Evidence-Based Medicine in Pediatric Endocrinology

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This is the second appearance of this *Yearbook* chapter on evidence-based medicine [1]. So what has changed over the past year? The total volume of publications in clinical pediatric endocrinology this year has been enormous, with many high quality publications, so how have we made the selection for this chapter? As before, selection has principally focused on identifying seminal studies demonstrating a well-defined rigorous evidence-based approach with direct relevance to our daily practice of pediatric endocrinology. This year has seen important joint consensus statements published by the European Society for Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society on GH treatment of children born small for gestational age [2], and on the use of continuous subcutaneous insulin infusions [3]. Recommendations on the use of newly launched rhIGF-1 were produced in a Lawson Wilkins Pediatric Endocrine Society review [4]. Additionally the large volume of published data on the efficacy and safety of rhGH treatment over 20 years in the KIGS pharmaceutically sponsored database cannot be ignored as an important source of evidence [5].

This chapter contains a selection of important randomized controlled trials (RCTs), but also several large cohort or population studies, often with prospectively collected data from the study population and specifically chosen parallel control groups. This is often the most appropriate way to test a hypothesis and to obtain sufficient statistical power. We must also not forget longitudinal follow-up programs, which have fewer subjects than population studies, but these give us the quality of the evidence-based information in pediatric endocrinology that can only be obtained from this type of platform. So therefore, this chapter contains quite a mix of sources of high quality evidence which we hope will stimulate and inform.

Mechanism of the year: insulin gene mutations – new mechanism and new hope

Insulin mutation screening in 1,044 patients with diabetes: mutations in the INS gene are a common cause of neonatal diabetes but a rare cause of diabetes diagnosed in childhood or adulthood

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Background: One to two percent of all diabetes is due to monogenic diabetes. Recently insulin gene (INS) mutations have been described as a cause of permanent neonatal diabetes (PND). The authors aimed to determine the prevalence, genetics, and phenotype of INS mutations in 1,044 patients with neonatal diabetes and permanent diabetes diagnosed in infancy, childhood, or adulthood.

Methods: INS gene sequencing was undertaken in: 285 patients with diabetes diagnosed before 2 years of age, 296 probands with maturity-onset diabetes of the young (MODY), and 463 patients with young-onset type 2 diabetes (non-obese, diagnosed <45 years). No patient had a previous molecular genetic diagnosis of monogenic diabetes.

Results: The authors identified heterozygous INS mutations in 33 of 141 probands diagnosed at <6 months, 2 of 86 between 6 and 12 months, and none of 58 between 12 and 24 months of age. Three known mutations (A24D, F48C, and R89C) account for 46% of cases. There were six novel mutations identified: H29D, L35P, G84R, C96S, S101C, and Y103C. INS mutation carriers were all insulin treated from diagnosis and were diagnosed later than K⁺ channel mutation carriers (11 vs. 8 weeks,

$p < 0.01$). In 279 patients with PND, the frequency of KCNJ11, ABCC8, and INS gene mutations was 31, 10, and 12%, respectively.

Conclusion(s): INS gene mutations are the second most common cause of PND and a very rare cause of MODY. The authors recommend INS gene mutation screening for all patients with diabetes diagnosed before 1 year of age.

Five different patient groups were studied with permanent diabetes at the time of referral: infancy, early childhood, MODY, type 2 diabetes and hyperinsulinism. This is the largest series of INS gene mutations identified to date through screening 1,044 patients diagnosed with diabetes from birth to 45 years old. It is now estimated that 1–2% of all diabetes is monogenic in origin. HLA studies and the association with ATP-sensitive K^+ channel mutations revealed that patients diagnosed with diabetes before 6 months of age are more likely to be monogenic than type 1 diabetes in origin [6, 7]. The original description of the INS mutations was from a previous paper from the same study group. This paper outlined 10 heterozygous mutations in the human insulin gene in 16 probands with neonatal diabetes and concluded that the identification of insulin mutations as a cause of neonatal diabetes will facilitate the diagnosis and treatment of this disorder [8]. Furthermore the introduction of glibenclamide in increasing doses to replace insulin has been successful in patients with mutations in Kir6.2 that may be managed on an oral sulfonylurea with sustained metabolic control rather than insulin injections, illustrating the principle of pharmacogenetics applied in diabetes treatment [7]. Mutations in Kir6.2 were the most frequent cause of PND in previous cohort studies. This new paper reports that the INS mutations are the second most common cause of PND and a rare cause of MODY. This report emphasizes the importance of revisiting a diagnosis, especially with the emergence of new gene mutations. In this scenario one must reconsider the diagnosis of type 1 diabetes. Furthermore, insulin gene mutation screening is recommended for all patients with diabetes diagnosed before 1 year of age. Perhaps the dreaded daily insulin injections will be replaced with new pharmacological agents in other monogenic diabetes, providing new hope for the future.

The study was designed as a large cohort study from the Neonatal Diabetes International Collaborative Group. Its strengths are the large number of patients, large power, and multiple international collaborators.

New paradigms – is biochemical management of GH treatment the way forward?

Insulin growth factor-based dosing of growth hormone therapy in children: a randomized, controlled study

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J Clin Endocrinol Metab 2007;92:2480–2486

Background: Since the introduction of biosynthetic rhGH, treatment regimens have centered on auxological criteria for dosing, mainly weight-based, despite IGF-1 being the main mediator of the actions of GH. This study was developed to ascertain whether IGF-1 levels attained during GH treatment were superior determinants of outcomes.

Methods: 172 prepubertal children were recruited, 147 completing the trial. Their mean age was 7.53 years, mean height SDS -2.64 , mean IGF-1 SDS -3.56 . They were entered into a 2-year open-label randomized IGF-1 concentration controlled 37 center GH dosing trial. There were two arms to the study, one titrating the GH dose to achieve mean IGF-1 levels ($n = 70$) and the other adjusting GH dose to attain IGF-1 levels at upper normal ($+2$ SD, high group, $n = 68$). They were compared with a group ($n = 34$) receiving conventional weight-based GH dosing ($40 \mu\text{g/kg/day}$). The principal outcome measure was the change in height SDS.

Results: It took 6–9 months to establish target IGF-1 levels in the dose titration groups. The high IGF-1 group showed a significantly ($p < 0.001$) greater height increase ($+1.6$ SD) compared with the low IGF-1 group ($+1.1$ SD) and the conventional treatment group ($+1.0$ SD). The dose of GH to achieve high IGF-1 levels was more than 2.5 times usual and was very variable (20 – $346 \mu\text{g/kg/day}$).

Multivariate analysis showed that the key factors were IGF-1 SDS level, GH dose and pretreatment stimulated GH peak.

Conclusion(s): This study demonstrates the possibility of IGF-1-based GH dosing with the target of maintaining IGF-1 in the desired range. This is now the approach used in adult GH replacement and it has now been demonstrated as a feasible approach in children.

This large multicentre open-label, randomized IGF-1-based GH dosing trial is the first set of evidence to support the feasibility of IGF-1-based dosing in children. However, significantly high doses of up to seven times the usual top of the range of GH regimens may be required to achieve top IGF-1 levels, and result in an improved growth response. Only two IGF-1 levels, mean and +2SD were targeted and not subtle variations in between which would reflect real life practice. Even within each study limb there was much variability in GH responsiveness. A significant growth improvement was noted in the high IGF-1 group over 2 years, and the lack of additional bone age advance in this group predicted that if this high level were maintained in the longer term, it would result in net height gain, something presumably could be extrapolated from the clinical situation of GH excess. The authors comment that the growth-promoting effects however could be independent of the rise in serum IGF-1 and be attributable to the cumulative dose of GH itself. They take considerable pains to discuss safety issues, especially with respect to high IGF-1 levels and cancer risk but longer term outcomes need a larger cohort and more than 2 years follow-up. Although there was no excess of short-term side effects seen in the high IGF-1 group, long-term outcomes need to be ascertained.

This was a large multicenter open-label RCT, the strengths of which were its rigorous methodology and clear endpoints. Its weaknesses were that it only looked at the mean and upper normal IGF-1 concentrations.

New hope – toddlers, Turners and GH

Growth hormone treatment of early growth failure in toddlers with Turner syndrome: a randomized, controlled, multicenter trial

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J Clin Endocrinol Metab 2007;92:3406–3416

Background: Height SD score (SDS) diminishes from birth relating to prenatal growth failure in Turner syndrome (TS). The authors aimed to determine whether GH treatment started before the age of 4 years in girls with TS would prevent further growth failure. Secondary aims were to identify factors associated with treatment response and discover if outcome could be predicted with regression modeling using these factors. Assess safety of GH in TS less than 4 years.

Methods: The authors undertook the Toddler Turner Study, August 1999 to August 2003 in 11 US pediatric endocrine centers, enrolling 88 girls with TS, aged 9 months to 4 years. The interventions were treatment with recombinant GH ($50 \mu\text{g}/\text{kg} \cdot \text{day}$; $n = 45$) or no treatment ($n = 43$) over a 2-year period. The primary outcome measure was the baseline to 2-year change in height SDS.

Results: Evidence of short stature was found at baseline (mean height SDS = -1.6 ± 1.0 at mean age 24.0 ± 12.1 months). There was a decrease in height SDS -1.8 ± 1.1 to -2.2 ± 1.2 (0.5 SDS decline) in the control group compared to mean height SDS gain 1.4 ± 1.0 to -0.3 ± 1.1 (1.1 SDS gain) in the GH group. Overall there was a 2-year between-group difference of 1.6 ± 0.6 SDS, which was statistically significant ($p < 0.0001$). The baseline variable with the strongest correlation to 2-year height gain was: the difference between mid-parental height SDS and subjects' height SDS ($r = 0.32$; $p = 0.04$). Actual height SDS at 2 years could be predicted with good accuracy based on baseline variables alone ($R^2 = 0.81$; $p < 0.0001$). However, the prediction of the 2-year change in height SDS required inclusion of initial treatment response data (4-month or 1-year height velocity) in the model ($R^2 = 0.54$; $p < 0.0001$). No new side effects were uncovered in association with GH treatment in this age group.

Conclusion(s): GH therapy is safe and effective at correcting growth failure and normalizing height in TS girls less than 4 years old.

The authors have a clear primary outcome: mean height SDS increased in the GH group (1.1 SDS gain) and decreased in the control group (0.5 SDS decline). Many previous studies have demonstrated GH-mediated improvements in height velocity and near adult or adult height; however, the previous controlled clinical trials have focused on older girls mean age 9–11 years. To date no RCT has been undertaken in TS girls less than 4 years. Other studies quote a mean age of starting GH in TS from 9.0 ± 3.8 to 10.1 ± 3.6 years.

The response to GH is highly variable from one individual to the next, therefore why is this study important in TS girls at a younger age? This hypothesis makes common sense when one considers the prenatal growth failure in TS; however, starting younger also maximizes growth potential if the safety profile is adequate in this age group. Delay in starting GH has potential negative impacts including progressive growth failure and delayed induction of puberty to maximize adult height. These events may in turn influence bone mineralization, cardiovascular health and may have significant psychological impact. Early diagnosis is essential to optimize the outcome in children with TS. This study reports younger children are highly responsive to GH therapy. What is the comparison in growth velocity in older Turner girls? A prediction model for height velocity in the first year of GH therapy in TS (1.52 cm/year) has previously been described by Ranke et al. [9]; however, this was in girls younger than 11 years of age precluding any direct comparison. Altogether, the data are promising but we must remember that these are short-term data and that long-term results on all end-points considered are necessary to reach a final conclusion.

This was a prospective, randomized, controlled, open-label, multicenter clinical trial. It had a good study design, and was a large multi-centre study with large numbers in this difficult age group (<4 years). RCTs of this size are unable to detect significant adverse events and therefore cannot conclude on GH safety profiles.

New concerns – inherited male reproductive problems

Risk factors for hypospadias

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Eur J Pediatr 2007;166:671–678

Background: The etiology of hypospadias, the most common and important condition of male under-masculinization still remains largely unknown. Many risk factors have been implicated, including parental health, fertility status and fertility treatments, characteristics of patient and parent pregnancies and lifestyle, exposure to drugs and environmental agents.

Methods: This was a large scale single-center retrospective population-based analysis ($n = 583$) with a prospectively recruited control group of boys of similar age and background ($n = 251$). Questionnaires about health status and exposure to the above risk factors were sent to the parents of both cases and controls. Analysis evaluating the independent contribution of each of risk factors was performed by logistic regression analyses.

Results: The most notable factor was the presence of hypospadias in the fathers of boys with hypospadias, odds ratio (OR) 9.7, and in low birth weight boys (OR 2.3) and multiple pregnancies (OR 2.0). Elevated risk was also present when mothers themselves had received diethylstilbestrol whilst in utero OR 3.5 (no increased OR on diethylstilbestrol-treated fathers). Infertility treatment was associated with overall OR of 2.3 (fathers only OR 1.8). Other factors associated with increased ORs for hypospadias in the 3 months prior to conception or the first trimester were maternal iron use (OR 2.2), maternal smoking (OR 1.5), paternal prescription drug use (OR 2.6), and paternal pesticide exposure (OR 2.1).

Conclusion(s): This study supports the multiple etiology hypotheses in the occurrence of hypospadias, namely substances which interfere with natural hormonal processes, but most noteworthy is the clear genetic predisposition in offspring of affected fathers.

Increased frequency of reproductive health problems among fathers of boys with hypospadias

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Hum Reprod 2007;22:2639–2646

Background: Previous investigations have indicated an association between paternal subfertility and the occurrence of hypospadias in their male offspring. This association has not been systematically investigated. This study looked at male reproductive health among a cohort of fathers of boys with hypospadias in comparison with fathers of unaffected boys.

Methods: Sixty-four fathers whose sons had hypospadias participated. The control group was 349 fathers with unaffected sons. All participants produced a semen sample, a blood sample, underwent a physical examination and completed a questionnaire.

Results: Fathers of boys with hypospadias had a significantly lower median sperm concentration ($54.1 \times 10^6/\text{ml}$) than the controls ($81.2 \times 10^6/\text{ml}$; $p = 0.004$) and their total sperm count (222.0×10^6) was also reduced (controls 326.0×10^6 ; $p = 0.009$). Furthermore, the fathers of boys with hypospadias reported more urogenital system disorders (hypospadias, cryptorchidism and testicular cancer; 11/64; $p < 0.001$) than the control group (16/349). There were no significant differences in time to conception. However, 15% of hypospadias boys' fathers had received fertility treatment.

Conclusion(s): Fathers with hypospadias produce an increased frequency of hypospadias in their sons. These men also demonstrate decreased semen quality and require more help with assisted conception. This suggests genes controlling reproductive function are directly inherited, but an additional impact of environmental factors cannot be excluded.

Reduced serum testosterone levels in infant boys conceived by intracytoplasmic sperm injection

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J Clin Endocrinol Metab 2007;92:2598–2603

Background: The health outcome for infants born by the newer generation of assisted conception techniques has been questioned. Intracytoplasmic sperm injection (ICSI) is a commonly used technique to treat male infertility. However it is not known whether aspects of impaired testicular function can be transmitted from father to son.

Methods: This study investigated testicular function in boys conceived by ICSI by evaluating the natural spontaneous testicular activity at 3 months of postnatal age. Testosterone, SHBG, inhibin B, FSH, LH and penile length were measured in a prospective longitudinal cohort study in 125 boys conceived by ICSI, 124 boys conceived by in vitro fertilization, and 933 boys conceived naturally.

Results: Boys with assisted conception had significantly lower median birth weight and birth lengths (ICSI 3.3 kg, $p < 0.001$; IVF 3.4 kg, $p < 0.05$; controls 3.6 kg), but this difference corrected by 3 months of age. Median penile length was significantly shorter at 3 months (ICSI 3.7 cm, IVF 3.5 cm, controls 3.9 cm). Those conceived by ICSI had significantly lower testosterone levels (median 2.4 nmol/l) compared with naturally conceived boys (3.3 nmol/l; $p < 0.001$) and additionally the LH:testosterone ratio was higher in the ICSI group (0.8 vs. 0.5 respectively; $p = 0.001$). No differences were found between controls and boys conceived by in vitro methods on account of maternal infertility. No differences in inhibin B, FSH and inhibin:FSH ratios were seen between the groups.

Conclusion(s): This study suggests that there is a mild impairment of Leydig cell function in boys conceived by ICSI but no equivalent dysfunction in Sertoli cells. It is possible that this is a paternally inherited phenomenon. Further study into other factors is required, especially as ICSI is used more frequently nowadays to treat male infertility.

These three papers, each one a large scale controlled cohort study, have independently concluded that not only are defects in masculinization of multifactorial etiology, but that there is also a hereditary element which requires further study. Brouwers et al. and Asklund et al. each demonstrated an

increased likelihood of hypospadias in sons of affected fathers by up to nearly ten times, and additionally these fathers showed other aspects of impairment of testicular function in the higher requirement for assisted conception techniques. The impairment of testicular function itself may be perpetuated if assisted conception, most notably ICSI, is used. Interestingly it is a subtle impairment of Leydig cell, not Sertoli cell and tubular function which is seen and this is the opposite of what would have been predicted. The lower testosterone levels were associated with slightly reduced penile growth. There are other factors such as maternal age and primiparity, gestational diabetes and twin pregnancies, each of which may have a different and independent effect. There is also an association between ICSI and hypospadias as demonstrated previously [10]. Overall, these studies have a common theme, that of subtle impairment of reproductive function with assisted conception techniques and with multiple possible environmental etiologies, but that these defects may become hereditary in some cases needs further clarification. The epigenetics of reproduction proves to be more complex than previously thought.

These studies had large population-based cohorts, prospectively collected in Mau et al., and Asklund et al. with prospectively identified controls groups. The strengths were the significant findings pointing to multiple etiologies, and the weaknesses were that some of the risk factors cited depended upon personal recall.

Concepts revised 1 – identifying children with growth disorders

Developing evidence-based guidelines for referral for short stature

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Arch Dis Child 2008;93:212–217

Background: Identifying growth disorders by population-wide public health monitoring programs as abnormal growth is a recognized indicator of poor health but there is little evidence for the effectiveness and efficacy of individual screening parameters.

Methods: Several different auxological screening criteria were developed and tested with longitudinal data from 4 different groups of patients: 542 referred to 2 hospitals for short stature; 777 girls with Turner syndrome; 216 children with cystic fibrosis, and 120 children with celiac disease, in comparison with 3 large samples from the general population.

Results: For infants 0–3 years, 30% of pathology can be detected with a height below -3 SDS or two serial measurements below -2.5 SDS with a false-positive rate of $<1\%$. For children aged 3–10 years, height below -2 SDS together with the height >2 SDS below target height had the best predictive value of pathology. These together, especially in cases of more severe short stature (-2.5 SDS) and additionally with slowing of growth rate on the chart, would identify 86% of children with Turner syndrome and 77% of children with organic disorders with a false-positive rate of 1.5–2%.

Conclusion(s): These proposed new guidelines for population growth monitoring demonstrate high sensitivity with a low false-positive rate in 3- to 10-year-old children. The most important criterion for identifying pathology in a short child is distance from target height. In infants below 3 years the sensitivity is much lower, low absolute height measurement being the best predictor. These guidelines have yet to be tested in developing countries.

Effectiveness and cost-effectiveness of height-screening programs during the primary school years: a systematic review

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Arch Dis Child 2008;93:278–284

Background: This study aimed to examine the effectiveness and cost-effectiveness of population height screening in primary school aged children (aged 4–11 years) in order to pick up growth-related pathology.

The outcome measures were diagnostic yield of height-related conditions and change in quality of life measured in QALYs (quality-adjusted life years) for early versus late identification and management of pathologies.

Methods: A systematic review of growth screening studies of any design was conducted as part of a population assessment. These studies were identified by literature searches of relevant publications and their bibliographies and contact with experts in the field. Economic modeling was applied to find the most cost-effective approach to diagnosis and treatment of growth-related disorders.

Results: Of 33,689 titles identified, 12 studies were found describing a height screening program and giving a diagnostic yield of new diagnoses of height-related conditions. Reports of GH deficiency varied from 0.05 per thousand (1 in 20,000) to 0.62 per thousand (1 in 1,500). Similar figures for Turner syndrome were between 0.02 per thousand (1 in 50,000) and 0.07 per thousand (1 in 14,000). Other pathological potentially treatable conditions were also detected as a secondary benefit, diagnostic yields between 0.22 and 1.84 per thousand children screened. The incremental cost-utility of height screening at school entry compared with no screening was EUR 12,500 per QALY. This is well below the commonly accepted willingness to pay threshold of EUR 38,000 per QALY.

Conclusion(s): This systematic review has demonstrated the utility and cost-effectiveness of population height screening which occurs through a greater pickup of primary and secondary growth disorders. Further research is needed to examine the benefits on quality of life intervention on early interventions for height-related disorders and to determine the exact role of growth screening in improving the health of children in general.

There is nothing more fundamental in pediatric practice and especially in pediatric endocrinology than the accurate assessment of childhood growth. Yet the evidence for introducing population-based growth monitoring interventions to identify growth-related disorders has been lacking. These two papers provide complementary evidence to the establishment of this important public health exercise. Grote et al. have published the latest in a series of papers examining the evidence base for the performance of different growth parameters, and come up with very clear and simple guidance, namely that short stature especially in combination with a height significantly below target height, has a very low false-positive rate in identifying growth-related pathology. Fayter et al. build on this by conducting a systematic review of published evidence, and in combination with economic modeling around quality of life gains have concluded that screening for growth disorders is a highly effective and cost-effective use of national health resources. These criteria have each yet to be tested in developing countries, but give a clear message to government health departments about this important aspect of child health surveillance.

The study designs were derived populations for analysis and a systematic review. The strengths were their systematic assessment of available evidence. The weakness were that OTH studies were dependent on available population data and published evidence. Prospective studies are required.

Concepts revised – endocrinology and diabetes combined

Classification of distinct baseline insulin infusion patterns in children and adolescents with type 1 diabetes on continuous subcutaneous insulin infusion therapy

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Diabetes Care 2007;30:568–573

Background: The authors hypothesized that systematic differences in the patterns of programmed basal insulin infusion rates in children and adolescents with type 1 diabetes on continuous subcutaneous insulin infusion (CSII). The study aims were classification of basal insulin infusion rate regimens and comparison of patients' clinical characteristics.

Methods: A prospective surveillance database based on the German/Austrian diabetes data acquisition system for pediatric diabetology was the main data source. Basal insulin infusion rates of all 1,248 patients with type 1 diabetes on CSII (0.38–18 years) were analyzed (dataset 1). Basal insulin infusion rates per hour were expressed relative to mean basal insulin infusion rates per 24 h. Unsupervised clustering was used to classify basal insulin infusion rate patterns. Patient clinical characteristics in distinct basal insulin infusion rates were clustered and compared by Kruskal-Wallis. A subset analysis was undertaken in 64 patients assessing changes in basal insulin infusion rates: from initial settings before CSII to most recent settings (dataset 2).

Results: There were 7 different basal insulin infusion rate patterns identified in dataset 1. The dawn-dusk pattern was the most frequently used in 708 patients (14.9 ± 2.4 years) with the peak basal insulin infusion rate at 5 a.m. Other basal patterns showed only one insulin infusion rate oscillation per 24 h with a backshift of peak basal insulin infusion rates in younger children ($p < 0.000001$; 1 a.m.: $n = 152$, 12.4 years and 9 p.m.: $n = 117$, 8.9 years). All but 2 children of a total of 64 patients in dataset 2 were commenced on dawn-dusk patterns. However, there was significant diversification of basal insulin infusion rates during follow-up with backshift of peak basal insulin infusion rates in younger children ($p < 0.01$).

Conclusion(s): Pediatricians often set basal insulin infusion rate profiles on CSII patients reflecting differences in age. These data strongly suggest that age-dependent endocrine changes during childhood (e.g., puberty) affect circadian distribution of insulin needs in CSII and this must be considered when setting basal insulin infusion rates in children and adolescents.

There have been many trials on MDI versus CSII insulin therapy in the pediatric setting. This paper focuses on the dramatic age-, sex- and puberty-related changes in their endocrine system from birth to adolescence. These changes are influenced by hormones antagonizing insulin, e.g. IGF-1, sleep patterns, puberty and circadian rhythms. These changes interact in an age-dependent manner with the pattern of insulin sensitivity thus giving rise to different basal insulin requirements and therefore programmable basal insulin infusion rates.

These data highlight the age-dependent changes in endocrinology that occur during childhood, which must be considered when choosing basal infusion rates for growing children on CSII therapy. These data are based on a large prospective surveillance of a nationwide diabetes registry based on 1,248 children with type 1 diabetes. However, only 65 patients were followed from initial settings before CSII to date. Seven different specific basal rate patterns were identified. The dawn-dusk pattern was the one most commonly used with peak insulin infusion at 5 a.m. There was a statistically significant backshift in peak insulin rates in younger children, ($p < 0.000001$). This study suggests that age-dependent endocrine changes such as puberty affect the circadian distribution of insulin and this should be kept in mind when calculating basal insulin infusion rates in children and adolescents on CSII. This study brings endocrinology and diabetes nicely together.

It was designed as a large prospective cohort study. Its strength is that it is a strong prospective surveillance of a nationwide diabetes registry. The weaknesses are that it is an observational study, and the individual clinical data cannot be accessed for reassessment.

Important for clinical practice 1 – can we manipulate growth during puberty?

Long-term observation of 87 girls with idiopathic central precocious puberty treated with gonadotropin-releasing hormone analogs: impact on adult height, body mass index, bone mineral content, and reproductive function

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J Clin Endocrinol Metab 2008;93:190–195

Background: This is a retrospective longitudinal single-center study to determine the long-term outcome of gonadotropin-releasing hormone analogs (GnRHa) therapy for central precocious puberty on adult height, body mass index, and bone mineral density.

Methods: GnRHa treatment was given for 4.6 ± 1.6 (range 3–7.9) years. Observation after treatment was finished continued for 9.9 ± 2.0 (range 4–10.6) years. Comparator was 32 untreated girls with CPP.

Results: All hormonal measures and uterine dimensions and bone mineral density returned to normal 1 year after treatment cessation. Mean age at menarche was 13.6 ± 1.1 years, 0.9 years after treatment stopped. Menses were normal, 6 patients having normal conceptions and pregnancies. Mean adult height of 159.8 ± 5.3 cm exceeded predictions made at the start of treatment by the method of Bayley and Pinneau by 5.1 ± 4.5 and 9.5 ± 4.6 cm, using advanced and average tables, respectively. Treatment effect did not differ whether older or younger than 7 years at the start. There was a nonsignificant increase in BMI SDS with therapy.

Conclusion(s): This study affirms the safety of GnRHa treatment on the reproductive system and allows an adult height to be attained near target height. Individual responses vary but decisions to start and stop treatment should also take into account the rate of pubertal progression, the effect on height velocity and psychological factors as well.

Final height outcome after three years of growth hormone and gonadotropin-releasing hormone agonist treatment in short adolescents with relatively early puberty

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J Clin Endocrinol Metab 2007;92:1402–1408

Background: This study aimed to evaluate the effect of the combination of GH and GnRHa treatments together on short adolescents in early puberty who were born either small for gestational age or who had idiopathic short stature.

Methods: This was an RCT, with a combined treatment duration of 3 years in 17 adolescents and 15 controls. Entry criteria: puberty at Tanner stage 2–3; bone age <12 years (girls) and <13 years (boys); height SDS <2.0, or between –1.0 and –2.0 SDS if predicted adult height <2.0 SDS. Adult heights were assessed at a minimum age of 18 years in girls and 19 years in boys.

Results: Combination treatment produced a greater height gain of 4.4 ± 4.9 cm at adult height compared with pretreatment predictions and compared with the controls -0.5 ± 6.4 cm. Adult height exceeded pretreatment predictions in 76% patients and 60% of controls. However over the follow-up period, the height advantage was lost with the mean height increment being 4.9 (range –4.0 to +12.3) cm over controls. BMI was unchanged. Hip bone mineral density was similar between the groups, but lumbar spine bone mineral density was slightly reduced in GnRHa-treated boys.

Conclusion(s): The total mean height gain of 4.9 cm resulting from this intervention does not justify the routine use of this intensive and expensive treatment in children with idiopathic short stature or born small for gestational age who are still short at the start of puberty. In addition the longer term effects of possible reduced peak bone mineral density are not known.

These two detailed longitudinal studies, one commencing as an RCT, have contrasted different approaches to manipulate pubertal growth in different patient populations. Both have demonstrated that that height gains resulting from the interventions are modest, yet the conclusions are quite different. The girls with central precocious puberty from the Italian study, many of whom we would currently classify as early normal puberty, may benefit from GnRHa in order to manage the complexities of early puberty including psychological and familial distress, and long-term consequences appear safe, even though growth is significantly improved (which was actually the primary aim). Delaying the process of puberty in older children who are starting puberty relatively earlier together with a GH boost produced disappointing benefits (and possible adverse sequelae on the bones). The patients in the van Gool et al. study are a group of children with different primary pathology who with hindsight would not have been expected to show a normal response to treatment, and despite the fact that GH was not continued to adult height after GnRHa was stopped. The rigor of this approach has left us with clear evidence that routine attempts to manipulate the pubertal growth spurt in this type of patient, whom we frequently see in our clinics, cannot be justified as a cost-effective treatment.

The Dutch study is a RCT, while the Italian study is a longitudinal study, both followed to adult height. They were well-managed cohorts with detailed follow-up. But GH/GnRHa treatment in short adolescents was limited to 3 years only.

Important for clinical practice 2 – same old complications: powerful new evidence

Arterial hypertension determined by ambulatory blood pressure profiles: contribution to microalbuminuria risk in a multicenter investigation in 2,105 children and adolescents with type 1 diabetes

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Background: Raised arterial blood pressure is important in the development of diabetes complications. The authors studies risk factors for abnormal 24-hour blood pressure regulation and microalbuminuria in children and adolescents with type 1 diabetes.

Methods: Ambulatory blood pressure monitoring was performed in 2,105 children and adolescents from 195 pediatric diabetes centers in Germany and Austria based on a nationwide database. Least median squares (LMS)-SD scores were calculated for diurnal and nocturnal systolic (SBP), diastolic (DBP), and mean arterial (MAP) blood pressure on all individuals and compared to normalized values of a reference population of 949 healthy German children. Nocturnal blood pressure reduction (dipping) was calculated for SBP as well as DBP.

Results: Children with diabetes showed significantly elevated nocturnal blood pressure (SBP +0.51, DBP +0.58, MAP +0.80 LMS-SD) and dipping of SBP, DBP, and MAP was significantly reduced ($p < 0.0001$). Age, duration of diabetes, gender, BMI, HbA1c and insulin dosage were related to altered blood pressure profiles; dipping, however, was only affected by age, female gender and HbA1c. Microalbuminuria was associated with nocturnal DBP ($p < 0.0001$) and diastolic dipping ($p < 0.01$).

Conclusion(s): The authors report a clear link between the quality of metabolic control and altered blood pressure regulation even in children with short diabetes duration. Nocturnal blood pressure is particularly associated with diabetes complications such as microalbuminuria.

Impact of physical activity on cardiovascular risk factors in children with type 1 diabetes: a multicenter study of 23,251 patients

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Diabetes Care 2007;30:2098–2100

Background: Type 1 diabetes is associated with a high risk for early atherosclerotic complications. The known risk factors for vascular complications include long duration of diabetes, age, poor glycemia, smoking, hypertension, obesity, and dyslipidemia. A recent study, identified 69% of the type 1 diabetes pediatric patients have one or more of these cardiovascular risk factors.

Methods: The authors focused on the impact of regular physical activity (RPA) on further cardiovascular risk factors such as plasma lipids and blood pressure in children with type 1 diabetes. In this cross-sectional study the following cardiovascular risk factors were evaluated: plasma lipids (cholesterol, HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), and triglycerides (TG), blood pressure, HbA1c, and BMI. Dyslipidemia was defined as cholesterol >200 mg/dl (5.2 mmol/l), HDL cholesterol <35 mg/dl (0.91 mmol/l), LDL cholesterol >160 mg/dl (4.1 mmol/l), or triglycerides >150 mg/dl (1.7 mmol/l). Normative blood pressure data developed by the Task Force on Blood Pressure Control in children served as reference values. For comparison, the HbA1c values were standardized and transformed to the Diabetes Control and Complications Trial normal range.

Results: Patients were grouped by the frequency of their self-reported RPA: RPA0 = none (n = 10,392), RPA1 = 1–2 times/week (n = 8,607), and RPA2 = ≥ 3 times/week (n = 4,252). At every visit to the diabetologist, the DPV software requires information about the frequency of the patient's RPA, which represents exercise performed at least once a week for at least 30 min. The frequency of RPA ranged from 0–9 per week (mean 1.29 per week). 44.7% of the children were not physically active, 37% undertook RPA 1–2 times/week and 18.3% performed RPA >2 /week. Dyslipidemia was present in 38% of children and adolescents, with elevation of cholesterol (24.3%) and TG (25.8%) being most frequent. LDL-C was elevated in 14.2% and HDL-C decreased in 3.1%. The authors report that increasing the frequency of RPA reduced dyslipidemia from 41.2% in RPA0 to 36% in RPA1 and 34.4% in RPA2 ($p < 0.0001$). Systolic and diastolic blood pressure was elevated in 8.1 and 3.1%, respectively. There was no difference in systolic or diastolic blood pressure between the different RPA groups. Multivariate analysis revealed that the percentage of children with elevated diastolic blood pressure was lower in groups RPA1 and 2 when compared to RPA0 ($p < 0.005$). Mean HbA1c was 7.9%. Frequency of RPA was the most important factor influencing HbA1c in multivariate analysis. HbA1c was lower in both genders at every age group with higher frequency of RPA ($p < 0.00001$). Higher HbA1c was associated with higher cholesterol, LDL-C and TG ($p < 0.001$) and lower HDL-C ($p < 0.01$).

Conclusion(s): Increasing physical activity is associated with a beneficial cardiovascular risk profile in children with type 1 diabetes such as lower lipoproteins and diastolic blood pressure and with better glycemic control. Physical activity should represent an important issue in education of children and adolescents with type 1 diabetes and be performed regularly by these patients.

Diabetic nephropathy in 27,805 children, adolescents, and adults with type 1 diabetes: effect of diabetes duration, A1C, hypertension, dyslipidemia, diabetes onset, and sex

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Diabetes Care 2007;30:2523–2528

Background: The authors' aims in this study were to provide a profile of nephropathy and associated risk factors in a large, prospective cohort of patients with type 1 diabetes with pediatric and adolescent onset of disease.

Methods: 27,805 patients from the nationwide, prospective German Diabetes Documentation System survey were analyzed. Inclusion criteria were at least two documented urine analyses with identical classification. Urine analyses, treatment regimens, diabetes complications, and risk factors were recorded prospectively. Baseline characteristics were median age at diagnosis 9.94 (interquartile range 5.8–14.3) years, age at last visit 16.34 (12.5–22.2) years, and follow-up time 2.5 (0.43–5.3) years. The cumulative incidence of nephropathy was analyzed with Kaplan-Meier and logistic regression was used to ascertain the association with risk factors.

Results: Baseline characteristics were drawn from a total number of 49,027 patients with type 1 diabetes being continuously followed and data collected. Nephropathy was classified as normal in 26,605, microalbuminuric in 919, macroalbuminuric in 78, and end-stage renal disease (ESRD) in 203 patients. 25.4% (95% CI 22.3–28.3) were identified with microalbuminuria and 9.4% (95% CI 8.3–11.4) had macroalbuminuria or ESRD over calculated diabetes duration of 40 years. The significant risk factors for microalbuminuria were: diabetes duration (odds ratio 1.033, $p < 0.0001$), HbA1c (OR 1.13, $p < 0.0001$), LDL (1.003, $p < 0.0074$), and blood pressure (OR 1.008, $p < 0.0074$) and the onset of diabetes in childhood was protective (OR 1.011, $p < 0.0001$). Male gender was associated with macroalbuminuria.

Conclusion(s): Diabetes duration, HbA1c, dyslipidemia, blood pressure, and male gender were identified as risk factors for nephropathy. Early diagnosis and prompt treatment of dyslipidemia and hypertension is mandatory in patients with type 1 diabetes.

All three of these large cohort studies help provide new and important information on the age old topic of complications of diabetes; however, we now have the benefit of huge nationwide diabetes registries, which makes these large cohort studies possible.

Dost et al. focus on ambulatory blood pressure monitoring and its contribution to microalbuminuria. Ambulatory blood pressure monitoring was performed in 2,105 children and adolescents from 195

pediatric diabetes centers. In children with diabetes, nocturnal blood pressure in particular was significantly elevated and dipping of SBP, DBP, and MAP was significantly reduced. Furthermore, the lack of nocturnal dipping was associated with elevated microalbuminuria.

Herbst et al. examine the influence of regular physical activity on cardiovascular risk factors in children and adolescents with type 1 diabetes. The authors recently reported that the frequency of regular physical activity (RPA) represents an important factor influencing HbA1c [11]. Dyslipidemia was present 38% of children and adolescents, with elevation of cholesterol (24.3%), TG (25.8%) LDL-C (14.2%), and HDL-C decreased in 3.1%. The authors report an increase in the frequency of RPA reduced dyslipidemia from 41.2% in RPA0 to 36% in RPA1 and 34.4% in RPA2 ($p < 0.0001$). Girls had higher concentrations of all measures of dyslipidemia than boys ($p < 0.001$). Multivariate analysis found HDL-C and TG were altered by the frequency of RPA; whereas cholesterol and LDL-C were not. Raile et al. focus on nephropathy and its associated risk factors. In adults, microalbuminuria and the risk factors, smoking, hypertension and poor glycemia control, predict increased risk from cardiovascular disease and early mortality. In childhood onset diabetes, young age at diagnosis and a longer prepubertal time, seem to delay the time to develop microalbuminuria, a phenomenon not fully understood. The authors reconfirm that significant risk factors for microalbuminuria were: diabetes duration, HbA1c, LDL-C, and blood pressure and the onset of diabetes in childhood was protective (1.011, $p < 0.0001$). The Dost and Raile papers overlap in this regard; Dost describes elevated SBP, DBP and MAP with a lack of nocturnal dipping in children and adolescents with type 1 diabetes, furthermore the lack of nocturnal dipping was associated with elevated microalbuminuria. Whereas Raile et al. reconfirm the association between elevated blood pressure and microalbuminuria.

Complications of type 1 diabetes (arterial hypertension, dyslipidemia, and nephropathy) are equally as prevalent as previously reported. These data report that complications of diabetes commence in childhood and need regular and early monitoring to identify those at risk. Herbst et al. report a considerable benefit from frequent RPA in reducing these complications and HbA1c. The protective effect of childhood onset diabetes against microalbuminuria is reassuring. Together these three studies remind us that good evidence can be obtained from large cohort studies and not all studies must be RCTs. The authors in these studies used prospective nationwide data registries to study cardiovascular risk factors in children and adolescents with type 1 diabetes.

All three studies are large population-based cohort studies. The power of the cohort study for statistical analysis is formidable. A mean HbA1c 7.9% from Herbst et al. lends great power to large cohort studies such as these. The weaknesses are that the RPA reported by the authors was based on self-reporting and the intensity of the sports activity and school sports were not included in the assessment. However, this is outweighed by the large numbers.

New mechanisms – the face of GH

A longitudinal study of craniofacial growth in idiopathic short stature and growth hormone-deficient boys treated with growth hormone

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Eur J Orthod 2007;29:243–250

Background: This study intended to examine the longitudinal effect of GH on craniofacial growth in boys with GH deficiency and idiopathic short stature.

Methods: This was a prospective, longitudinal controlled study of 46 boys, mean age 11.8 years (25 GH deficient, 21 ISS), GH treatment randomized to 33 or 67 $\mu\text{g/kg/day}$. Controls were a semi-longitudinal group of 130 boys aged 7–21 years. Lateral radiographs were taken annually and cephalometric measurements were performed and converted to SDS. GH continued until the cessation of growth, mean follow-up 6.4 (SD 1.8) years.

Results: Pretreatment cranial morphology demonstrated reduced measurements for facial structures in the patient groups together with a retrognathic facial type. Enhancement of the growth of the facial

bones was a notable feature of GH treatment. GH produced a more prognathic growth pattern, a more anterior position of the jaws when compared with the base of the skull. Thirty-five percent had orthodontic treatment which was associated with lesser growth in the height of the mandibular ramus. The length of the body of the mandible and height of the face was greater with GH treatment compared with the controls. There was no difference in facial growth parameters between GH treatment doses, nor between GH deficient and ISS groups.

Conclusion(s): GH treatment produced an overall increase in growth toward normal levels for 71% of variables. The study shows that GH treatment in short boys has a favorable effect on craniofacial growth and does not induce acromegalic features.

How often do we read about descriptions of the crowding of mid-facial structures in GH deficiency and indeed this is an important clinical sign. There have been worries that standard GH treatment could have acromegalic-like effects on the skeleton [12] producing concerns about replacement treatment. This very elegant, prospective, longitudinal, controlled study has been able to demonstrate that there is increased facial growth compared with controls, but that this is not excessive, even with higher GH doses, and that GH treatment serves to ameliorate the facial architecture. Therefore there appears to be no worry of distortion of facial growth and development of acromegalic features with standard GH treatment regimens.

The study was designed as a prospective RCT of two GH dosage regimens (high and low). Its strengths lie in the detailed assessment of craniofacial growth, and a weakness is the small size of the study.

Clinical trials, new treatments – MDI versus CSII: the never-ending story

Comparison of continuous subcutaneous insulin infusion (CSII) and multiple daily injections (MDI) in pediatric type 1 diabetes: a multicenter matched-pair cohort analysis over 3 years

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Diabet Med 2008;25:80–85

Background: Continuous subcutaneous insulin infusion (CSII) has been available since the 1970s; however, it has really only been widely used in pediatric patient populations from the 1990s to date. There are limited numbers of prospective studies comparing CSII with multiple daily injections (MDI) in pediatrics, therefore the authors undertook a multicenter, matched-pair cohort study to assess glycemic control and side-effect profiles in these insulin modalities.

Methods: In a cohort of 434 matched pairs over a 3-year period the following parameters were analyzed prospectively: HbA1c, insulin dose, body mass index–standard deviation score (BMI–SDS), hypoglycemic rate, diabetic ketoacidosis (DKA) rate and intensity of care after initiation of MDI or CSII.

Results: There was a significant difference with lower HbA1c in the CSII group for the first year only (CSII 7.5 ± 0.05 vs. MDI 7.7 ± 0.06 ; $p < 0.05$), but this difference was not present by year 3, even though insulin requirements remained significantly lower in the CSII group. The BMI–SDS increased in both study groups. Severe hypoglycemia decreased significantly after the change of regimen (CSII 17.87 ± 2.85 vs. MDI 25.14 ± 3.79 ; $p < 0.05$) and over the 3-year period especially when compared with baseline (-21 vs. -16%). DKA rate was lower at baseline in the CSII group and remained significantly lower over the 3-year period.

Conclusion(s): Over a 3-year period CSII has been proven to be a safe modality of insulin therapy with similar glycemic effects, but with significantly reduced hypoglycemia and DKA rates and overall a lower insulin requirement when compared with MDI.

The authors argue that RCTs do not always apply to 'real life' situations. For example in choice of insulin therapy in diabetes, one cannot simply choose CSII or MDI and patient choice must be considered and individualized in each scenario. Quality of life must be considered along with cost-effectiveness of the insulin modality selected. Other papers agree with these conclusions including a

5-year prospective longitudinal paper by Hanas et al., previously reviewed in this chapter [1]. The authors conclude that as an intensive insulin modality CSII is safe, with lower insulin requirements and reduced DKA and hypoglycemia rates compared to MDI. Although this is a large cohort study with similar results to previous studies, the CSII versus MDI debate continues.

The study was designed as a multicenter, matched-pair cohort study. It has a good design, and is a large cohort study from German/Austrian nationwide diabetes registry. The weakness is that there were significant drop outs in the CSII numbers from 434 at baseline to 199 at 3 years when compared to 434 and 309 in the MDI group.

Reviews – controversies in GH treatment

A randomized, double-blind study to assess the efficacy and safety of valtropin, a biosimilar growth hormone, in children with growth hormone deficiency

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Horm Res 2007;68:288–293

Background: Valtropin is one of the 'biosimilar' GH compounds produced by a novel yeast expression system. In this study its efficacy is compared with Humatrope, a standard recombinant human GH preparation.

Methods: 146 previously untreated GH-deficient children were randomized to 1-year treatment with Valtropin (n = 98) or Humatrope (n = 49) at a dose of 0.3 mg/kg/week in a multicenter, multinational study. Baseline data between the groups was similar. IGF-1; IGFBP-3 and GH antibodies were assayed in a central laboratory.

Results: One-year height velocity on Valtropin was 11.3 ± 3.0 cm/year and on Humatrope was 10.5 ± 2.8 cm/year, the difference within the predefined non-inferiority criterion of -2.0 cm/year. HSDS increased in both groups with no difference in bone maturation. IGF-1 and IGFBP-3 concentrations increased by a similar amount. Safety data showed no differences between the groups as was the detection of anti-GH antibodies in 3.1% of Valtropin- and 2.0% of Humatrope-treated patients.

Conclusion(s): This new biosimilar GH Valtropin exhibits a similar efficacy and safety profile to the comparator hGH Humatrope over this 1-year study. The longer term efficacy and safety profiles have yet to be determined.

Recombinant growth hormone for idiopathic short stature in children and adolescents

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Cochrane Database Syst Rev 2007;3:CD004440

Background: Idiopathic short stature (ISS) is defined as height 2 SD below the mean with a reduced adult height prognosis. As there are no precise diagnostic criteria, the exact prevalence cannot be determined. As GH has been considered for ISS children (and has a product license currently in the USA), objective outcome criteria need to be determined.

Methods: A systematic review of the current available evidence performed according to Cochrane Metabolic and Endocrine Disorders Group methods from MEDLINE, EMBASE, the Cochrane Library, Science Citation Index, BIOSIS and Current Controlled Trials. Trials needed to have included GH treatment for a minimum of 6 months in short-term studies or until adult height (or near adult height; height velocity <2 cm/year) and be compared with placebo or no treatment.

Results: Ten studies, all RCTs met the review criteria. Only four contained more than 50 participants. Dosage ranges were very variable. Short-term studies report gains ranging from 0 to 0.7 SD over the first year. One trial reported near adult height in girls and found that girls treated with GH were 7.5 cm

taller than untreated controls (GH group 155.3 ± 6.4 cm; control 147.8 ± 2.6 cm; $p = 0.003$). Another trial which reported the adult height standard deviation score found that children treated with GH were 3.7 cm taller than children in a placebo-treated group (95% confidence intervals 0.03–1.10; $p < 0.04$). Only one study examined quality of life and demonstrated no changes over 2 years on GH treatment. The incremental cost-effective ratios gave the estimated cost for each centimeter gained at adult height to be between EUR 9,400 and 18,930. Few adverse events were noted.

Conclusion(s): Published RCTs show that GH is effective in promoting growth in children with ISS in the short-term. Data on children treated and followed to adult height are limited so conclusions about the longer term effects of GH are tenuous. Height gains being modest are such that treated individuals remain relatively short when compared with peers of normal stature. The only study considering quality of life could provide no evidence to support the commonly held assumption that GH benefits children with ISS. Greater evidence from more detailed and appropriately constructed RCTs is needed before the clinical and cost benefit of GH treatment in ISS can be fully evaluated.

These two papers present important evidence in two controversial areas of GH treatment. Peterkova et al. provide that this is the first clinical report on the safety and efficacy of this new biosimilar rhGH preparation. Since the recent licensing in Europe of these compounds, debate has continued as to their safety and appropriateness of treatment given the shortened licensing process [for a full review see, 13]. Time will tell, but this study begins the quest for parallel, rigorous accrual of evidence which will eventually confirm or disprove the clinical parity of biosimilar rhGH preparations in the same way that the initial *Escherichia coli* genetically produced rhGH brands were first received with appropriate caution at their launch.

The merest mention of treatment of children with ISS either brings a loud chorus of support or fierce opposition. Bryant et al. in this *Cochrane Systematic Review* examine the latest evidence. It is disappointing that even now there are so few studies with adult height data. It is clear that GH is effective in producing short-term acceleration in growth in children with ISS and that some of this height gain can be maintained. No evidence of an improvement in quality of life is available. Whether this is an indication for GH treatment which will gain a European license and general acceptance is still not clear. This will depend on results of more extensive RCTs, demonstration of improved quality of life and favorable economic evaluation.

The studies were an RCT and a systematic review. Both had rigorous evidence-based approaches but they lack long-term data.

Food for thought – VLBW and insulin at birth and in young adults

Early elective insulin therapy can reduce hyperglycemia and increase insulin-like growth factor-I levels in very low birth weight infants

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Background: IGF-I is the dominant hormone involved in fetal growth, and low levels have been implicated in neonatal morbidities, such as retinopathy of prematurity.

Methods: Infants of very low birth weight (VLBW) were assessed with the use of insulin introduced early and used throughout the first week of life: to improve glucose control and increase IGF-I. This was a prospective RCT with the intervention group ($n = 8$) receiving insulin (0.025 U/kg/h) on days 1–7, with 20% dextrose to maintain normoglycemia and the control infants ($n = 8$) receiving conventional neonatal care. All infants underwent continuous glucose monitoring (CGM) for 7 days.

Results: There was little difference between the intervention and conventional care groups for mean gestational age ($\pm$ standard deviation, 26.2 ± 2.5 vs. 26.9 ± 2.7 weeks) and birth weight (0.79 ± 0.26 vs. 0.73 ± 0.16 kg). The authors quote a dramatic 36 versus 7.6% difference in the percentage of total time >10 mmol/l (hyperglycemia) in standard versus early intervention arm respectively ($p = 0.035$).

Despite this there was no difference in the percentage of total time <2.6 mmol/l (hypoglycemia) between the 2 groups ($p = 0.746$). During the 7-day monitoring period the early insulin treatment group had significantly lower mean glucose, less glucose variance and higher percentage glucose in target range (4–8 mmol/l). The insulin-treated group had a 2.4-fold increase in mean IGF-I bioactivity ($p = 0.005$).

Conclusion(s): The use of early insulin therapy improves blood glucose control and increases IGF-I bioactivity levels. This may lead to reduced morbidity associated with hyperglycemia and diminished IGF-I concentrations.

The authors hypothesize that early use of insulin therapy with dextrose would improve glycemia and IGF-I levels in VLBW infants in neonatal intensive care. This novel study combines a simple hypothesis in premature infants (23.7–28.2/40) with new technology: continuous glucose monitoring (CGM). Although manufacturers recommend the use of the CGM sensors for a 72-hour period, in this study all infants tolerated the sensor for 7 days, with no side effects and adequate monitoring. The IGF-I kinase receptor activation bioactivity assay used is based on cells transfected with human IGF-I receptor gene which has recently been validated and shown to be highly sensitive and specific.

Early insulin replacement may be important in prematurity not only for normoglycemia but also to improve IGF-I generation and bioavailability. There was no significant difference in total IGF-I protein concentrations between the groups; however, IGFBP-I was lower and IGF-I was 2.4-fold higher in the insulin treatment group ($p = 0.005$). However, the endogenous bioactivity of IGF-I was estimated by the ability of serum to activate (i.e. phosphorylate) the IGF-I receptors in vitro; this does not necessarily reflect IGF-I bioactivity at the local tissue level. Reduced IGFBP-I could also contribute to increased IGF-I bioactivity, because IGFBP-I is a potent IGF-I inhibitor in vitro.

Improved IGF-I bioactivity may have short- and long-term health benefits in premature infants: decrease retinopathy of prematurity, poor weight gain, head growth and insulin resistance. Although this study was a RCT, it was too small to assess these clinical outcomes, which require a larger prospective study. The fact that all infants tolerated the CGM for 7 days is another indication that CGM is a valid, safe and useful research tool well recognized in glycemia assessment. It is well known the CGM sensor is less sensitive <3.0 mmol/l; however, the authors ensured that all these periods of hypoglycemia were matched with plasma blood glucose measurements. Because the sensor tends to read lower and lags behind plasma glucose, one can be assured that these periods of hypoglycemia are over rather than underrepresented. The findings in this small randomized controlled study support the hypothesis that hyperglycemia can be prevented with early elective insulin therapy in VLBW infants, without the increased risk of further hypoglycemia, similar to the intensive therapy arm in the DCCT trial without the hypoglycemic side effects [14].

This was a RCT with a small number of patients ($n = 16$). The strengths are that it is a RCT with a novel focus on new technology with IGF-I bioactivity. How accurate the IGF-I bioassay is as a measure of bioactivity in extremes of prematurity and whether it reflects IGF-I activity at the local tissue level are weaknesses. Seven of the 8 patients in the conventional therapy arm also received insulin therapy.

Glucose regulation in young adults with very low birth weight

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N Engl J Med 2007;356:2053–2063

Background: Infants born preterm birth with very low birth weight (VLBW) are associated with insulin resistance in childhood. When insulin resistance persists into adulthood, preterm birth with VLBW may also be associated with an increased risk of disease in adulthood. The authors assessed glucose tolerance, insulin sensitivity, serum lipid concentrations and blood pressure in young adults with VLBW.

Methods: Standard 75-gram oral glucose-tolerance testing, measuring insulin and glucose at baseline and 120 min, was undertaken in 163 young adults (age range 18–27 years) with VLBW and in 169 term appropriate for gestational age patients. The 2 groups were matched for age, sex, and birth hospital. The authors measured blood pressure and serum lipid levels in all subjects, and in 150 VLBW subjects and 136 term patients body composition by means of dual-energy X-ray absorptiometry was also measured.

Results: When comparing term patients to those with VLBW, the VLBW subjects had raised 2-hour glucose concentration (6.7%), fasting insulin concentration (16.7%), 2-hour insulin concentration (40.0%), insulin-resistance index determined by homeostatic model HOMA-IR (18.9%), and an increase of 4.8 mmHg in systolic blood pressure. Adjustment for the lower lean body mass in the VLBW subjects did not weaken these relationships.

Conclusion(s): VLBW compared to term infants are prone to higher indices of insulin resistance, glucose intolerance and systolic blood pressure in young adult life.

This study follows on from the Beardsall et al. paper [15], further assessing the well-known effect of VLBW on insulin resistance and disease in adulthood. Those born VLBW had significantly higher fasting insulin, 2-hour OGTT, 2-hour insulin, higher HOMA-IR and higher systolic blood pressure, when compared to those born at term. These differences were not due to body size, composition or fat distribution based on DEXA scanning. This large study confirms the well-known association between VLBW and adult disease especially cardiovascular and diabetes. The authors also assessed systolic blood pressure and lipid profiles using DEXA scanning in subset analysis of this population. Serum lipids including mean total cholesterol ($p = 0.37$), HDL-cholesterol ($p = 0.71$) and triglycerides ($p = 0.95$) were no different between the 2 groups. None of the subjects in the VLBW or term group had a diagnosis of type 2 diabetes; however, 10 in the VLBW and 8 in term group had impaired glucose tolerance.

Adults born VLBW may be more prone to type 2 diabetes and cardiovascular disease later in life. Lifestyle interventions can be effective in preventing these disease states, thus early identification of these at risk patients provides an opportunity for disease prevention in the future. Perhaps young adults born with VLBW would benefit from a targeted preventive interventional approach.

This was a large, well-constructed, prospective, population-based cohort study from birth to adult life.

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