Mitochondrial DNA point mutation is associated with lower bone turnover markers

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Introduction

We previously showed that the mitochondrial DNA point mutation mtDNA3243A>G is associated with lower BMD and altered bone structure.

The aim of this study was to assess biochemical bone turnover markers in individuals with the mutation and controls.

Background

Mitochondrial dysfunction is implicated in the human ageing process and is associated with several clinical outcomes including diabetes, myopathy and hearing loss.

Mitochondrial dysfunction causes increased levels of reactive oxygen species and oxidative stress[1,2,3], which is associated with:

- Increased apoptosis of osteoblasts and osteocytes[4].
- Increased osteoclastogenesis[4].
- BMD negatively correlated with oxidative stress in postmenopausal women[5].

Mitochondrial dysfunction could affect purinergic signalling, which is involved in parathyroid hormone signalling, osteoclast fusion and bone cell response to mechanical stimuli of the bone[8].

Mitochondrial mutations cause osteoporosis in mouse models and affect both osteoblasts, osteocytes and osteoclasts[6,7,8].

I humans mitochondrial dysfunction may be associated with subclinical disturbances in calcium metabolism, i.e. basal ganglia calcifications and hypo- and hyperparathyroidism[5].

[1] Li, J. et al. Genet Mol Res 2008. [2] Ishikawa, K. et al. Circ J 2005. [3] Ikawa, M. et al. Eur Neurol 2012. [4] Manolagas, S.C. Endocr Rev 2010. [5] Cervellati, C. et al. Clin Chem Lab Med 2013. [6] Trifunovic, A. et al. Nature 2004. [7] Miyazaki, T. Et al. J Biol Chem 2012. [8] Rumney, R. et al. Front Endocrinol 2012. [9] Finsterer, J. et al. Metab. Brain Disease 2005.

Study design

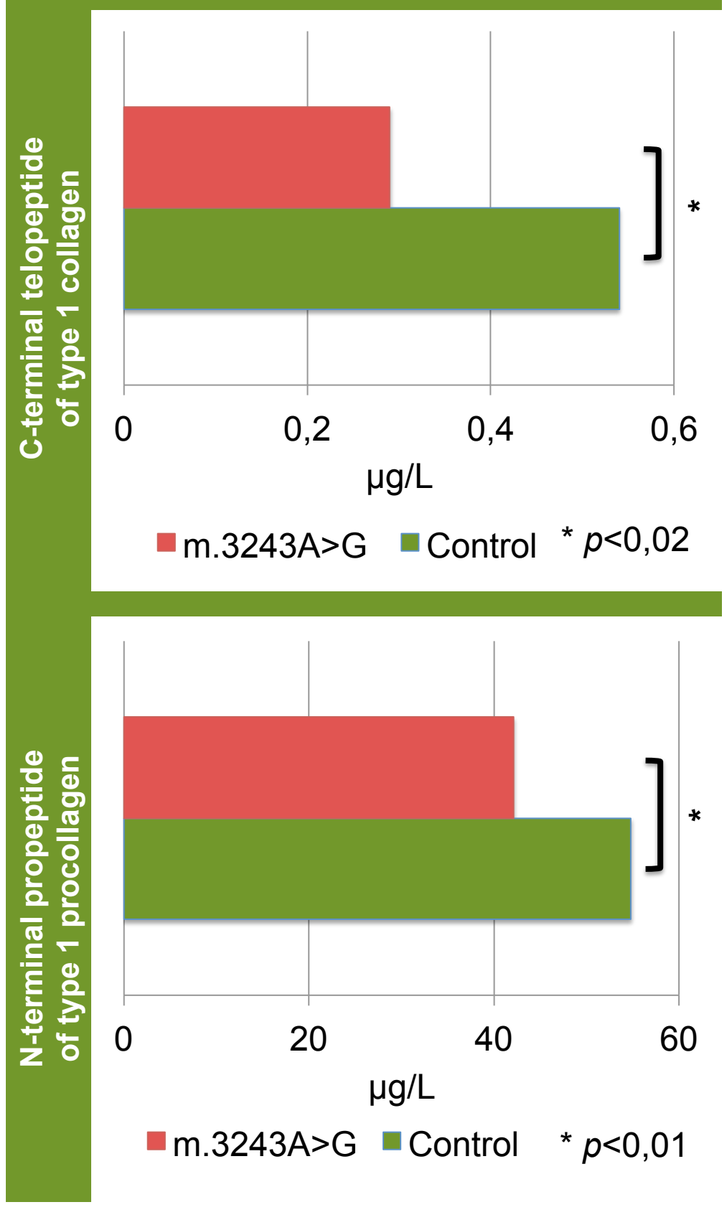
Participants:

- 45 subjects carrying m.3243A>G.
- 45 healthy controls matched with respect to sex, age, height and menopausal status.

Examinations:

- Dual-energy X-ray Absorptiometry (DXA).
- High-Resolution peripheral Quantitative Computed Tomography (HR-pQCT).
- Biochemical markers of bone turnover, i.e. CTX and P1NP.

Results – Bone turnover markers



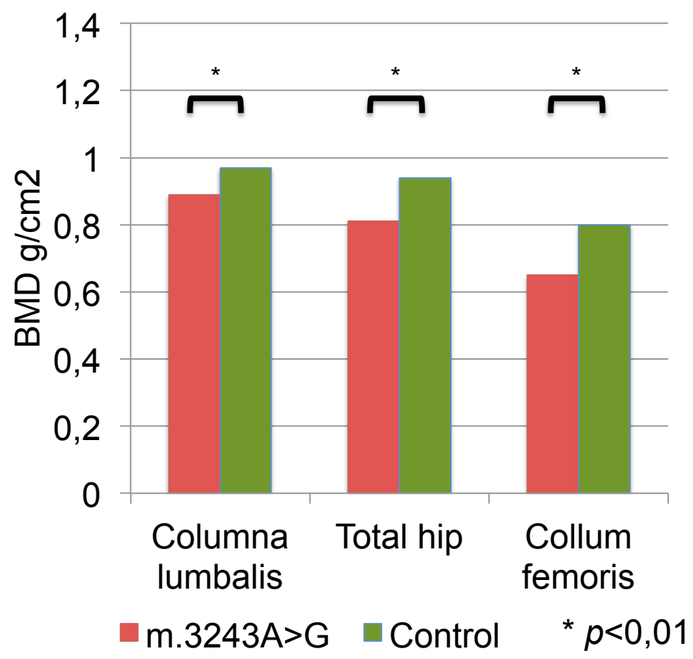
Conclusion and perspectives

We have previously shown that carriers of the m.3243A>G mitochondrial mutation had lower bone mineral density and thinner cortical bone assed by HR-pQCT scan and additionally decreased estimated bone strength.

In the present study we have shown that mitochondrial dysfunction is associated with lower levels of biochemical bone turnover markers. These results can possibly in part be explained by lower body mass and diabetes, however the difference in s-P1NP, but not s-CTX, remained significant after adjusting for weight and sex. Stratifying according to DM-status s-CTX and s-P1NP was significantly lower in cases with DM compared to their controls, whereas levels of bone turnover markers were the same in non-DM cases and their controls.

Further studies are needed to describe the effects of mitochondrial dysfunction on bone remodelling.

Results – DXA scan



Results – HR-pQCT scan

	m.3243A>G	Control	*p*-value
Number of participants	45	45	
Sex (n) male / female	16 / 29	16 / 29	1.00
Age (years)	47.6 ±15.2	47.8 ±14.4	0.91
Height (cm)	165.4 ±9.3	166.4 ±8.4	0.61
Weight (kg)	59.1 (52.7-72.1)	72.6 (62.1-83.0)	<0.01
BMI (kg/m^2)	21.4 (20.1-25.0)	26.3 (23.9-28.7)	<0.01
Diabetes status (n) DM/non-DM	25 / 20	0 / 45	
Previous fractures (n) yes / no	15 / 30	13 / 32	0.65
Daily calcium intake (mg)	1300 (775-1700)	600 (400-850)	<0.01
Vitamin D supplements (n) yes / no / unknown	29 / 16 / 0	4 / 40 / 1	<0.01

Mean ±SD / Median (Inter Quartile Range)

Results – HR-pQCT scan

Radius

	m.3243A>G	Control	*p*-value
Total bone density (mg/cm^3)	312.6 ±57.7	370.8 ±71.3	**<0,01**
Cortical density (mg/cm^3)	888.8 (844.7-924.6)	913.9 (882.6-935.4)	**0.02**
Trabecular density (mg/cm^3)	154.4 ±43.3	172.2 ±41.6	0.09
Total bone area (mm^2)	272.0 (239.4-344.4)	259.2 (215.7-327.7)	0.22
Cortical area (mm^2)	56.0 (48.6-64.4)	64.2 (58.1-76.2)	**<0.01**
Trabecular area (mm^2)	220.9 (186.8-267.6)	193.9 (146.5-239.8)	0.08
Estimated failure load (kN)	3864.3 (3201.7-4899.4)	4285.3 (3665.7-5520.2)	0.11

Mean ±SD / Median (Inter Quartile Range)

Tibia

	m.3243A>G	Control	*p*-value
Total bone density (mg/cm^3)	275.8 ±64.2	316.2 ±62.3	**<0,01**
Cortical density (mg/cm^3)	874.0 (829.2-911.3)	886.0 (845.8-909.6)	0.31
Trabecular density (mg/cm^3)	154.1 ±41.2	176.8 ±39.3	**0.02**
Total bone area (mm^2)	675.5 (579.2-764.5)	686.1 (615.5-816.8)	0.33
Cortical area (mm^2)	98.4 (83.8-128.1)	134.6 (107.4-158.4)	**<0.01**
Trabecular area (mm^2)	102.2 ±10.9	105.0 ±11.1	0.29
Estimated failure load (kN)	8514.1 (7323.5 -11108.9)	10689.3 (9446.0 -12809.0)	**<0.01**

Mean ±SD / Median (Inter Quartile Range)

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