

TOTAL SERUM LEVEL OF OSTEOPROTEGERIN AND TOTAL sRANKL IN ADOLESCENTS WITH TYPE 1 DIABETES MELLITUS



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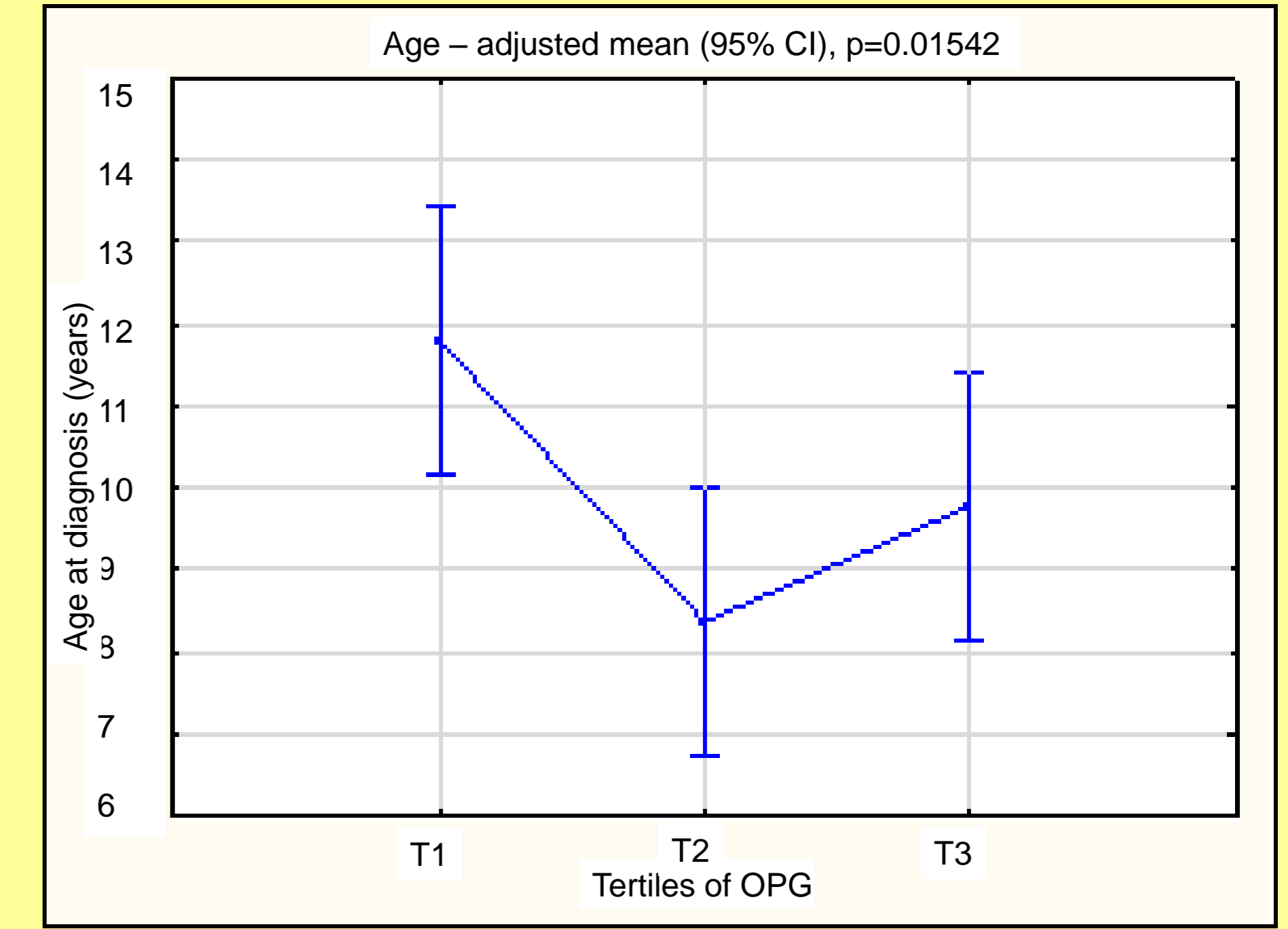
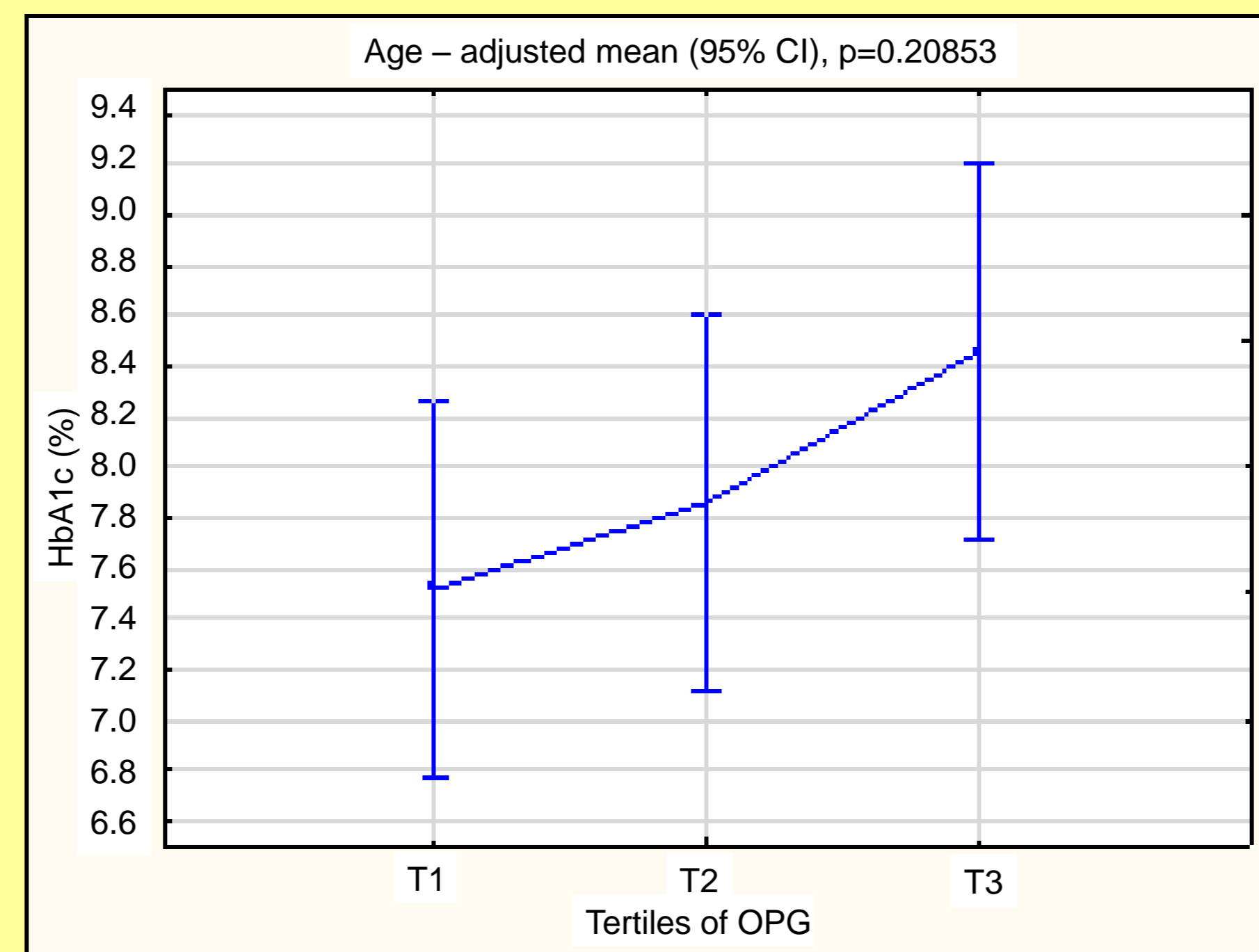
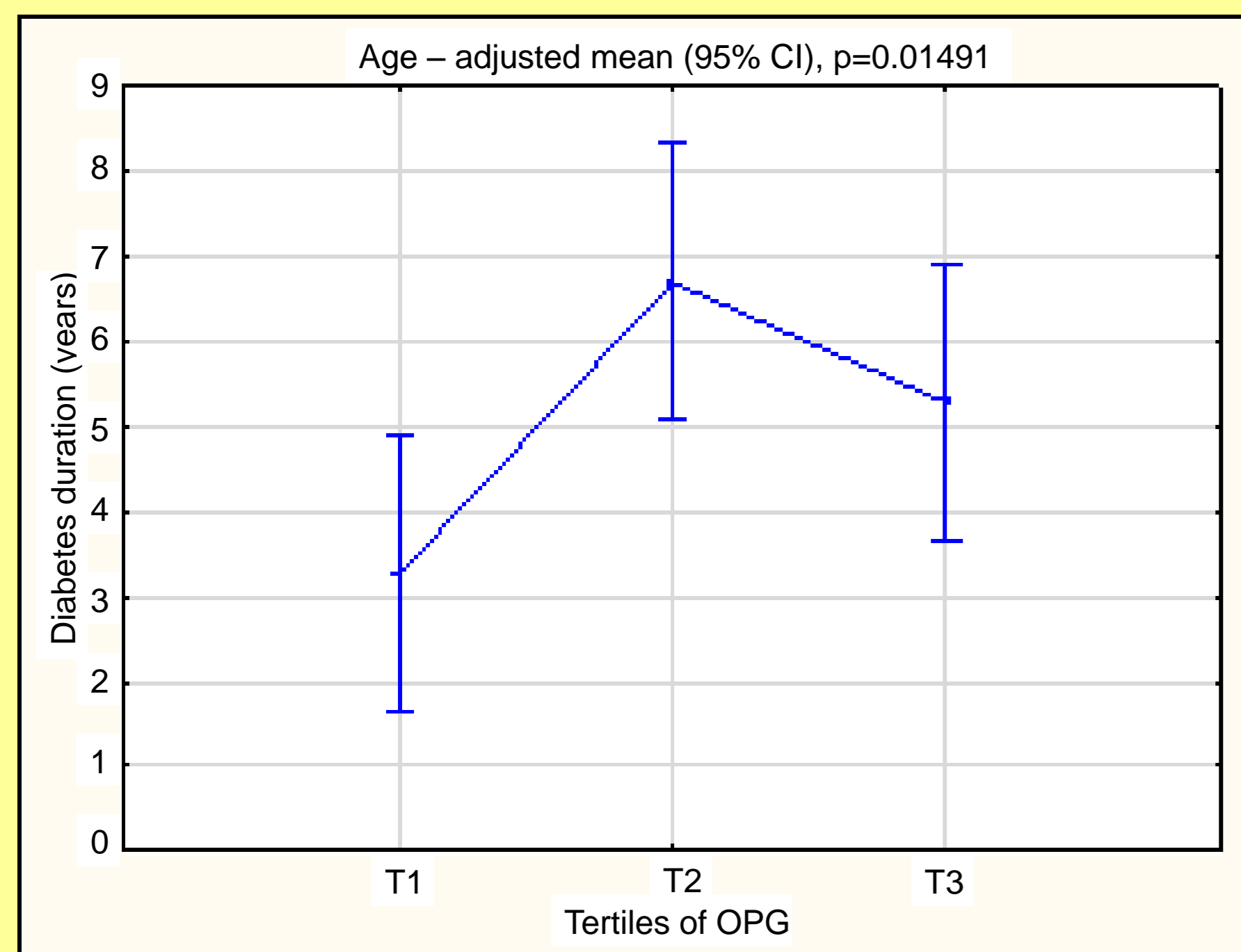
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BACKGROUND

There is a still little clinical data regarding the influence of Insulin Dependent Diabetes Mellitus (IDDM) on bone structure, bone density and biochemical markers of bone turnover.

OBJECTIVE

To evaluate the potential role of osteoprotegerin (OPG)/sRANKL system in adolescents with IDDM and the influence of age, sex, metabolic control, diabetes duration and age of IDDM diagnosis on OPG/sRANKL system, cross tertiles of OPG levels.



METHODS

Serum concentrations of OPG and total sRANKL (tsRANKL) were measured in 60 children (25 boys, 33 girls) with IDDM duration of 5.1 ± 3.9 years (min. 1.0, max. 11.8), age 15.0 ± 1.9 (11.4 – 17.8), age of IDDM diagnosis 9.9 ± 3.9 (2.5 – 17.0) and mean HbA1c level in the last year of $7.8 \pm 1.7\%$ (5.1 – 13.6). Control group consisted of 17 healthy, age and sex matched children. OPG concentration and tsRANKL (free and bound) were measured by EIA and ELISA commercial kits, respectively.

| Serum level of OPG, sRANKL, OPG/sRANKL (ratio), and sRANKL/OPG (ratio) in adolescents with type 1 diabetes and control group according to tertiles of OPG | | | | |
|---|--------------------------|-----------------------------------|----------------------------|--|
| | Tertile 1 Low (<2.45) | Tertile 2 Medium (2.45 – 2.96) | Tertile 3 High (> 2.96) | p value* |
| DIABETIC | | | | |
| OPG (pmol/L) | 2.07 ± 0.27 | 2.72 ± 0.12 | 3.55 ± 0.4 | 0.001 (T1 vs.T2 vs.T3) |
| tsRANKL (pmol/L) | 346.6 ± 133.8 | 457.1 ± 274.1 | 412.4 ± 185.8 | 0.0901 (T1 vs.T2) |
| OPG/tsRANKL (ratio) | 0.0070 ± 0.0037 | 0.0085 ± 0.0059 | 0.0103 ± 0.0044 | 0.0277 (T1 vs.T3) |
| tsRANKL/OPG (ratio) | 170.9 ± 69.2 | 169.1 ± 105.1 | 116.1 ± 52.5 | 0.0279 (T1 vs.T3) 0.0335 (T2 vs.T3) |
| Age (y) ¹⁾ | 15.3 ± 2.0 | 15.1 ± 1.8 | 14.6 ± 2.2 | ns |
| CONTROL | | | | |
| OPG (pmol/L) | 1.99 ± 0.21 | 2.79 ± 0.36 | 3.76 ± 0.66 | 0.001 (T1 vs.T2 vs.T3) |
| tsRANKL (pmol/L) | 429.0 ± 124.6 | 425.6 ± 146.5 | 486.1 ± 311.6 | ns |
| OPG/tsRANKL (ratio) | 0.0050 ± 0.0018 | 0.0074 ± 0.0036 | 0.0114 ± 0.009 | ns |
| tsRANKL/OPG (ratio) | 220.2 ± 77.5 | 156.7 ± 59.4 | 129.7 ± 75.6 | 0.0629 (T1 vs.T3) |
| Age (y) ¹⁾ | 13.6 ± 2.5 | 12.8 ± 0.8 | 14.9 ± 1.7 | 0.0540 (T2 vs.T3) |

| Baseline characteristics of the study population | | |
|--|-----------------|-----------------|
| | DIABETIC (N=60) | CONTROL (N=18) |
| Gender (% females) | 53.3 | 66.7 |
| Age (y) | 15.03 ± 1.96 | 14.02 ± 1.87 |
| OPG (pmol/L) | 2.78 ± 0.67 | 3.10 ± 0.89 |
| Total sRANKL (pmol/L) | 405.4 ± 207.8 | 456.6 ± 233.2 |
| OPG / total sRANKL (ratio) | 0.0086 ± 0.0048 | 0.0089 ± 0.0070 |
| sRANKL / OPG (ratio) | 152.0 ± 81.5 | 157.3 ± 76.9 |
| Age at diabetes diagnosis (y) | 9.9 ± 3.9 | - |
| Diabetes duration (y) | 5.1 ± 3.9 | - |
| HbA1c (%) – 1-year period | 7.9 ± 1.4 | - |

| Serum concentration mean ± SD (95% CI) of OPG, total sRANKL, OPG / total sRANKL (ratio), total sRANKL/OPG (ratio) in diabetes patients in comparison with healthy subjects control, and the age-adjusted distribution of diabetes (D), gender (S) and their interaction (D x S) | | | | | | | |
|---|-----------------|-----------------|-----------------|-----------------|----------------|----------------|--|
| | Girls | | Boys | | p value* | | |
| | DIABETIC | CONTROL | DIABETIC | CONTROL | P _D | P _S | P _{DxS} |
| OPG (pmol/L) | 2.95 ± 0.64 | 2.99 ± 0.85 | 2.59 ± 0.67 | 3.30 ± 1.01 | 0.066 | 0.878 | 0.031 (boys D vs. C) |
| total sRANKL (pmol/L) | 433.0 ± 210.9 | 462.1 ± 116.2 | 373.8 ± 203.3 | 445.7 ± 393.8 | 0.614 | 0.748 | 0.759 |
| OPG / total sRANKL (ratio) | 0.0081 ± 0.0039 | 0.0068 ± 0.0026 | 0.0070 ± 0.0114 | 0.0014 ± 0.0246 | 0.228 | 0.037 | 0.036 (girls D vs. boys C) 0.019 (girls C vs. boys C) |
| total sRANKL / OPG (ratio) | 153.5 ± 80.0 | 163.9 ± 55.8 | 150.3 ± 84.6 | 144.2 ± 113.8 | 0.831 | 0.832 | 0.683 |

| Characteristics of determinants (age, gender, age at diagnosis, diabetes duration and metabolic control) in adolescents with type 1 diabetes according to tertiles of serum OPG | | | | | |
|---|--------------------------|-----------------------------------|----------------------------|-------------|------------------|
| | Tertile 1 Low (<2.45) | Tertile 2 Medium (2.45 – 2.96) | Tertile 3 High (> 2.96) | p value* | |
| Sex | girls | 21.9 | 31.3 | 46.9 | 0.038 |
| subjects (%) | boys | 46.4 | 35.7 | 17.9 | |
| Age (years) | x ± SD | 15.3 ± 2.0 | 15.1 ± 1.8 | 14.6 ± 2.2 | ns |
| subjects (%) | 12-15y | 32.3 | 32.3 | 35.5 | ns |
| | ≥ 15y | 34.5 | 34.5 | 31.0 | |
| Age at diagnosis (years) | x ± SD | 11.9 ± 3.1 | 8.4 ± 4.2 | 9.6 ± 3.7 | 0.0034 (T1vs.T2) |
| | (95% CI) | (10.5 - 3.4) | (6.5 - 10.4) | (7.9 - 1.3) | 0.0486 (T1vs.T3) |
| subjects (%) | < 7 y | 14.3 | 50.0 | 35.7 | |
| | 7-12 y | 27.6 | 34.5 | 37.9 | 0.083 |
| | ≥ 12 y | 58.8 | 17.6 | 23.5 | |
| Diabetes duration (years) | x ± SD | 3.4 ± 3.1 | 6.7 ± 4.3 | 5.0 ± 3.8 | 0.0048 (T1vs.T2) |
| | (95% CI) | (2.0 - 4.9) | (4.7 - 8.8) | (3.2 - 6.8) | |
| subjects (%) | < 2 y | 50.0 | 22.2 | 27.8 | |
| | 2-5 y | 37.5 | 25.0 | 37.5 | 0.063 |
| | 5-10 y | 29.4 | 29.4 | 41.2 | |
| | ≥ 10 y | 0.0 | 77.8 | 22.2 | |
| HbA1c (%) | x ± SD | 7.7 ± 1.7 | 7.8 ± 1.0 | 8.2 ± 1.4 | 0.093 (T1vs.T3) |
| | (95% CI) | (7.0 - 8.6) | (7.3 - 8.3) | (7.5 - 8.8) | |
| subjects (%) | < 9% | 34.8 | 37.0 | 28.3 | ns |
| | ≥ 9% | 28.6 | 21.4 | 50.0 | |

Mean ± SD (95% CI); statistically significant differences (p<0.05)

* age-adjusted p-value for ANCOVA (post-hoc tests using Fisher's Least Significant Difference test)

¹⁾ p-value for ANOVA (post-hoc tests using Fisher's Least Significant Difference test)

* age-adjusted p-value for ANCOVA (post-hoc tests using Fisher's Least Significant Difference test); statistically significant differences (p<0.05)

Mean ± SD (95% CI) or percentage of subjects (%); statistically significant differences (p<0.05)

*Chi² test for categorical variables, Fisher's Least Significant Difference post-hoc test for continuous variables

RESULTS

Both serum OPG and tsRANKL and also OPG/tsRANKL ratio were lower in diabetic children, but not in a statistically significant way. OPG concentration in IDDM boys was significantly lower than in the control group. Negative correlation was observed between OPG level and the age of diagnosis of diabetes and positive correlation was found with diabetes duration. tsRANKL did not correlate with sex, metabolic control, diabetes duration or age of diagnosis. However, a negative correlation between serum tsRANKL and the age was observed. The OPG/tsRANKL ratio values depend only on the age in IDDM children. Statistical analysis showed that higher level of OPG (third and/or second vs. first tertile) was associated with an earlier age of diagnosis, longer diabetes duration and poor metabolic control.

CONCLUSION

OPG/tsRANKL system may be used as a prediction marker of bone and cardiovascular system status in children and adolescents with IDDM, but precise reference data for children in relation to age, sex and puberty status should be determined first. **Supported by grant NCN: N N312433140**