



DIABETIC PROFILE, COGNITIVE IMPAIRMENT, AND ALZHEIMER’S RISK: METFORMIN TREATMENT EFFECTS ON OLFACTORY NEUROEPITHELIUM

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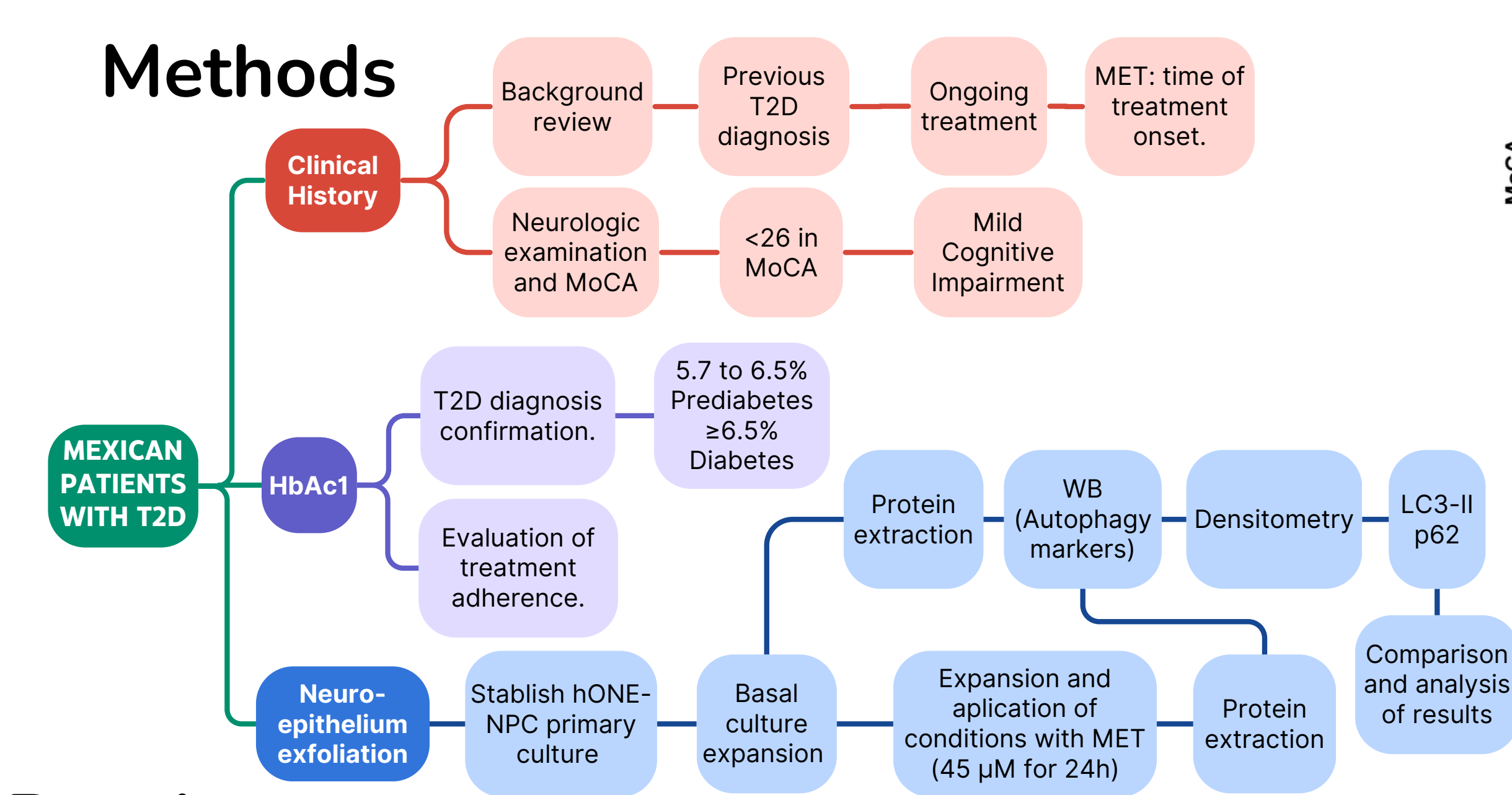
Metformin (MET) acts as an inducer of the autophagic pathway in human olfactory neuroepithelium cells (hONE-NPCs), with its modulating effects persisting up to two years after treatment cessation. The cellular response to *in vitro* metformin treatment varies significantly based on patient history: cells from patients without prior metformin exposure show decreased p62 expression (indicating successful autophagic flux), whereas cells from patients with a history of prior use show increased p62 expression, signaling autophagic pathway dysfunction. Furthermore, clinical data reveals a correlation trend linking higher HbA_{1c} levels (poorer glycemic control) to lower MoCA scores, reinforcing the connection between type 2 diabetes and an increased risk of mild cognitive impairment (MCI). Ultimately, while the results highlight metformin's potential neuroprotective role through autophagy regulation, the authors emphasize the need for a larger sample size to overcome statistical limitations and account for treatment adherence issues caused by gastrointestinal side effects.

Introduction

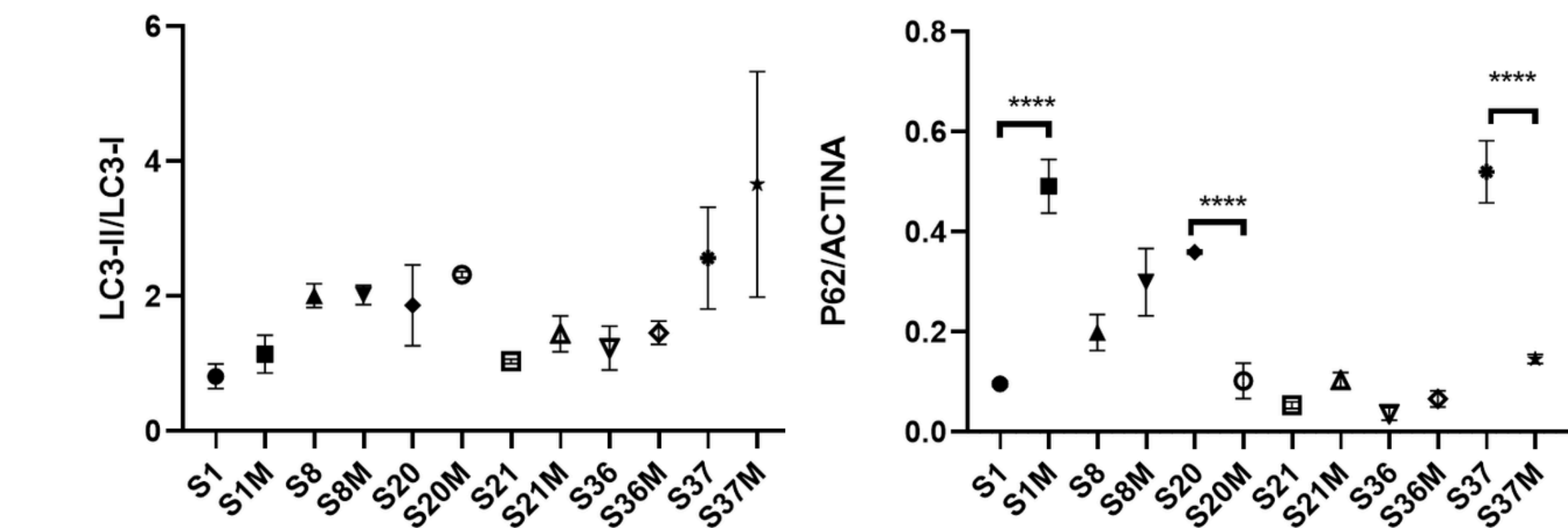
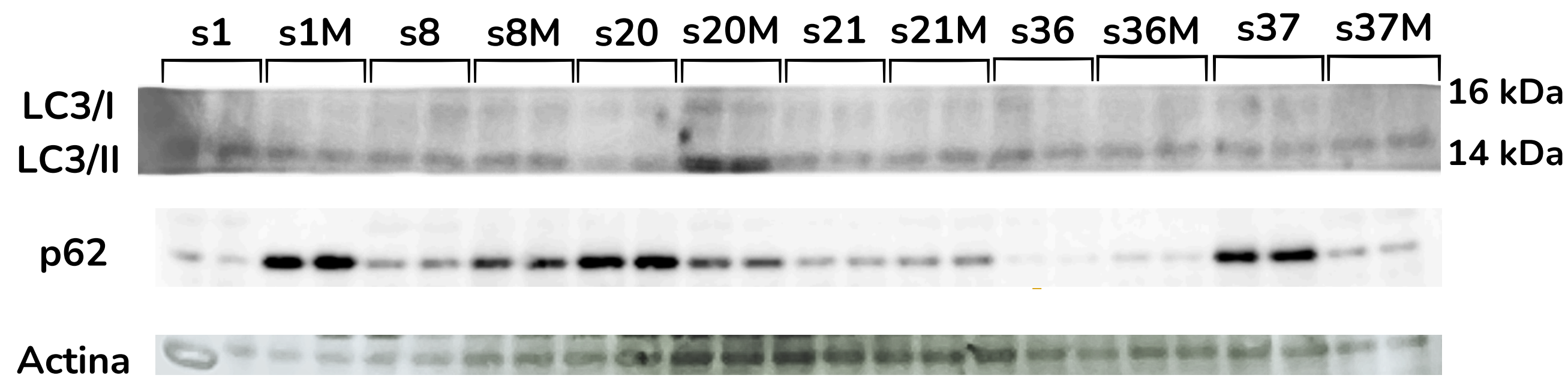
Type 2 Diabetes (T2D) is a metabolic disorder characterized by chronic hyperglycemia. This high glucose concentration saturates insulin receptors, preventing its utilization in neural tissues; because of this, chronic diabetes doubles the risk of dementia (Hamzé et al., 2022). Dementia is preceded by **Mild Cognitive Impairment (MCI)**, where patients present alterations in higher mental functions but preserve functionality in daily activities (Biessels-Geert-Jan, 2014). Furthermore, robust evidence highlights a pathophysiological link between T2D and **Alzheimer’s disease (AD)**, where T2D actively exacerbates neurodegenerative mechanisms. (Wu et al, 2026)

AD pathology initiates decades before clinical dementia, often manifesting through olfactory deficits. Present in up to 85% of cases, olfactory dysfunction reliably predicts cognitive decline. Pathologically, this sensory loss is driven by neurocircuit homeostasis breakdown. In early stages, a prominent degeneration of noradrenergic axon fibers from the locus coeruleus occurs within the **olfactory bulb (OB)**. This loss is orchestrated by an aberrant innate immune response, where OB microglia clear hyperactive projections via lysosomal phagocytosis before widespread amyloid deposition (Meyer et al. 2025). Therefore, olfactory testing and clinical tools like the MoCA serve as critical, non-invasive early biomarkers.

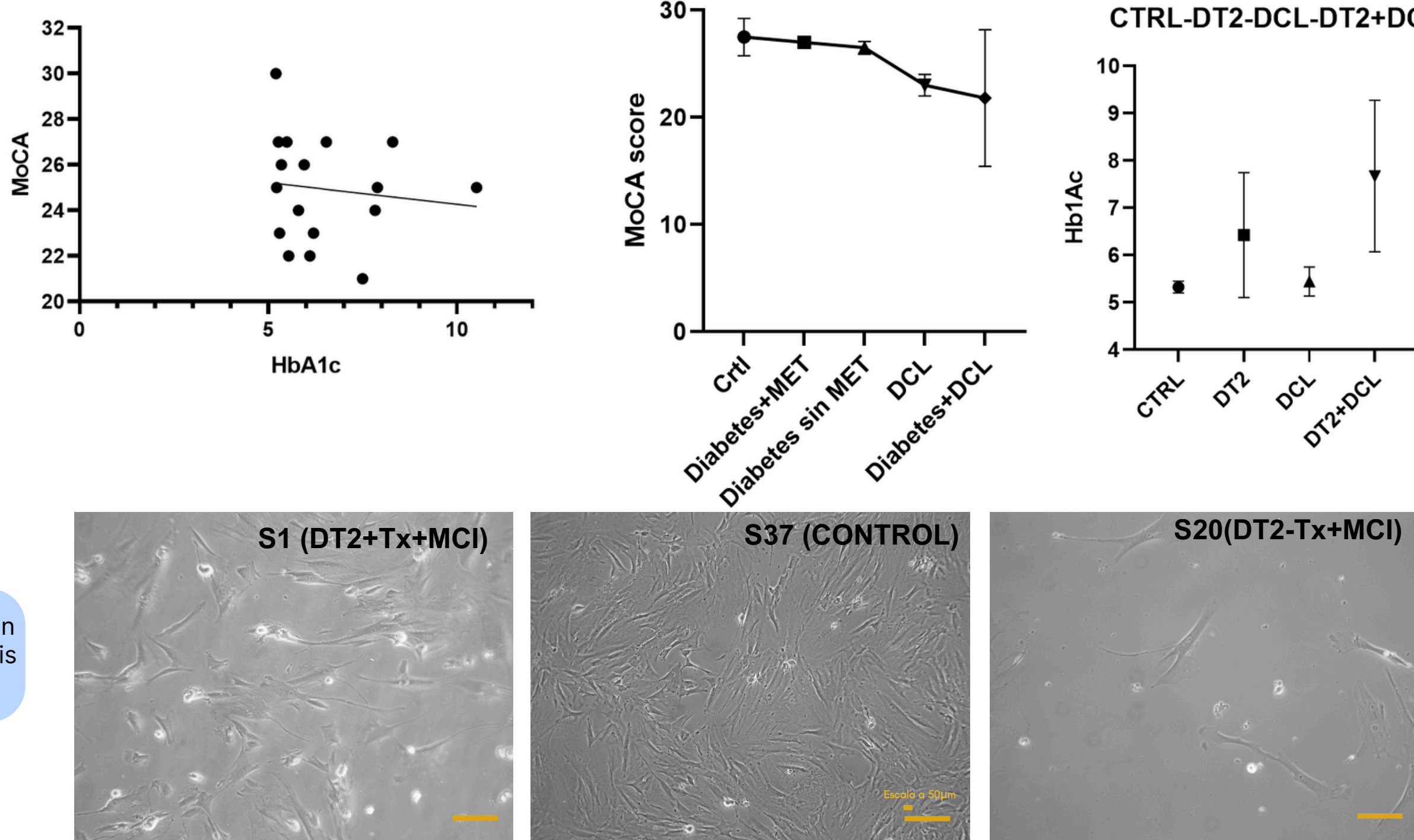
To study these mechanisms, patient-derived **human olfactory neuroepithelium neural progenitor cells (hONE-NPCs)** offer a useful model to analyze cellular integrity, cell death, and autophagy. Autophagy is an intracellular lysosomal degradative survival mechanism that maintains cellular homeostasis by recycling damaged organelles and clearing misfolded proteins. During active autophagy, levels of the adapter protein p62/SQSTM1 decrease as it links ubiquitinated cargo to LC3-II for degradation. **Metformin (MET)**, a first-line T2D drug, induces this pathway (Kodali et al., 2021) and could counteract cognitive dysfunction. This study aims to evaluate the effects of oral versus in vitro metformin treatment on autophagic pathway activation in hONE-NPCs by evaluating p62 and LC3-II levels.



Results



Subject ID	MCI	DT2	MET-Pretratment	hONE-NPC response to MET (Inhibition of Autophagy flux, detected by an increase in p62 levels)	Induction of Autophagy in response to MET treatment (evaluated by LC3-II increase)
S1	No	Yes	Yes	Yes	No
S8	No	Yes	Yes	Yes	No
S20	Yes	No	No	No	Yes
S21	Yes	Yes	No	No	No
S36	Yes	Yes	No	No	No
S37	No	No	No	No	Yes



Discussion and Conclusions

Metformin sensitization was found in the cells of patients with a history of prior metformin use. The magnitude of the effect was related to the duration of use and adherence to treatment.

While in patients without prior metformin treatment (S37 control, S20 untreated diabetic), a decrease in p62 expression was found when cells were treated with metformin, which correlates with an increase in the autophagic pathway, detected by an increase in LC3-II. Among the patient groups studied, there were differences in the MoCA score depending on whether they were diabetic or not and whether or not they had taken metformin.

It is advisable to repeat this study in larger populations to confirm the protective effect of metformin in patients at risk of developing cognitive impairment, considering that this drug has gastrointestinal side effects that may discourage patients from taking it or lead to poor adherence to treatment.

References

Contact

