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Letter to the Editor

# Brain-muscle-adipose tissue triad crosstalk in childhood obesity: In the service of predictive medicine

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## Dear Editor-in-Chief

The global epidemic of childhood obesity continues to challenge healthcare systems, with recent epidemiological data confirming a tenfold increase in prevalence over four decades. While the complications of pediatric obesity are well documented, the field of predictive medicine urgently requires reliable biomarkers that identify at-risk children before irreversible metabolic dysfunction develops. The Journal of Exercise & Organ Cross Talk has consistently highlighted the importance of inter-organ communication in metabolic health. Herein, we propose that the brain-muscle-adipose tissue triad represents a pivotal axis for developing predictive strategies in childhood obesity.

Recent evidence has substantially advanced our understanding of adipose tissue signaling in pediatric populations. A study of 104 children aged 7-18 years demonstrated that circulating spexin and adiponectin are significantly associated with insulin resistance in pediatric obesity. Notably, spexin exhibited a biphasic pattern characterized by an initial compensatory increase followed by a decompensated decrease, suggesting its potential as an early warning signal for metabolic deterioration. Adiponectin emerged as an independent determinant of HOMA-IR ($\beta=-0.577$, $p=0.005$), reinforcing the central role of adipose-derived signals in systemic insulin sensitivity (Lian et al., 2026). These findings position adipokines as accessible biomarkers for stratifying risk in children with obesity.

Expanding beyond adipose tissue, large-scale proteomic analyses have revealed multi-organ signatures of cardiometabolic risk. In a cross-sectional study of 4,024 children and adolescents, Stinson and colleagues identified protein signatures linking obesity to dyslipidemia, insulin resistance, and hypertension. Using machine learning approaches, a three-protein panel (CDCP1, FGF21, HAOX1) combined with liver enzymes improved prediction of steatotic liver disease compared to enzymes alone (ROC-AUC=0.83 vs. 0.77, $p<0.05$). Importantly, reductions in adiposity during a one-year intervention were associated with decreased inflammatory cytokines, demonstrating the modifiable nature of these biomarkers (Stinson et al., 2026). This work underscores that circulating proteomic signatures reflect integrated signals from multiple organs, including liver, adipose tissue, and potentially skeletal muscle.

The central nervous system's role in this crosstalk cannot be overlooked. A comprehensive Mendelian randomization study investigating the fat-brain axis revealed bidirectional causal relationships between body fat measures and brain phenotypes. Body fat composition showed negative genetic correlations with intelligence and cognitive performance, while positive correlations emerged with attention-deficit/hyperactivity disorder, stroke, and depression. These genetic insights suggest that the brain is not merely a passive recipient of peripheral metabolic signals but actively participates in a bidirectional dialogue with adipose tissue. For predictive medicine, this implies that neurobehavioral assessments could complement biochemical markers in identifying children at greatest metabolic risk (Baranova et al., 2025).

The convergence of these findings carries translational implications. First, the identification of early biomarkers such as spexin and adiponectin enables risk stratification before frank insulin resistance develops. Second, proteomic signatures incorporating multiple organ-derived proteins offer enhanced predictive accuracy for specific outcomes like steatotic liver disease. Third, genetic evidence linking brain phenotypes to body fat measures suggests that predictive models should incorporate both biochemical and neurobehavioral parameters.

For JEOCT readers, these advances highlight opportunities for exercise-based interventions targeting inter-organ communicat-

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-ion. Physical activity potently modulates the secretome of skeletal muscle, adipose tissue, and potentially the brain. Understanding how exercise-induced signals influence the brain-muscle-adipose triad could inform personalized exercise prescriptions for children with obesity. Future research should prioritize longitudinal studies mapping the temporal dynamics of these biomarkers during childhood development and in response to lifestyle interventions.

In conclusion, the brain-muscle-adipose tissue triad represents a conceptual framework for predictive medicine in childhood obesity. By integrating adipose-derived signals, multi-organ proteomic signatures, and brain-body genetic links, we can move toward early identification of at-risk children and targeted preventive strategies. The Journal of Exercise & Organ Cross Talk is ideally positioned to advance this research agenda.

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