Relationship among plasminogen activator inhibitor-1, bone mineral density, metabolic and bone turnover markers in postmenopausal women with type 2 diabetes mellitus

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BACKGROUND

Women with type 2 diabetes mellitus (T2DM) have a higher risk of fractures despite increased bone mineral density (BMD). In experimental studies a potential role of plasminogen activator inhibitor-1 (PAI-1) in bone remodeling is suggested but studies in humans are lacking.

OBJECTIVE

This is a first study in humans investigating whether circulated levels of PAI-1 in postmenopausal women with T2DM are related to BMD and adiposity.

RESULTS

Diabetic patients with normal BMD had significantly higher BMI, greater waist circumference and lower bone turnover markers than diabetics with osteopenia and osteoporosis (p<0,01). PAI-1 was lower in diabetics with osteoporosis and osteopenia compared with diabetics with normal BMD (p<0,05). In the multiple regression models the strongest determinants of PAI-1 among metabolic parameters were triglyceride and insulin levels and the duration of T2DM, among therapy beta blockers, and among bone markers pyrilinks (p<0,05). Final regression analysis model revealed insulin (p=0.003), triglycerides levels (p=0.0002) and pyrilinks (p=0.0002) to be the strongest predictors of PAI-1 levels in all patients.

METHODS

Anthropometric variables, PAI-1 and insulin levels, serum lipids and bone turnover markers were measured in 117 postmenopausal women with T2DM. A total of 117 female patients were divided according to lumbar spine BMD measurements via dual-energy x-ray absorptiometry in three groups: 47 with osteopenia, 21 with osteoporosis and 49 with normal BMD.

Table 1. Baseline characteristics of study subjects

	Osteoporosis n=21		Osteopenia n=47		Normal BMD n=49		p
Age (year)	65,3	10,2	67,4	8,04	64,9	8,7	NS
Waist (cm)	89,8	11,2	96,0	8,2	98,3	12,0	‡ 0,03; †0,003
BMI (kg/m²)	27,5	5,6	29,1	3,9	31,3	5,1	*0,02; †0,002
Menopause duration (year)	17,8	9,2	18,3	8,5	14,7	7,9	*0,049
Diabetes duration (year)	9,1	6,3	12,2	7,1	12,1	7,3	NS
HbA1c (%)	10,2	2,24	10,1	1,59	9,95	1,9	NS
Cholesterol (mmol/l)	5,45	1,62	5,13	1,25	4,97	1,41	NS
HDL cholesterol (mmol/l)	1,29	0,25	1,22	0,25	1,19	0,27	NS
LDL cholesterol (mmol/l)	3,39	1,02	3,03	1,02	2,76	1,12	*† 0,042
Triglicerydes (mmol/l)	1,98	1,32	1,96	0,79	2,37	1,43	NS
Osteocalcin (ng/ml)	10,22	7,67	8,37	3,84	6,32	2,87	*0,025; †0,0013
Insulin (mIU/l)	8,94	4,14	9,97	4,82	10,62	5,69	NS
Pyrilinks (nMPD/mMc)	7,8	3,1	7,41	2,9	5,5	2,1	*0,001; †0,0015
Crosslaps (ng/ml)	0,54	0,25	0,49	0,29	0,35	0,21	*0,012; †0,0092
PAI-1 (U/l)	3,3	2,1	3,5	2,1	4,4	1,9	*0,042; †0,052
Fibrinogen (g/L)	4,1	1,0	4,3	0,8	4,0	0,8	NS
CRP (mg/L)	5,77	11,6	3,89	3,67	3,74	4,25	NS
Lumbar BMD (g/cm²)	0,707	0,07	0,856	0,04	1,036	0,09	*† ‡ <0,05
Hip BMD (g/cm²)	0,746	0,13	0,838	0,109	0,985	0,147	*‡; † <0,05

Associations of PAI-1 levels with metabolic parameters, BMD and bone turnover markers

PAI-1	r	p
Age (year)	-0,2375	0,011
BMI (kg/m²)	,3453	0,000
Diabetes duration (year)	-,3046	0,002
Insulin (mIU/L)	,4411	0,000
Triglycerides (mmol/L)	,4704	0,000
HDL (mmol/L)	-,3331	0,001
Osteocalcin (ng/ml)	-,2976	0,002
Pyrilinks (nMPD/mMc)	-,2897	0,002
Crosslaps (ng/ml)	-,2955	0,002
Lumbar BMD (g/cm²)	,1990	0,046
Hip BMD (g/cm²)	,3530	0,000

Final stepward forward regression analysis model with therapy (including age, BMI, diabetes duration, menopause duration, insulin, triglycerides, femoral and lumbar BMD)

Dependent variable: PAI-1	Beta	p	adjusted R²
Triglycerides (mmol/L)	0.314	0.0002	0.574
Insulin (mIU/L)	0.250	0.0033	
Pyrilinks (nMPD/mMc)	-0.308	0.0002	
BMI (kg/m²)	0.310	0.0035	
Waist circumference (cm)	-0.278	0.0097	
Age (years)	-0.364	0.0201	
Diabetes duration (years)	-0.187	0.0185	
Menopause duration (years)	0.283	0.0688	
Beta blockers (%)	0.224	0.0045	

CONCLUSION

Conclusions: Our findings suggest that the PAI-1 has a protective effect on bone loss by suppression of bone turnover in obese diabetic patients, and the effect is primarily mediated through the influence of metabolic factors, hyperinsulinemia, hypertriglyceridemia and obesity. However, the fact that pyrilinks is also independently correlated to PAI-1 implies its direct involvement in bone metabolism influencing bone mass and strength.