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Letter to the Editor

Comment on "Clinical and laboratory characteristics of nephropathic cystinosis in a resource-limited region": Linear growth retardation as a clinically important signal

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Introduction

I read with great interest the article by Köksoy and Görükmez (1). Longitudinal data on nephropathic cystinosis from regions of high consanguinity, with constrained access to leukocyte cystine monitoring and uninterrupted cysteamine supply, are scarce, and the authors provide a valuable real-world account of presentation, tubular phenotype, genetics, and renal trajectory. The cohort is especially informative because the recurrent CTNS variant c.681G>A was observed in homozygous form in most genotyped patients.

A particular strength of this cohort is the early age at diagnosis, at a median of around 11 months, which the authors note compares favorably with other series from developing settings and likely reflects heightened regional awareness of consanguinity-related disease (1). This makes the outcomes all the more thought-provoking: despite early diagnosis, estimated glomerular filtration rate (eGFR) declined significantly (116.66 to 77.40 mL/min/1.73 m², p=0.007) and height SDS fell further over follow-up, from −2.8 to −3.9 (p=0.034), while weight SDS did not change significantly and body bass index (BMI) SDS remained around −2.0 (1). This gap between early diagnosis and subsequent growth and renal outcome suggests that what determines outcome is not only how early cystinosis is recognized, but what is done after diagnosis to protect growth and bone. Growth retardation was in fact the leading presenting complaint in this cohort, and I would like to use this growth signal to draw attention to three areas that the study, by its scope, could not detail but that are central to that question.

Before doing so, one nuance on the data should be addressed. The authors appropriately frame the height decline as multifactorial, citing chronic hypokalemia, persistent acidosis, phosphate loss with defective bone mineralization, reduced caloric intake, and hormonal factors (1). I read the magnitude cautiously given the small sample and heterogeneous follow-up, but the direction is informative: weight did not decline and rose numerically, BMI was stable, and only height fell further behind. To the extent that reduced caloric intake is invoked, this dissociation suggests that it is unlikely to be the principal driver of the linear growth deficit, although the absence of detailed nutritional data in a retrospective cohort precludes a firm conclusion. Either way, linear growth deserves attention as an outcome in its own right.

First, the bone-mineral observations may be usefully unified under a single framework. The authors discuss rickets in four patients, nephrocalcinosis in six, and the delicate balance between correcting mineral depletion and overtreatment with active vitamin D, calcium, and phosphate (1). These are facets of what is increasingly recognized, though not yet widely familiar in general practice, as a distinct entity: cystinosis-associated metabolic bone disease (CMBD), which differs from conventional chronic kidney disease (CKD)-mineral and bone disorder (2). Mechanistically, tubular phosphate wasting, reduced 1.25-dihydroxyvitamin D, and chronic metabolic acidosis impair growth-plate mineralization and induce relative resistance to the growth hormone and insulin like growth factor-1 (IGF-1) axis (3). The entity also carries a disease-specific mineral signature with a direct monitoring implication: because persistent tubular phosphate leak keeps serum phosphate low, fibroblast growth factor-23 (FGF-23) remains paradoxically low rather than rising as it does early in typical CKD, so secondary hyperparathyroidism tends to appear late and can be missed if sought only on the usual CKD timeline (4). Bone turnover is additionally altered across CKD stages and deteriorates with age (5). Much of this evidence derives from overlapping European cohorts,

so independent confirmation in populations such as the one studied here would be genuinely valuable.

Second, the growth hormone axis deserves explicit emphasis. The authors note, appropriately, that effects within this axis may become more evident as chronic kidney disease progresses, consistent with the three patients who reached stage 3 CKD and the three requiring replacement therapy (1). I would add that recombinant human growth hormone (rhGH) may be an actionable option in selected patients before advanced CKD develops. International consensus recommends considering rhGH when adequate cysteamine therapy, nutrition, and symptomatic treatment fail to prevent growth retardation, including in selected patients without advanced renal failure; CKD-specific recommendations support its use once treatable risk factors are corrected and growth potential remains (2,6). In nephropathic cystinosis specifically, long-term rhGH has been reported to roughly double height velocity and to raise height SDS by about 1.6 over three years in prepubertal children on conservative treatment (7). Documenting whether eligible children with persistent growth failure were assessed for rhGH, after optimization of Fanconi replacement, nutrition, cysteamine, and thyroid status, would meaningfully enrich the interpretation of growth outcomes in future cohorts. This last point connects to a feature of the cohort worth underlining: the authors themselves link the relatively high incidence of renal failure to adherence shaped by socioeconomic conditions, and report poorer adherence among those who progressed to advanced CKD (1). Extending their reasoning, I would suggest the same treatment and monitoring gap may also bear on linear growth, since initiation of cysteamine is not equivalent to adequate, adherent, cystine-guided treatment: early initiation and lower leukocyte cystine levels are associated with better linear growth, and outcome depends more on early, presymptomatic intervention than on genotype (8,9). As the authors candidly acknowledge that adherence was assessed subjectively and leukocyte cystine could not be measured locally, this is best read as an association rather than established causation, and likely a bidirectional one; even so, it identifies a modifiable target and reframes early diagnosis as a window of opportunity rather than an endpoint (1).

Third, standing height alone may underestimate the burden, because growth in this disease is disproportionate. Compared with other pediatric CKD entities, children with nephropathic cystinosis show disproportionate linear growth and reduced upper-arm fat area, pointing to cystinosis-specific contributors beyond reduced glomerular filtration rate (10). In practice, sitting height and the sitting-height-to-total-height ratio, subischial leg length, the upper-to-lower segment ratio, and upper-arm fat area, together with height velocity, bone age, and pubertal staging, would characterize the deficit far better than standing height SDS alone, and would help distinguish disproportionate, rickets-driven leg shortening from the more harmonious growth deficit of other CKD.

These observations are intended to complement rather than detract from the authors' valuable real-world data. Their findings carry a clear message for pediatricians, pediatric nephrologists, endocrinologists, and dietitians: in nephropathic cystinosis, preserving kidney function and preserving growth potential are parallel therapeutic goals, and early diagnosis delivers its benefit only when followed by adherent, cystine-guided treatment and active protection of growth and bone. I would suggest that future cohorts adopt a standardized growth and bone-mineral module, organized under CMBD, capturing standing and sitting height with segmental measurements, height velocity, mineral-bone biochemistry including FGF-23 and parathyroid hormone where feasible, treatment adherence, leukocyte cystine where available, and growth hormone eligibility. Such a framework would help separate the renal, skeletal, endocrine, and nutritional contributors to growth failure and prompt earlier multidisciplinary intervention during the narrow window before loss of height potential becomes difficult to reverse.

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