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Growth after organ transplantation

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Growth is an important feature of childhood, but it is usually impaired before and after organ transplantation. Modest catch-up growth often occurs after renal transplantation. Nevertheless, patients remain short due to the effects of steroids used for immunosuppression. Children with chronic liver failure are also growth impaired, although not to the same extent. They also frequently have poor catch up growth after transplantation, again due to steroids. There are several randomized controlled clinical trials reporting growth hormone (GH) use after renal transplantation. These consistently show a beneficial effect of GH on linear growth. Patients with histories of frequent acute rejections before GH may have increased risk of acute rejection during treatment. Few data exist on liver transplant patients, although GH also appears effective. GH use may be safe and effective for renal transplant recipients who have been stable without acute rejection episodes. There needs to be long-term study of GH use in liver and renal transplant patients. It is critical to focus efforts on improving growth in renal failure before transplantation through GH use and to improve posttransplant growth in all recipients by minimizing steroid exposure.

Solid organ transplantation is a frequently used modality for the treatment of a wide variety of diseases in children, involving an increasing number of organ systems. In the United States, there were over 25,000 organ transplant procedures in 2003.[1] Pediatric patients received 13% of the kidney transplants in one center,[2] and 10% of liver transplants went to children in another report.[3] Cardiac transplantation has long been used in children, and one author estimated that over 2600 pediatric heart transplants were performed in the last 10 years.[4] The frequencies of lung, small intestine, and multivisceral transplants in children are also increasing. With the large number of children receiving transplants, increasing attention is being devoted to long-term follow up. Although growth in healthy children is often taken for granted, organ transplant recipients frequently have significant growth failure, both before and after transplantation. This article will first review the basic endocrine control of growth and then discuss mechanisms for abnormal growth seen before and after organ transplantation. Finally, I will review treatment efforts to improve growth, focusing on studies of growth hormone (GH).

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Physiology of normal growth (Figure 1)

The hypothalamus regulates pituitary secretion of GH through two opposing hormones: GH releasing hormone (GHRH) and somatostatin. The pituitary gland secretes GH in a pulsatile manner, with the majority of GH released at night. Circulating GH concentrations thus vary widely, and a low level at any given time does not necessarily indicate GH deficiency. In the liver, GH promotes the synthesis of insulin-like growth factor-1 (IGF-1) and its primary carrier protein, IGF binding protein-3 (IGFBP-3). IGF-1 has important effects on the growth plates, stimulating cartilage

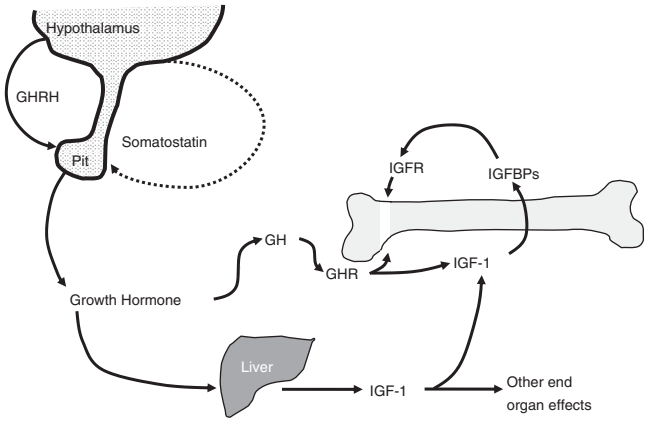

Figure 1 Schematic of growth hormone secretion and action. GH is produced by the pituitary under the influence of the hypothalamic hormones GHRH and somatostatin. In the circulation, GH travels to the liver, where it promotes secretion of circulating IGF-1. At the growth plate, GH acts through its receptor, resulting in locally produced IGF-1 in the bone. GH has direct effects on bone through its receptor as well. IGF-1 acts in concert with its binding proteins to promote growth by stimulating cartilage proliferation. Pit, pituitary gland; GHR, growth hormone receptor; IGFBPs, insulin-like growth factor binding proteins, IGFR, IGF-1 receptor.

matrix production and the multiplication and hypertrophy of chondrocytes. GH itself has direct actions on the bone, and it stimulates local production of IGF-1 in the growth plate. This locally produced IGF-1 may be more important in growth promotion than hepatic IGF-1.[5] The action of GH depends on a wide variety of other factors as well. These include many other growth factors, including a number of fibroblast growth factors and epidermal growth factors; normal levels of other hormones, including glucocorticoids, thyroid hormone, and sex steroids; a normal metabolic state, with appropriate acid-base balance; and the availability of precursors for protein and lipid synthesis.

Effects of chronic organ failure on growth pre-transplantation

Children with a rapidly evolving condition may not have growth impairment at the time of transplantation. If the condition is chronic, however, growth failure is nearly universal. This may be for several reasons, including the abnormal organ function itself, such as uremia, acid-base abnormalities, and electrolyte problems seen in patients with chronic renal failure (CRF). Nutritional deficiencies are common in children with chronic disease, both in terms of macronutrients (protein, carbohydrates, and fats) and micronutrients such as vitamins, cofactors, and trace elements. The genetic background is an important factor in the evaluation of growth in any child, including those suffering from organ failure. Many short children have relatively short parents, and very few studies of growth in transplant patients take this into account.[6] Finally, many chronic diseases are treated with high-dose glucocorticoids. These medications, including most commonly methylprednisolone and prednisone, impair growth on many levels. In the GH/IGF-1 system, pharmacologic doses of steroids increase the release of the inhibitory factor somatostatin, thus decreasing GH secretion. They also act on the GH receptor gene to decrease its expression and decrease the transduction signal from the receptor, resulting in relative GH insensitivity.[7] Similarly, they lead to relative loss of IGF-1 bioactivity.[8] Following transplantation, virtually all patients receive high doses of steroids for prolonged periods, ranging from several weeks to years, depending on the individual institutional protocol, potentially resulting in long-term growth failure.

Chronic renal failure

Growth failure tends to be more severe in children with renal failure than in those with diseases in other organ systems. It has been estimated that for every mg/dL increase in the serum creatinine, there is loss of 0.17 standard deviation units (SD) in height in patients with chronic renal failure.[9] Data from the North American Pediatric Renal Transplantation Cooperative Study (NAPRTCS) indicate that even if a child starting dialysis is not short, the height deficit as expressed by SD score doubles after 2 years.[10] The heights of children with CRF often are more than 3 SD below the mean for age. Furthermore, long-term follow up of adolescents with CRF reveals the absence of the pubertal growth spurt, which normally accounts for 28 to 31 cm (about 12 inches) of an individual's adult height.[11] This severe growth failure led to trials of GH administration, and it was approved for this indication in the mid-1990s. However, it is underused, with only 11% of patients overall having received treatment.[10] An analysis of GH use in patients with CRF showed that treatment results in a height increase of 0.8 SD during the first year.[12] It appears that children below 6 years of age have a better response to GH treatment before transplantation.[10]

Chronic liver failure

Liver failure patients as a group are not as short as CRF patients. Many studies of spontaneous growth before and after liver transplantation have been published. Mean height SD scores before transplantation ranged from −1.1 to −1.8.[13-18] Younger patients with liver failure often have more severe growth impairment.[19] No studies of GH use in patients with liver failure before transplantation have been published.

Other chronic organ failure

Patients with organ failure in other systems often experience growth failure as well. Cardiac transplant recipients are