METABOLIC SIGNATURES IN PLASMA, URINE AND SALIVA IN ALZHEIMER´S DISEASE: SYSTEMIC INSIGHTS AND GENE INTEGRATION

Cadaxo, AS1; Cotrin, JC1; De Oliveira, LA1; Valente, AP2; Lopes, FG3; Vera, RP4; Santos Junior, GC1; Santos-Rebouças, CB1

1Departamento de Genética, Instituto de Biologia Roberto Alcantara Gomes, Universidade do Estado do Rio de Janeiro

2CENABIO I, Instituto de Bioquímica Médica, CNRMN, BioNMR, Universidade Federal do Rio de Janeiro

3Unidade de Atendimento à Pessoa Idosa, Universidade do Estado do Rio de Janeiro

4Núcleo do Envelhecimento Humano, Universidade do Estado do Rio de Janeiro

*cbs@uerj.br

(21) 999154982

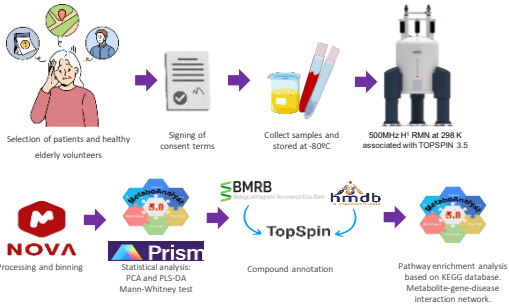
INTRODUCTION

Alzheimer's disease (AD) is the most prevalent age-related neurodegenerative condition worldwide. It is characterized by the gradual accumulation of beta-amyloid (βA) and the hyperphosphorylation of tau proteins, leading to progressive neuronal decline in the cognitive areas of the affected brain. Currently, definitive diagnosis relies on postmortem brain analysis. Given the multifactorial nature of AD, the identification of noninvasive metabolic biomarkers can significantly improve early diagnosis and deepen our understanding of its causes, progression, and possible treatments.

This study aimed to compare individuals with AD and healthy controls by identifying metabolic alterations in plasma, urine, and saliva using Nuclear Magnetic Resonance (NMR).

METHODOLOGY

Figure 1: Work flowchart



RESULTS AND DISCUSSION

Plasma and urine samples were collected from 34 AD patients, along with 13 saliva samples. For healthy matched controls (without metabolic diseases, no history of neurological disorders, and with depression or hypertension under control, 48 plasma and urine samples and 28 saliva samples were obtained.

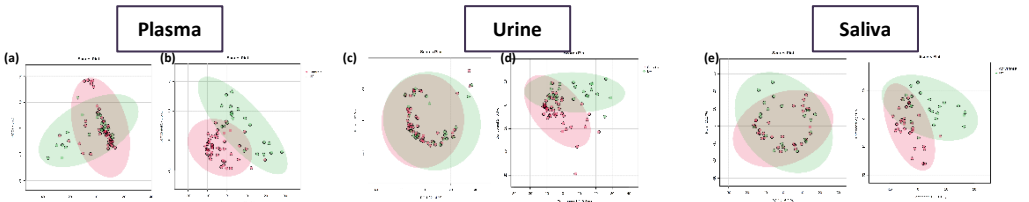


Figure 2: Samples from Control group are shown in red, and samples from DA group in green. (a) PCA of plasma samples (b) PLS-DA of plasma samples (c) PCA of urine samples (d) PLS-DA of urine samples (e) PCA of saliva samples (f) PLS-DA of saliva samples. All data are normalized by the sum of intensities

Across plasma, urine, and saliva, AD patients showed distinct metabolic alterations involving energy metabolism, amino acid metabolism, synaptic regulation, inflammatory response, lipid, and purine pathways. Key metabolites included pyruvate, phenylalanine, alanine, proline, histidine, glycerol, and creatinine. Network analysis integrated these findings with AD-associated genes from GWAS, highlighting *AQP4,* a gene involved in blood–brain barrier function and beta-amyloid clearance, which appears in the three of the biofluids enrichments analysis.

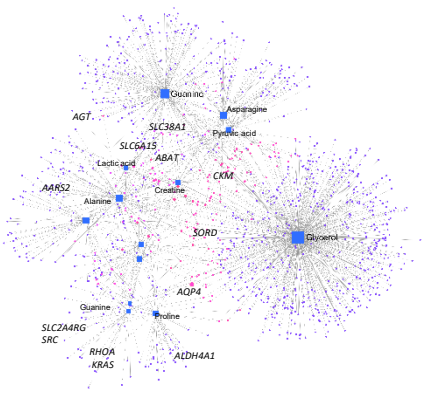


Figure 3: Interaction network between genes and the identified compounds. The nodes (blue diamonds) represent the main identified compounds, while the edges indicate their interactions with the genes (purple/pink circles)

Energy metabolism - glycolysis/gluconeogenesis

Lipoproteins, pyruvate, glucose, pyruvate lactic acid, creatinine, glycerol, glycolic acid

Amino acid metabolism

Histidine, creatinine, creatine, choline, phenylalanine, guanine, proline

Inflammation and immune modulation

Histidine, glycerol, silo-Inositol, lipoproteins

Microbiota

Silo-Inositol, pipoproteins, pyruvate, choline, lactic acid

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