LETTER TO EDITOR

Insulin paradox, aging, bone health and growth in the context of mitochondrial function

Dear Editor,

Insulin paradox (as it is generally referred to) has recently been reported to show up in more than expected scientific investigations. This puzzle has also involved studies in bone health and longevity. Increase in lifespan of mice and C. elegans knockouts of growth hormone receptor gene has opened an interesting area of research. To this effect, an interesting paper seems to integrate certain cardinal aspects of aging, bone health, and growth with mitochondrial function and insulin; indicating role for insulin signaling at several levels in differentiation, growth and maintenance of osteocytes and life span determination. It has been found that growth hormone receptor knockout (GHRKO) mice display increased insulin, insulin like growth factor-1 (IGF-1), cytoplasmic/mitochondrial reactive oxygen species (ROS), life span and decreased mitochondrial membrane potential, glucose transporter-1 (GLUT-1) expression, steady state ATP, NADH redox index, glutathione, oxygen consumption rate, mitochondrial reserve capacity and skeletal health span. Association of increased insulin and IGF-1 with extended life span is a novel finding seemingly not in agreement with previous reports. An imperative facet of these findings is reduced mitochondrial volumetric density and mitochondrial intensity density in vivo with a parallel finding of no reduction in mitochondrial volumetric density and reduced mitochondrial intensity density in the primary osteocyte cultures.

It could be argued that physical activity in mice (which may be conjectured to the phenomenon of exercise in humans) has much to do with skeletal dynamics and may affect mitochondrial volumetric density when viewed in context of bioenergetic demands (in addition to the argument of osteocytes being deep buried and relatively less proliferative as suggested by Yakar et al., 2018 and Liu et al., 2019). It appears that physical activity has a role to play in determining mitochondrial volume with a caveat that investigators have reported these findings in various cells (while this scenario with osteocytes has not been reported yet). As physical activity cannot be assessed in cell lines it would be worthwhile to study rodent/mouse models by subjecting them to various exercise practices. Also, the elevation of insulin and IGF-1 in GHRKO mice and increased adiposity and insulin sensitivity (though the evaluation of the expression of insulin receptor in these experiments have not been explicated in comprehensive detail) is relevant. Change in insulin sensitivity can be interpreted in terms of hyperinsulinemia observed in these mice yet it may also be due to altered expression of insulin receptors (IR). So IR expression pattern may well be a parallel and presumably a cardinal biological feature in osteocyte health, pertinent to GHRKO mice. This rationale has important implications in clinical management of diabetes, bone health and metabolic syndrome. To add to this logic, insulin has been shown to improve mitochondrial function in a PI3K/Akt-dependent manner and increase in insulin levels might also be interpreted as a response (or associated factor) to alterations in mitochondrial volume density. Also, insulin prevents oxidative stress which primary osteocyte cultures.

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may be one of the mechanisms for prevention/delay of senescence/aging in the osteocytes presenting as extended life span.

Mitochondria have important role to play in insulin sensitivity\(^\text{17}\). ROS formation may have maladaptive consequences that increase the rate of mutagenesis and stimulate proinflammatory processes. This provides a cogent rationale to evaluate inflammatory and immune aspects of GHRKO mediated bone impairments and osteocyte dysfunction. This may have implications in autoimmune disorders like rheumatoid arthritis (though the idea needs to be acknowledged with some caution). In addition, ROS, genetic factors, aging, and reduced mitochondrial biogenesis all contribute to altered expression of IRs. These factors contribute to changes in insulin signaling in classic and non-classic insulin target tissues. The prolonged life span and antiaging effect of GHRKO may also be explained in terms of insulin resistance mediated hyperinsulinemia (though the logic seems to run counterintuitive). On an additional note, mutations in Klotho have been associated with aging and bone loss. Why we assert Klotho is because its expression is controlled by insulin\(^\text{19}\). This integrates growth hormone receptor loss, mitochondrial dysfunction, insulin/IGF-1 elevation and IR expression into a single conceptual outlook. It is pertinent to mention that Klotho downplays insulin/IGF-1 pathway, Wnt pathway, TNF-α, and TGFβ signaling thus acting as a co-receptor for FGF23 signal transduction. It also plays a role in sialidase activity mediated ion channel function\(^\text{19}\). It is interesting to note that Klotho polymorphisms have been associated with longevity and risk of disease in humans\(^\text{19}\).

In the backdrop of all this, a coherent concept seems to emerge where bone health is being orchestrated by insulin signaling (bringing bone mineralization, trabecular spacing and, therefore, skeletogenesis, bone remodeling, mechanosensing and bone-cell crosstalk into a single picture). Experiments aimed at siRNA mediated knockout or CRISPR mediated knockout of pivotal insulin signaling genes (like PI3K, IR, IGF-1, GSK-3β) in osteocytes in culture and selected gene knockout in animals combined with experiments based on physical activity are likely to yield a wealth of information and suggest therapeutic measures in relevant bone diseases. Hence insulin paradox may appear as a biological conundrum at the outset but it presents an unexpected opportunity to be exploited for clinical applications in bone diseases, aging and endocrine health.

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