Growth following solid organ transplantation in childhood

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Abstract: One of the ultimate goals of successful transplantation in pediatric solid organ transplant recipients is the attainment of optimal final adult height. This manuscript will discuss the attainment of height following solid organ transplantation in pediatric recipients of kidney, liver, heart, lung, and small bowel transplantation. Age is a primary factor with younger recipients exhibiting the greatest immediate catch up growth. Graft function is a significant contributory factor with a reduction in glomerular filtration rate correlating with poor growth in kidney recipients and the need for re-transplantation with impaired growth in liver recipients. The known adverse impact of steroids on growth has led to modification of steroid dosage and even to steroid withdrawal and steroid avoidance. In kidney and liver recipients, this has been associated with the development on occasion of acute rejection episodes. In infant heart transplantation, avoidance of maintenance corticosteroid immunosuppression is associated with normal growth velocity in the majority of patients. With marked improvement in patient and graft survival rates in pediatric organ graft recipients, it is timely that the quality of life issues, such as normal adult height, receive paramount attention. In general, normal growth post-transplantation should be an achievable goal that results in normal adult height for many solid organ transplantation recipients.

Kidney

What factors influence post-transplant growth in renal allograft recipients? The three major factors are age at transplantation, allograft function, and corticosteroid dosage. Chronological age at transplantation is predictive of the magnitude of post-transplant growth. The most recent data from NAPRTCS that delineates growth in children 0–1, 2–5, 6–12, and >12 yr of age, shows that the two younger age groups of children, those <6 yr of age, all show catch up growth for the initial 1–2 yr following transplantation and then a plateau after that time interval. However, the children who are 6–12 and >12 yr of age at the time of transplantation show no catch up growth. Therefore, the older children do not exhibit any catch up growth and their final adult height is frequently suboptimal in pediatric recipients of kidney, liver, heart, lung, and small bowel transplants. As the overwhelming majority of recipients are prepubertal at the time of transplantation, it is imperative that post-transplant growth be optimized with the frequent need to affect catch up growth if the target adult height is to be achieved. The following will review the current status of growth following successful solid organ transplantation in children.
height will be determined by the height at the time of transplantation (1).

Reduction in renal allograft function has a significant effect on growth velocity. Studies by Tejani et al (2), almost two decades ago, showed that renal function has a profound impact on growth with a –0.17 decrease in Z score (SDS) being associated with a 1.0 mg per deciliter increase in the serum creatinine level. These data would indicate that as kidney function deteriorates following renal transplantation long-term growth velocity will decrease. Likewise, the data emphasize the need for optimal graft function to achieve optimal adult target height in pediatric renal allograft recipients.

Steroid dosage has a significant impact on growth in pediatric allograft recipients. Switching from daily to alternate day steroids (3), steroid withdrawal, and steroid avoidance (4, 5) have all been associated with improvement in growth velocity. A randomized controlled trial of early steroid withdrawal (TWIST Study) randomized 98 patients to daclizumab induction followed by tacrolimus and mycophenolate mofetil with steroid discontinuation on day 5 vs. 98 patients randomized to receive tacrolimus, mycophenolate mofetil, and steroids with steroids being tapered but continued at a daily dose of 10 mg per meter squared. The patients enrolled in this study were primarily prepubertal patients. At six months, the standard deviation scores improved by 0.13 in the steroid withdrawal group compared with the group that continued daily steroids (6). All clinical parameters were similar in the two groups except for an increase in infection rate and anemia in the group with steroid withdrawal on day 5. As further long-term results of this study continue to show that there is an improvement in growth following early steroid withdrawal without any adverse impact on allograft function, it is likely that steroid-minimizing regimens will become a standard of care in the future. An alternative to steroid withdrawal is total steroid avoidance that was accomplished by Li et al. at Stanford in 2009 (5). This study showed a greater improvement in growth on a steroid-free protocol with six months of extended daclizumab induction in comparison with those on a steroid-based protocol. This improvement in growth was especially evident in the youngest of the transplant recipients as they demonstrated catch up growth that exceeded growth rates of healthy peers. The TWIST and Stanford studies both showed a significant improvement in height with steroid withdrawal and avoidance but importantly, they also displayed comparable rates of rejection and transplant survival when steroid avoidance groups were compared with steroid-based groups. There was no significant difference in rejection-free survival at six months in the TWIST study (difference of steroid withdrawal versus steroid based of –0.02, p = 0.46). Furthermore, in the first post-transplant year of the Stanford trial, there was no significant difference in the incidence of acute rejection between the steroid-free group and the steroid-based group. Still, because both the Stanford and TWIST trials conducted induction using daclizumab, which is no longer available on the market, further investigation is needed to ensure that these differences are maintained with alternate induction agents such as basiliximab.

Recently, Sarwal et al (7). reported the three-yr follow-up from a multicenter NIAID sponsored randomized controlled study of 130 children enrolled from 12 pediatric transplant centers in the United States. The change in standard deviation score at three yr from all recipients was not different in the steroid-free group compared with the steroid-based group. However, if one analyzed the change in standard deviation score at three yr in the 27 children <5 yr of age and adjusted for baseline height, there was a significantly greater growth velocity in the steroid-free group in comparison with the steroid-based group (p = 0.019). Biopsy-proven acute rejection at three yr was similar in the steroid-free group (16.7%) and the steroid-based group (17.1%). Patient survival was 100% in both groups, and graft survival was similar in both groups; steroid-free group was 95%, and steroid-based group was 90%. The systolic blood pressure and cholesterol levels were lower in the steroid-free group. This randomized controlled study certainly indicates that steroid avoidance does not adversely affect long-term graft function or increase the incidence of biopsy-proven acute rejection episodes. However, the impact on growth was less than anticipated in that the steroid-free group only demonstrated a salutary effect on growth in the recipients <5 yr of age. This study emphasizes that there are obviously factors other than steroids that affect growth velocity and catch up growth especially in older pediatric transplant recipients. A strategy to address the factors that require amelioration to enhance growth in the older recipients will need to be a significant focus for the future.

The ultimate goal with respect to growth in pediatric renal allograft recipients is attainment of normal final adult height. Recent data from the NAPRTCS registry (1) have shown that over the past quarter century, there has been
significant increase in the final adult height of recipients entered into the registry. From 1987 to 1991, those patients who reached adult height had a standard deviation score of −1.93, whereas for the patients who were entered in the registry between 2002 and 2010 and reached final adult height, their standard deviation score was −0.94; almost one standard deviation improvement in final adult height over a 15–20 yr period. This certainly is a remarkable achievement and indicates that pediatric renal allograft recipients now have a final adult height that is approaching target heights.

One of the primary factors that have led to improved final adult height has been that the height deficit at the time of transplantation has improved markedly during the past decade. The most recent NAPRTCS registry data (1) indicate that in 1987 the standard deviation score (Z score) for patients at the time of transplantation was approximately −2.5. Whereas, in those patients who were transplanted in 2009, the standard deviation score (Z score) at transplantation was between −1 and −1.5. Again, over this interval of a quarter of a century, the standard deviation score of children at the time of transplantation has improved more than one standard deviation that is similar to the improvement in adult height during the same period for the same patient population. Along with baseline height at transplantation, the age at transplantation also plays a role in the achievement of a normal adult height. Klare et al (8) showed that of 74 patients with good graft function and successful weaning of steroids within six months, 94% achieved a normal adult height in the prepubertal group compared with 77% in the pubertal group. Also, the pre-pubertal group was more likely than the pubertal group to achieve a height consistent with their genetic potential. Similar to the NAPRTCS data, having a greater height at the time of transplantation was also shown to be associated with improved final adult height. Per Klare et al., age at transplantation and height at transplantation explained 48% of the variability in final adult height, thus demonstrating the importance of both early transplantation and maximization of pre-transplant growth.

As indicated previously, the overwhelming majority of children over six yr of age at the time of transplantation do not exhibit any catch up growth following transplantation. Therefore, if those patients are to achieve normal adult height some intervention to stimulate growth will be required. This dilemma raises the question as to whether the use of an rhGH improves the growth in growth-retarded renal allograft recipients. There have been four (9–12) randomized controlled studies that have addressed the issue of rhGH treatment in growth-retarded renal transplant patients. The growth velocity in most of the studies doubled with rhGH treatment compared with the control group. A recent systematic review and meta-analysis by Wu et al. (13) pooled 401 pediatric patients from the available randomized controlled trials on rhGH and demonstrated a greater height SDS at one-yr post-transplant in the rhGH group compared with controls (mean difference in SDS of 0.68, p = 0.002). Despite the well-documented improvements in height SDS associated with rhGH treatment, concern still exists with its use. One of the concerns regarding the use of rhGH following renal transplantation has been prior anecdotal information that rhGH may stimulate the immune system and precipitate acute rejection episodes. In the previous meta-analysis, a non-significant difference in acute rejection episodes of 17% in the rhGH group vs. 10% in controls (p = 0.07) was found though the use of biopsy confirmation of acute rejection was not consistent between each study. Thus, it is important to accurately weigh the perceived risks of rhGH with its benefits, specifically in older transplant recipients who, as shown by Sarwal et al. (7), demonstrate poor growth despite the use of steroid-free immunosuppression.

A concern with one of the newer immunosuppressant drugs, sirolimus, was that the use of this immunosuppressive agent impaired linear growth in pediatric solid organ transplant recipients. There are two studies (14, 15) that addressed this issue. It was raised primarily because animal models have shown a decrease in longitudinal growth due to sirolimus by inhibition of cell proliferation and vascular endothelial growth factor expression at the long bone growth plate that blocks IGF intracellular signaling of chondrocytes (16). The study by Gonzalez et al. (14) looked at 34 renal transplant recipients who received sirolimus for 24 months and had their height standard deviation scores compared with a control group. There was no difference in the height standard deviation score in the sirolimus and control group at any time from the inception of the study to 24 months. However, the change in height was significantly decreased in the sirolimus group at all follow-up times compared with the control group. The authors concluded that growth velocity is significantly decreased in the sirolimus group compared with the control group. In contrast, Hymes and Warshaw (15) looked at 25 renal transplant recipients on sirolimus who were followed for 24 months and
compared their height standard deviation scores with a control group who received tacrolimus. The height standard deviation score was no different at baseline and 24 months in either the sirolimus or tacrolimus group. The height standard deviation score increased by 52% in the sirolimus group and the authors concluded that sirolimus does not impair growth in renal allograft recipients.

Liver

The current status of growth following liver transplantation was summarized in 2009 by Al-Sinani and Dhawan (17). They evaluated 20 reports between 1987 and 2008. The number of patients in each report varied between 21 and 236, and the follow-up period in each report varied between 1 and >8 yr. The number of recipients who exhibited catch up growth varied between 39 and 100%. The steroid dosage in the various reports varied from daily to a tapering dose, alternate day steroid therapy to steroid withdrawal and steroid-free regimens. Therefore, it was quite difficult to specifically analyze each group. However, the authors attempted to identify the factors from these 20 reports that impacted growth. Their assessment was that steroid dosage did impact growth with the cumulative dose, timing of tapering of withdrawal, and the presence of daily steroid treatment having an adverse impact on growth. Height at the time of transplantation also had an impact on catch up growth with those who had a decrease in growth standard deviation score at the time of transplantation having an increase in catch up growth following transplantation. Age was also a factor impacting on growth with children <2 yr old at the time of transplantation having an increase in catch up growth. The primary diagnosis whether cholestasis, fulminant liver failure, sclerosis or metabolic disease had an impact on growth. Patients with cholestasis and hepatitis had a better post-transplant growth. Graft dysfunction also impacted post-transplant growth with those liver transplant recipients who required retransplantation or developed PTLD having a reduced growth velocity following transplantation.

Alonso and colleagues (18) reviewed the data from the SPLIT registry on 1143 recipients. The standard deviation score was −1.55 at transplant, and at 24 months, it was −0.87, and at 36 months, it was −0.68. This would indicate a significant improvement in height standard deviation score following liver transplantation. Subsequent follow-up, however, showed limited catch up growth after 36 months. The factors that impacted negatively on growth were more than 18 months of steroid therapy following transplantation and a primary metabolic or non-biliary atresia cholestatic disease. They found that when compared to metabolic liver disease, a pretransplant diagnosis of biliary atresia was associated with decreased risk of growth impairment (OR 4.4 [CI: 1.83–10.59]). Other studies have also shown that a diagnosis of biliary atresia, which may account for up to 50% of the cases in pediatric liver transplant studies, has a favorable impact on post-transplant growth with higher rates of catch up growth being reported post-transplant. For instance, Saito et al. (19) reported a change in z score for height of −1.34 at liver transplantation to −0.61 at one yr and −0.21 by the second yr post-transplant (Fig 1). As with mixed groups of liver transplant recipients, within the biliary atresia groups, Saito et al. found that lower height z score at the time of liver transplantation was associated with higher catch up growth post-transplant and this finding was more pronounced in those younger than two yr at transplant. Therefore, those with a diagnosis of biliary atresia show significant post-transplant growth, which is more pronounced with younger age and lower height z score at the time of transplantation.

The role of graft dysfunction in post-transplant growth was evaluated by El Moghazy et al. (20), who adopted a regimen of rapid tapering of steroids to 0.1 mg/kg/day by four week post-transplant followed by rapid removal of steroids by 3–6 months. In looking at 237 pediatric patients, they demonstrated that post-transplant change in z score decreased in the presence of
graft dysfunction. Those without graft dysfunction showed more dramatic increases in final Z score at 15-yr post-transplant, a change from $-1.795$ at baseline to $-0.291$ at 15 yr versus a change in those with graft dysfunction from $-1.607$ at baseline to $-0.836$ at 15-yr post-transplant. SPLIT data also displayed an association between graft dysfunction and poor growth by demonstrating the association of elevated GGTP at 12 months, an indicator of poor graft function, with poor post-transplant catch up growth (18).

Because the liver is thought to be less immunogenic than other organs, steroid withdrawal has been utilized therapeutically in pediatric liver transplant recipients in the past to maximize linear growth. There have been five uncontrolled studies with cyclosporine as the primary immunosuppressive agents where steroids were withdrawn between 3 months–58 months following transplantation and acute rejection episodes occurred in seven to 27% of the patients. Chronic rejection, which occurred in <18 months, was present following steroid withdrawal in four to 13% of the patients and graft loss in three to 13% of the patients. More recently, steroid withdrawal was attempted in three series of patients with tacrolimus as the primary immunosuppression (21, 22) (personal communication). In a study from John Hopkins (21), the steroid was withdrawn at six months in 29 patients with a 29% acute rejection rate, and in Kyoto (22), it was withdrawn at eight months in 156 patients all of whom were recipients of live related donors with a 14% acute rejection rate. In Pittsburgh (personal communication), it was withdrawn within the first year in 166 patients and in 21% of these patients reinstitution was required within five yr because of rejection. The SPLIT data (18) indicated that at 24 months post-transplant, if steroids were withdrawn at <6 months, that the increment in standard deviation score was 1.7 compared with steroids being withdrawn at more than 18 months with only a 0.9 increase. Furthermore, those with pretransplant growth failure in addition to steroid usage for more than 18 months were 14.1 times more likely to have linear growth impairment at 24 months when compared to those without pretransplant growth failure and with steroid usage of <6 months. These data would seem to indicate that steroid withdrawal especially if performed early will result in an improvement in the standard deviation score and potentially lead to improved adult height. However, there is a risk of rejection and potential graft loss with steroid withdrawal.

What can one anticipate as the final adult height in pediatric liver transplant recipients? The study by Scheenstra et al (23), in 2008 looked at 23 recipients with a median age of 13.3 yr at transplantation. The standard deviation score was $-1$ at transplant and $-1.4$ at the final height, and the median target height was $-1.3$: 12 of the 23 had a final adult height below 1.3 standard deviations of their target height. These data would indicate that a significant number of liver transplant recipients cannot reach their adult target height. As a number of liver transplant recipients exhibit suboptimal post-transplant growth, one could question whether or not there is any effective treatment for improving growth in this population. Growth hormone has been utilized in eight recipients with a standard deviation score of more than two who were treated with rhGH for more than five yr. The standard deviation score improved from $-3.6$ to $-2.7$ (24). There were no rejection episodes, and one patient who had elevated liver enzymes prior to rhGH treatment was diagnosed with chronic rejection at three yr. This one study on a limited number of patients would seem to indicate that severely growth-retarded liver transplant recipients could benefit from prolonged rhGH treatment post-transplant without any adverse impact on graft function.

**Heart**

Chinnock and Baum (25) more than a decade ago looked at the recipients of heart transplants at their institution and delineated three factors that they determined impacted post-transplant growth. The number of days in the hospital during the first post-transplant year, the number of treated rejection episodes after the first post-transplant year and something that is quite important and had not been delineated by prior authors which was mid-parental height, which was the genetic potential for each individual. They looked at 77 infants who were transplanted at <6 six months of age, and these patients received no maintenance steroid therapy. Catch up growth was quite prevalent during the first post-transplant year, and only six of 51 who were more than five-yr post-transplant were less than the fifth percentile. This study demonstrated that the use of a steroid-free maintenance protocol can provide normal growth for very young infants transplanted at <6 months of age. Importantly, steroid-free immunosuppression has been shown to be achievable without increased rates of rejection or decreased patient or graft survival. Singh et al. (26) evaluated 55 transplant patients
who underwent induction with rabbit thymocyte globulin and 3–6 days of methylprednisolone. Maintenance immunosuppression was achieved with tacrolimus and MMF; there was no maintenance steroid usage. Surveillance biopsies showed a rejection rate of 14.5% (8/55) and a one-yr freedom from rejection rate of 87%. These rejection rates compare well with time-matched data reported from the International Society for Heart and Lung Transplantation in 2009 (27), which showed a freedom from rejection rate of 64% at one yr using polyclonal antibody induction. This demonstrates that the avoidance of maintenance steroids for immunosuppression is associated with comparable rates of rejection thus, making it possible to attempt steroid avoidance to maximize growth.

Whereas Chinnok and Baum showed highly favorable growth post-transplantation, Peterson et al. (28), when looking at 46 heart transplant recipients who were <11 yr of age at the time of transplantation, showed no significant change in the height standard deviation score up to 24 months post-transplant. The authors noted that the younger age at transplant had a positive impact on growth and the length of steroid treatment had a negative impact on the change in the standard deviation score post-transplant (Fig 2). Their current practice was to wean the patients off steroids at one yr in low-risk patients who had no rejection episode. More recently, Bannister et al. (29) from Toronto Sick Kids looked at 130 heart recipients who were transplanted between 1990 and 2005 with a mean follow-up of 4.4 yr. Their mean height Z score was unchanged from transplant to last measurement and was a mean of −1.3. The authors felt that enteral feeding support did lead to an increase in height standard deviation score in patients who were identified as not consuming sufficient calories. There are limited data on the use of rhGH in growth-retarded pediatric heart transplant recipients. Mital et al. (30) reported from the program at Columbia on 10 recipients with a mean age of 7.8 yr at transplant and a mean age at the initiation of rhGH treatment of 13 yr with a mean duration of rhGH treatment of 2.5 yr. The growth velocity increased from 2.5 cm per yr at baseline to 8.6 cm per yr during rhGH treatment. The authors noted an increase in left ventricular shortening fraction, left ventricular volume and cardiac output in those patients with rhGH treatment. The left ventricular volume remained increased following discontinuation of rhGH, and therefore, it was felt to be physiologic and not pathologic.

**Lung**

Recently, Elizer et al. (31) from St. Louis Children’s Hospital reported on 36 infants <1 yr of age and 26 toddlers 1–3 yr of age who received lung transplantation between 1990 and 2004. At transplant, the infants had a height standard deviation score of −1.76 and the toddlers −1.72; at one-, three-, and five-yr post–transplant, the standard deviation score was more negative from −1.89 at one yr to −1.91 at three yr and to −2.14 at five yr. Obviously, this report would indicate that catch up growth does not occur and indeed an increase in the growth retardation occurs following lung transplantation. Because of this, rhGH has been utilized in a small series at St. Louis Children’s Hospital. Sweet and his colleagues (32) reported eight of nine lung transplant recipients who received rhGH developed bronchiolitis obliterans syndrome and this was an increased incidence compared with the group who did not receive rhGH. Therefore, Sweet and his colleagues caution on the use of rhGH to enhance growth velocity in lung transplant recipients.

**Small bowel**

Linear growth in those undergoing small bowel transplantation is severely retarded prior to transplant and shows a limited ability to achieve normal height Z scores post-transplant. Venick et al. (33) showed that of 33 patients that underwent intestinal transplantation, the mean height Z score improved from −3.1 at transplant to between −2 and −2.5 after four-yr post-transplant. This finding shows the severe impairment in linear growth at the time of transplantation and the lack of achievement of a normal height, defined as growth > −2 SDS, even
over four yr of follow-up. Of those who demonstrated positive linear growth, it was shown to be associated with early cessation of parenteral nutrition, low steroid dosage and use of a peptide-based formula instead of an amino acid-based formula. Because steroids have been associated with poor linear growth, Nucci et al. (34) studied the difference in linear growth between patients receiving steroid-based immunosuppression and those receiving steroid-free immunosuppression. Over time, they found a decrease in the prevalence of patients with growth failure in the steroid-free group, but no change in the number of patients with growth failure in the steroid-based group. Furthermore, in evaluating the steroid-free group for number of days of steroid treatment for rejection, those who received steroids for a total of 120 days or less showed a greater positive change in linear growth. Similarly, Nayyar and colleagues (35) evaluated 76 small bowel transplant recipients who received a transplant at a mean age of 2.6 yr; 34 of them received standard immunosuppression of tacrolimus and steroids, and 42 had a combination of ATG induction followed by tacrolimus and only received steroids with acute rejection. Forty-eight percent of the patients who received ATG remained steroid free during the follow-up period, and the height standard deviation score improved at two yr in this steroid-free group. These studies would seem to indicate that similar to findings in other solid organ transplantation, steroid-free immunosuppression has a beneficial effect in the small bowel transplant population. The long-term outcomes in growth following small bowel transplantation have yet to be widely elucidated though Lacaille et al. (36) have provided some insight into the ability to achieve a normal final adult height. Of six children in their study population to reach adult height, five were able to reach a normal adult height, though they failed to reach a height consistent with mid-parental height. Though the baseline Z scores were not as severely delayed as with other study populations, these findings seem promising as they suggest the ability to achieve a normal adult height that may improve quality of life even if the height is less than genetic potential.

**Conclusion**

There are universal factors that impact growth velocity, catch up growth, and final adult height in pediatric solid organ transplant recipients. The height at transplant is certainly an important factor with more severe growth retardation at transplant as a potential for greater catch up growth following transplant. Normal target height at transplant has the potential to result in normal final adult height. The latter has certainly been shown in selected renal transplant populations.

The age at transplant also impacts growth with younger recipients tending to be more growth retarded at transplant, and therefore, they may exhibit greater catch up growth. Graft dysfunction, likewise, impacts growth with the number of acute rejection episodes, the number and length of hospitalization, the need for retransplantation and the need for surgical re-exploration all having an adverse effect on growth.

Renal dysfunction, whether in renal allograft recipients or recipients of other solid organ transplants, may have an adverse impact on growth. In the renal allograft recipients, primary renal dysfunction certainly has been associated with an adverse effect on growth. In recipients of other solid organ transplants, renal dysfunction secondary to drug toxicity, whether it be calcineurin inhibitors, antibiotics, antivirals or other reasons, can have an adverse impact on growth. Bone dysfunction may impact growth, whether a persistent abnormality of bone that has resulted from the primary disease or acquired bone dysfunction following solid organ transplantation.

Corticosteroids certainly can impact growth in all pediatric solid organ transplant recipients. Steroid-free regimens are optimal with steroid withdrawal being a secondary option. It should be noted that in those studies where steroid withdrawal has been effective, it is noted that earlier is better. Those cases who received alternate day steroid therapy demonstrated a positive impact on growth; however, one must be concerned about adherence to the treatment regimen when an alternate day treatment is given. One of the major factors that may adversely affect ultimate adult height is a suboptimal pubertal growth spurt. This occurs to a significant degree in renal allograft recipients and may also occur in other solid organ transplant recipients. One potential therapeutic option to enhance pubertal growth is the use of rhGH to enhance the magnitude of the pubertal growth spurt; however, to our knowledge, there are no studies that have addressed this issue. It is important to remember when one is determining the factors that affect growth following transplantation that the genetic potential is a major factor that will determine target height and one should assess mid-parental height when one is determining the anticipated target height of any recipient. In addition, one should also be
cognizant of the fact that if the patient has significant growth retardation that there may be a genetic abnormality causing primary short stature rather than the growth retardation being a consequence of the primary disease or other factors following organ transplantation.

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