

Plasma microRNA Dysregulation Targeting Neuroinflammatory and Metabolic Pathways in Alzheimer's Disease and Type 2 Diabetes



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Circulating neuroinflammatory microRNAs are altered in individuals with T2DM. The significant upregulation of miR-155-5p, together with the upward trend observed for let-7c-5p, supports the presence of systemic inflammatory processes that may contribute to neurodegenerative pathways. These findings highlight the potential of circulating microRNAs as early biomarkers linking metabolic dysfunction to Alzheimer's disease risk.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD) share metabolic and inflammatory disturbances that may be reflected in circulating microRNAs¹⁻².

This study assessed the plasma expression of two microRNAs linked to neuroinflammatory signaling, **let-7c-5p** and **miR-155-5p**, in controls, individuals with T2DM, AD, and combined AD-T2DM.

Both microRNAs are mechanistically linked to neuroinflammation²⁻³. miR-155 promotes pro-inflammatory microglial activation (M1 phenotype) and enhances NF-κB-dependent cytokine production, while let-7c can act as an extracellular ligand for TLR7, amplifying inflammatory cascades and contributing to neuronal stress³⁻⁴. Their dysregulation in metabolic disease suggests that systemic inflammation may prime or exacerbate neuroinflammatory pathways relevant to AD⁴.

METHODS

Plasma samples from 148 participants were analyzed: CTRL (n=60), T2DM (n=60), AD (n=17), and AD-T2DM (n=11). MicroRNA expression was quantified by RT-qPCR using SNORD48 as the endogenous control and calculated with the Pfaffl method. Group and age-stratified comparisons were performed using non-parametric statistical analyses.

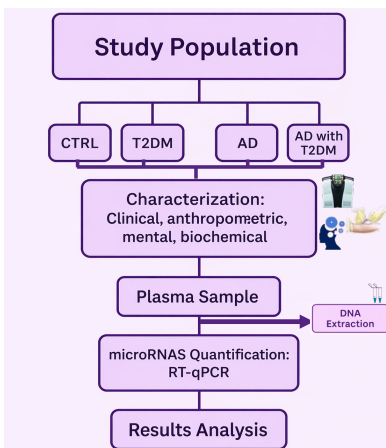


Fig. 1. Scheme of the experimental strategy for the microRNAs quantification.

RESULTS

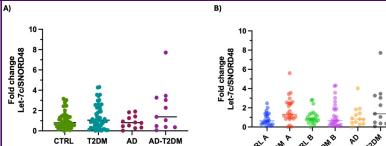


Figure 1. Plasma hsa-let-7c-5p expression in CTRL, T2DM, AD, and AD-T2DM subjects. Expression was quantified by qRT-PCR, normalized to SNORD48, and expressed relative to CTRL. Group differences were analyzed using the Kruskal-Wallis test. (A) Overall group comparison. (B) Age-stratified analysis in CTRL and T2DM groups.

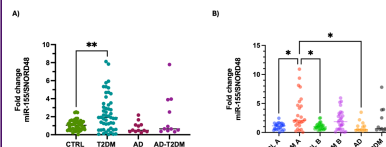


Figure 3. Plasma hsa-miR-155-5p expression in CTRL, T2DM, AD, and AD-T2DM subjects. Expression was quantified by qRT-PCR, normalized to SNORD48, and expressed relative to CTRL. Significant differences were observed between groups ($p < 0.05$), as determined by the Kruskal-Wallis test. (A) Overall group comparison. (B) Age-stratified analysis in CTRL and T2DM groups.

Let-7c-5p showed a non-significant upward trend in the T2DM and AD-T2DM groups, with no statistically significant differences in global or age-stratified comparisons (Figure 2). In contrast, **miR-155-5p was significantly upregulated in T2DM vs. controls** ($p = 0.002$) (Figure 3). Participants aged 30-59 years with T2DM exhibited up to a threefold increase relative to age-matched controls ($p = 0.001$), while older adults displayed a consistent but non-significant elevation. AD alone did not show similar increases.

CONCLUSIONS

The marked overexpression of miR-155-5p in T2DM, together with a mild nonsignificant increase of let-7c-5p, supports their role as circulating indicators of metabolic-driven inflammatory activation, with potential implications for early neuroinflammatory processes at the intersection of T2DM and AD.

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