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Relative Fat Mass as a Determinant of Insulin Resistance in Children on Hemodialysis: Review Article

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ABSTRACT

Background: Insulin resistance (IR) is a prevalent metabolic abnormality in children with end-stage renal disease (ESRD) receiving hemodialysis (HD). Relative fat mass (RFM), an emerging anthropometric measure, is increasingly recognized as a sensitive indicator of adiposity, potentially more accurate than traditional indices like BMI in pediatric populations. Children on HD often experience body composition alterations, including increased fat mass and muscle wasting, which may contribute to the development of IR. Understanding the association between RFM and IR is critical for risk stratification, prevention of metabolic complications, and optimization of care in this vulnerable group. This review aims to synthesize current evidence regarding the role of relative fat mass as a determinant of insulin resistance in children undergoing hemodialysis. It explores pathophysiological mechanisms, assessment techniques for RFM and IR, prevalence data, clinical consequences, and the impact of various interventions. The review also discusses challenges in research and practice and outlines future directions for improving metabolic health in pediatric HD patients.

Conclusion: Emerging data indicate a strong association between elevated RFM and IR in children on hemodialysis, mediated by chronic inflammation, adipokine dysregulation, and impaired glucose metabolism. Accurate assessment of body composition, early identification of IR, and targeted interventions aimed at modulating fat mass are essential steps in improving outcomes. However, gaps remain in standardized assessment methods and long-term interventional studies. Future research should focus on refining diagnostic tools for RFM in CKD, investigating mechanistic pathways, and developing personalized management strategies to address the complex interplay between adiposity and insulin resistance in this unique pediatric population.

Keywords*:* Relative Fat Mass, Insulin Resistance, Children on Hemodialysis

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INTRODUCTION

Children with ESRD on hemodialysis (HD) are exposed to unique metabolic and nutritional challenges. The interplay of chronic inflammation, uremic milieu, and hormonal dysregulation significantly alters their metabolic landscape compared to healthy peers. These children frequently present with altered body composition, often characterized by increased fat mass despite stunted growth or malnutrition, complicating both clinical management and prognosis. The increasing prevalence of obesity and metabolic syndrome in the pediatric CKD population further exacerbates this risk, making the study of adiposity and its metabolic consequences highly relevant [1].

Recent years have seen a paradigm shift in how adiposity is assessed in this population. While BMI has long been the standard, it fails to distinguish between fat and lean mass, especially in children affected by growth failure or abnormal hydration states. Relative fat mass (RFM) has emerged as a promising alternative, offering better correlation with actual adiposity and ease of use in clinical settings. Despite its growing use, the relationship between RFM and insulin resistance (IR) specifically in children on HD remains under-explored. This gap highlights the importance of synthesizing available evidence to improve both risk assessment and patient care [2].

Furthermore, pediatric nephrology faces the challenge of translating adult-centric research into meaningful strategies for children. Developmental differences in metabolism, body composition, and hormonal axes mean that findings from adult populations often cannot be directly applied to pediatric patients. The critical periods of growth and development experienced by children on HD may amplify the effects of IR and excess adiposity on long-term outcomes, underscoring the need for tailored research and interventions [3].

Given these considerations, this review seeks to clarify the association between relative fat mass and insulin resistance in pediatric HD patients. By highlighting mechanisms, prevalence data, assessment tools, and management strategies, we aim to provide clinicians with a comprehensive understanding of this complex and pressing issue. Identifying children at risk for IR through improved assessment of fat mass could allow for earlier interventions and ultimately better health outcomes [4].

Overview of Insulin Resistance in Pediatric Hemodialysis

Insulin resistance is a metabolic condition wherein insulin fails to elicit its normal physiological response in target tissues. In pediatric HD patients, IR develops through a combination of factors, including chronic inflammation, accumulation of uremic toxins, and impaired glucose metabolism. The resulting hyperinsulinemia and hyperglycemia drive a cascade of metabolic disturbances that increase cardiovascular risk and hinder growth [5].

Studies have demonstrated that IR is prevalent even in early stages of CKD, but the risk escalates as patients progress to ESRD and initiate dialysis. Dialysis-related factors, such as inadequate clearance

10.48047/jocaaa.2024.33.06.68

of inflammatory mediators and altered insulin pharmacokinetics, may further worsen IR. The use of glucose-containing dialysate and the stress of regular treatments can contribute to metabolic dysregulation, particularly in the pediatric population, who may be more vulnerable to these changes [6].

Children on HD also exhibit unique hormonal disturbances. Growth hormone resistance, alterations in IGF-1, and increased cortisol levels have all been implicated in the development of IR in this population. These hormonal imbalances can disrupt normal insulin action and contribute to the accumulation of adipose tissue, especially in the visceral compartment. Notably, IR in pediatric HD patients is associated with higher rates of hypertension, dyslipidemia, and microvascular complications, all of which increase long-term morbidity and mortality [7].

Additionally, IR can affect nutritional status by promoting protein-energy wasting and muscle catabolism, a phenomenon sometimes termed "malnutrition-inflammation-atherosclerosis syndrome." This paradoxical coexistence of obesity (increased fat mass) and muscle wasting further complicates management and highlights the need for accurate assessment of body composition [8].

The impact of IR extends beyond physical health, with studies linking metabolic disturbances to impaired neurocognitive development, reduced school performance, and lower health-related quality of life in children with CKD. Early recognition and targeted management of IR are thus crucial components of comprehensive pediatric HD care [9].

Assessment of Body Composition and Relative Fat Mass in Children

Accurate assessment of body composition is fundamental to understanding and managing metabolic risk in children on HD. Traditional anthropometric indices, such as BMI and weight-for-age z-scores, are commonly used but have notable limitations in pediatric CKD. These measures do not account for changes in hydration status, which can confound interpretation, especially in the presence of fluid overload or edema [10].

RFM, calculated using height and waist circumference, has gained attention as a more reliable indicator of adiposity in children. Unlike BMI, RFM is less influenced by fluid status and better reflects actual fat distribution, particularly visceral fat, which is more metabolically active and closely linked to IR. Research shows that RFM has stronger correlations with direct imaging techniques, such as DXA and MRI, compared to BMI or waist-to-hip ratio in children with CKD [11].

The utility of RFM extends beyond clinical research and is increasingly being incorporated into routine clinical practice. It allows for the identification of children with excessive fat accumulation who may be at increased risk for metabolic complications. Importantly, RFM can detect subtle changes in body composition over time, enabling early intervention before significant clinical consequences arise [12].

10.48047/jocaaa.2024.33.06.68

Despite its advantages, RFM is not without limitations. There is a need for pediatric-specific reference ranges, as current cut-offs are largely derived from adult or general pediatric populations. Further, factors such as ethnicity, puberty, and chronic illness may influence RFM values, necessitating the development of validated, age- and disease-specific nomograms for children on HD [13].

In addition to RFM, advanced imaging modalities such as DXA, bioelectrical impedance analysis (BIA), and MRI are used in research settings to provide detailed assessments of fat and lean mass. However, their high cost, limited availability, and the need for sedation in younger children restrict their routine use. Therefore, RFM offers a pragmatic, accessible alternative for risk stratification in clinical practice [14].

Prevalence of Insulin Resistance in Children on Hemodialysis

The prevalence of IR among pediatric HD patients varies widely in the literature, reflecting differences in diagnostic criteria, methods of assessment, and study populations. HOMA-IR is the most commonly used surrogate marker in clinical studies, with cut-off values adjusted for age and pubertal stage. Estimates suggest that between 30% and 70% of children on HD exhibit evidence of IR, a significantly higher rate than in the general pediatric population [15].

Several factors contribute to the high prevalence of IR in this group. Chronic inflammation, physical inactivity, poor nutritional status, and excess adiposity all play critical roles. Children with longer durations on dialysis, greater degrees of fat mass (as assessed by RFM), and higher levels of inflammatory markers are particularly susceptible to developing IR. Moreover, children with genetic predisposition or family history of diabetes may be at even greater risk [16].

Comparative studies have shown that children on peritoneal dialysis (PD) may have slightly different metabolic profiles, but the risk of IR remains elevated regardless of dialysis modality. Notably, higher RFM scores are consistently associated with higher HOMA-IR values in both HD and PD populations, supporting the role of adiposity as a central determinant of metabolic risk [17].

Socioeconomic factors and access to care also influence the prevalence and severity of IR in pediatric HD patients. Children from lower-income backgrounds or with limited access to specialized care may experience higher rates of obesity and poorer metabolic control. This underscores the need for comprehensive, multidisciplinary approaches to care that address both medical and social determinants of health [18].

Finally, longitudinal studies indicate that IR often persists or worsens over time in children on HD, with a tendency to progress to overt glucose intolerance or type 2 diabetes, particularly in those with high RFM. Early identification and intervention are therefore crucial to modifying long-term outcomes [19].

Mechanisms Linking Relative Fat Mass to Insulin Resistance

10.48047/jocaaa.2024.33.06.68

The relationship between increased relative fat mass and IR is mediated by a complex interplay of metabolic, hormonal, and inflammatory pathways. Adipose tissue, particularly visceral fat, is metabolically active and secretes a range of pro-inflammatory cytokines, including TNF-α, IL-6, and C-reactive protein. These molecules disrupt insulin signaling by promoting serine phosphorylation of insulin receptor substrates, thereby reducing glucose uptake in muscle and liver [20].

Adipose tissue also produces adipokines such as leptin, adiponectin, and resistin. In children with increased RFM, leptin levels are typically elevated, leading to leptin resistance and impaired regulation of appetite and energy expenditure. Adiponectin, which enhances insulin sensitivity, is often reduced in obese children with CKD, further exacerbating IR. Resistin, another adipokine, has been implicated in the promotion of hepatic gluconeogenesis and systemic inflammation [21].

In pediatric HD patients, chronic exposure to uremic toxins amplifies these metabolic derangements. Uremic solutes such as indoxyl sulfate and p-cresyl sulfate inhibit insulin signaling pathways and promote oxidative stress, creating a vicious cycle of inflammation and IR. This effect is compounded by the altered gut microbiome frequently observed in children with CKD, which may contribute to both systemic inflammation and metabolic dysregulation [22].

Physical inactivity, common among children on HD due to fatigue and treatment-related constraints, further contributes to increased fat mass and decreased muscle mass. The resulting imbalance in body composition not only increases IR but also heightens the risk for cardiovascular disease and poor physical functioning [23].

Additionally, hormonal disturbances characteristic of CKD, such as resistance to growth hormone and alterations in the IGF-1 axis, may promote central adiposity and impair glucose metabolism. These hormonal shifts, combined with the effects of chronic inflammation and uremic toxins, underscore the multifactorial nature of IR in children with high RFM on HD [24].

Clinical Implications of Insulin Resistance in Pediatric HD Patients

The presence of IR in children on HD is associated with a host of adverse clinical outcomes. Cardiovascular disease is the leading cause of morbidity and mortality in this population, and IR is a recognized contributor to the development of left ventricular hypertrophy, arterial stiffness, and accelerated atherosclerosis. Children with IR are more likely to have elevated blood pressure, dyslipidemia, and abnormal endothelial function, all of which increase cardiovascular risk [25].

IR also impacts growth and nutritional status in pediatric HD patients. Hyperinsulinemia may impair growth hormone signaling and contribute to protein-energy wasting, leading to stunted growth and decreased muscle mass. This "double burden" of obesity and malnutrition is particularly challenging to manage and is associated with poorer quality of life and increased risk of hospitalization [26].

10.48047/jocaaa.2024.33.06.68

Metabolic complications, such as glucose intolerance and the progression to type 2 diabetes, are increasingly recognized in children on HD, particularly those with elevated RFM. Early identification of IR allows for timely intervention, potentially preventing the onset of overt diabetes and its associated complications. Moreover, IR may increase susceptibility to infections and impair immune function, further complicating the clinical course of these children [27].

Neurocognitive function is also affected by metabolic disturbances in pediatric HD patients. IR and its associated metabolic abnormalities have been linked to lower cognitive performance, reduced attention, and impaired academic achievement. These effects are particularly concerning given the critical periods of neurodevelopment that occur during childhood and adolescence [28].

Given these wide-ranging clinical implications, routine screening for IR and accurate assessment of fat mass are essential components of comprehensive care for children on HD. Early intervention targeting both IR and adiposity may improve short- and long-term outcomes [29].

Interventions Targeting Relative Fat Mass and Insulin Resistance

Interventions aimed at reducing fat mass and improving insulin sensitivity in pediatric HD patients must be holistic and individualized. Nutritional counseling is foundational, with an emphasis on achieving a balance between adequate energy intake to support growth and avoiding excess caloric consumption that promotes adiposity. Dietitians play a critical role in tailoring meal plans that address the unique needs of children with CKD, including electrolyte and fluid restrictions [30].

Physical activity, although often limited by fatigue and treatment schedules, is a powerful tool for improving insulin sensitivity and reducing fat mass. Even moderate-intensity activities, such as walking, swimming, or cycling, can confer significant metabolic benefits. Structured exercise programs, where feasible, have been shown to improve body composition and cardiovascular health in children on HD [31].

Pharmacological interventions for IR, such as metformin, have been used in select cases, but data in pediatric HD populations are limited. The risks and benefits must be carefully weighed, and pharmacotherapy should generally be reserved for children with persistent IR despite lifestyle modifications. In addition, optimization of dialysis prescription, including consideration of nocturnal or more frequent HD, may improve metabolic outcomes by reducing the burden of uremic toxins and inflammation [32].

Behavioral and psychosocial interventions are also important, as children on HD may experience depression, low self-esteem, or family stressors that impact dietary choices and activity levels. Multidisciplinary approaches that incorporate psychological support, social work, and peer support can enhance adherence to lifestyle interventions and improve overall well-being [33].

10.48047/jocaaa.2024.33.06.68

The success of interventions is dependent on early identification and consistent follow-up. Regular monitoring of RFM, insulin sensitivity, and related metabolic markers should be integrated into routine care to enable timely adjustments to management plans and support long-term health [34].

Challenges in Research and Practice

Despite advancements, significant challenges remain in both research and clinical practice regarding the assessment and management of RFM and IR in pediatric HD patients. Heterogeneity in study populations, variations in diagnostic criteria, and differing methodologies for assessing body composition limit the comparability of results and the ability to draw definitive conclusions [35].

Fluid shifts inherent to the HD process, as well as growth abnormalities, can confound anthropometric measurements and complicate the interpretation of RFM and related indices. There is also a lack of consensus on appropriate cut-off values for RFM in children with CKD, further complicating clinical decision-making. Standardization of assessment tools and protocols is urgently needed to facilitate both research and practice [36].

The psychosocial context of pediatric HD patients must also be considered. Barriers to lifestyle modification, such as limited access to recreational facilities, food insecurity, and family stress, can impede the implementation of effective interventions. Cultural factors, health literacy, and disparities in healthcare access further contribute to variability in outcomes and must be addressed through comprehensive, culturally sensitive care models [37].

Additionally, many studies in this area are cross-sectional or involve small sample sizes, limiting the strength of evidence. Longitudinal and interventional studies are needed to better understand the causal pathways linking RFM and IR and to evaluate the efficacy of different management strategies [38].

Finally, there is a need for greater collaboration among pediatric nephrologists, endocrinologists, dietitians, and researchers to advance knowledge and improve care for children with CKD and associated metabolic disturbances. Multidisciplinary efforts are essential to overcoming the complex challenges faced by this vulnerable population [39].

Future Directions and Recommendations

Future research should prioritize the development and validation of pediatric-specific RFM reference ranges and assessment tools for children with CKD. Efforts should also focus on longitudinal studies tracking changes in body composition, IR, and clinical outcomes over time, with an emphasis on identifying modifiable risk factors and evaluating the impact of targeted interventions [40].

Mechanistic studies exploring the roles of adipokines, inflammation, genetic predisposition, and the gut microbiome in the development of IR among children with increased RFM on HD are needed to better elucidate the underlying pathways. Such research could inform the development of novel therapeutic strategies and personalized interventions [41].

10.48047/jocaaa.2024.33.06.68

In clinical practice, routine screening for IR and the integration of RFM assessment into standard care protocols are recommended. Multidisciplinary care models that include dietary, physical, and psychosocial support should be implemented to address the complex needs of pediatric HD patients. Education for families and caregivers is also vital to support lifestyle modifications and adherence to treatment plans [42].

Healthcare systems and policy makers should work to reduce disparities in access to care, nutrition, and physical activity resources for children with CKD. Advocacy for research funding, improved clinical guidelines, and public health initiatives targeting childhood obesity and metabolic syndrome in this population is essential for long-term progress [43].

Ultimately, a personalized, proactive approach that addresses the unique metabolic, developmental, and psychosocial needs of children on HD will be critical to improving health outcomes and quality of life for this vulnerable group [44].

Conclusion

The relationship between relative fat mass and insulin resistance in children on hemodialysis is a complex, multifactorial, and clinically significant issue. Increased RFM serves as a key determinant of metabolic risk in pediatric HD patients, contributing to cardiovascular disease, impaired growth, and reduced quality of life. Advances in assessment tools, early identification, and multidisciplinary interventions offer hope for improved outcomes. Continued research and innovation are needed to close the current knowledge gaps and ensure that all children with CKD receive optimal, personalized care [45].

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