Effects of Fructose-induced Metabolic Syndrome and Metformin in the Skeleton of Wistar Rats

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INTRODUCTION
- Metabolic Syndrome (MS) is a heterogeneous disorder produced by different combinations of dyslipidaemia, elevated blood pressure, abdominal obesity and glucose intolerance.
- MS has been associated with a reduction in bone strength and increased non-vertebral osteoporotic fractures.
- The insulin-sensitizer metformin (MET) is one of the most widely-used agents to treat metabolic disturbances related to MS. However, the effects of MET on bone metabolism are not well established.

HYPOTHESIS
MS-induced decrease in the osteogenic potential of bone marrow mesenchymal stromal cells (MSC), could alter the structure, composition and metabolism of bone tissue. Additionally, that these alterations could be prevented by oral treatment with MET.

GOALS
To investigate the effect of experimental MS and treatment with MET, on MSC osteogenic commitment, bone micro-architecture and biomechanics.

METHODS
- 38 male 12-wk-old Wistar rats were randomized into four groups (n=8-10): 1) autolced drinking water (DW) control (Veh), 2) Veh + oral MET (100 mg kg BW/day) (MET), 3) DW with 20% fructose (F) and 4) DW with simultaneous F + MET treatments (F+MET). (Figure 1).
- MSC were isolated from humen to determine their osteogenic potential ex vivo.
- Tibiae were excised for pQCT, and static and dynamic histomorphometric analyses.
- Femora were excised for biomechanical analyses.
- Maxillae were histologically processed to assess alveolar bone loss (ABL) at interradial molars (M1) and M2/M3.

RESULTS
- At 12 weeks of F treatment, rats had metabolic abnormalities compatible with MS that were reverted by co-treatment with MET (Table 1).
- MSC derived from F-treated rats had lower levels of type 1 collagen synthesis (COL), and decreased formation of mineral nodules (MIN) after 15 days of osteogenic cultures.
- MET-derived MSC displayed a reduction in alkaline phosphatase activity (ALP) and COL syntheses compared to Veh-derived MSCs (Table 2).
- pQCT and bone histomorphometric analyses revealed no differences in cortical and cancellous bone histomorphometric parameters between F-treated and Veh-treated rats.
- Decreased trabecular bone mineral content and density in MET rats compared to Veh rats (Figure 2).
- Reduced trabecular BTV, Tb.Th and Tb area in MET-treated rats (groups F and F+MET) compared to Veh rats (Fig. 3 and 4).
- No differences between groups were observed for biomechanical measurements, nor for cortical static and dynamic bone histomorphometric parameters.
- F+MET rats had greater ABL at M1+2 compared to Veh rats, and MET rats had greater ABL at M2/M3 compared to Veh and F, respectively (Fig. 5 and 6).

CONCLUSIONS
- 12 weeks of F treatment in Wistar rats induced metabolic abnormalities characteristic of MS, but not skeletal changes. Furthermore, 10 weeks of MET treatment reverted the MS metabolic disturbances but, rather than protecting the skeleton, induced detrimental effects in some of the structural parameters of cancellous bone but not of cortical bone and accelerate ABL.

REFERENCES