LETTER

# Metabolites as frailty biomarkers in older adults

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We recently read, with great interest, the article by Kameda et al. (1). They conducted untargeted metabolomics analysis of whole blood samples of 19 older adults; identified 22 markers for frailty, cognition, and hypomobility; and find the following: 1) Metabolite profiles can efficiently distinguish frailty from nonfrailty; 2) antioxidant ergothioneine is neuroprotective; and 3) oxidative stress may be key to frailty and age-related illnesses. While this study makes a significant contribution to the current understanding of metabolomics and frailty, we have a few concerns.

First, in this study, frailty was diagnosed using the Edmonton Frail Scale (EFS), which includes cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence, and functional performance (2). This scale is recommended for screening rather than assessment of frailty, in the latest version of the International Conference of Frailty and Sarcopenia Research guidelines (3). EFS might confuse concepts of physical frailty, comorbidity, and subtypes of frailty; thus, frailty markers based on EFS cannot distinguish the types of frailty (physical, cognitive, social, and psychosocial). A highly validated physical frailty phenotype is recommended, to assess frailty (4).

Second, this study shows that lipid metabolism is not involved in cognition or mobility with respect to frailty, while, recently, in the English Longitudinal Study of Aging, Rattray et al. (5) identified 12 different metabolites of frail phenotypes and confirmed the significance of the carnitine shuttle and vitamin E pathways in the risk of frailty, based on their levels in the serum of 1,191 older subjects. Given that most studies used plasma (6) or serum (7) instead of whole blood in metabolomics research, further studies on the comparison between metabolites of frailty in whole blood and plasma/serum would be beneficial.

Third, a metabolite composite score based on 37 metabolites associated with the Scale of Aging Vigor in Epidemiology was recently developed to predict mortality of frailer individuals, in the Health, Aging, and Body Composition study, in which a metabolite composite score higher by 1 SD was associated with 46% higher mortality (8). The predictive ability of the model was validated among older adults, using the Cardiovascular Health Study All Stars study, which shows the potential clinical application of metabolomics markers of frailty. Further longitudinal studies are needed to verify the clinical usage of these markers.

Finally, the sample size was relatively small, with a lack of matching factors, such as age, sex, and chronic diseases. Besides, the study only excluded patients who were bedridden or had abnormal kidney or liver function; the effects of cancer, rheumatic diseases, and diabetes mellitus on metabolomics should not be neglected (9, 10).


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