A Plasma Cuprome Exists With Predictors of Copper Status in Nepalese Children

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Objectives: Copper (Cu) is an essential micronutrient but, due to difficulties of measuring Cu by atomic absorption spectroscopy (AAS), plasma Cu status is rarely assessed in low income countries. A less costly assay is needed. We have explored whether plasma Cu concentration can be predicted by modelling strongly associated plasma proteins, assessed by mass spectrometry (MS), that could be assayed with other nutriproteomic biomarkers on one platform in the future.

Methods: In plasma samples from 500 Nepalese children 6–8 y of age, the mean (SD) plasma Cu concentration measured by AAS was 23.3 ± 5.7 mmol/L, with 13.6% classified as deficient (< 10 mmol/L). We quantified relative abundance of 982 plasma proteins by iTRAQ tandem MS following affinity depletion of six high abundance proteins (Cole J Nutr 2013) and correlated their relative abundance with plasma Cu by linear mixed effects regression. We defined a stringent *plasma cuprome* comprising proteins associated with Cu at a false discovery rate (q) < 0.01. Missing values were imputed and proteins were fit by forward, stepwise regression analysis, meeting an AIC reduction of ≥ 30, to model plasma Cu status.

Results: There were 134 (q < 0.01) proteins in the plasma cuprome. Among 62 positive correlates were ceruloplasm (r = 0.65), 9 complement proteins (r = 0.29 to 0.45), 4 serpin protease inhibitors (r = 0.31 to 0.43) with others involved in coagulation, 5 LRR structural motifs as found in toll-like receptors (r = 0.35 to 0.58), signaling enzymes such as CDC42BPA (r = 0.70) and proinflammatory reactants and regulators such as CRP, AGP, amyloids and TNIP1 (r = 0.40 to 0.56). Among 72 negative correlates (r = −0.29 to −0.42) are lipid and sterol binding and transport proteins including apolipoproteins/lipocalins, enzyme regulating proteins, extracellular adhesion, signaling and matrix proteins. Different members of serine peptidase inhibitor members were among + and – correlates. Forward stepwise regression fit 6 proteins (CP, CDC42BPA, LRRC47, TDRD9, LLRIQ1, LRRCC1) that explain 76.5% of the variance (R2) in plasma Cu, sufficient for predicting plasma Cu status of a population.

Conclusions: A large, diverse plasma cuprome exists, as revealed in young Nepalese children, from which six proteins may adequately predict plasma Cu status.

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