A Metabolomics Approach to Biomarker Discovery Reveals That Tocotrienols Have Potential Beneficial Impact on Maintenance Hemodialysis Population

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Objectives: Cardiovascular disease is considered major comorbidity in the maintenance hemodialysis (MHD) population. A dietary supplement such as tocotrienols have shown to improve cardiovascular health in these patients. In our study, we hypothesized that the tocotrienols may possess potential beneficial impacts on MHD patients by improving their metabolomic profile.

Methods: Changes in plasma metabolomic profile of the MHD patients with or without tocotrienol rich fraction (TRF) supplements (300 mg/day) for 12 months period on plasma metabolomic profile of the US (n = 85) and Malaysian (n = 80) MHD was investigated using ^{1}H-NMR based metabolomics approach followed by Receiver Operating Characteristics (ROC) curve based biomarker model validation.

Results: Partial linear square discriminant analysis showed a significant difference in the metabolomic profile of the MHD patients between the placebo and the TRF supplemented groups over 12 months in both US and Malaysian cohorts. According to metabolite identification and quantification proline, 4-hydroxyproline, ornithine, glutamate, 4-aminobutyrate, 3-aminoisobutyrate, acetoacetate, and 3-hydroxybutyrate were found to be significantly ($p < 0.05$) altered between the placebo group and TRF groups over 12 months. The biomarker models created using these key metabolites had shown good predictive accuracy (Area under the ROC curve > 0.8) in both cohorts with high sensitivity (79% and 78%) and specificity (84% and 80%) in the US and Malaysian cohorts, respectively. Further model validation relied on the permutation test with 1000 permutations ($p < 0.001$), validating the predictive ability of the created biomarker models in both cohorts. The biomarker meta-analysis revealed that trans-4-hydroxyproline, proline, acetoacetate, ornithine, 3-hydroxybutyrate, 3-aminoisobutyrate, and glutamate had similar expression patterns in both cohorts.

Conclusions: Metabolites linked to arginine and proline metabolism and synthesis and degradation of ketone bodies pathways were altered in MHD patients over 12 months. TRF modulated these changes in a favorable direction, indicating the potential beneficial impact of TRF supplements in these patients. These metabolites may serve as biomarkers for kidney disease and/or for evaluating the efficacy of TRF supplementation in MHD patients.

Funding Sources: PEMANDU, Malaysia