Low bone mineral density is associated to poor glycemic control and increased dickkopf-1 (DKK-1) serum levels in children and adolescents with type 1 diabetes

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The authors disclose any conflict of interest

BACKGROUND

Decreased bone mineral density (BMD) and increased fracture risk have consistently been observed in type 1 diabetes mellitus (T1DM). The influence of T1DM on BMD seems to depend on gender or age of patients and to occur early after T1DM diagnosis. The mechanisms of decreased BMD in T1DM patients are still unknown. Dickkopf-1 (DKK-1) is a Wnt signaling inhibitor which decreases bone formation and increases bone resorption (fig. 1), thus it strongly affects BMD in murine models and human diseases.

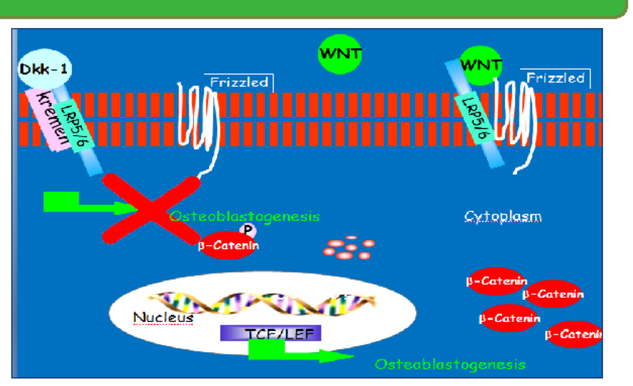

Figure 1. Inibition of Wnt signaling mediated by DKK-1

OBJECTIVE AND HYPOTHESES

We aimed to investigate the serum levels of DKK-1 in T1DM children and adolescents and to evaluate the relationship with glycemic control, BMD and bone biomarkers.

METHODS

This cross-sectional study included 53 T1DM children and adolescents (mean age 12.1 ± 3.3 years) and 50 sex and age-matched controls (Table 1). Phosphorus, calcium, osteocalcin, alkaline phosphatase (ALP), PTH and 25(OH)-Vitamin D values were determined. DKK-1 was measured in the sera of T1DM patients and controls by ELISA. Bone mineral status was measured by Quantitative ultrasonography (QUS), and reported as AdSos-Z-score and BTT-Z-score.

Table 1

	T1DM n=53	CONTROLS n=50	P-VALUE
Age (years)	11,58±4,58	10,61±3,63	ns
Sex (M/F)	26/27	28/22	ns
Height (cm)	148,27±19,74	147,33±14,59	ns
Height SDS	0,18±0,97	0,17±0,80	ns
Weight (kg)	46,32±17,33	46,30±18,42	ns
Weight SDS	0,75±0,72	0,79±0,53	ns
BMI (kg/m²)	20,08±4,25	20,33±3,24	ns
BMI SDS	0,8±1,69	0,9±1,04	ns
HbA1c (%)	7.98±1.20	-	-

RESULTS

Bone parameters in T1DM patients and controls

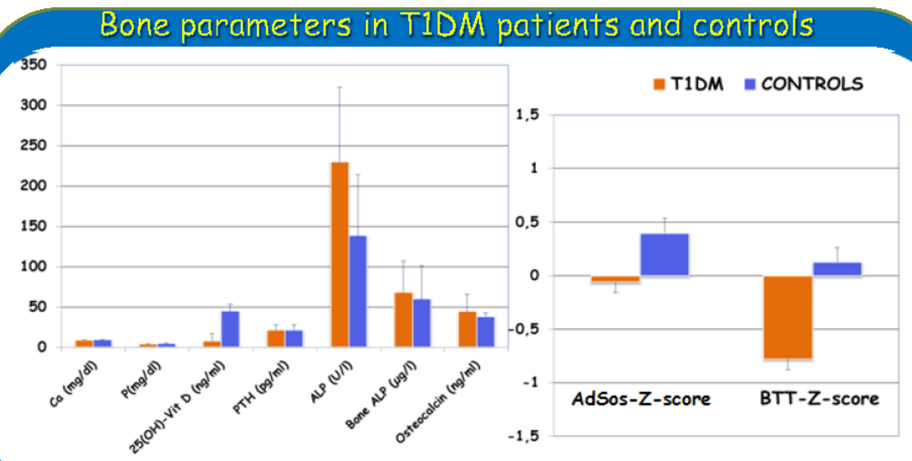

Figure 2. T1DM patients showed a lower BMD than controls (p>0.01).

DKK-1 serum levels in T1DM patients and controls

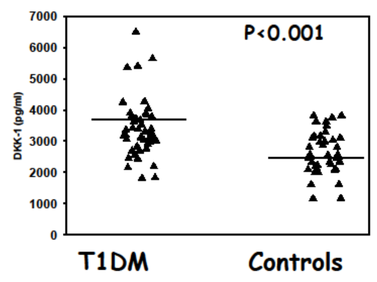

Figure 3. T1DM patients had higher DKK-1 serum levels compared with controls.

DKK-1 correlation with HbA1C and BMD

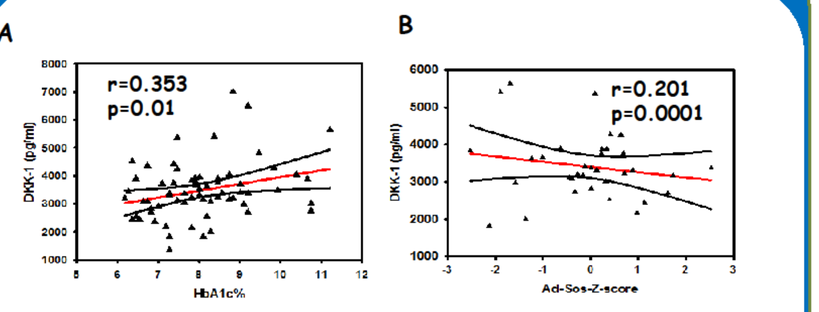

Figure 4. DKK-1 levels directly correlated with HbA1c values (A) and inversely with AdSos-Z-score (B).

HbA1c correlation with BTT-Z-score, AdSos-Z-score, osteocalcin and 25(OH)-Vitamin D

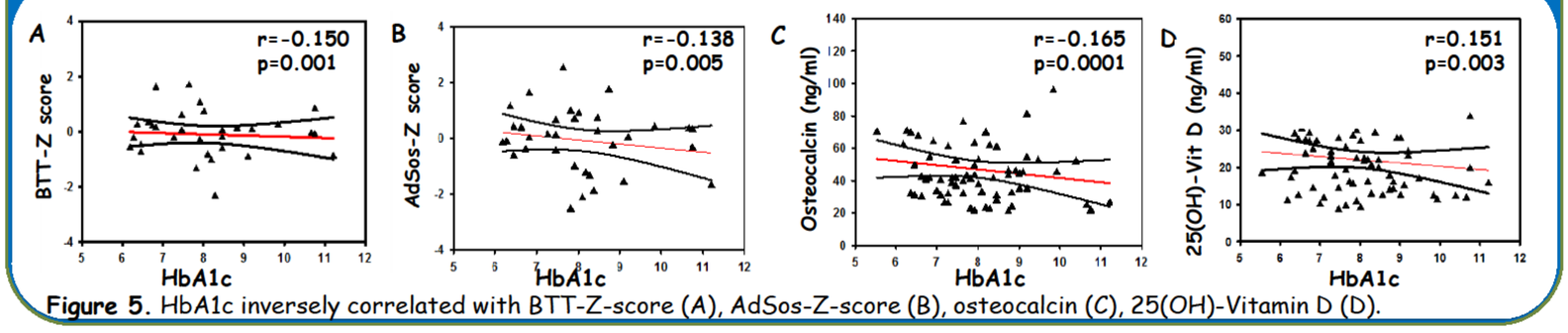

Figure 5. HbA1c inversely correlated with BTT-Z-score (A), AdSos-Z-score (B), osteocalcin (C), 25(OH)-Vitamin D (D).

Table 2

DEPENDENT VARIABLE	INDEPENDENT VARIABLE	β	p	r
DKK-1			0.001	0.61
	AdSos-Z-score	-0.141	0.005	
	ALP	-0.289	0.0001	
	25-(OH) Vit. D	-0.098	0.045	
	HbA1c	0.321	0.0001	

T1DM patients showed a significant reduction of BTT-Z-score compared to controls (p=0.01) (Fig. 2). Higher DKK-1 levels were found in patients than in controls (3344±961 vs 2450±684 pg/ml, p<0.001) (Fig. 3). The DKK-1 levels directly correlated with HbA1c values (r=0.353, p=0.01) (Fig. 4A) and inversely with AdSos-Z-score (r=0.201, p=0.0001) (fig. 4B). Furthermore, with adjustment for age, HbA1c inversely correlated with BTT-Z-score, AdSos-Z-score, osteocalcin, 25(OH)-vitamin D (Fig. 5) and ALP (r=0.35, p<0.0001), as well as directly correlated with daily insulin dosage (r=032, p<0.01) and T1DM duration (r=0.22, p<0.01). Multiple regression analysis showed that DKK-1 serum levels were best predicted by AdSos-Z-score, ALP, 25(OH)-vitamin D and HbA1c (r=0.61, p<0.0001) (Table 2).

CONCLUSIONS

In conclusion, children and adolescents with T1DM showed a reduction of bone mineral status associated to poor glycemic control and increased DKK-1 serum levels.

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