Pubertal Status in Children and Adolescents with End-Stage Renal Disease on Hemodialysis

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Abstract

the potential effects of renal dysfunctions and its related pathophysiological pathways especially hemodialysis on dysregulation of hormonal systema is expected leading naturally growth abnormalities and even delaying puberty in adolescents.

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Introduction:

Chronic kidney disease, height velocity is most affected during periods of rapid growth (i.e., the first 2 years of life and the pubertal age). In the pre-pubertal years, the appearance of secondary sexual characteristics is delayed and the growth rate is disproportionately decreased. The pubertal growth spurt is later than normal and its degree impaired, resulting in loss of growth potential and reduced final height. Over the last 20 years, although these basic principles remain, new concepts for improving pubertal development have been established (1).

Pubertal Status in End-Stage Renal Disease:

Pubertal delay was reported in more than half of the girls and one-third of the boys with end-stage renal disease (ESRD). Variable mechanisms were attributed to delayed puberty in these children including neuroendocrine impairment in the pituitary-gonadal axis, peripheral alterations due to uremia, gonadal damage and impaired regulation of gonadotropin secretion (2).

Pubertal development is frequently delayed or disordered in children with chronic renal failure. Both neuroendocrine and peripheral alterations due to uremia have been hypothesized to explain the impairment in the pituitary-gonadal axis (3).

Chronic renal failure (CRF) was found to be associated with gonadal damage and decreased testosterone and estradiol levels together with impaired regulation of gonadotropin secretion (4).

In pediatric patients with CRF, only a few studies have been performed to evaluate the status of the hypothalamo–pituitary–gonadal axis. Most of these deal with the endocrine changes that occur during adolescence. The problem is unsolved if in CRF hormonal alterations comparable to those of adult patients occur before the onset of puberty or not (5).

Sexual dysfunction is common in adolescents with ESRD. Disturbances of pubertal development are commonly encountered in adolescent patients with chronic renal failure (6).

Delayed puberty is also a common finding with CRF, half of the girls and one-third of the boys with CRF reach sexual maturity later than 95% of the normal population. The onset of puberty is usually delayed in adolescents with CKD. At least 50% of adolescents with ESRD enter puberty later than the normal range and achieve the pubertal milestones beyond the normal age range. Late puberty is observed both in children on dialysis and after renal transplantation. In the Cooperative Study for Pubertal Development in CKD, the onset of puberty was delayed by 2–2.5 years on average (7).

The start of genital maturation was delayed by 1.8 years in uremic and 2.5 years in transplanted boys. Full genital maturation was achieved with a delay of 2.2 and 3.2 years, respectively. Thus, once started, puberty appears to proceed at a normal rate. However, in individual patients, particularly on long-term dialysis, pubertal maturation may arrest for years. Almost half of the girls treated by

dialysis or renal transplantation fail to menstruate before the upper normal age limit of 15 years. Menarche even tends to occur later in transplanted than in dialyzed girls (8).

In El-Gamasy et al. (7) study, serum testosterone and estradiol levels were found significantly lower in patients than in controls. Low plasma testosterone and estradiol levels were reported in boys and girls with chronic renal failure.

The endocrine system plays an integral role in normal male sexual function supplying adequate penile blood flow and intact neural input for an erectile response. Disturbances in the pituitary-gonadal axis are induced by only moderate reductions in the glomerular filtration rate and progressively worsen as kidney failure progresses which are manifestations in men with chronic kidney disease, and unfortunately these disorders rarely normalize with initiation of hemodialysis or peritoneal dialysis and, in fact, often progress. By comparison, a well-functioning kidney transplant is much more likely to restore normal sexual activity, although some features of reproductive function may remain impaired (9).

In CKD the plasma concentrations of testosterone (T) and Estradiol (E2) are usually low or low normal, due to reduced synthesis and perhaps, increased metabolic clearance rate. In prepubertal children with predialytic renal failure, low total and free T and dihydrotestosterone (DHT) plasma concentrations have been reported. However, since the adrenal cortex is the major site of androgen production before puberty and specific adrenal androgens are also low in children with CKD. Low prepubertal plasma androgen levels do not provide evidence for gonadal damage before puberty. In pubertal patients, normal or slightly subnormal plasma Testosterone concentrations are observed. In late puberty, however, DHT concentrations are significantly reduced in children with CKD compared with healthy or post transplanted children. Impaired conversion of T to DHT due to decreased 5-reductase activity has been suggested (7).

In Estradiol the plasma concentrations in the low normal range are observed in females with CKD. In pubertal girls with CKD, estradiol plasma levels were normal or low when related to pubertal stage. An inverse correlation between serum creatinine levels and estradiol concentrations was found in patients with predialytic CKD (2).

Reproductive Pathophysiology in girls with Kidney Disease. The precise processes of hormone disruption in women with kidney disease are poorly understood. Women with kidney disease have demonstrated preserved basal levels of GnRH, LH, and FSH but are unable to secrete GnRH in a pulsatile manner that is required for ovulation. The downstream effects of this include lack of LH/FSH rise consequently blunting estradiol synthesis and secretion. With low levels of estradiol, girls are unable to reach a mid-cycle LH peak, which leads to anovulation. The etiology of GnRH inhibition remains ill-defined but is likely multifactorial from reduced clearance of leptin, prolactin, endorphins, and gonadotropins (10).

The main endocrine disorders in boy is Reduced testosterone concentration in CKD. The cause of hypogonadism in CKD is not fully understood. Both the synthesis of testosterone and its secretion are reduced with a decrease of renal function. In patients with CKD, the ability of testosterone binding and SHBG concentrations are normal, but the concentrations of free and total testosterone are reduced. Decreased testosterone concentrations are due to dysfunction of the hypothalamic-pituitary-gonadal axis. Inappropriate cyclic release of gonadotropin-releasing hormone (GnRH) by the hypothalamus leads to a loss of correct LH release by the pituitary gland and reduced testosterone synthesis. Low testosterone concentrations in CKD may be caused by the resistance to the action of LH at the Leydig cell level. Haemodialysis does not remove testosterone from the circulation (11).

Low testosterone concentrations in CKD are associated with sexual disorders such as decreased libido, erectile dysfunction, and inability to achieve orgasm. Other disturbances in CKD such as decreased muscle mass and mineral bone density, anaemia, All these derangements may also contribute to the changes of mood and to the development of depression in CKD patients (12).

The height gain achieved during the pubertal growth spurt is usually reduced. In a longitudinal analysis of the growth curves of 29 adolescents with various degrees of CKD, the growth spurt started with an average delay of 2.5 years. The degree of the delay was correlated with the duration of uremia. Although a distinct acceleration of growth during puberty occurred, the total pubertal height gain was reduced in both sexes to approximately 50% of normal maturing children.

This reduction was due to a marked suppression of the late prespurt height velocity, a subnormal peak height velocity, and a shortening of the pubertal growth period by 1 year in boys and 1.5 years in girls. Notably, the prolonged prepubertal growth phase, resulting from the delayed onset of the pubertal growth spurt (3).

Multiple factors can lead to impaired growth in CKD patients, and there are disturbances of the growth hormone/ Insulin-like growth factor 1 (GH/IGF1) axis in CKD. In these patients, the serum level of GH is expected to be normal or elevated, while total and free (bioactive) IGF1 may be decreased .During uremia, loss of normal balance between total IGF1 and Insulin-like growth factor binding protein 3 (IGFBP3) plays a significant role in growth failure in children with CKD (13).

Most children with CKD have short stature and are in the 3-10 percentile for height with a height velocity below the 25 percentile. If CKD with GFR <15 occur before the first year of birth, the risk of short stature would be higher. Patients with CKD demonstrate delayed or abnormal pubertal spurt due to direct toxic effects of uremia on gonadal hormones and endorgan resistance to sex steroids (14).

Growth impairment is a common problem in children with Chronic Kidney Disease (CKD). Approximately 40% of children with CKD have a reduced final height. Growth impairment affects school attendance, duration of hospitalization, adult height, and a higher risk of death (15).

Anemia is a major complication in children with chronic kidney disease (CKD). Anemia is an important risk factor for the development and progression of cardiovascular disease, including left ventricular hypertrophy. In addition, anemia negatively affects the quality of life of patients and their caregivers. The chronic inflammatory state in patients with CKD results in decreased erythropoiesis in the bone marrow, reduced production of erythropoietin (EPO) in the kidneys, and impaired iron absorption and mobilization due to increased production of hepcidin in the liver. Uremia, oxidative stress, and nutritional deficiencies also contribute to anemia in CKD (16).

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