
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