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Adipolin: a potential early biomarker of vascular injury in children with obesity

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Pediatric Research; https://doi.org/10.1038/s41390-026-05368-8

In the past three decades, the global combined prevalence of pediatric obesity has tripled, and in 2021, 93.1 million children aged 5–14 years were diagnosed with obesity.[1] Obesity-related comorbidities, such as cardiometabolic complications, increase with age and with the severity of obesity.[2] Cardiovascular complications are thought to be a result of multifactorial mechanisms, such as oxidative stress, reduced nitric oxide, and chronic low-grade inflammation. Accumulation of excessive macronutrients in adipose tissue leads to the excessive release of inflammatory mediators such as interleukin (IL)-6, IL-1β, tumor necrosis factor-α (TNF-α), leptin, and monocyte chemoattractant protein-1 (MCP-1). MCP-1 reduces the production of adiponectin.[3] Recently, adipolin, which is encoded by the FAM132A gene, has been found to have beneficial metabolic effects such as improving insulin resistance and reducing proinflammatory gene expression in obese mice.[4] However, the correlation between adipolin levels and obesity is conflicting in adults and children. While the older obese population has reduced adipolin levels,[5] a recent article by Jin et al.[6] demonstrates that children with obesity have elevated adipolin levels. Jin et al.'s article "Serum FAM132A/Adipolin Correlates with Endothelial Dysfunction in Children with Obesity" in the recent issue of *Pediatric Research* represents the initial step in elucidating the relationship between FAM132A levels and markers of endothelial dysfunction.[6] In this commentary, we evaluate the strengths and limitations of this study and propose areas for future research.

Jin et al. conducted a case–control study[6] in a cohort of 132 Chinese individuals comprising 82 patients with obesity and 50 age- and sex-matched normal-weight controls. Anthropometric and blood pressure values were systematically measured to limit the amount of intra- and inter-operator variability. Venous samples were collected after a 10-h fast. Several biochemical markers were obtained, including fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and fasting insulin (FINS). FINS was measured by chemiluminescence immunoassay, whereas the other biochemical markers were measured using an automated biochemical analyzer. Serum adipolin, adiponectin, leptin, and three markers for endothelial dysfunction (Vascular Cell Adhesion Molecule [VCAM]-1, endothelial [E]-selectin, and Endothelial Cell-Specific Molecule [ESM]-1/endocan) were measured by commercial enzyme-linked immunosorbent assay (ELISA) kits. Each assay was repeated, which demonstrated intra-assay and inter-assay coefficients of variation (CV) less than 8% and 10%, respectively.

The obese cohort had statistically significantly increased markers of anthropometric indices and blood pressure compared to their matched controls. In addition, the obese cohort had pro-atherogenic profiles with statistically significant elevated TG, TC, ALT, AST, FINS, and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR). Serum FAM132A levels were higher in children with obesity compared to their normal-weight controls. Using simple linear regression analyses, FAM132A had a positive correlation with all three markers of endothelial dysfunction ($p < 0.05$ in all markers). To adjust for potential confounding variables, multiple linear regression analyses were conducted controlling for factors such as age, sex, HOMA-IR, and leptin. FAM132A remained independently associated with VCAM-1, E-selectin, and ESM-1. Finally, FAM132A had a positive correlation with serum leptin and a negative correlation with serum adiponectin. The authors proposed that their findings suggest a "Compensatory Upregulation" role for FAM132A in the early phase of obesity to maintain homeostasis in pediatric populations. In contrast, adults likely have prolonged exposure to metabolic surplus, leading their adipose tissue to become "exhausted" or fibrosed, resulting in decreased FAM132A synthesis.

This study demonstrates several notable strengths and addresses a major gap in the literature, as it is among the first to address FAM132A in a human pediatric cohort. Prior research on FAM132A focused primarily on adult populations or on murine models. As per the American Heart Association (AHA), early identification and treatment of risk factors are important for youth because they are more prone to premature cardiovascular disease.[7] In addition, Jin et al.[6] used three markers of endothelial dysfunction, which are activated at distinct parts of the endothelial activation pathway. This approach suggests that FAM132A is associated with generalized endothelial activation and was not isolated to a singular activation marker. Furthermore, this study's exclusion criteria were robust, addressing potential confounding factors. However, other conditions, such as autoimmune or renal diseases associated with obesity, can also independently affect endothelial activation. Another key strength is the study's use of multiple linear regression models, specifically adjusting for HOMA-IR and leptin. FAM132A has been found to be an insulin-sensitizing adipokine, so adjusting for endothelial activation associated with insulin resistance establishes that the results are not a reflection of insulin resistance. Similarly, adjusting

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Received: 22 July 2026 Accepted: 29 July 2026
Published online: 11 August 2026

for leptin, a mediator for endothelial activation in obesity, helps isolate the independent contribution of FAM132A.

Despite these strengths, there are a few limitations to recognize. Jin et al.'s sample group was exclusively of Chinese descent from a single center. This may limit the generalizability to other populations and other centers with varied practice guidelines and associated co-morbidities. As noted by the authors, the adipokines were measured at a single time-point, which makes it challenging to determine if elevated FAM132A precedes or follows endothelial activation. Future studies should also address longitudinal validation. Moreover, the lack of functional assessment of endothelial function limits the ability to determine if the elevated endothelial markers are from true endothelial dysfunction or secondary to a systemic inflammatory response. Importantly, previous studies have demonstrated the feasibility of performing endothelial functional studies in obese children.[8] By acquiring functional vascular status, there would be direct physiological evidence for the authors' "Compensatory Upregulation" hypothesis that elevated FAM132A represents a compensatory upregulation during early obesity. The exhaustion theory proposed by the authors to explain the paradoxical relationship between FAM132A/adipolin levels and obesity in adults and children may not fully account for the observed differences. Both adipolin and adiponectin are protective adipokines. While the association between adiponectin levels and obesity is similar in both adults and children, the relationship between FAM132A/adipolin levels and obesity differs between these groups. The secretion and expression of these adipokines and their receptors may be regulated by distinct mechanisms.[9] Additionally, these adipokines may be secreted at different stages of the disease. It is also possible that adipolin is secreted by non-adipose cells.

Jin et al.[6] address a gap in the literature by elucidating the relationship between FAM132A/adipolin and endothelial markers in children with obesity. Future studies should aim to decrease reliance on surrogate markers for endothelial dysfunction by incorporating vascular assessment. In addition, using a prospective longitudinal cohort study would help determine the temporal relationship between FAM132A and endothelial biomarkers. Addressing these limitations in subsequent studies would help clarify whether FAM132A is a clinically relevant biomarker for early vascular injury in children with obesity. If FAM132A were to be determined as a biomarker for cardiovascular risk stratification, these findings could have implications in early detection, potential therapeutic targeting, and decreased morbidity and mortality in pediatric patients.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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