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EDITORIAL

Growth hormone axis in patients with chronic kidney disease

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Kidneys play an essential role in the metabolism of the majority of hormones. Chronic kidney disease (CKD) causes endocrine disturbances, which develop already at the early stages, but become more prominent as renal failure progresses. Alterations in the homeostasis of calcium, phosphorus, vitamin D, and parathyroid hormone are the most common endocrine disorders observed in these patients and they have been extensively described in the literature. However, a variety of other primary or secondary endocrinopathies are also present in these patients, including growth hormone (GH) axis derangement.

Data from the NAPRTCS (North American Pediatric Renal Trials and Collaborative Studies) database revealed that 36.9% of children with chronic kidney disease present with severe growth impairment (height below the third percentile). Growth retardation is more pronounced in younger patients and even more severe in male subjects [1–3]. The growth retardation seen in patients with chronic kidney disease is also associated with increased morbidity and mortality. It has been demonstrated that each standard deviation decrease in height among pediatric patients who are on dialysis or after transplantation contributes to an increase in mortality by 14% [4].

The mechanisms leading to growth retardation in patients with CKD are thought to be multifactorial. Undernutrition with inadequate protein and calorie intake, water and electrolyte losses, vitamin D deficiency with secondary hyperparathyroidism and renal osteodystrophy, anemia, metabolic acidosis, as well as long-term therapy with glucocorticoids seem to be the main contributory factors [5–7]. However, even with optimal medical and nutritional therapy, children with CKD cannot approach normal height without growth hormone supplementation therapy [1]. This fact highlights the importance of detection of changes in the GH and insulin-like growth factor (IGF-1) axis to assess the growth failure.

Decreased appetite, which is often present in patients with CKD, is associated with decreased levels of ghrelin, a GH secretagogue and a potent orexigenic factor that stimulates feeding by interaction with hypothalamic nuclei [8]. However, GH levels are usually normal or even elevated in these patients [9, 10], suggesting that CKD is mainly a state of GH resistance and not GH deficiency. A number of factors leading to GH resistance have been proposed, and they include: (1) reduced GH receptors numbers in target tissues, (2) post-receptor defects in GH signaling [Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling], and (3) reduced levels of free IGF-1 [5]. GH binding to the growth hormone receptor (GHR) results in its dimerization and the auto-phosphorylation of the tyrosine kinase JAK, which then stimulates phosphorylation of STAT proteins. These phosphorylated proteins translocate into the nucleus and activate certain GH-regulated genes. In uremia, the density of GHR is low, while the JAK/STAT pathway is impaired, probably through suppression by cytokine signaling (SOCS) proteins [11–13].

GH actions are mostly mediated by IGF-1, which is mainly produced in the liver and acts as an anabolic hormone after binding to the IGF-1 receptor (IGF-1R) [14]. Only 1% of IGF-1 normally circulates in a free bioactive form, the rest being bound to IGF-binding proteins (IGFBPs) which can either potentiate (IGFBP3, IGFBP5) or inhibit (IGFBP1, IGFBP2, IGFBP4) its action. In patients with CKD, increased levels of inhibitory IGFBPs have been shown to be associated with the degree of renal dysfunction [15]. Levels of IGFBP3, which is the most

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abundant IGFBP and potentiates IGF-1 action, are normal but mainly fragmented, with the final result being reduced levels of free IGF-1 [16].

Furthermore, metabolic acidosis, which is a characteristic of patients with CKD, inhibits pituitary GH secretion [17] and down-regulates hepatic IGF-1 and GH receptor mRNA expression [18]. Many patients with CKD are also undergoing long-term therapy with steroids, which both affects pulsatile GH secretion and inhibits hepatic production of IGF-1 [19]. Moreover, increased gonadal steroids during puberty are key factors for pubertal growth spurt. Puberty seems to start 2 to 3 years later in children with CKD, which may further contribute to a dysfunctional GH axis and growth retardation [5].

Previous studies have demonstrated that treatment with recombinant human growth hormone (rhGH) is efficacious and safe in children with CKD, resulting in an increase of growth rate and improvement of final height. Nevertheless, the potential genetic target is not achieved in most cases [20, 21]. The defects in impaired phosphorylation of JAK2/STAT signaling and IGFBP concentrations after rhGH administration seem to persist, resulting in lower IGF-1 bioavailability than normally expected, even if sound clinical evidence is as yet missing [22]. A meta-analysis including 16 randomized controlled clinical trials suggested a dose of 28 IU/m^2 (0.35 mg/kg) per week as optimal [23], and this is the recommended and approved dose for treatment of growth failure in CKD [2, 24–26]. After more than two decades of experience with rhGH, a greater number of patients (~40%) now seem to almost reach their target adult height. The average increase is 4 cm every year, with the greatest gain observed during the first year of therapy [11, 26]. Many patients with chronic kidney disease undergo renal transplantation, but even then growth retardation may persist. Patients under the age of 6 years seem to benefit most, presenting a substantial increase in IGF-1 levels and catch-up growth [9].

As chronic kidney disease is mainly a state of GH resistance and not GH deficiency, future treatment strategies with recombinant human IGF-1 (rhIGF-1), a combination of rhGH and rhIGF-1, or recombinant human IGFBP displacers, may prove to be more effective and beneficial for both short- and long-term outcomes [5, 26]. Until then, early diagnosis and treatment of relevant derangements are important and can improve prognosis and the quality of life of these patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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