Fast & furious: the consequential role of the mitochondria in mesenchymal stromal/stem cell (MSC) osteogenic commitment

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One of the most important functions of mesenchymal stromal/stem cells (MSCs) is osteogenesis, a capacity which has been shown to decline with age as well as by replicative senescence. Alarmingly, while there is correlative evidence that adolescents consuming greatest amounts of simple sugars—the most common being glucose—have the lowest bone mass, there is no mechanistic understanding on the causality of this correlation. We therefore sought to elucidate the impact of overconsumption of simple sugars on bone health, which peaks in adolescence/early adulthood and correlates with osteoporosis (OP) and fracture risk decades later. Using human cellular data, bioinformatics analyses revealed glucose-related metabolic and mitochondrial pathways as integral to MSC osteo-/adipo-lineage commitment. Functionally, *in vitro* addition of high levels of glucose (HG) alone without differentiation induction was sufficient to decrease both young/non-senescent MSC mitochondrial activity and osteogenesis while enhancing adipogenesis by 8 hours' time due to rapid depletion of nicotinamide adenine dinucleotide (NAD^+), a vital mitochondrial coenzyme and also activator for Sirtuin (SIRT) 1, a longevity gene also involved in osteogenesis through its role as co-factor to RUNX2, the master osteogenic transcription factor. *In vivo*, HG intake in young mice depleted MSC NAD^+, with oral NAD^+ precursor supplementation rapidly reversing both mitochondrial decline and osteo-/adipo-commitment in a SIRT1-dependent fashion within 1 to 5 days. These findings have strong implications on global OP and disability risks in light of current worldwide overconsumption of simple sugars. We recently have sought to utilize this knowledge to enhance MSC osteogenesis by boosting mitochondrial activity *ex vivo* in 3D systems as a more a practical strategy to improve MSC therapy for bone regeneration.