

# Growth Velocity, Final Height and Bone Mineral Metabolism of Short Children Treated Long Term with Growth Hormone

Roberto Lanes\*

Unidad de Endocrinología Pediátrica, Hospital de Clínicas Caracas, Caracas, Venezuela



**Abstract:** Since human recombinant growth hormone (GH) became available a large number of short GH deficient and GH-sufficient children have been treated with growth hormone. Growth hormone deficient patients have been followed to final height and several studies have shown that even when treated with GH from very early on in life they tend to end up shorter than their target height. There is, however, a clear increase in their growth velocities particularly during the first 4-5 years of GH therapy so that patients end up with a height-SD score of approximately -0.8. Recent studies have demonstrated decreased bone mineral densities (BMD) in children with growth hormone deficiency, both by areal and volumetric analysis. Therapy with growth hormone clearly increases their BMD with an increase in bone formation markers, as will be reviewed in detail. Growth hormone therapy of non-growth hormone deficient short children has increased their growth velocity short term, particularly in girls with Turner's syndrome and in children with chronic renal insufficiency. Recent final height data by Rosenfeld *et al.* and by Swedish and Dutch groups have demonstrated a gain of 8-12 cm in girls with Turner's syndrome treated with GH or with a combination of GH and oxandrolone. Neely *et al.* and we have demonstrated that growth hormone treated prepubertal age girls and adolescents with Turner's syndrome have normal BMD and Shaw *et al.* has suggested that they have normal BMD despite GH or estrogen therapy. However, we found the BMD of a group of previously GH treated young women with Turner's syndrome on estrogen replacement to be decreased compared to both age and gender matched controls and to controls of the same weight and pubertal status. Growth hormone therapy increases the growth velocity and the final height of children with chronic renal insufficiency, particularly in prepubertal children treated with GH before dialysis. We have demonstrated how the BMD of these patients, which at baseline is low when compared to healthy age matched controls, but normal when compared to height and bone age matched controls, increases with growth hormone treatment significantly, moreso than in untreated uremic controls or in untreated healthy controls paired for height and bone age.

Short, slowly growing, non growth hormone deficient patients (idiopathic short stature) have been treated for prolonged periods of time with GH. We and others have demonstrated a clear increase in their growth velocity short term, but improvement of their final height remains unclear and controversial. After 4-8 years of GH treatment, Hintz *et al.* have found a 5-6 cm increase in final height compared to the predicted adult height before beginning therapy, but most patients did not reach their target heights. Other studies, however, have found no improvement in final height and Kawai *et al.* even suggests that GH therapy diminishes the final height of treated children due to an earlier puberty and a shorter pubertal growth spurt. We, have found decreased BMD in children with idiopathic short stature when compared to controls of their same height and bone age with a significant increase in BMD following 12 months of GH and with an increase in bone turnover as measured by bone formation and resorption markers. Recent short term studies in patients with hypophosphatemic rickets and osteogenesis imperfecta treated with rhGH have also yielded similar results which will be specified in the review. Some 10-20% of children born with intrauterine growth retardation (IUGR) end up short and we had already demonstrated 20 years ago how 2 years of GH therapy were capable of increasing their growth velocities significantly with an improvement of their height-SD scores. Recent studies mainly from Europe have corroborated this data long term, so that IUGR children have been shown by de Zegher *et al.* to increase their growth velocities and their height for age after 6 years of treatment, entering into the low normal centiles of their growth curves for age. Long term studies of these children to final height will be necessary to determine the usefulness and safety of this form of therapy.

Until recently, the supply of growth hormone was so limited that it was exclusively used to treat GH-deficient patients so that short, slowly

growing, GH-sufficient patients, many of which failed to reach their midparental target height, could not be treated. With the advent of the commercial application of recombinant DNA technology there is an unlimited supply of growth hormone, so that medical indications, costs and ethics are the only factors limiting the prescription of growth hormone. Multiple studies have evaluated the effect

\* Address correspondence to this author at the M-209, P.O. Box 020010; Miami, Florida 33102, U.S.A.; Phone and fax: 58-2-5749232; E-mail: lanes@telcel.net.ve

of short term GH treatment in both GH-deficient and GH-sufficient children, demonstrating that most of them had increase in growth rate, SD-scores for height and predicted adult heights after 1-3 years of therapy. Final height data are, however, only recently becoming available, particularly in many non GH-deficient short children treated with growth hormone, and results have been mixed and somewhat controversial. We will review this data, as well as the recent reports on the effects of growth hormone treatment on the bone mineral density and the bone markers of short children.

## GROWTH HORMONE DEFICIENCY

Successful treatment of growth hormone deficiency with human growth hormone was initially reported by Raben in 1958 [1] and by 1964 it was clear that GH stimulated linear growth in children with GH-deficiency. Studies from Britain, the United States, Canada and Germany reported a significant negative relationship between the linear growth response following GH therapy and chronological age, height, bone age and weight [2]. The minimal effective dose of human growth hormone extracted from the pituitary gland was found to be 0.03-0.06 IU/Kg/week by Frasier *et al.* [3]; the same dose of GH was found to be less effective in accelerating the growth velocity after 6-12 months of therapy, but Gertner *et al.* [4] demonstrated how renewed catch-up growth could be obtained with increased replacement doses of human growth hormone (from 0.1 U/Kg to 0.3 U/Kg three times weekly). However, while the only source of human GH was cadaver pituitaries, treatment efforts were limited by GH supply and treatment outcomes in terms of adult height were not satisfactory with 50% of treated patients failing to attain heights above the third percentile [5].

The introduction of GH, prepared by recombinant DNA techniques, has allowed for children to be treated with larger doses and in a continuous fashion until final height. Near adult height was recently determined by Blethen *et al.* [6] in 121 GH-deficient children who were prepubertal when they began treatment; GH was administered at a dose of 0.3 mg/Kg/week initially three times weekly and then daily. Adult height as a SD score was  $-0.7 \pm 1.2$ , significantly greater than the pretreatment height SD score of  $-3.1 \pm 1.2$ , the predicted adult height SD score of  $-2.2 \pm 1.2$  and the height SD score at the start of puberty ( $-1.9 \pm 1.3$ ). The etiology of GH-deficiency and the presence or absence of spontaneous puberty did not affect the outcome. Adult height in this study was positively

dependent on height and negatively dependent on age at the start of the study; statistically significant variables included duration of treatment with GH, age, and height at the start of GH and the growth rate during the first year of therapy.

So, as to assess the efficacy of GH therapy in GH-deficient children treated before the age of 3 years, Rappaport and collaborators [7] treated 49 children with isolated GH-deficiency or multiple pituitary hormone deficiency with daily injections of 0.6 IU/Kg/week of GH. The mean height SD score had increased from  $-3.6 \pm 1.0$  to  $-0.9 \pm 1.2$  after 4 years of treatment; during the fourth year the mean height gain of  $0.2 \pm 0.2$  SD was significant and after 5 years a plateau was reached with a height SD score  $-0.8 \pm 1.2$  SD. Although this value remained below normal for age indicating incomplete catch-up, only 16% of patients remained below  $-2$ SD for chronological age. Similar results have been reported in other studies, so that even in GH-deficient children, diagnosed quite late in life, results are satisfactory. Cacciari *et al.* [8] in GH-deficient children diagnosed at an age of  $12.2 \pm 1.7$  years reports a significant improvement in height-SDS from a baseline of  $-2.2$  to  $-1.3$  after at least 2 years of treatment with recombinant human growth hormone.

The capacity of combined treatment with growth hormone and gonadotropin releasing hormone analog (GnRH) to preserve the height potential of patients with GH deficiency and early puberty was recently evaluated by Adan *et al.* [9] and Cassorla *et al.* [10]. They later found a greater height gain in height prediction in patients treated with GH and GnRH than in patients treated with GH and placebo after 3 years of therapy (mean of  $14.0 \pm 1.6$  vs  $8.0 \pm 2.4$  cm;  $p < 0.05$ ) suggesting that delaying epiphyseal fusion with GnRH analog in pubertal GH-deficient children treated with GH increases height prediction and may increase final height compared to treatment with GH alone. Adan *et al.* concluded from their study that combination treatment in patients with GH-deficiency and early puberty leads to a normal adult height ( $-0.5 \pm 0.2$ SD), similar to predicted height at the onset of therapy but lower than target height.

Growth hormone influences not only skeletal growth and maturation but also bone turnover and mineral deposition and several recent studies have suggested that GH is probably also involved in the buildup and the maintenance of bone mass. In 1991, Zamboni *et al.* [11] reported that GH therapy for 6 months at a dose of 0.5 IU/Kg/ week administered subcutaneously 6 times per week

increased IGF-1 and osteocalcin levels, as well as the bone mineral content of growth hormone deficient children, but not reaching the values found in normal children of the same age. Saggese and collaborators [12] in 1993 treated 26 GH-deficient children with growth hormone (0.6 IU/Kg/week) for 12 months. Before therapy bone mineral density was reduced for chronological, statural and bone ages, as were the levels of osteocalcin, carboxyl-terminal propeptide of procollagen type I (PICP) and 1,25-dihydroxyvitamin D. During GH treatment, BMD significantly improved at 12 months, with a complete recovery in 46.2% of the children and an increase in osteocalcin, PICP, intact serum parathyroid and 1,25-dihydroxyvitamin D.

Saggese [13] further evaluated the effect of long term GH treatment on bone mass by treating 32 GH-deficient children aged 7.2-16.3 years with GH for a mean of  $48.2 \pm 13.2$  months and measuring radial and lumbar BMD by dual energy x-ray absorptiometry; results were corrected for bone age and lumbar BMD was corrected for the estimated vertebral volumes. Before treatment patients showed significantly reduced radial and lumbar BMD ( $-1.7 \pm 0.4$  and  $-1.5 \pm 0.5$  Z-score, respectively) which increased significantly with therapy, so that in patients, treated for the longest time, the BMD was 0.5 SD of age-matched mean levels. They concluded that GH plays an important role in the attainment of peak bone mass in children with GH-deficiency and suggested that GH treatment should be continued until the attainment of peak bone mass irrespective of the height was achieved.

Similar findings were reported by Boot *et al.* [14] after studying the effect of 2-3 years of GH-therapy in 40 GH-deficient children; volumetric BMD, calculated to correct for bone size increased during treatment, as did lean tissue mass and 1,25-dihydroxyvitamin D levels. Osteocalcin, PICP and the cross-linked telopeptide of collagen I did not differ from normal at baseline, but increased after 6 months, while fat mass SDS decreased during the first 6 months and remained stable thereafter.

Similar results have been reported in GH-deficient adults, [15-17] with a reduction of bone density at both distal and proximal sites, a decrease in osteocalcin and procollagen III levels, a significant cardiac impairment supported by a reduction of left ventricular mass index and left ventricular systolic function and an increase in fat mass percentage, before therapy. Low dose GH-treatment (70ug/Kg/week) normalized body composition, echocardiographic findings,

osteocalcin and procollagen III levels as well as proximal BMD, with an increase, though not to normal distal BMD.

## TURNER'S SYNDROME

Poor growth velocity and short stature are hallmarks of Turner's syndrome with final heights of 140-143 cm reported in the European and North-american literature. Conflicting reports on the GH secretion of patients with Turner's syndrome have been published. Several studies reported that a low GH response to provocative tests and diminished GH secretion as determined by 24 hour overnight sampling may contribute to the limited stature of these girls. While Zadik *et al.* [18] found an increase in the integrated GH concentration (IC) with age and progression of puberty in normal controls, he failed to find such an increase in girls with Turner's syndrome so that the IC-GH concentration was significantly lower in this group of patients, but normalized with estrogen replacement. However, Van Es *et al.* [19] and we [20] found normal spontaneous GH levels in prepubertal and pubertal age girls with Turner's syndrome when compared with controls. Decreased metabolic clearance of endogenous GH and specific alterations in the pulsatile mode of growth hormone secretion have also been reported in girls with Turner's syndrome [21]. IGF-1 levels have been found to be similar to those in bone age-matched, but lower than those in chronological age-matched controls. GH-binding protein levels have been reported to be elevated [22] and Zadik suggested a possible end organ resistance to IGF-1 in these patients [18].

As early as 1980 Rudman *et al.* [23] reported a synergistic effect between oxandrolone and GH in stimulating growth in Turner syndrome. Ross *et al.* [24] in 1986 concluded that 0.15 U/Kg of GH three times weekly stimulated short term growth in patients with Turner's syndrome and that same year Raiti and collaborators [25] and Rosenfeld *et al.* [26] using pituitary derived and methionyl human growth hormone, respectively, found similar growth promoting effects after 12 months of treatment. We [27] found the growth velocity of 12 prepubertal girls with Turner's syndrome to increase from  $3.5 \pm 0.4$  cm/yr to  $6.4 \pm 0.3$  and  $5.7 \pm 0.4$  cm/yr following 12 and 24 months of growth hormone therapy at a dose of 0.5IU/Kg/week.

The beneficial effect on height velocity increment of adding estrogen to the GH therapy was

small and even very low estrogen doses were shown to induce breast development at an early age and to accelerate bone maturation [22]. Recent studies have suggested that yearly increments of the growth hormone dose results in a better growth response during 4 years in girls with Turner's syndrome, so that a stepwise GH-dosing approach reduced the "waning" effect of the growth response after 4 years of treatment without undue bone maturation [28]. Irrespective of the GH dose used initiation of GH treatment at a younger age was shown to be beneficial when expressed as cm gained or as final height prediction.

Several recent studies have followed girls with Turner's syndrome treated with growth hormone for several years to final height. A final height of  $150.4 \pm 5.5$  cm,  $8.4 \pm 4.5$  cm taller than their mean projected adult height at enrollment in subjects receiving GH alone and of  $152.1 \pm 5.9$  cm,  $10.3 \pm 4.7$  cm taller than their mean adult projected height in patients receiving GH and oxandrolone, was reported by Rosenfeld, *et al.* [29]. A similar response has been noted by the Swedish group [30] with a net gain in height of 8.5 cm over the projected adult height and a mean final height of  $154.2 \pm 6.6$  cm using 0.1IU/Kg/day of growth hormone and 0.05 mg/Kg/day of oxandrolone; addition of 100 ng/Kg of ethinyl estradiol resulted in a net gain in height of only 3 cm with an increment in bone age of  $4.9 \pm 0.8$  years after 4 years of treatment.

However, studies by Van den Broeck [31] and Dacou-Voutetakis *et al.* [32] starting treatment at a relatively advanced age (>10 years) resulted in a modest mean gain of 3 and 2.1 cm, with wide inter-individual variation. Several authors have suggested that starting GH therapy at an early age, as soon as the growth velocity starts decreasing and girls with Turner's syndrome start falling of their growth curves would be beneficial, as a better final height may be attained and estrogen replacement could be initiated earlier. However, Joss *et al.* [33] found that starting growth promoting therapy early may not be beneficial, as in many girls with a Turner-specific bone age below 9 years at the onset of therapy, the increase in height did not outweigh the advancement in bone age.

As to the bone mineral status of girls and adolescents with Turner syndrome, Ross *et al.* [34] in 1991 evaluated the bone mineral content of the wrist and lumbar spine of seventy eight prepubertal girls (4-13 years old) using both single and dual photon absorptiometry and found them to have normal bone density for height age, but significantly decreased bone density of the wrist for

chronological age, bone age and BMI, with an increased fracture rate of the wrist. Mora *et al.* [35] found radial bone mineral content values to be below the 95% normal confidence interval in 44 of 49 untreated patients age  $10.8 \pm 3.5$  years. In 9 girls with Turner's syndrome on growth hormone therapy for 3.2 years we [27] found normal bone mineral densities when compared to healthy controls paired for height, bone age, weight and BMI ( $0.739 \pm 0.05$  and  $0.791 \pm 0.04$  g/cm<sup>2</sup> for femoral and lumbar spine BMD in Turner patients vs  $0.750 \pm 0.05$  and  $0.699 \pm 0.02$  g/cm<sup>2</sup> in the controls). Similar results were reported in growth hormone treated adolescents by Neely *et al.* [36] who concluded that Turner syndrome adolescents receiving growth hormone were not osteopenic. Shaw *et al.* [37] recently concluded after following 18 girls aged 4-17 years over a period of 2.5 years that there is little evidence of reduced bone mineral density in girls with Turner's syndrome, regardless of whether they were untreated or treated with growth hormone or estrogens.

Osteoporosis is considered a common complication of Turner syndrome in the adult and the exact cause of the decreased mineralization is unknown. It seems possible that the lifelong estrogen deficiency characteristic of Turner syndrome might be the cause of the osteopenia. Davies *et al.* [38] found vertebral BMD in women with Turner syndrome to be similar to that of other causes of primary amenorrhea and considered osteopenia not to be an intrinsic feature specific to this disorder, but rather a result of extreme estrogen deprivation. Mora *et al.* [35] evaluated the effect of beginning estrogen replacement early in 16 girls who were started on estrogens before the age of 11 years and found that although still deficient compared to controls, early treated subjects had better mineralization; they then followed 9 of these patients for 3.2 years during replacement therapy and although their bone mineral content improved it did not normalize.

We [39] studied 8 of our original patients who had been found to have normal bone densities as prepubertal girls on growth hormone therapy, now as young adults having reached their final height and on estrogen replacement for over 4 years; despite the 6 year time and almost 19 cm height difference between the 2 studies their BMD had not changed and was decreased compared to both age and gender or weight and pubertal status paired controls. They were also found to have decreased serum concentrations of the bone formation marker PICP and elevated levels of the bone resorption marker ICTP, so that they did not reach their peak

bone mass despite long term estrogen replacement. Controlled studies using estrogen or placebo will be necessary to determine the exact role of estrogens on the bone mineralization of these girls.

## IDIOPATHIC SHORT STATURE

This is a group of children who are very short, are GH sufficient as determined by provocative testing and are growing at a subnormal velocity for their age.

Several studies have focused on possible disturbances in the neuroendocrine regulation of episodic GH release of these children, but Veldhuis *et al.* [40] reported that the overall dynamics of GH secretion and clearance in boys with idiopathic short stature (ISS) could not be distinguished from physiological patterns observed in prepubertal boys of normal height. One possible explanation for the growth failure of children with ISS is a reduced peripheral responsiveness to GH; in a recent study [41] in 573 ISS children 90% had growth hormone binding protein (GHBP) below the age and sex adjusted mean for controls and 20% had GHBP concentrations below the normal range. Patients with ISS and low GHBP had lower standardized levels of insulin-like growth factor 1 and higher mean 12 hour GH levels compared with those with normal GHBP levels, suggesting partial GH insensitivity.

The increasing availability of growth hormone has made it possible to conduct clinical trials on a large variety of short children who are growing poorly and are not GH deficient. As early as 1983 and 1987 Van Vliet *et al.* [42] and Gertner *et al.* [43] demonstrated how human growth hormone administered at a dose comparable to that used for the treatment of hypopituitarism increased the growth velocity of some short children without growth hormone deficiency. A multicenter randomized 1 year trial of human recombinant GH treatment at a dose of 0.1 mg/Kg/three times a week carried out in 1989 in 121 children with ISS reported a significant increase in mean growth rate from  $4.6 \pm 1.1$  cm/yr to  $7.5 \pm 1.2$  cm/yr, whereas the growth rate of untreated children did not change significantly; they concluded that children who have significant short stature and slow growth may benefit from a trial of growth hormone therapy [44]. However, that same year Wit *et al.* [45] in a 2 year study in which 30 short, slowly growing children with normal plasma growth hormone response to standard provocation tests were

randomly assigned to either a treatment or a control group, concluded that although GH therapy appeared to be safe and efficacious in increasing growth velocity, its efficacy in terms of increasing final height remained uncertain as treatment resulted in an unchanged height standard deviation score for bone age and ambiguous results on final height prediction. In our experience in 32 prepubertal children with ISS treated with GH hormone at a dose of 0.1 IU/Kg/day for 2 years the height velocity increased from  $3.8 \pm 0.9$  cm/yr to  $7.3 \pm 1.3$  and  $7.1 \pm 0.9$  cm/yr at 12 and 24 months, while H-SD scores decreased from  $-2.4 \pm 0.4$  to  $-1.8 \pm 0.5$ ; predicted adult height changed from  $160.2 \pm 9.8$  to  $164.7.9$  cm during this period [46].

Studies evaluating the final height of children with ISS treated long term with GH have yielded conflicting results. Loche *et al.* [47] in 1994 reported on the effect of GH treatment (1.0 IU/Kg/week) for 4-10 years in 15 prepubertal non GH-deficient short children, concluding that GH treatment did not increase their final height over target height. Hintz *et al.* [48] followed 80 ISS patients to final height after treatment with 0.3 mg/kg/week of GH for 2-10 years and found that their mean standard-deviation score for height increased from -2.7 to -1.4 with a mean difference between predicted adult height before therapy and achieved final height of  $5.0 \pm 5.1$  cm in males and  $5.9 \pm 5.2$  cm in females; they concluded that the long term administration of growth hormone to children with ISS can increase adult height to a level above the predicted adult height and above the adult height of untreated historical controls. Similar findings were recently reported by Buchlis *et al.* [49] who found that the mean height gain of 6.8 cm in girls and 3 cm in boys, though modest and variable provided significantly better height outcomes for the majority of children with ISS.

Rekers-Mombarg *et al.* [50] in a recent study found increasing doses of GH for 4 years (3 IU/m<sup>2</sup>/day or 4.5 IU/m<sup>2</sup>/day equivalent to 0.2 and 0.3 mg/Kg/week) to increase the H-SD score for age by a mean of 2.5 (ISS standards) or 1.2 (British standards) but with an increase of bone age of 4.8 years during this period so that any effect on final height was expected to be modest. Kawai *et al.* [51] even suggested recently that there is a unfavorable effect of GH therapy on the final height of boys with short stature not caused by GH deficiency, as puberty begins earlier and the pubertal spurt is shortened, so that the final height of children treated for 4.2 years was  $154.2 \pm 4.2$  cm, while the final height of untreated patients was  $162.0 \pm 5.4$  cm. Lesage *et al.* [52] recently

administered large GH doses (0.3 U/Kg/day) for 2 years to 10 prepubertal children before puberty and found it to promote sustained acceleration of growth rate allowing near normalization of height. A significant increase of insulin secretion induced by exogenous GH which continued to progress during the 2 years of treatment was noted; this hyperinsulinemia and relative insulin resistance was reversible after GH therapy was discontinued and apparently had no effect on plasma lipid substrate.

In an attempt to increase the final height of short non growth hormone deficient children who enter into normally timed puberty, several groups have administered a GnRH analog to slow pubertal progression while attempting to increase the growth velocity often decreased by the use of the analog with the simultaneous use of growth hormone. While Saggese *et al.* [53] found a beneficial effect of combined therapy on predicted final height, both Balducci *et al.* [54] and ourselves [55] have found no improvement in final height over predicted height or over target height after 2-3 years of recombinant human growth hormone and GnRH analog treatment. Longer studies in a larger population of patients and with appropriate controls will be needed in order to clarify this issue.

There is no clear way of predicting which children with ISS will respond to exogenous GH therapy by increasing their growth velocity. Responses to therapy could not be reliably predicted from baseline anthropometric variables, plasma insulin- like growth factor 1 or growth hormone levels. Young children, with a greater delay in bone age and a slower pretreatment growth rate may, however, respond better to GH therapy.

The effect of GH treatment on the bone mineral status of ISS children has to our knowledge only been evaluated in 2 studies. Ogle *et al.* [56] in 1994 followed 11 short children without GH deficiency treated with GH at a dose of  $0.5 \pm 0.08$  IU/Kg/week for 24 weeks. They found mean L2-L4 BMD to be essentially unchanged at 8 weeks and to increase by a mean of  $0.03$  g/cm<sup>2</sup> at 24 weeks, while the expected increase in lumbar spine BMD was  $0.02$  g/cm<sup>2</sup> over 24 weeks. An increase rate of bone turnover was suggested by the rise in hydroxyproline excretion (bone resorption) and the trend towards an increase in alkaline phosphatase levels (bone formation). We, [57] recently evaluated 14 prepubertal non growth hormone deficient short children who were growing poorly and found them to increase their growth velocity significantly from  $3.9 \pm 1.1$  to  $8.1 \pm 1.9$  cm/yr following 1 year of GH treatment with and

improvement in height-SDS from  $-2.2 \pm 0.5$  to  $-1.8 \pm 0.5$ . Their lumbar spine BMD was significantly reduced before therapy, when compared to a group of healthy controls paired for bone age and height ( $0.645 \pm 0.09$  in ISS patients vs  $0.730 \pm 0.08$  g/cm<sup>2</sup> in controls) and increased after 1 year of therapy reaching levels similar to those of the control group followed without therapy for the same period ( $0.808 \pm 0.4$  vs  $0.760 \pm 0.08$  g/cm<sup>2</sup>). Serum concentrations of PICP, a bone formation marker, were similar to controls before therapy and increased significantly during GH therapy, while serum levels of ICTP, a bone resorption marker, were increased before therapy in children with ISS compared to controls and increased further with treatment. We [57] concluded from this study that short term GH treatment increases the growth velocity and the bone mineral density of short, slowly growing non growth hormone children, but that long term studies in a larger population were needed to determine the benefits of this form of therapy on the final height and the peak bone mass of these patients.

## UREMIA

Growth retardation associated with chronic renal insufficiency (CRI) has been identified for many years. The etiology of the growth retardation in children with CRI is considered to be multifactorial with age at onset, primary renal disease, fluid and electrolyte abnormalities, acidosis, renal osteodystrophy, inadequate caloric intake and alterations of growth factors, all implicated [58].

In CRI endogenous GH levels are elevated as a result of reduced renal clearance; despite elevated GH concentrations the IGF-1 secretory rate by the liver is reduced possibly due to a reduction in the number of hepatic GH receptors, with a reduction in the number of the GH binding protein levels (which represents the extracellular domain of the GH receptor). Additionally, due to a reduced clearance the insulin growth factor binding proteins (IGFBP's) are elevated, primarily IGFBP2 and IGFBP3, with a reduction of the available free IGF levels [58].

Exogenous growth hormone has been found to increase the IGF-1 levels to a greater extent that it increases the IGFBP concentrations, thereby increasing the free IGF levels and enhancing bone growth. Melhs and Ritz in 1983 [59] demonstrated how recombinant human growth hormone improved the growth velocity of uremic rats and initial studies by Koch *et al.* [60] in 5 boys with

CRI demonstrated how 1 year of growth hormone accelerated the growth velocity with an improvement of height for age. In 1991 Fine *et al.* [61] reported that 9 boys with growth retardation consequent to renal failure treated for 12-36 months with GH prior to dialysis demonstrated a significant improvement in growth velocity achieving a height-SD score of less than -2.0 or above the 5th percentile in the growth curve; the mean calculated creatinine clearance did not decrease significantly during the 36 months of therapy and there was no exacerbation of the glucose intolerance of uremia following GH administration.

In a placebo-controlled double blind, cross-over trial in which 6 months of subcutaneous GH injections were either preceded or followed by 6 months of placebo injection, Hokken-Koelega *et al.* [62] found 16 prepubertal uremic children to increase their growth velocity so that the GH-induced height-velocity increase exceeded that of placebo by 2.9 cm per 6 months without affecting bone maturation. IGF-1 and IGFBP3 levels increased significantly, though the change in IGFBP3 concentrations was significantly smaller than the GH-induced IGF-1 increase. Fructosamine, lipid and parathyroid concentrations remained constant and renal function deterioration did not accelerate. We [63], treated 13 prepubertal children prior to dialysis with 1 IU/Kg/week of GH for 2 years with an increase of their growth velocity from  $4.3 \pm 2.1$  to  $9.1 \pm 2.0$  cm/yr at 12 months and  $8.6 \pm 1.8$  cm/yr at 24 months of treatment. Mean height-SDS improved from  $-3.5 \pm 1.0$  to  $-2.6 \pm 1.3$  and  $-2.0 \pm 1.0$  during this period and mean serum creatinine and blood urea nitrogen levels remained stable; however, 2 subjects had a significant deterioration of their renal function at 6 and 9 months of GH requiring discontinuing treatment.

To determine the usefulness of GH treatment among children with renal allografts, Van Drop *et al.* [64] treated 9 children <16 years of age with poor growth with an improvement of growth velocity from  $1.9 \pm 1.1$  to  $7.2 \pm 1.8$  cm/yr without acceleration of skeletal or pubertal maturation. During treatment serum creatinine concentrations rose and creatinine clearance decreased, but then remained stable; they concluded that although GH treatment may be useful as adjunctive therapy for increasing growth rates in selected children with renal allografts, creatinine concentrations should be monitored closely during treatment in these children.

Hokken-Koelega and collaborators [65] found GH therapy at a dose of 4 IU/m<sup>2</sup> to induce and maintain better catch-up growth during 2.5 years than a smaller dose of 2 IU/m<sup>2</sup> without evidence of adverse effects and suggested that this higher dose may be beneficial for children with severe growth retardation secondary to uremia. Fine *et al.* [66] evaluated the impact of a pause in GH treatment once target height (50th percentile for mid-parental height) was reached and the impact of GH cessation after successful renal transplant; he found that maintenance of height SDS was achieved in 27% and a marked reduction in growth velocity, requiring reinstatement of GH therapy was noted in 73% of uremic patients prior to transplant and that discontinuing GH treatment at the time of transplantation did not result in substantive post-transplantation "catch down" growth. In our experience [63] discontinuing GH after 2 years of therapy in prepubertal children with uremia prior to dialysis, resulted in a significant reduction of their growth velocity and loss of height for age. Long term (>5 years) therapy with GH has demonstrated that although the magnitude of improvement in growth velocity was not sustained at the same level obtained during the initial years, continued improvement in standardized height has been noted during long term treatment [66].

As to side effects, although no significant change in fasting or 2 hour post-prandial glucose was noted with GH therapy, fasting and 2 hour post-prandial insulin levels were significantly increased compared to baseline at 24, 48 and 60 months following initiation of GH treatment, with a slight increase in HbA1c but no clinical consequences. The risk of slipped femoral epiphyses and avascular necrosis in children with uremia receiving GH remains equivocal, so that it is advisable to obtain radiographs of the osseous structures prior to initiating GH treatment and to repeat the radiographic studies if clinical symptoms appear [58]. Several episodes of an acute rise in the serum creatinine level shortly after initiation of GH and of an acute rejection episode or allograft dysfunction during therapy have been reported, but this incidence does not seem to be increased compared to that seen prior to therapy.

Only 2 reports have evaluated the BMD of children with CRI prior to transplantation, at baseline and during growth hormone treatment. We [63,67] treated 13 prepubertal children for 2 years with GH and found bone mineral content as well as bone mineral density in the lumbar spine and in the femoral neck to be significantly reduced in our patients compared to healthy controls paired for

chronological age and similar to those of a healthy control group paired for bone and height. Both these parameters increased significantly during GH treatment so that at 12 months our patients had values similar those seen in a healthy control population paired to our patients for chronological age. While trabecular BMD did not change in a group of untreated uremic controls during follow up, the percent of BMD change in trabecular bone in our uremic patients during 24 months of therapy was very significant ( $p < 0.001$ ) and larger to that noted in a group of healthy controls paired for bone age and height during 24 months of follow up.

Boot *et al.* [68] also found baseline mean lumbar spine and total body BMD of uremic patients not significantly different from normal and these parameters did not change during GH treatment; height-SDS and biochemical markers of both bone formation and bone resorption increased significantly during GH treatment. However, their uremic patients treated with GH had a tendency to increase lumbar spine BMD, with a tendency towards a decrease in BMD in uremic untreated patients. It is difficult to compare the results of both these studies, as our uremic patients were much shorter and were growing slower than theirs and as different methods were used to evaluate BMD; additionally bone densities in the study by Boot are compared to healthy controls paired for chronological age and not controls paired for height or bone age.

As to the effect of renal transplantation on the BMD of uremic children, Feber and collaborators [69] reported a significant decrease of BMD during the first 6 months after surgery, despite normal graft function and improvement in growth; all these patients were receiving a combination of immunosuppressive therapy which may have contributed to these changes. In conclusion, longer studies in a much larger number of patients will be necessary to clarify the effects of GH on the bone mineral status of children with CRI.

## **INTRAUTERINE GROWTH RETARDATION**

In approximately one fifth of significantly short children, postnatal growth failure is believed to be related to intrauterine growth retardation (IUGR). GH has been detected in the fetal circulation by 10 weeks of gestation, rises significantly by midgestation and decreases subsequently by term birth. This GH secretion is pulsatile and is under hypothalamic control through GHRH and

somatostatin secretion. The intense GH secretion towards mid-gestation is thought to be related to an earlier responsiveness to GHRH compared to GH-inhibiting factors; the gradual decrease in fetal GH secretion towards birth may be due to inhibition by circulating IGF-1. During the first postnatal days hypersomatotropinemia is seen with a hyperresponse to GHRH and increased circulating levels of IGF-1; this intense activity of the somatotrophic axis is probably one of the mechanisms driving the postnatal catch-up growth that occurs in most these patients. Approximately 85-90% of term newborns with a birth weight or length below -2 SDS display sufficient catch-up growth to attain a height above -2SDS by 2 years of age [70].

The prevalence of GH insufficiency seems to be increased in children with IUGR. This insufficiency may consist of classical GH deficiency or of subtle abnormalities in GH secretion as reported by Boguszewski *et al.* [71] in 106 patients who were found to secrete less GH than healthy children of short stature born with a height and weight appropriate for gestational age. They appear to have low normal circulating IGF-1, suggesting an altered sensitivity to the growth-promoting actions of IGF's and their binding proteins.

As early as 1971 and 1972, Tanner *et al.* [72] and Grunt *et al.* [73] treated some IUGR patients with human growth hormone with disappointing results possibly due to the low frequency of administration. Foley *et al.* [74] in 1974 using growth hormone substitution doses found GH to be an effective therapeutic agent in some young patients who have intrauterine growth retardation. In 1979 we [75] reported on our experience treating 19 prepubertal patients with IUGR. Growth rates were  $4.8 \pm 1.4$  cm/yr before therapy,  $7.6 \pm 2.3$  and  $5.9 \pm 1.4$  cm/yr in the first and second year of treatment. Height-SD scores increased from  $-4.5 \pm 1.1$  to  $-3.9 \pm 1.6$  ( $p < 0.05$ ) compared to a control group of untreated IUGR children who were  $-4.4 \pm 1.2$  height-SDS before and  $-4.2 \pm 1.3$  after follow up (NS).

Attempts to treat this group of patients with higher doses of growth hormone began once recombinant human growth hormone became available. In 1994 Chatelain *et al.* [76] reported on their experience treating 95 short prepubertal children with non-GH deficient IUGR in a double blind, controlled study comparing the effects of placebo or two doses of GH (0.4 or 1.2 IU/Kg/week). A significant GH dose-dependent

growth acceleration was noted with a mean height gain of  $0.66 \pm 0.07$  SD in the low dose group and of  $1.25 \pm 0.07$  in the subjects receiving the high dose, but with a faster bone maturation progression in this latter group ( $30.2 \pm 1.5$  months over 24 months of treatment). High dose GH administration over two years was reported to be effective by de Zegher and collaborators [77] with a near doubling of growth velocity and weight gain and a mean height increment of more than 2 SDS; the GH-induced catch-up was associated with elevated serum concentrations of insulin, insulin-like growth factor 1 and insulin-like growth factor binding protein.

In a meta analysis of four independent European randomized, controlled, multicenter studies in 244 patients treated for 2 years with GH, de Zegher *et al.* [78] conclude that GH administration is a promising therapy for normalizing short stature and low weight after insufficient catch-up growth in children born small for gestational age. In 1998 Boguszewski [79] reported on the findings of the Nordic multicenter trial which demonstrated that within 3 years of GH given at a dose of 0.2 IU/kg/day the target height of IUGR patients can be achieved and de Zegher [80] very recently concluded, after a 6 year follow up of his patients, that most patients can be brought to the normal centiles for age after 2-3 years of GH therapy and that a good percentage of them will then follow this percentile into puberty; for the subjects falling of the curve a second treatment course would be suggested. It remains to be seen if the final height of these patients improves as follow up continues during their pubertal development and growth spurt. Results from France in 70 IUGR children treated with lower GH dosages ( $0.4 \pm 0.1$  U/Kg/week) for  $4.6 \pm 2.5$  years showed a very limited effect on final height [81].

Side effects with the high dose use of GH include an increase in insulin levels without negative effects on fasting glucose levels or glycosylated hemoglobin. As insulin resistance has been reported in small for gestational age children, fasting insulin and glycosylated hemoglobin concentrations need to be carefully monitored during and after GH treatment in this group of patients. Although high dose GH induces an acceleration of bone maturation, a gain in height-SD scores for bone age has also been shown. As to predictors of the growth response to GH in this group of children low baseline IGF-1 and IGFBP3 levels, low integrated GH concentrations and slow growth velocities before therapy appear to be useful in predicting response to GH [82,83].

To our knowledge, there is no information available in the literature as to the effects of GH on the bone mineral density and on bone markers of children with intrauterine growth retardation.

## OTHER ENTITIES

Renal hypophosphatemic rickets is characterized by growth failure with disproportionate short stature, owing mainly to bowing of the lower limbs associated with skeletal deformities and reduced bone mineralization. Although combined treatment with high doses of inorganic oral phosphate salts and the more biologically active form of vitamin D have resulted in a rise of serum phosphate concentrations and in the healing of rickets, it does not always promote linear growth so that many children do not grow appropriately.

GH administration stimulates renal phosphate reabsorption and  $1,25(\text{OH})_2\text{D}$  production, but data on the therapeutic effects of GH in patients with hypophosphatemic rickets are still limited. In 1990 we [84] demonstrated how 14 months of recombinant human growth hormone therapy resulted in an increase of the growth velocity, predicted adult height and serum phosphate levels of a prepubertal boy with hypophosphatemic rickets already on vitamin D and phosphate salts. These results were then confirmed by Wilson *et al.* [85] who treated 9 children with GH alone for 4 weeks and with combined therapy for 24 weeks.

Saggese *et al.* [86] in 1995 reported on their experience in treating 12 prepubertal children with hypophosphatemic rickets, 6 of whom received 0.6 IU/Kg/ week of GH combined with conventional treatment, while the remaining 6 received conventional therapy alone; both were followed for 3 years. Height SD-scores, growth velocity SD-scores, predicted adult height, serum values of phosphate, bone alkaline phosphatase isoenzyme, osteocalcin, propeptides of type I and type III procollagen, intact parathyroid hormone,  $1,25$ -dihydroxyvitamin D and TmpP/GRF, as well as radial bone density improved significantly only in patients treated with GH and conventional therapy, without any side effects. They concluded that long term GH administration may benefit growth, phosphate retention and bone density in this group of patients, but long term follow up will be needed to determine if final height and bone mass are improved by this form of therapy.

Not all short children with hypophosphatemic rickets seem to benefit from GH treatment.

Cameron *et al.* [87] very recently reported treating 5 prepubertal children who were well controlled on oral phosphate and calcitriol, with GH at a dose of 0.03 mg/Kg/day. After 12 months of therapy no significant biochemical or radiological benefits were observed, without an increase in the growth velocity SD score and no significant decreases in mean height SD or growth velocity SD scores were noted when GH therapy was ceased.

Osteogenesis imperfecta is a heritable disorder of connective tissue with bone fragility as its main feature. Severe growth deficiency is always present in type II and is frequently seen in moderate type IV and mild type I osteogenesis imperfecta. The growth hormone and somatomedin axis was evaluated by Marini and collaborators [88] in nine children with osteogenesis imperfecta, demonstrating a decreased GH responsiveness to growth hormone releasing hormone and a blunted somatomedin response to exogenous GH; mean 24-hour GH values and mean peak growth hormone response to provocative agents were within the normal range.

Antoniazzi *et al.* [89] treated 7 prepubertal children with osteogenesis imperfecta with 0.6 IU/Kg/week of GH for 12 months. Linear growth velocity in treated patients increased significantly from  $3.57 \pm 0.55$  to  $6.04 \pm 0.69$  cm/year, while bone age did not advance faster than chronological age. Serum levels of osteocalcin and of the carboxyterminal propeptide of type I procollagen were significantly reduced before therapy and rose after 12 months of GH. Before therapy, patients with osteogenesis imperfecta had lower anteroposterior, lateral, and calculated true bone density than the normal population of the same sex compared for both age and height, and after GH bone density increased significantly in all these areas; fracture risk was not increased in these patients. Again, long term studies, in a larger population of patients and in a controlled environment will be needed before GH treatment can be recommended for the treatment of children with osteogenesis imperfecta.

## ABBREVIATIONS

GH	=	Growth Hormone
BMD	=	Bone mineral density
ISS	=	Idiopathic short stature
IUGR	=	Intrauterine growth retardation
CRI	=	Chronic renal insufficiency

PICP = Carboxy-terminal propeptide of type 1 collagen

ICTP = Carboxy-terminal cross linked telopeptide of type 1 collagen

## REFERENCES

- [1] Raben MS. Treatment of a pituitary dwarf with human growth hormone. (1958) *J. Clin. Endocrinol. Metab.* **18**, 901.
- [2] Frasier SD. Human pituitary growth hormone (hGH) therapy in growth hormone deficiency. (1983) *J. Clin. Endocrinol. Metab.* **4**, 155-170.
- [3] Frasier SD, Aceto T, Hayles AB and Mikity VG. Collaborative study of the effects of human growth hormone in growth hormone deficiency, IV. Treatment with low doses of human growth hormone based on body weight. (1977) *J. Clin. Endocrinol. Metab.* **44**, 22-31.
- [4] Gertner JM, Tamborlane WV, Gianfredi SP and Genel M. Renewed catch-up growth with increased replacement doses of human growth hormone. (1987) *J. Pediatr.* **110**, 425-429.
- [5] Dean HJ and Friesen HG. Long-term growth of children with growth hormone deficiency and hypoglycemia. (1989) *J. Pediatr.* **115**, 597-603.
- [6] Blethen SL, Baptista J, Kuntze J, Foley T, LaFranchi S and Johanson A. Adult height in growth hormone (GH)-deficient children treated with biosynthetic GH. (1997) *J. Clin. Endocrinol. Metab.* **82**, 418-420.
- [7] Rappaport R, Mugnier E, Limoni C, Crosnier H, Czernichow P, Leger J, *et al.* A 5 year prospective study of growth hormone (GH) deficient children treated with GH before the age of 3 years. (1997) *J. Clin. Endocrinol. Metab.* **82**, 452-456.
- [8] Cacciari E, Cicognani A, Pirazzoli P, Zucchini S, Salardi S, Balsamo A, *et al.* Final height of patients treated for isolated GH deficiency, examination of 83 patients. (1997) *Europ. J. Endocrinol.* **137**, 53-60.
- [9] Adan L, Souberbielle JC, Zucker JM, Pierre-Kahn A, Kalifa C and Brauner R. Adult height in 24 patients treated for growth hormone deficiency and early puberty. (1997) *J. Clin. Endocrinol. Metab.* **82**, 229-233.
- [10] Cassorla F, Mericq V, Eggers M, Avila A, Garcia C, Fuentes A, Rose SR and Cutler GB. Effects of luteinizing hormone-releasing hormone analog-induced pubertal delay in growth hormone (GH) deficient children treated with GH, preliminary results. (1997) *J. Clin. Endocrinol. Metab.* **82**, 3989-3992.
- [11] Zamboni G, Antoniazzi F, Radetti G, Musumeci C and Tato L. Effects of two different regimens of recombinant human growth hormone therapy on the bone mineral density of patients with growth hormone deficiency. (1991) *J. Pediatr.* **119**, 483-485.

- [12] Saggese G, Baroncelli GI, Bertelloni S, Cinquanta L and Di Nero G. Effects of long-term treatment with growth hormone on bone mineral metabolism in children with growth hormone deficiency. (1993) *J. Pediatr.* **122**, 37-45.
- [13] Saggese G, Baroncelli GI, Bertelloni S and Barsanti S. The effects of long-term growth hormone treatment on bone mineral density in children with GH deficiency. Role of GH in the attainment of peak bone mass. (1996) *J. Clin. Endocrinol. Metab.* **81**, 3077-3083.
- [14] Boot AM, Engels MAMJ, Boerma GJM, Krenning EP, de Muinck Keizer-Schrama SMPF. Changes in bone mineral density, body composition and lipid metabolism during growth hormone treatment in children with GH-deficiency. (1997) *J. Clin. Endocrinol. Metab.* **82**, 2423-2428.
- [15] Baroncelli GI, Bertelloni S, Ceccarelli C and Saggese G. Measurement of volumetric bone mineral density accurately determines degree of lumbar undermineralization in children with growth hormone deficiency. (1998) *J. Clin. Endocrinol. Metab.* **83**, 3150-3154.
- [16] Amato G, Izzo G, La Montagna G and Bellastella A. Low dose recombinant human growth hormone normalizes bone metabolism and cortical bone density and improves trabecular bone density in growth hormone deficient adults without causing adverse effects. *Clin. Endocrinol.* **45**, 27-32 (1996).
- [17] Johannsson G, Rosen T, Bosaeus I, Sjostrom L and Bengtsson BA. Two years of growth hormone treatment increases bone mineral content and density in hypopituitary patients with adult-onset GH deficiency. (1996) *J. Clin. Endocrinol. Metab.* **81**, 2865-2873.
- [18] Zadik Z, Landau H, Chen M, Altman Y and Lieberman E. Assessment of growth hormone axis in Turner's syndrome using 24-hour integrated concentrations of GH, insulin-like growth factor 1, plasma GH-binding activity, GH binding to IM9 cells and GH response to pharmacological stimulation. (1992) *J. Clin. Endocrinol. Metab.* **75**, 412-416.
- [19] Van Es, Massarano AA, Wit JM. 24 hour growth hormone secretion in Turner syndrome. In Ranke MB, Rosenfeld RG, eds. Turner syndrome, growth promoting therapies. Amsterdam, Elsevier, 29-33.
- [20] Lanes R, Brito S, Suniaga M, Moncada G and Borges M. Growth hormone secretion in pubertal age patients with Turner's syndrome. (1992) *J. Clin. Endocrinol. Metab.* **71**, 770-772.
- [21] Veldhuis JD, Sotos JF, Sherman BM. Decreased metabolic clearance of endogenous growth hormone and specific alterations in the pulsatile mode of growth hormone secretion occur in prepubertal girls with Turner's syndrome. (1991) *J. Clin. Endocrinol. Metab.* **73**, 1073-1080.
- [22] Massa G, Bouillon R and Vanderschueren-Lodeweyckx. Serum growth hormone-binding protein and insulin-like growth factor 1 levels in Turner's syndrome before and during treatment with recombinant human GH and estradiol. (1992) *J. Clin. Endocrinol. Metab.* **75**, 1298-1302.
- [23] Rudman D, Goldsmith M, Kutner M and Blackston D. Effect of growth hormone and oxandrolone singly or together on growth rate in girls with X chromosome abnormalities. (1980) *J. Pediatr.* **96**, 132-135.
- [24] Ross JL, Myerson L, Skerda M, Cassorla F, Loriaux DL and Cutler GB. Growth response relationship between growth hormone dose and short term growth in patients with Turner's syndrome. (1986) *J. Clin. Endocrinol. Metab.* **63**, 1028-1030.
- [25] Raiti S, Moore WV, Van Vliet G, Kaplan SL. Growth-stimulating effects of human growth hormone therapy in patients with Turner syndrome. (1986) *J. Pediatr.* **109**, 944-949.
- [26] Rosenfeld RG, Hintz R, Johanson AJ, Brasel JA, Burstein S, Chernauek SD, et al. Methyonil human growth hormone and oxandrolone in Turner syndrome; preliminary results of a prospective randomized trial. (1986) *J. Pediatr.* **109**, 936-943.
- [27] Lanes R, Gunczler P, Paoli M and Weisinger JR. Bone mineral density of prepubertal age girls with Turner syndrome while on growth hormone therapy. (1995) *Horm. Res.* **44**, 168-171.
- [28] Teunenbroek AV, Muinck Keizer-Scharma SMPF, Stijnen T, Jansen M, Otten BJ, Delemarre-Van de Waal HA, et al. Yearly stepwise increments of the growth hormone dose results in a better growth response after four years in girls with Turner syndrome. (1996) *J. Clin. Endocrinol. Metab.* **81**, 4013-4021.
- [29] Rosenfeld R, Attie KM, Frane J, Brasel JA, Burstein S, Cara JF. Growth hormone therapy of Turner's syndrome, beneficial effect on adult height. (1998) *J. Pediatr.* **132**, 319-324.
- [30] Nilsson KO, Albertsson-Wikland K, Alm J, Aronson S, Gustafsson J, Hagenas L, et al. Improved final height in girls with Turner's syndrome treated with growth hormone and oxandrolone. *J. Clin. Endocrinol. Metab.* (1996) **81**, 635-640.
- [31] Van den Broeck J, Massa GG, Attanasio A, Matranga A, Chaussain JL, Price DA, et al. Final height after long term growth hormone treatment in Turner syndrome. (1995) *J. Pediatr.* **127**, 729-735.
- [32] Dacou-Voutetakis C, Karavanaki-Karanassiou K, Petrou V, Georgopoulos N, Maniati-Christidi M and Mavrou A. The growth pattern and final height of girls with Turner syndrome with and without human growth hormone treatment. (1998) *Pediatrics* **101**, 663-668.
- [33] Joss EE, Mullis PE, Werder EA, Partsch CJ and Sippell WG. Growth promotion and Turner-specific bone age after therapy with growth hormone and in combination with oxandrolone, when should therapy

- be started in Turner syndrome? (1997) *Horm. Res.* **47**, 102-109.
- [34] Ross JL, Meyerson Long L, Feuillan P, Cassorla F and Cutler GB. Normal bone density of the wrist and spine and increased wrist fractures in girls with Turner syndrome. *J. Clin. Endocrinol. Metab.* (1991) **73**, 355-359.
- [35] Mora S, Weber G, Guarneri MP, Nizzoli G, Pasolini D and Chiumello G. Effect of estrogen replacement therapy on bone mineral content in girls with Turner syndrome. *Obstet. Gynecol.* (1992) **79**, 747-751.
- [36] Neely EK, Marcus R, Rosenfeld RG and Bachrach LK. Turner syndrome adolescents receiving growth hormone are not osteopenic. (1993) *J. Clin. Endocrinol. Metab.* **76**, 861-866.
- [37] Shaw NJ, Rehan VK, Husain S, Marshall T and Smith CS. Bone mineral density in Turner syndrome—a longitudinal study. (1997) *Clin. Endocrinol.* **47**, 367-370.
- [38] Davies M, Gulekli B and Jacobs HS. Osteoporosis in Turner syndrome and other forms of primary amenorrhea. *Clin. Endocrinol.* (1995) **43**, 741-746.
- [39] Lanes R, Gunczler P, Esaa S, Martinis R, Villaroel O and Weisinger JR. Decreased trabecular bone mineral density in young women with Turner syndrome despite estrogen replacement and previously normal bone densities. (1999) *Fertil and Steril*, **72**, 896-899.
- [40] Veldhuis JD, Blizzard RM, Rogol AD, Martha PM, Kirkland JL, Sherman BM and the Genentech Collaborative Group. Properties of spontaneous growth hormone secretory bursts and half life of endogenous growth hormone in boys with idiopathic short stature. (1992) *J. Clin. Endocrinol. Metab.* **74**, 766-773.
- [41] AttieKM, Carlsson LMS, Rundle AC and Sherman BM. Evidence for a partial growth hormone insensitivity among patients with idiopathic short stature. (1995) *J. Pediatr.* **127**, 244-250.
- [42] Van Vliet G, Styne DM, Kaplan S and Grumbach MM. Growth hormone treatment for short stature. (1983) *N. Engl. J. Med.* **309**, 1016-1022.
- [43] Gertner JM, Genel M, Gianfredi RN, Hintz RL, Rosenfeld RG and Tamborlane WV. Prospective clinical trial of human growth hormone in short children without growth hormone deficiency. (1984) *J. Pediatr.* **104**, 172176.
- [44] Genentech Collaborative group. Idiopathic short stature, Results of a one-year controlled study of human growth hormone treatment. (1989) *J. Pediatr.* **115**, 713-719.
- [45] Wit JM, Fokker MH, de Muinck Keizer-Schrama MPF, Oostdijk W, Gons M, Delemarre HA *et al.* Effects of two years of methionyl growth hormone therapy in two dosage regimen in prepubertal children with short stature, subnormal growth rate, and normal growth hormone response to secretagogues. (1989) *J. Pediatr.* **115**, 720-725.
- [46] Lanes R. Effects of two years of growth hormone treatment in short, slowly growing non-growth hormone deficient children. (1995) *J. Pediatr. Endocrinol. Metab.* **8**, 167-171.
- [47] Loche S, Cambiaso P, Setzu S, Carta D, Marini R, Borrelli and Cappa M. Final height after growth hormone therapy in non-growth-hormone deficient children with short stature. (1994) *J. Pediatr.* **125**, 196-200.
- [48] Hintz RL, Attie KM, Baptista J and Roche A. Effect of growth hormone treatment on adult height of children with idiopathic short stature. (1999) *N. Engl. J. Med.* **340**, 502-507.
- [49] Buchlis JG, Irizarry L, Crotzer BC, Shine BJ, Allen L and Macgillivray MH. Comparison of final heights of growth hormone treated Vs. untreated children with idiopathic growth failure. (1998) *J. Clin. Endocrinol. Metab.* **83**, 1075-1079.
- [50] Rekers-Mombarg LTM, Massa GG, Wit JM, Matranga AMC, Buckler JMH, Butenandt O *et al.* Growth hormone therapy with three dosage regimens in children with idiopathic short stature. (1998) *J. Pediatr.* **132**, 455-460.
- [51] Kawai M, Momoi T, Yorifuji T, Yamanaka C, Sasaki H and Furusho K. Unfavorable effects of growth hormone therapy on the final height of boys with short stature not caused by growth hormone deficiency.
- [52] Lesage C, Walker J, Chatelain P, Chaussain JL and Bougneres PF. Near normalization of adolescent height with growth hormone therapy in very short children without growth hormone deficiency. (1991) *J. Pediatr.* **119**, 29-34.
- [53] Saggese G, Cesareretti G, Barsanti S and Rossi A. Combination treatment with growth hormone and gonadotropin-releasing hormone analogs in short normal girls. (1995) *J. Pediatr.* **126**, 468-473.
- [54] Balducci R, Toscano V, Mangiantini A, Municchi G, Vacaro F, Picone S *et al.* Adult height in short normal adolescent girls treated with gonadotropin-releasing hormone analog and growth hormone. (1995) *J. Clin. Endocrinol. Metab.* **80**, 3596-3600.
- [55] Lanes R and Gunczler P. Final height after combined growth hormone and gonadotropin releasing hormone analogue therapy in short healthy children entering into normally timed puberty. (1998) *Clin. Endocrinol.* **49**, 197-202.
- [56] Ogle GD, Rosemberg AR, Calligerosd and Kainer G. Effects of growth hormone treatment for short stature on calcium homeostasis, bone mineralisation and body composition. (1994) *Horm. Res.* **41**, 16-20.
- [57] Lanes R, Gunczler P and Weisinger JR. Decreased trabecular bone mineral density in children with idiopathic short stature. Normalization of bone density and increased bone turnover after one year of growth hormone treatment. (1999) *J. Pediatr.*, **135**, 177-181.

- [58] Fine R. Growth hormone treatment of children with chronic renal insufficiency, end-stage renal disease and following renal transplantation. (1997) *J. Pediatr. Endocrinol. Metab.* **10**, 361-370.
- [59] Mehls O, and Ritz E. Skeletal growth in experimental uremia. (1983) *Kidney Int.* **21** (suppl), S53-S62.
- [60] Koch VH, Lippe BM, Nelson PA, Boechat MI, Sherman BM and Fine RN. Accelerated growth after recombinant human growth hormone treatment of children with chronic renal failure. (1989) *J. Pediatr.* **115**, 365-371.
- [61] Fine R, Pyke-Grimm K, Nelson PA, Boechat MI, Lippe BM, Yadim O and Kamil E. Recombinant human growth hormone treatment of children with chronic renal failure, long term (1 to 3 year) outcome. *Pediatr.* (1991) *Nephrol.* **5**, 477-481.
- [62] Hokken-Koelega ACS, Stijnen T, de Muinck Keizer-Schrama SMPF, Wit JM, Wolff ED, de Jong MCJW, *et al.* Placebo-controlled, double-blind, cross over trial of growth hormone treatment in prepubertal children with chronic renal failure. (1991) *Lancet* **338**, 585-590.
- [63] Lanes R, Gunczler P, Orta N, Bosquez M, Scovino R, Dominguez L, *et al.* Changes in bone mineral density, growth velocity and renal function of prepubertal uremic children during growth hormone treatment. (1996) *Horm. Res.* **46**, 263-268.
- [64] Van Dop C, Jabs KL, Donahoue PA, Bock GH, Fivush Ba and Harmon WE. Accelerated growth rates in children treated with growth hormone after renal transplantation. (1992) *J. Pediatr.* **120**, 244-250.
- [65] Hokken-Koelega ACS, Stijnen T, de Jong MCJW, Donckerwolcke RA, de Muinck Keizer-Schrama SMPF, *et al.* Double blind trial comparing the effects of two doses of growth hormone in prepubertal patients with chronic renal insufficiency. (1994) *J. Clin. Endocrinol. Metab.* **79**, 1185-1190.
- [66] Fine RN, Brown DF, Kuntze J, Wooster P, Kohaut EE. Growth after discontinuation of recombinant human growth hormone therapy in children with chronic renal failure. (1996) *J. Pediatr.* **129**, 883-891.
- [67] Lanes R, Gunczler P, Orta N, Bosquez M, Scovino R, Dominguez L *et al.* Incremento en la velocidad de crecimiento y en la mineralización ósea de niños con insuficiencia renal crónica durante 2 años de tratamiento con hormona de crecimiento; desaceleración marcada de su velocidad de crecimiento al discontinuar terapia. (1997) *Endocrinología* **44**, 355-360.
- [68] Boot AM, Nauta J, de Jong MCJW, Groothof JW, Lilien MR, van Wijk JAE, *et al.* Bone mineral density, bone metabolism and body composition of children with chronic renal failure, with or without growth hormone treatment. (1998) *Clin. Endocrinol. Metab.* **49**, 665-672.
- [69] Feber J, Cochat P, Braillon P, Castelo F, Martin X, Glastre C, *et al.* Bone mineral density after renal transplantation in children. (1994) *J. Pediatr.* **125**, 870-875.
- [70] De Zegher F, Francois I, van Helvort and Van den Berghe G. Small as fetus and short as child, From endogenous to exogenous growth hormone. (1997) *J. Clin. Endocrinol. Metab.* **82**, 2021-2026.
- [71] Boguszewski M, Rosberg S and Albertsson-Wikland. Spontaneous 24-hour growth hormone profiles in prepubertal small for gestational age children. (1995) *J. Clin. Endocrinol. Metab.* **80**, 2599-2606.
- [72] Tanner JM, Whitehouse RH, Hughes PCR and Vince FP. Effect of human growth hormone treatment for 1 to 7 years on growth of 100 children, with growth hormone deficiency, low birthweight, inherited smallness, Turner's syndrome, and other complaints. (1971) *Arch. Diseases Child* **46**, 745-781.
- [73] Grunt JA, Enriquez AR and Daughday WH. Acute and long term responses to hGH in children with idiopathic small-for dates dwarfism. (1972) *J. Clin. Endocrinol. Metab.* **35**, 157-168.
- [74] Foley TP, Thompson RG, Shaw M, Baghdassarian A, Nissley SP and Blizzard RM. Growth responses to human growth hormone in patients with intrauterine growth retardation. (1974) *J. Pediatr.* **84**, 635-641.
- [75] Lanes R, Plotnick LP and Lee PA. Sustained effect of human growth hormone therapy on children with intrauterine growth retardation. (1979) *Pediatrics* **63**, 731-735.
- [76] Chatelain PC, Job JC, Blanchard J, Ducret JP, Olivier M, Sagnard L, *et al.* Dose-dependent catch-up growth after 2 years of growth hormone treatment in intrauterine growth-retarded children. (1994) *J. Clin. Endocrinol. Metab.* **78**, 1454-1460.
- [77] de Zegher F, Maes M, Gargosky SE, Heinrichs C, Caju MVD, Thiry G, *et al.* High-dose growth hormone treatment of short children born small for gestational age. (1996) *J. Clin. Endocrinol. Metab.* **81**, 1887-1892.
- [78] de Zegher F, Albertsson-Wikland K, Wilton P, Chatelain P, Jonsson B, LOfstrom A, *et al.* Growth hormone treatment of short children born small for gestational age, metanalysis of four independent, randomized, controlled, multicentre studies. (1996) *Acta Paediatr Suppl* **417**, 27-31.
- [79] Boguszewski M, Albertsson-Wikland K, Aronsson S, Gustafsson J, Hagenas L, Westgren U, *et al.* Growth hormone treatment of short children born small-for-gestational age, the Nordic multicentre trial. (1998) *Acta Paediatr* **87**, 257-263.
- [80] de Zegher F, Du Caju MVL, Heinrichs C, Maes M, De Schepper J, Craen M. Early, discontinuous, high dose growth hormone treatment to normalize height and weight of short children born small for gestational age, results over 6 years. (1999) *J. Clin. Endocrinol. Metab.* **84**, 1558-1561.
- [81] Coutant R, Carel JC, Letrait M, Bouvattier C, Chatelain P, Coste J and Chaussain JL. Short stature associated with intrauterine growth retardation, Final height of untreated and growth hormone-treated children. (1998) *J. Clin. Endocrinol. Metab.* **83**, 1070-1074.

- [82] Boguszwesky M, Jansson C, Rosberg S and Albertsson-Wikland K. Changes in serum insulin-like growth factor 1, and IGF-binding protein-3 levels during growth hormone treatment in prepubertal short children born small for gestational age. (1996) *J. Clin. Endocrinol. Metab.* **81**, 3902-3908.
- [83] Frank GR, Cheung PT, Horn JA, Alfaro MP, Smith EP and Chernausek SD. Predicting the growth response to growth hormone in patients with intrauterine growth retardation. (1996) *Clin. Endocrinol.* **44**, 679-685.
- [84] Lanes R and Harrison HE. Growth hormone therapy in a poorly growing child with hypophosphatemic rickets. (1990) *J. Endocrinol. Invest.* **13**, 833-837.
- [85] Wilson DM, Lee PDK, Morris AH. Growth hormone therapy in hypophosphatemic rickets. (1991) *AM. J. Dis. Child.* **145**, 1165-1170.
- [86] Saggese G, Baroncelli GI, Bertelloni S and Perri G. Long-term growth hormone treatment in children with renal hypophosphatemic rickets, Effects on growth, mineral metabolism and bone density. (1995) *J. Pediatr.* **127**, 395-402.
- [87] Cameron FJ, Sochett EB, Daneman A and Kooh SW. A trial of growth hormone therapy in well-controlled hypophosphatemic rickets. (1999) *Clin. Endocrinol.* **50**, 577-582.
- [88] Marini JC, Bordenick S, Heavner G, Rose S, Hintz R, Rosenfeld R and Chrousos GP. The growth hormone and somatomedin axis in short children with osteogenesis imperfecta. (1993) *J. Clin. Endocrinol. Metab.* **76**, 251-256.
- [89] Antoniazzi F, Bertoldo F, Mottes M, Valli M, Sirpresi S, Zamboni G, *et al.* Growth hormone treatment in osteogenesis imperfecta with quantitative defect of type I collagen synthesis. *J. Pediatr.* **129**, 432-439.