Fructose vs. Glucose: Modulating Mesenchymal Stem Cell Growth and Cytokine Expression Through Sugar Supplementation

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Mesenchymal stem cells (MSCs) have been increasingly spotlighted in recent therapeutic research due to their multipotency and ability to be isolated from various sources, such as adipose tissue and bone marrow1. These cells can differentiate into a myriad of cell types, including adipocytes, chondrocytes, hepatocytes, and osteoblasts 2-5.

Furthermore, their capacity to be reprogrammed into induced pluripotent stem cells underscores their vast potential in regenerative medicine. The overarching aim of our research was to unravel the influences of fructose and glucose on MSC differentiation and cytokine production, given the prevalence of these sugars in cell culture mediums. We initiated our investigation by substituting glucose with fructose under standard culture conditions. The ensuing data pinpointed a reduction in MSC growth rate with fructose as opposed to glucose.

From a therapeutic perspective, MSCs are recognized for their immunomodulatory function, secreting pivotal cytokines and hormones6. Prompted by this, we explored if fructose could amplify cytokine production in MSCs compared to glucose. Our experiments revealed enhanced IGFBP3 and HGF expression at distinct fructose concentrations. These cytokines play important roles in the development and resolution of liver inflammation7,8. Enhancement of these cytokines was intrinsically tied to elevated HIF1a expression increased IGFBP3 expression was observed when MSCs were grown in hypoxia, regardless of the type of sugar used. Conversely, silencing HIF1a caused a decrease in both IGFBP3 and HGF at the transcript level. These results point to the important role of the metabolic microenvironment in MSC growth and culture, where oxygen and nutrient availability can modulate the immune properties of these cells.

In conclusion, our findings clarify the nuanced effects of fructose and glucose on MSC proliferation and cytokine output. These revelations not only broaden our understanding of cellular responses in the presence of these sugars but also accentuate the pivotal role of HIF1a in orchestrating MSC function. This research potentially paves the way for tailoring MSC function through strategic sugar supplementation.

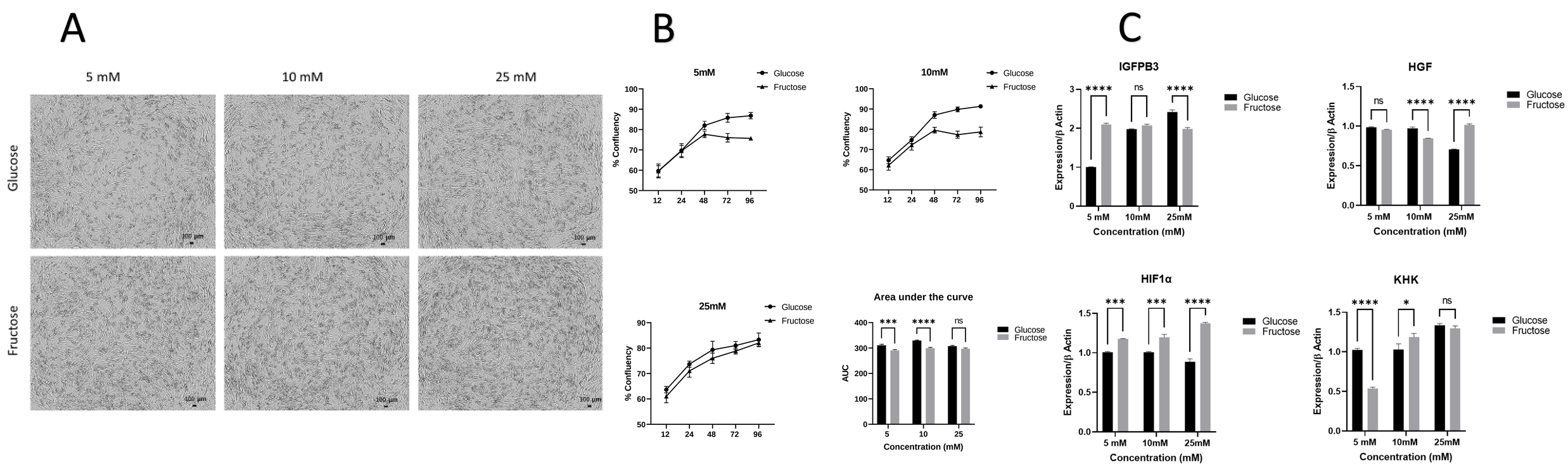

Figure 1. **Fructose boosted cytokines production but decreased cellular growth.** The present study involved quantifying the growth rate of MSCs at concentrations of 5, 10, and 25 mM in both glucose and fructose, (A &B) . MSCs grow faster in glucose when compared to fructose at equivalent concentrations. Conversely, MSCs cultured in fructose demonstrated elevated mRNA levels for *IGFBP3* and *HGF* as well as *HIF1α* (C).

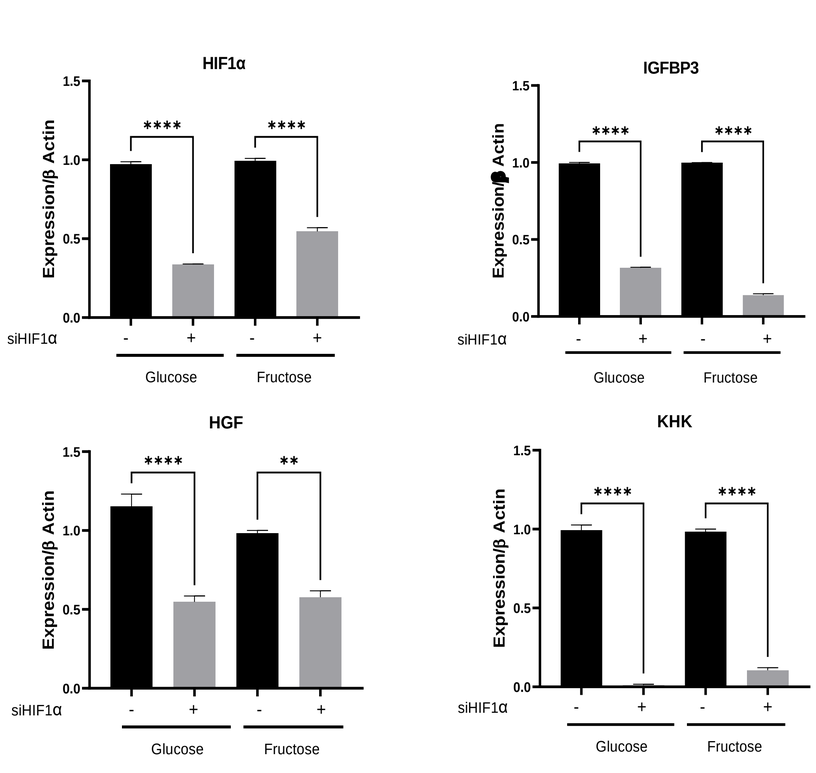

Figure 2. ***Hif1a* knockdown reduces *Igfbp3* and *Khk*.** Based on the earlier experiment, we noticed an upregulation of *Hif1a* in MSCs when they were cultured in a fructose-rich environment. To delve deeper, we conducted a knockdown of *Hif1a*, which resulted in the downregulation of both *Khk* and *Igfbp3*. This indicates that Hif1a plays a pivotal role in regulating the expression of both *Khk* and *Igfbp3* in MSCs

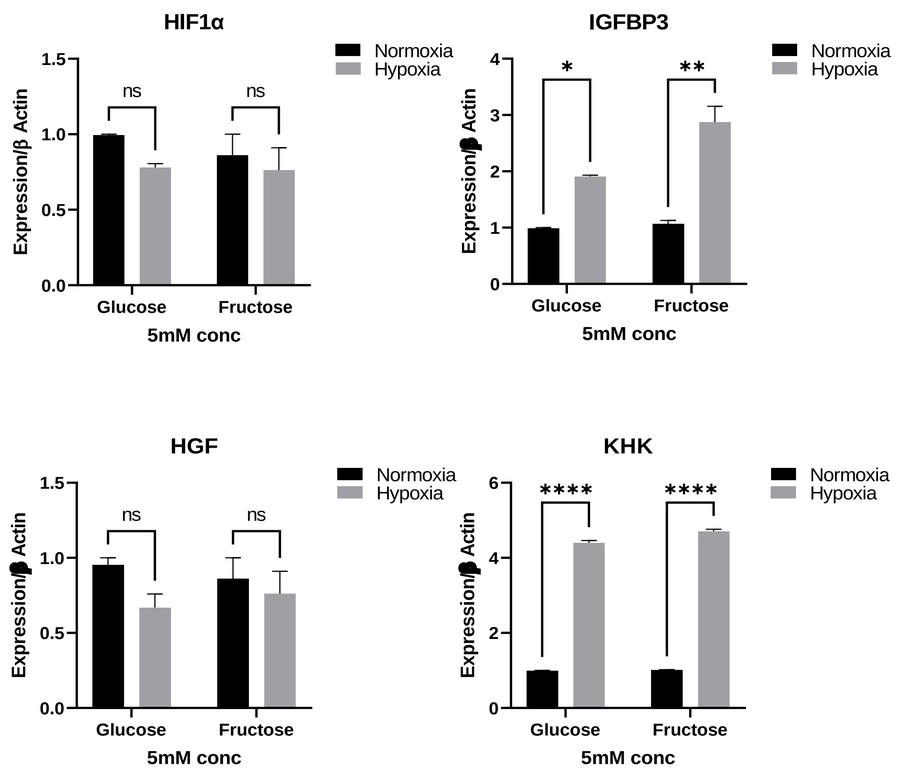

Figure 3. **Hypoxia induced *Igfbp3* and *Khk* expression.** Under hypoxic conditions (1% O2), MSCs exhibited upregulation in both *Khk* and *Igfbp3*, regardless of the type of hexose used (glucose or fructose). Notably, this upregulation did not extend to *Hif1a*. These findings confirm the critical role of *Hif1a* in regulating the expression of both *Khk* and *Igfbp3* in MSCs.

Our research aimed to understand how fructose and glucose impact MSC differentiation and cytokine production, given their common use in cell culture. Substituting glucose with fructose reduced MSC growth rate. Fructose enhanced the production of specific cytokines, such as IGFBP3 and HGF. This was influenced by HIF1a.

In conclusion, our findings highlight the nuanced effects of fructose and glucose on MSCs, underscoring HIF1a's pivotal role. This research opens possibilities for customizing MSC function through sugar supplementation in regenerative medicine.

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