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Higher Parathyroid Hormone Level Is Associated With Increased Arterial Stiffness in Type 1 Diabetes

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Vascular calcification is a common consequence of aging, hypercholesterolemia, chronic renal insufficiency, and diabetes (1). Stiffening of the large arteries is a result of vascular calcification. Carotid–femoral pulse wave velocity (cfPWV) is considered the gold standard measure of arterial stiffness (2) and has been shown to be a strong predictor of mortality and cardiovascular outcome.

We evaluated the association between arterial stiffness (evaluated by cfPWV) and bone mass density (evaluated with dual-energy X-ray absorptiometry at the femoral neck), as well as a comprehensive panel of bone markers, in a well-characterized cohort of 347 persons with type 1 diabetes. We hypothesized that vascular calcification is linked to decalcification of the bones.

The participants were recruited from the outpatient clinic at Steno Diabetes Center, Gentofte, Denmark. Written informed patient consent and ethical approval of the study were obtained.

A total of 164 (47%) participants were women, mean ± SD age was 55.8 ± 9.6 years and cfPWV was 11.0 ± 3.4 m/s, and median (interquartile range) parathyroid hormone (PTH) was 39.1 (29.1, 57.3) pg/mL.

Table 1 shows the unadjusted and stepwise adjusted associations between cfPWV and bone mineral density, clinical bone markers (PTH, 25-hydroxyvitamin D, calcium, and phosphorus), and markers of bone mineral metabolism (endostatin, sclerostin, Dickkopf 1, and osteoprotegerin). In unadjusted analyses, bone mineral density, all clinical bone markers, and markers of mineral metabolism—except calcium, phosphorus, and Dickkopf 1—were associated with cfPWV ($P \leq 0.041$). After adjustment for age, sex, and mean arterial pressure, the level of bone mineral density, PTH, and sclerostin remained associated with cfPWV ($P \leq 0.027$). After adjustment for additional risk factors (HbA_{1c}, total cholesterol, BMI, antihypertensive treatment, urinary albumin excretion rate, estimated glomerular filtration rate, and smoking), PTH remained positively associated with cfPWV ($P = 0.014$).

In the search for a link between bone and vascular disease, we demonstrated an association between arterial stiffness and bone mineral density, clinical bone markers, and markers of mineral metabolism. These associations lost significance after comprehensive adjustment, except for the relationship between higher PTH and increased arterial stiffness.

PTH is one of the main regulators of calcium homeostasis. Secretion of PTH from the parathyroid gland is triggered by low serum calcium. PTH secretion results in raised serum calcium through its release from the bones, reduced renal excretion, and increased small intestine absorption (3). Aside from its well-established role in calcium homeostasis, elevated PTH has been linked to presence of hypertension and cardiac hypertrophy (4), and PTH excess may be related to development of cardiovascular disease (5).

Our study consisted of a well-characterized group of persons with type 1 diabetes. Arterial stiffness was evaluated using the gold standard method, analyzed as a continuous variable and with proper adjustment. Bone mineral density was evaluated with robust methods, and all bone markers were analyzed as continuous variables; no arbitrary cutoffs were applied.

Our findings highlight PTH as a potential mediator for the cross talk between bone and vascular disease. However, our findings need validation, and prospective studies investigating the relationship between PTH and cardiovascular outcome in type 1 diabetes are warranted. Depending on the results of such studies, therapies known to reduce PTH (e.g., cinacalcet) could potentially reduce the cardiovascular risk in

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Table 1—Unadjusted and stepwise-adjusted associations between cfPWV and measures of bone/mineral metabolism

	Unadjusted		Adjusted for age, sex, and mean arterial pressure		Adjusted for age, sex, mean arterial pressure, and other risk factors	
	β	*P*	β	*P*	β	*P*
Bone mineral density						
Femoral neck bone mineral density	−0.23	<0.001	−0.15	0.027	−0.06	0.43
Clinical bone markers						
PTH*	0.23	<0.001	0.28	<0.001	0.17	0.014
25-Hydroxyvitamin D	0.12	0.041	−0.12	0.09	−0.10	0.17
Ionized calcium	−0.01	0.08	−0.06	0.37	−0.02	0.77
Phosphorus	0.07	0.19	0.11	0.13	0.001	0.98
Markers of bone mineral metabolism						
Endostatin*	0.16	0.003	0.12	0.09	0.05	0.49
Sclerostin*	0.14	0.011	0.16	0.022	0.01	0.85
Dickkopf 1*	0.007	0.90	0.06	0.43	0.12	0.15
Osteoprotegerin*	0.36	<0.001	0.13	0.08	0.02	0.77

Other risk factors included HbA_{1c}, total cholesterol, BMI, antihypertensive treatment, urinary albumin excretion rate, estimated glomerular filtration rate, and smoking. cfPWV was measured with the SphygmoCor (AtCor Medical, Sydney, Australia). Plasma vitamin D [25(OH)D3] levels were determined by high-performance liquid chromatography–tandem mass spectrometry. Plasma PTH levels were analyzed using a second-generation electrochemiluminescence immunoassay (Cobas e601, Roche Diagnostics). Serum endostatin, sclerostin, Dickkopf 1, and osteoprotegerin were measured by sandwich ELISA (Biomedica Medizinprodukte, Austria). *Log_2 transformed for analyses. The β estimates represent standardized effect.

subjects with type 1 diabetes with elevated PTH.

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Author Contributions. E.H.Z. analyzed and interpreted the data and drafted the manuscript. S.T. and M.L. researched data, analyzed and interpreted the data, and made critical revision of the manuscript for key intellectual content. B.J.v.S. and T.W.H. analyzed and interpreted the data, performed statistical analysis, and critically revised the manuscript for key intellectual content. F.P. analyzed and interpreted the data and made critical revision of the manuscript for key intellectual content. L.T. conceived and designed the research, analyzed and interpreted the data, and made critical revision of the manuscript for key intellectual content. P.R. conceived and designed the research, analyzed and interpreted the data, handled funding and supervision, made critical revision of the manuscript for key intellectual content, and supervised the study. E.H.Z. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Staessen J, Amery A, Fagard R. Isolated systolic hypertension in the elderly. J Hypertens 1990;8:393–405
2. Laurent S, Cockcroft J, Van Bortel L, et al.; European Network for Non-invasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 2006;27:2588–2605
3. Fraser WD. Hyperparathyroidism. Lancet 2009;374:145–158
4. Saleh FN, Schirmer H, Sundsfjord J, Jorde R. Parathyroid hormone and left ventricular hypertrophy. Eur Heart J 2003;24:2054–2060
5. Folsom AR, Alonso A, Misialek JR, et al. Parathyroid hormone concentration and risk of cardiovascular diseases: the Atherosclerosis Risk in Communities (ARIC) study. Am Heart J 2014; 168:296–302