Impact of Cholinesterase Inhibitor Therapy on Metabolomic Biomarkers of Alzheimer's Disease

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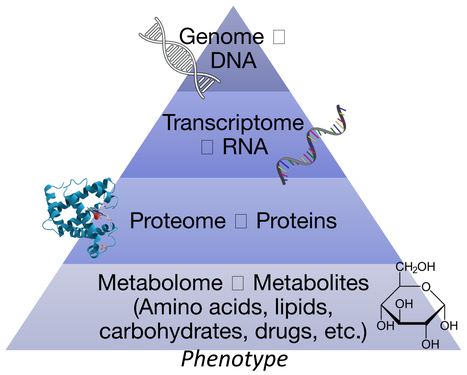
Introduction

- Alzheimer's disease (AD) is a progressive neuro-degenerative disorder characterized by cognitive decline, memory loss, and behavioral changes.[1]
- Inability to detect AD prior to symptom onset limits opportunities for early therapeutic intervention.
  - Metabolomics offers a promising, noninvasive strategy for identifying diagnostic biomarkers of AD.[2]
- Yilmaz et al. identified significant concentration changes in 22 salivary and urinary metabolites distinguishing individuals with AD from healthy controls.[3-4]
  - These findings led to the development of a diagnostic model with 94% sensitivity and 78% specificity.[4]

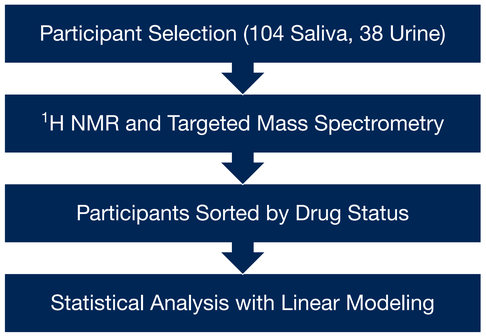


- Cholinesterase inhibitors are first-line symptomatic treatments for AD.[5]
  - Nearly half (46.7%) of AD patients in the Corewell Health System are prescribed a cholinesterase inhibitor.
  - These medications are primarily metabolized in the liver via cytochrome P450 enzymes and eliminated in urine.[5]
- To validate previously identified biomarkers, it is necessary to investigate the effect of cholinesterase inhibitors on the salivary and urinary metabolome of AD patients.
- We hypothesized that cholinesterase inhibitors would not affect previously identified biomarkers of AD.

Aims and Objectives

- Primary Aim: Determine whether previously identified metabolomic differences in AD are attributable to disease status or medication effects.
  - Specifically, perform a retrospective analysis of existing urinary and salivary metabolomics datasets to better characterize the impact of cholinesterase inhibitors on the AD patient metabolome.

Methods



- Data for each metabolite (250 total) were preprocessed and normalized to reduce technical variability, followed by log transformation and autoscaling. Differential metabolite abundance between drug groups was assessed using covariate-adjusted linear regression models.
  - Urinary and salivary metabolomes were analyzed separately.
  - Analyses were adjusted for age, sex, and batch effects.
  - False discovery rate correction was applied using the Benjamini-Hochberg method.

	Controls	AD	p value
Age	77.91	81.15	0.62
Sex: Male	35	13	0.73
Race: White	59	33	0.58
Education (years)	14.68	14.62	0.39
MMSE	28.7	20.11	0.00009
SLUMS Score	24.63	14.03	0.00012
Depression Score	2.33	2.28	0.37
Cholinesterase Inhibitor	0	13	0.0023

Table 1. Clinical and demographic variables of study subjects for urine metabolomics analysis, grouped by disease status (control n=68, AD n=38).

Results

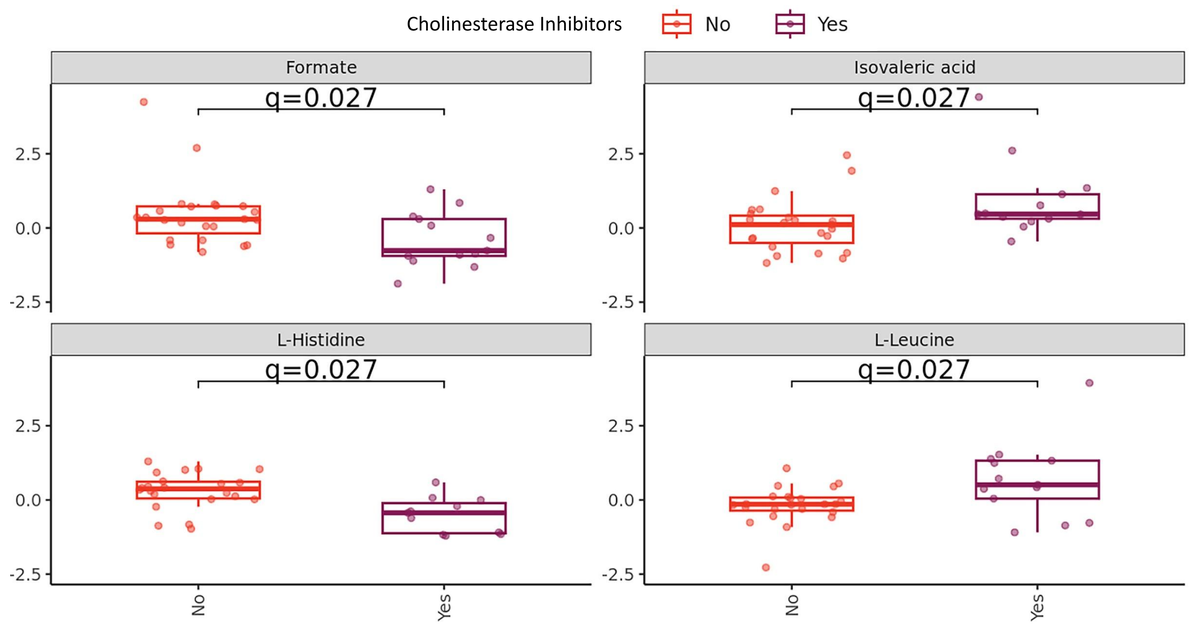


Figure 1. Distributions of statistically significant urinary metabolite changes associated with cholinesterase inhibitor use among individuals with AD.

Conclusions

- Analysis of salivary samples revealed no significant differences between cholinesterase inhibitor users and non-users among individuals with AD.
- Cholinesterase inhibitor use was associated with significant changes in urinary metabolite concentrations, including increased isovaleric acid and L-leucine and decreased formate and L-histidine (q=0.027 for all).
  - These urinary metabolites have not been identified as candidate biomarkers for AD and do not affect the previously developed diagnostic model.
- Limitations of this study include the use of cross-sectional metabolomic data; longitudinal studies are needed to examine changes before and after initiating cholinesterase inhibitors.
  - Future research should also explore the impact of other commonly prescribed medications on the AD patient metabolome, including antidepressants and medications for diabetes.
- Overall, these findings support the persistence of disease-specific metabolomic signatures in AD, independent of cholinesterase inhibitor treatment.
  - This work reinforces the potential of metabolomic patterns as a non-invasive diagnostic tool for AD.

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