Evidence-Based Medicine in Pediatric Endocrinology

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This has been an outstanding year of publications in pediatric endocrinology and diabetes since last year’s *Yearbook* chapter on evidence-based medicine [1]. The selection process has been very challenging given the space available but we have endeavored to feature the key publications, chosen on the quality of the methodology, and the significance of the outcome, especially with regard to day-to-day clinical practice. Additionally, we have tried to produce a balance of topics in pediatric endocrinology and diabetes. Many other high-quality evidence-based studies, however, can also be found in other chapters in this book. There have also been consensus statements published on the diagnosis and management of children with idiopathic short stature, and optimal management of undescended testes [2, 3]. This chapter contains a selection of important RCTs, but also randomized trials of other designs, more appropriate for the population under study. This year we are beginning to see the first reports of well-designed clinical studies of growth hormone treatment that include final adult height status, which is surely the best evidence of efficacy of any growth intervention. We also include systematic reviews and very large-scale population studies. We hope these selected publications will help with understanding and improve both knowledge and the clinical care of patients.

Mechanism of the year – new technologies in diabetes

Continuous glucose monitoring and intensive treatment of type 1 diabetes

Tamborlane WV, Beck RW, Bode BW, Buckingham B, Chase HP, Clemons R, Fiallo-Scharer R, Fox LA, Gilliam LK, Hirsch IB, Huang ES, Kollman C, Kowalski AJ, Laffel L, Lawrence JM, Lee J, Mauras N, O’Grady M, Ruedy KJ, Tansey M, Tsalikian E, Weinzimer S, Wilson DM, Wolpert H, Wysocki T, Xing D

Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group

N Engl J Med 2008;359:1464–1476

Background: The value of continuous glucose monitoring (CGM) in the management of type 1 diabetes has not yet been determined.

Methods: A multicenter clinical trial randomly assigned 322 adults and children already receiving intensive therapy for type 1 diabetes to CGM or a control group performing home monitoring. Patients were stratified into three groups according to age and had a glycated hemoglobin level of 7.0–10.0%. The primary outcome was the change in the HbA1c at 26 weeks.

Results: The changes in HbA1c levels in the two study groups varied markedly according to age group ($p = 0.003$), with a significant difference among patients 25 years of age or older that favored the continuous-monitoring group (mean difference in change -0.53% ; 95% confidence interval [CI] -0.71 to -0.35 ; $p < 0.001$). The between-group difference was not significant among those who were 15–24 years of age (mean difference 0.08 ; 95% CI -0.17 to 0.33 ; $p = 0.52$) or among those who were 8–14 years of age (mean difference -0.13 ; 95% CI, -0.38 to 0.11 ; $p = 0.29$). Secondary HbA1c outcomes were better in the CGM group than in the control group among the oldest and youngest patients but not among those who were 15–24 years of age. The use of CGM averaged ≥ 6.0 days/week for 83% of patients 25 years of age or older, 30% of those 15–24 years of age, and 50% of those 8–14 years of age. The rate of severe hypoglycemia was low and did not differ between the two study groups.

Conclusions: CGM can be associated with improved glycemic control in adults with type 1 diabetes. Future research is warranted to identify barriers to effective continuous monitoring in children and adolescents.

Continuous glucose monitoring system in children with type 1 diabetes mellitus: a systematic review and meta-analysis

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Diabetologia 2008;51:233–240

Background: The authors investigated the potential effects of the Continuous Glucose Monitoring System (CGMS), as compared with self-monitoring of blood glucose (SMBG), on glycemic control in children with type 1 diabetes.

Methods: MEDLINE, EMBASE and The Cochrane Library electronic databases were searched in June 2007. Additional references were obtained from reviewed articles. Only randomized controlled trials were included.

Results: Five trials involving 131 type 1 diabetic patients were included in the study. Combined data from all trials showed that the CGMS did not significantly reduce HbA1c levels compared with control groups. The pooled weighted mean difference was -0.02% (95% CI -0.29 to 0.25) with a fixed model and remained insignificant in the random effect model. Sensitivity analysis-determined results were stable. There was a trend towards a longer time under the CGMS curve for glucose <3.89 mmol/l in the CGMS group compared with the control group (mean difference 49.00 min, 95% CI -18.00 to 116.00). The CGMS significantly increased the number of insulin dose changes per patient per month for those managed with CGMS compared with the control groups (mean difference 6.3 changes, 95% CI 2.88 – 9.72).

Conclusions: The CGMS is not better than SMBG with regard to improvement of metabolic control in children with type 1 diabetes. Because of the small number of participants and methodological limitations of the studies included, findings of this meta-analysis must be interpreted with care.

Validation of continuous glucose monitoring in children and adolescents with cystic fibrosis: a prospective cohort study

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Diabetes Care 2009;32:1020–1022

Background: This study aimed to validate continuous glucose monitoring (CGM) in children and adolescents with cystic fibrosis.

Methods: Over a 24-month period, 102 children (aged 9.5–19.0 years) with cystic fibrosis (CF) undertook oral glucose tolerance tests (OGTTs) and CGM monitoring at the same time. These paired tests were completed at baseline (CGM1) and 12 months later (CGM2). CGM validity was assessed by reliability, reproducibility, and repeatability.

Results: Bland-Altman agreement analysis was undertaken to assess reliability. CGM was found to be reliable with a between CGM and OGTT of 0.81 mmol/l (95% CI for bias ± 2.90 mmol/l) and a good correlation coefficient between the OGTT and CGM ($r = 0.74$ – 0.9 ; $p < 0.01$). CGM was reproducible with no significant differences in the coefficient of variation of the CGM assessment between visits and repeatable with a mean difference between CGM1 and CGM2 of 0.09 mmol/l (95% CI for difference ± 0.46 mmol/l). Discriminant ratios were also undertaken to confirm reproducibility, the results were of 13.0 at visit 1 and 15.1 at visit 2.

Conclusions: In children and adolescents with CF, CGM performed on two occasions over a 12-month period was reliable, reproducible, and repeatable.

All three papers above highlight the utility of new technology in the form of continuous glucose monitoring (CGM) in the modern management of intensive diabetes care. When CGM technology was introduced it was supposed to revolutionize the safety and effectiveness of intensive insulin therapy in type 1 diabetes. This new tool could allow patients with diabetes to optimize basal insulin requirements and precisely define mealtime insulin boluses. However, the initial CGM system was suboptimal and sensor accuracy was in question. Today, real-time glucose sensing allows CGM integration into the everyday intensive management of children and adolescents with diabetes, allowing for improved mean glucose, reduction in glycemic variability and reduction in HbA1c.

The recent paper by Tamborlane et al. highlights the utility of CGM in young adults (>25 years) when used continuously. However, the use of CGM averaged ≥ 6.0 days/week for 83% of patients >25 years age, 30% of those 15–24 years old, and 50% of the children in the age group 8–14 years. These results were disappointing for the child and adolescent arm of this cohort study, however there were not separate child and adolescent age groups but a combination of both. Based on the evidence suggested from this paper, CGM does not have a role in everyday management of children (8–14 years) unless used continuously. However, the *NEJM* paper reveals significant bias in its selection criteria and in the HbA1c start point for the children and adolescent (60 and 57% HbA1c <8.0%) versus the very well-controlled adult cohort (83% HbA1c <8.0%) [4].

Based on current evidence, CGM is useful in adults when used continuously and there is not enough evidence for children and adolescents. However, new data presented at the American Diabetes Association in New Orleans in 2009 highlights that patients of all ages including children and adolescents who were willing to use CGM 6/7 days over a 6-month period showed an equal reduction in HbA1c of 0.5%. All three age groups were followed for a further 6 months, i.e. 12 months in total and sustained these lower HbA1c when CGM was in high use [5]. These results are more positive and conclude that CGM does have sustained and long-term beneficial effects on glycemic control in all age groups.

A small meta-analysis by Golicki et al. reports that CGM is no better than routine home blood glucose monitoring in children with type 1 diabetes. Once again, this is a good study design; however there were very few studies, five in total, able to be included in this meta-analysis. The authors admit that due to the small number of participants and methodological limitations of the studies included, findings of this meta-analysis must be interpreted with care. We await other ongoing prospective trials on CGM utility in the care of children and adolescents with diabetes.

CGM is being used in a wide variety of scenarios in pediatric endocrinology, one of these specialized areas is cystic fibrosis and cystic fibrosis-related diabetes (CFRD). The authors report that CGM is valid for use in children with CF and CFRD. The paper by O’Riordan et al. describes the valid components of CGM for use in children with CF under the headings: reliability, reproducibility and repeatability. The study was a prospective multicenter cohort study of 102 children and adolescents with CF and CFRD. The study was undertaken over a 24-month period with two glycemic measures, OGTT and CGM, at the same time 12 months apart. When CGM was performed on two occasions over a 12-month period, it was found to be reliable, reproducible, and repeatable. Thus the novel use of CGM in assessment of glycemic dysregulation is valid in children and adolescents with CF.

These papers provide different and sometimes conflicting evidence focused on the utility and validity of CGM in childhood diabetes. All three papers provide food for thought and acknowledge that this new technology may be useful and valid in diabetes management in certain populations (type 1 diabetes and CFRD). Until large international prospective randomized control trials in children and adolescents are done, CGM cannot be regarded as fully effective by evidence-based criteria.

New paradigms

Control of childhood congenital adrenal hyperplasia and sleep activity and quality with morning or evening glucocorticoid therapy

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J Clin Endocrinol Metab 2008;93:4707–4710

Background: In most patients with congenital adrenal hyperplasia (CAH), hydrocortisone (HC) replacement therapy is given three times a day. Although a higher morning dose mimics physiological diurnal variation in cortisol secretion, giving the higher dose in the evening has been advocated to suppress the early morning surge in adrenal activity. However, giving larger doses of HC later on has been claimed to be associated with sleep disturbances and insomnia. This study aimed to evaluate giving the high HC dose in the evening versus morning with respect to disease control, sleep pattern, and daytime activity in children with CAH.

Methods: This study was an open-label, cross-over, randomized trial in 15 children with classical CAH. Patients were randomized to receive 50% of the daily HC either in the morning or in the evening for 2 weeks; the other two doses each containing 25% of the total daily dose. Disease control was assessed by 08:00 h 17-hydroxyprogesterone, testosterone, androstenedione, and dehydroepiandrosterone sulfate levels on the last day of each treatment schedule. Sleep and daytime activity were assessed by a 7-day ActiGraph.

Results: There were no significant differences in basal hormone values between the high-morning and high-evening HC treatment schedules. No significant differences in sleep or daytime activity between the schedules were recorded.

Conclusions: Neither disease control, sleep quality nor daytime activity were affected by the timing of the peak HC dose. The authors recommend the high-morning dose schedule in replacement therapy of children with CAH as being more physiological.

Managing replacement HC well in children and adolescents with CAH is one of the biggest challenges facing a pediatric endocrinologist. This elegant and well-designed randomized cross-over trial aimed at answering a simple and practical question. Does giving a reverse physiological HC dosing schedule in order to achieve better disease control cause upset to sleep parameters and changes to a child's waking activity levels? The ActiGraph was able to record time in bed, total sleep time, total wake time, sleep onset latency, sleep efficiency, arousal and activity indices. No differences were recorded between the different treatment schedules. Single morning hormone profiles could not distinguish differences in disease control between the schedules, although, as the authors admit, this does not reflect hormone status throughout the day. However, the hypothesis that a reverse HC regimen causes disturbances in wakefulness in children as has been reported in adults can therefore be rejected. Answering this simple question can bring us the evidence for reassuring our patients and families that any necessary alterations in HC schedule merited on clinical or biochemical grounds should not cause disturbance to a child's lifestyle. Very important for clinical practice.

Bone mineral density in adolescent females using injectable or oral contraceptives: a 24-month prospective study

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Fertil Steril 2008;90:2060–2067

Background: This study aimed to determine whether young female adolescents using hormonal-contraceptive methods have a lower bone mineral density (BMD) than an untreated comparison group.

Methods: This was an observational, prospective cohort study of 24-month duration in adolescent clinics in a Midwestern US city. 433 postmenarcheal girls, 12–18 years of age, who were on depot medroxyprogesterone acetate (DMPA; $n = 58$), or were on oral contraceptives containing 100 μg of levonorgestrel and 20 μg of ethinyl estradiol (OCs; $n = 187$), or were untreated ($n = 188$) were studied. Measurements of BMD at spine and femoral neck were obtained by using dual x-ray absorptiometry at baseline and 6-month intervals and were corrected for volumetric variations in bone content.

Results: Over the 24-month period, the mean percentage change in spine BMD in each group was: DMPA -1.5% , OC $+4.2\%$, and untreated $+6.3\%$. The mean percentage change in femoral neck BMD in each group was: DMPA -5.2% , OC $+3.0\%$, and untreated $+3.8\%$. A statistical significant fall in BMD was seen between the DMPA group and the other two groups. In the DMPA group, the mean percentage change in spine BMD over the first 12 months was -1.4% , but the rate of change slowed to -0.1% over the second 12 months. No measures of bone density loss reached the level of clinical osteopenia.

Conclusions: Adolescent girls receiving DMPA showed a significant loss in BMD, in contrast with the bone gain in both the OC and the untreated groups. However, the clinical significance of this finding is mitigated by slowed bone loss after the first year of DMPA use and general maintenance of bone density values within the normal range in the DMPA group over time.

Why has this paper been included in the *Yearbook*, as it is a report from adolescent medical services? We as pediatric endocrinologists are keen to optimize bone health in our adolescent patients. This observational, prospective cohort study was conducted principally to examine the effect of DMPA on

bone health. The reduction in BMD should sound a note of caution, despite the unlikelihood of reaching clinical osteopenia. No increased fracture rate has been reported in premenopausal adult women. However, the 20 µg of ethinyl estradiol combined OC is the mainstay of most sex steroid replacement regimens in hypogonadism and ovarian dysfunction disorders, for example, in Turner syndrome. This study states that this treatment regimen is likely to be satisfactory to develop adequate bone mineralization in the 12- to 18-year group, but that further studies are required using different OC doses and estrogen types. DMPA is prescribed as it is the most effective contraceptive in adolescent girls. If we are required to consider this treatment in the presence of other risk factors for osteopenia such as immobility or dietary disorders, then the authors recommend that BMD status should be assessed. Yet, osteopenia has to be prevented rather than treated, and assessing alone is a poor preventive measure. There was no discussion of either the etiology or an approach to the prevention of progestagen-induced osteopenia. This requires further evaluation via appropriately designed clinical trials.

New hope – prolonging endogenous insulin secretion

Etanercept treatment in children with new onset type 1 diabetes: pilot randomized, placebo-controlled, double-blind study

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Diabetes Care 2009;32:1244–1249

Background: The authors conducted a feasibility and efficacy study of etanercept therapy to prolong endogenous insulin production in newly diagnosed pediatric patients with type 1 diabetes mellitus.

Methods: A 24-week double-blind, randomized, placebo-controlled study was undertaken in 18 children (11 M/7 F, age 7.8–18.2 years). Children were randomized to receive either placebo (P) or etanercept (E). Inclusion criteria were age 3–18 years, GAD-65 and/or ICA positivity, HbA1c >6%, 3 insulin injections per day, WBC 3,000–10,000, platelets >100,000, and normal liver and renal function. Intention-to-treat analysis was used.

Results: HbA1c at week 24 was lower in the etanercept ($5.91 \pm 0.5\%$) compared with the placebo group ($6.98 \pm 1.2\%$; $p < 0.05$) with a higher percent decrease from baseline compared with the placebo (E 0.41 ± 0.1 vs. P $0.18 \pm 0.21\%$; $p < 0.01$). The percent change in C-peptide AUC from baseline to week 24 showed a 39% increase in the etanercept group and a 20% decrease in the placebo group ($p < 0.05$). Baseline to week 24 insulin dose decreased 18% in the etanercept group compared with a 23% increase in the placebo group ($p < 0.05$).

Conclusions: In this small pilot study, treatment of pediatric patients newly diagnosed with type 1 diabetes with etanercept reduced HbA1c, increased endogenous insulin production, suggesting preservation of β -cell function.

Etanercept is a subcutaneously administered biological response modifier that binds and inactivates tumor necrosis factor- α , a proinflammatory cytokine. In patients with early active rheumatoid arthritis, etanercept is associated with rapid improvement in disease activity. This is a double-blind, randomized, placebo-controlled study. Although only a small pilot study of the use of etanercept as a novel therapy in newly diagnosed children with type 1 diabetes, the results are promising; suggesting lower HbA1c, increased endogenous insulin production and β -cell preservation. One case in the literature highlighted that etanercept may be associated with the onset of type 1 diabetes in a 7-year-old girl, 5 months after the initiation of etanercept therapy. However, larger randomized controlled trials are warranted to confirm these preliminary results and to explore the safety and efficacy profiles in childhood.

Management and 1-year outcome for UK children with type 2 diabetes

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Arch Dis Child 2009;94:206–209

Background: This paper is a report of the 1-year outcome in the UK for children newly diagnosed with type 2 diabetes.

Methods: All children under the age of 17 years diagnosed as having type 2 diabetes from 1 October 2004 to 31 October 2005 were reported as part of a follow-up study of a UK national cohort.

Results: Follow-up data were available on 73 of 76 children. The mean age at follow-up was 14.5 years, with mean duration of diabetes 1 year. The revised incidence of type 2 diabetes in the UK in children under 17 years is 0.6/100,000/year. The mean body mass index (BMI) SDS at diagnosis was 2.89, and mean change at 1 year was –0.11 (range –1.53 to +1.37). At 1 year, only 58% achieved within target HbA1c $\leq 7.0\%$ (ADA and EASD). No relationship between improvement in BMI and improvement in HbA1c was identified. There was wide variation in choice of treatments and regimens. Hypertension was a common comorbidity (34%) and nephropathy less common (4%). Evidence of polycystic ovarian disease was identified in 26% of girls. In the first year after diagnosis, 22% of children had not been screened for nephropathy or retinopathy.

Conclusions: Pediatricians use a wide variety of treatment regimens to reduce HbA1c, however systematic screening for complications of diabetes is incomplete. Evidence-based treatment and management protocols are urgently needed to reduce the risks of long-term micro- and macrovascular complications of diabetes.

Shield et al. describe the difficulties young children have in the first year after diagnosis with type 2 diabetes, indicating that many children find it hard to make the necessary lifestyle changes needed to positively affect metabolic health. This follow-up national cohort study redefines the UK incidence of childhood type 2 diabetes in children under 17 years is 0.6/100,000/year. Pediatricians are noted to use a wide variety of treatment regimens to reduce HbA1c, however systematic screening for complications of diabetes is lacking. In the USA among African-American youths aged 10–19 years, prevalence (per 1,000) of type 2 diabetes was 1.06 (0.93–1.22) with an annual incidence of 19.0/100,000. Although the age ranges (<17 vs. 10–19 years) do not allow exact comparison, it seems that the USA is farther ahead with more new cases of type 2 diabetes in childhood. This paper is important as the epidemic of type 2 diabetes continues to emerge across Europe. It highlights the urgent need for evidence-based treatment and management protocols to reduce the risks of long-term complications of type 2 diabetes in these children. Large national-based audits and follow-up audits are essential to develop evidence-based treatment and management protocols in this challenging group of children.

Concepts revised – thyroid disease in childhood

Perinatal outcome of children born to mothers with thyroid dysfunction or antibodies: a prospective population-based cohort study

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J Clin Endocrinol Metab 2009;94:772–779

Background: The authors prospectively investigated the effects of thyroid dysfunction or antibody positivity on perinatal outcome.

Methods: Population was the Northern Finland Birth Cohort 1986 (9,247 singleton pregnancies). First-trimester maternal serum samples were analyzed for thyroid hormones [TSH, free T₄ (fT₄)] and antibodies [thyroid-peroxidase antibody (TPO-Ab) and thyroglobulin antibody (TG-Ab)]. Mothers were classified by their hormone and antibody status into percentile categories based on laboratory data and compared. Outcome variables were perinatal mortality, preterm delivery, absolute and gestational age-adjusted birth weight, and absolute and relative placental weight.

Results: Children from TPO-Ab- and TG-Ab-positive mothers had higher perinatal mortality which was not affected by thyroid hormone status. Unadjusted and adjusted (for maternal age and parity) risk for increased perinatal mortality was an odds ratio of 3.1 and 3.2 (1.4–7.1) in TPO-Ab- and 2.6 and 2.5 (1.1–5.9) in TG-Ab-positive mothers. TPO-Ab-positive mothers had more large infants, $p = 0.017$, as did mothers with low TSH and high fT₄ concentrations vs. reference group (6.6 vs. 2.5%, $p = 0.045$). Significantly higher placental weights were observed in mothers with low TSH and high fT₄ or high TSH and low fT₄ levels as well as among TPO-Ab-positive mothers.

Conclusions: First-trimester antibody positivity is a risk factor for perinatal death but not altered thyroid hormone status. Thyroid dysfunction early in pregnancy affects fetal and placental growth.

Thyroid autoimmunity in schoolchildren in an area with long-standing iodine sufficiency: correlation with gender, pubertal stage, and maternal thyroid autoimmunity

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Thyroid 2008;18:747–754

Background: The aim of this study was to determine the prevalence of thyroid autoimmunity (TA) in children and adolescents, and to determine if there are relationships between the period of onset of TA and gender and between TA and maternal autoimmunity.

Methods: Antithyroperoxidase antibodies (anti-TPO Ab), antithyroglobulin antibodies (anti-Tg Ab), thyrotropin, thyroxine, triiodothyronine, and urinary iodine were determined in 440 healthy schoolchildren (200 boys and 240 girls), aged 5–18 years, and in 123 mothers.

Results: The prevalence of positive anti-TPO and anti-Tg Ab was 4.6 and 4.3%, respectively. In girls, the prevalence of positive anti-TPO Ab was higher in Tanner stage 2–5 compared with Tanner stage 1 (8.2 vs. 2.2%; $p < 0.05$). No difference was detected with regard to anti-Tg Ab. In girls, positive anti-TPO and anti-Tg Ab levels were associated with significantly greater thyroid volume. Hypoechogenicity was detected in 52.6 and 36.8% of the children with positive anti-TPO or anti-Tg Ab, respectively ($p = 0.0005$). The prevalence of autoimmune thyroiditis, as defined by positive serum anti-TPO and/or anti-Tg and an echographic pattern of the thyroid gland having diffuse or irregular hypoechogenicity, was 2.5%. Mothers of anti-TPO Ab-positive children had positive anti-TPO Ab more frequently compared with mothers of anti-TPO Ab-negative children (82 vs. 18%; $p = 0.0005$). Mothers of anti-Tg Ab-positive children had positive anti-Tg Ab more frequently compared to mothers of anti-Tg Ab-negative children (75 vs. 25%; $p = 0.0005$).

Conclusions: These findings demonstrate that TA positivity in children was significantly associated with maternal autoimmunity and their development in girls emerges at puberty. Because genetic background, female gender and puberty are strongly associated with TA, girls with a family history of TA should be reassessed at the onset of puberty.

Two different papers were reviewed together as these disorders of the thyroid are common in childhood. There are few large population-based studies assessing the effects of thyroid antibody positivity on perinatal outcome. This work by Mannisto et al. is a prospective population-based Northern Finland Birth Cohort 1986, including 9,247 singleton pregnancies. The increased risk of perinatal mortality quoted in this paper is high with odds ratios of 3.1 and 2.5 for TPO and TG antibody-positive mothers. The authors conclude that first-trimester antibody positivity is a risk factor for perinatal death but not altered thyroid hormone status. Thus, thyroid dysfunction early in pregnancy affects fetal and placental growth. The next report from Athens, Greece, demonstrates that thyroid autoimmunity (TA) positivity in children was significantly associated with maternal autoimmunity and their development in girls emerges at puberty. These data are derived from thyroid autoantibodies, thy-

roxine, triiodothyronine, and urinary iodine measurements which were determined in a large cohort of 440 healthy schoolchildren (200 boys and 240 girls), aged 5–18 years, and in 123 mothers. Hypoechogenicity was detected in more than one-half and one-third of the children found to be positive anti-TPO or anti-Tg Ab, respectively ($p = 0.0005$). The prevalence of TA, defined by positive serum anti-TPO and/or anti-Tg and an echographic pattern of the thyroid gland being diffuse or irregular hypoechogenicity was 2.5%. The authors conclude that because genetic background, female gender, and puberty are strongly associated with TA; girls with a family history of TA should be reassessed at the onset of puberty. These papers were chosen based on good study design, large population-based datasets or large cohort studies. All describe known anecdotal associations in various aspects in thyroid disease in childhood and adolescence. However, these reports provide good evidence to support and confirm these associations.

Concepts revised – GH treatment to final adult height

Dose-dependent effect of growth hormone on final height in children with short stature without growth hormone deficiency

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J Clin Endocrinol Metab 2008;93:4342–4350

Background: This study aimed at defining the response to GH treatment in children without GH deficiency, focusing especially in those described as having idiopathic short stature (ISS) who were treated in a controlled trial until final height. The study also aimed at examining the effect of two different doses of GH.

Methods: This was a randomized controlled, long-term, multicenter trial from Sweden. Children were all short (-2 SD) and GH deficiency and organic disease were excluded. Although 177 subjects were initially enrolled, after exclusion of those born small for gestational age (SGA) the final group included 126 children in the intention-to-treat population and 68 subjects who observed the study protocol exactly. The principal outcomes were final height SD score (SDS), difference in SDS to midparenteral height, and gain in height SDS. Two doses of GH (Genotropin) were administered, 33 or 67 $\mu\text{g/kg/day}$; control subjects were untreated.

Results: GH therapy was given for a mean of 5.9 ± 1.1 years. The final height SDS in the protocol observing population treated with GH was -1.5 ± 0.81 (33 $\mu\text{g/kg/day}$ -1.7 ± 0.70 , and 67 $\mu\text{g/kg/day}$ -1.4 ± 0.86 ; $p < 0.032$) vs. -2.4 ± 0.85 in the controls ($p < 0.001$). The difference in SDS to midparenteral height was -0.2 ± 1.0 vs. -1.0 ± 0.74 ($p < 0.001$), and the gain in height SDS was 1.3 ± 0.78 vs. 0.2 ± 0.69 ($p < 0.001$). The time to the onset of puberty was unchanged. A dose-response relationship identified after 1 year continued to final height for all growth outcome variables in all populations studied.

Conclusions: GH treatment significantly increased final height in ISS children with a clear dose responsiveness. Although the mean treatment gain was 1.3 SDS (8 cm), there was a broad range of response from no gain to +3 SDS compared with a mean increase of +0.2 SDS in the untreated controls. The distance from initial target height predicted greater gains in height. GH therapy was monitored and found to be safe.

A randomised study of the effect of two doses of biosynthetic human growth hormone on final height of children with familial short stature

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Horm Res 2008;70:89–92

Background: This randomized trial aimed to ascertain the dose-dependent effect of two different doses of recombinant human GH in children with familial short stature (FSS) who were not GH-deficient.

Methods: The age range of the 29 (24 male, 5 female) FSS children at presentation was 5.1–10.5 years, height <1.5 standard deviation scores (SDS) below the mean, height velocity SDS >–1.5 and peak growth hormone response to provocative testing >13.5 mU/l. GH was randomized in two doses, 20 or 40 IU/m² body surface area/week (33 or 67 µg/kg/day) by daily subcutaneous injection of GH and continued until the endpoint which was assessment of adult height.

Results: Adult height data (SDS) were similar at 16.5 ± 2.1 years for the low-dose group –1.06 (SD 0.75) and at 16.1 ± 1.1 years for the high-dose group –1.02 (SD 0.83) (no significant difference, *p* = 0.88 for adult height). The incremental effect of both doses on stature was minimal (low-dose actual minus predicted difference in height 0.79 (SD 0.94), high dose 1.27 (SD 0.88); *p* = 0.12).

Conclusions: Neither GH dosing schedule produced beneficial effects either in short-term gains in height or in long-term increases in adult stature in this group of children with FSS.

These two papers reporting randomized trials of GH treatment in non-GH-deficient short statured children followed up to adult height seem at first glance to show opposite results. However, on closer inspection that is not the case. They represent carefully designed and executed clinical trials begun over 20 years ago which have run to completion with the ultimate endpoint of measured adult height thus providing the highest level of evidence in this situation. Albertsson-Wikland's paper is a remarkable achievement, as it has a randomized untreated group. In what ways are they similar? Both studies randomized patients to the same standard and high doses of GH, and one of the studies showed a dose-dependent increase in stature with a similar non-significant trend in the other study. In the study of Coelho et al. the recruited patients were more homogeneous, being less short and not as far below target height as those in Albertsson-Wikland et al. In this latter study there was a greater range of responses to GH with short children of non-familial short stature families showing the best height gains on GH treatment in a dose-dependent manner. Thus the conclusions of both trials is that slightly short children of short parents do not show good responsiveness to GH treatment, whereas Albertsson-Wikland et al. demonstrate that ISS patients furthest below target height at diagnosis gain the most in height. However, despite the demonstration of gains in height, additional evidence is needed on cost effectiveness and quality-of-life gains before GH can be advocated.

A randomised study of two doses of biosynthetic human growth hormone on final height of pubertal children with growth hormone deficiency

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Horm Res 2008;70:85–88

Background: This study was a randomized clinical trial to determine the effectiveness of two different doses of GH therapy (standard and high dose) during puberty in children undergoing treatment for growth hormone deficiency (GHD).

Methods: 49 children with GHD who showed a spontaneous onset of puberty were allocated randomly using a random number table to one of two groups: 15 IU/m²/week (25 µg/kg/day) or 30 IU/m²/week (50 µg/kg/day). Patients were also included if they had received hGH daily at a dose of 15 IU/m²/week for at least 1 year before randomization.

Results: Both groups showed similar height standard deviation score (SDS) increases (standard dose: 1.1; high dose: 1.2; *p* = 0.81). Time to mid-puberty was similar, but the high-dose group attained adult height 1.1 year earlier at 16.1 years (*p* = 0.026).

Conclusions: Doubling the dose GH from the start of puberty until adult height does not appear to have a significant effect on adult height of children with GH deficiency.

Studies of the nocturnal physiological pattern of GH secretion during puberty have demonstrated a 2- to 4-fold increase in total GH secretion. The corollary of this is that this physiological pattern of normal growth should be reproduced by doubling the pubertal GH replacement dose in patients with GHD. Interestingly, this common sense idea is rejected by this study, and has not been upheld in earlier short-term studies. The GH dose has not previously been found to be a significant factor in modeling total pubertal growth gains. Although there was a reduction in the duration of the pubertal growth spurt with high-dose treatment, this was not during the acceleration phase, time to mid-puberty being similar between the groups. This lack of ability to significantly manipulate the magnitude of adolescent growth remains one of the unmet challenges of pediatric endocrinology. The authors suggest that altering pubertal tempo with GnRH analogues or aromatase inhibitors, or intensifying prepubertal hGH therapy may be more promising approaches to improving final height in children with GH deficiency, but this remains speculative until evidence is provided.

Important for clinical practice – highs, lows and carbs!

Cognitive function is disrupted by both hypo- and hyperglycemia in school-aged children with type 1 diabetes: a field study

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Background: The authors developed a field procedure using personal digital assistant (PDA) technology to test the hypothesis that naturally occurring episodes of hypo- and hyperglycemia are associated with deterioration in cognitive function in children with type 1 diabetes.

Methods: A total of 61 children aged 6–11 years with type 1 diabetes received a PDA programmed with two brief cognitive tests (mental maths and choice reaction time), which they completed just before home glucose readings. The computer recorded speed of each test and number of correct answers. Children undertook multiple tests daily over 4–6 weeks for a total of 70 tests. Performance variables were compared across glucose ranges. Individual impairment scores were calculated from the SD between performance during euglycemia and that during glucose extremes.

Results: Hypoglycemia increased time to complete both mental maths and reaction time. During hyperglycemic episodes, time to complete maths was significantly longer and there was a trend towards increased reaction time ($p = 0.053$). No differences on task accuracy were found. Decline in mental maths performance was equal at glucose levels <3.0 and >22.2 mmol/l. Individual impairment scores varied greatly across children, with no age or sex differences.

Conclusions: Mental efficiency declines with naturally occurring hypoglycemic and hyperglycemic fluctuations in children with type 1 diabetes. There are equal declines in performance for low and high blood glucose concentrations >22.2 mmol/l. These effects can be detected using PDA technology.

Impact of carbohydrate counting on glycemic control in children with type 1 diabetes

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Background: To study the association between parent carbohydrate counting knowledge and glycemic control in children with type 1 diabetes (T1D).

Methods: The authors assessed 67 youth ages 4–12 years with T1D (duration ≥ 1 year). Parents estimated carbohydrate content of children's meals. The ratio of parent estimates to computer analysis defined

carbohydrate counting knowledge; the mean and SD of these ratios defined accuracy and precision, respectively. HbA1c defined glycemic control.

Results: Better accuracy and precision were associated with lower HbA1c in bivariate analyses ($p < 0.05$). In a multivariate analysis ($R^2 = 0.25$, $p = 0.007$) adjusting for child age, sex, and type 1 diabetes duration, precision ($p = 0.02$) and more frequent blood glucose monitoring ($p = 0.04$), but not accuracy ($p = 0.9$), were associated with lower HbA1c. HbA1c was 0.8% lower among youth whose parents demonstrated precise knowledge of carbohydrate counting.

Conclusions: Parental precision with carbohydrate counting and increased blood glucose monitoring were associated with lower HbA1c in children with type 1 diabetes.

The first report by Gonder-Frederick et al. provides good evidence on practical everyday management of patients in the pediatric diabetes clinic. The authors report declining mental performance and efficiency with naturally occurring hypo- and hyperglycemic glucose fluctuations in children with type 1 diabetes. However, what is most interesting about this paper is that the authors highlight the equal decline in performance for low (<3.0 mmol/l) and high blood glucose concentrations >22.2 mmol/l. These effects can be detected using PDA technology. The impact of severe hypoglycemic episodes on cognitive development in children with diabetes is well known; however, practical demonstration of similar effects from hyperglycemia >22.2 mmol/l has not been previously described. Prevention of extremes of hypo- and hyperglycemia are important as both impact equally on the mental performance and efficiency of the developing brain in childhood diabetes. Mehta et al. demonstrate that precision with carbohydrate counting by parents and increased blood glucose monitoring were associated with lower HbA1c in children with type 1 diabetes. This paper reminds us that in this age group <12 years old, the parent is the primary caregiver and the huge responsibilities that are included in intensive diabetes care for children, including precise carbohydrate counting. The reported reduction in HbA1c by 0.8% was significantly associated with precise carbohydrate counting and more frequent blood glucose measurements. This reduction in HbA1c (almost 1%) is important, according to the Diabetes Complications and Controls Trial (DCCT), which demonstrated that intensive diabetes care effectively delays the onset and slows the progression of diabetic retinopathy (76%), nephropathy (39%), and neuropathy (60%) in patients with type 1 diabetes [6]. These two papers report practical data for the everyday management of children and highlight the importance of carbohydrate counting and prevention of extremes of glucose fluctuations. These papers reflect some of the NICE guidelines [7]. These papers are neither randomized nor population-based but both provide sound important practical evidence on more than 60 children in each cohort <12 years old with type 1 diabetes.

Clinical trials, new treatments

Nasal insulin to prevent type 1 diabetes in children with HLA genotypes and autoantibodies conferring increased risk of disease: a double-blind, randomised controlled trial

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Background: In mouse models of diabetes, prophylactic insulin reduced incidence of the disease. The authors investigated whether administration of nasal insulin decreased the incidence of type 1 diabetes, in children with HLA genotypes and susceptibility autoantibodies.

Methods: At three university hospitals in Turku, Oulu, and Tampere (Finland), cord blood samples were analyzed of 116,720 consecutively born infants, and 3,430 of their siblings, for the HLA-DQB1 susceptibility alleles for type 1 diabetes. 17,397 infants and 1,613 siblings had increased genetic risk, of whom 11,225 and 1,574, respectively, consented to screening of diabetes-associated autoantibodies at every 3–12 months. During this double-blind trial, patients were randomly assigned 224 infants and 40 siblings positive for two or more autoantibodies, in consecutive samples, to receive short-acting human

insulin (1 unit/kg; n = 115 and n = 22) or placebo (n = 109 and n = 18) once a day intranasally. Restricted randomization was used, stratified by site, with permuted blocks of size two. Primary endpoint was diagnosis of diabetes. Analysis was by intention to treat. The study was terminated early because insulin had no beneficial effect.

Results: Median duration of the intervention was 1.8 years (range 0–9.7). Diabetes was diagnosed in 49 index children randomized to receive insulin, and in 47 randomized to placebo (hazard ratio [HR] 1.14; 95% CI 0.73–1.77). 42 and 38 of these children, respectively, continued treatment until diagnosis, with yearly rates of diabetes onset of 16.8% (95% CI 11.7–21.9) and 15.3% (10.5–20.2). Seven siblings were diagnosed with diabetes in the insulin group, versus 6 in the placebo group (HR 1.93; 0.56–6.77). In all randomized children, diabetes was diagnosed in 56 in the insulin group, and 53 in the placebo group (HR 0.98; 0.67–1.43, p = 0.91).

Conclusions: In children with HLA-conferred susceptibility to diabetes, administration of nasal insulin, started soon after detection of autoantibodies, does not prevent or delay type 1 diabetes.

In this large double-blinded randomized controlled trial from Finland, 11 225 and 1574 infants and their siblings were finally included to assess their HLA susceptibility to diabetes. Administration of nasal insulin, started soon after detection of autoantibodies does not prevent or delay type 1 diabetes. This paper has a good study design but the problem lies in the very indirect assessment (diabetes or not) of the immune tolerance that is meant to be induced by intra-nasal administration. At time of writing, nasal insulin that was meant to deliver hormonally active (rather than immunologically active) insulin has been withdrawn from the retail market. Perhaps if rapid acting analogues were used instead of nasal insulin the results might be more relevant to clinical practice and diabetes care. This study highlights that even with national screening in Finland and early autoantibody susceptibility screening the prophylactic use of nasal insulin does not prevent the onset of diabetes and that new schemes should be evaluated to induce immune tolerance in type 1 diabetes.

New mechanisms – novel GH regimens in SGA

Growth response to an individualised versus fixed dose GH treatment in short children born small for gestational age: the OPTIMA study

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Eur J Endocrinol 2009;160:149–156

Background: This randomized, open-label, multicenter study compared the effect of an individually adjusted GH dose versus a fixed high GH dose over 1 year in 194 prepubertal children born small for gestational age (SGA) who failed to show catch-up growth and were severely short. Initial GH-induced catch-up growth is highly variable in short SGA children and is mainly influenced by age at start of therapy and GH dose.

Methods: The fixed high GH dose group received 67 µg/kg/day GH continuously throughout the 12-month study. The individually adjusted GH dose group initially received 35 µg/kg/day GH. After 3 months of treatment, if predicted annual change was <0.75 SDS using the Cologne Growth-Prediction Model, then the dose of GH was increased to 67 µg/kg/day for the remaining 9 months, otherwise the initial dose was continued.

Results: In the individually adjusted GH dose group, 38 out of the 80 patients required a GH dose increase from month 3 following the prediction model application. From an ANCOVA for non-inferiority, mean difference in change in height SDS between individually adjusted GH dose and fixed high GH dose groups was –0.24 (95% confidence interval (CI) –0.35: –0.12), the CI for height SDS being above the predefined non-inferiority margin of –0.5 SDS based on reasonable expectations. Safety data were similar between groups but a reduction of GH dose due to IGF-I SDS >0.5 and IGFBP-3 SDS <–0.5 was made in 4/99 fixed high GH dose patients, but not in any of the individually adjusted GH dose group patients.

Conclusions: There was a statistically significant mean difference of 1 cm lower total growth over the full year in the individually adjusted GH dose compared with the fixed high GH dose group, although this was considered non-inferior as per the predetermined endpoint. The authors suggest that early growth prediction may be used to tailor the dose to the individual patient's needs, thus resulting in a lower overall GH dose.

European multicentre study in children born small for gestational age with persistent short stature: comparison of continuous and discontinuous growth hormone treatment regimens

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Background: This was a multinational randomized, prospective, 2-year parallel group study designed to investigate the most effective GH treatment regimen for increasing height in short children born SGA.

Methods: A total of 151 SGA children aged 3–8 years, height below -2.5 standard deviation scores) were randomized into three groups: low-dose GH continuously for 2 years ($33 \mu\text{g/kg/day}$, $n = 51$); high-dose GH for 1 year ($100 \mu\text{g/kg/day}$, $n = 51$) and then no treatment for 1 year; or were left untreated for 1 year then received mid-dose GH for 1 year ($67 \mu\text{g/kg/day}$, $n = 47$). Height, bone age and adverse events were determined during 3 monthly assessments.

Results: The additional height increase with GH after 1 year, compared with untreated controls, was greater with high-dose than with low-dose GH (mean (SD) gain 6.5 ± 0.2 vs. 3.3 ± 0.2 cm). After 2 years, the additional height gain was similar between high- and low-dose GH groups (between-group treatment difference = 0.2 cm, 95% CI = -0.8 to 1.2 cm, $p = 0.702$). Patients treated exclusively in the last year with mid-dose GH had a similar height gain to those in the other treatment groups ($p = 0.604$). The total height gain in all three groups was 1.1 – 1.2 SDS. Maximum IGF-1 levels rose to 0.9 SD in the low-dose group, 3.3 SD in the high-dose group, and 2.9 SD in the mid-dose group.

Conclusions: In short SGA children, continuous low-dose and discontinuous high-dose GH regimens were associated with similar height gain. Treatment with mid-dose GH for 1 year also led to a similar improvement in growth. GH treatment allowed approximately half the children in each group to achieve a stature above -2 SDS after 2 years from pretreatment values below -3.1 SDS.

Maximizing height gain with the minimum of GH dosing in short SGA children who demonstrate a degree of GH resistance is a tricky challenge, and these two studies show imaginative, yet different approaches. Each is a large-scale multinational randomized trial with novel treatment strategies. Both sought to augment the all-important period of catch-up growth over the first 2 years. Phillip et al. confirmed that double and triple the conventional dose of GH for 1 year achieved similar height gains to 2 years' treatment at standard low dose ($33 \mu\text{g/kg/day}$), but at what cost? The high-dose regimen produced impressively quick catch-up growth, showing that supraphysiological GH doses can override the GH-IGF axis into a maximal response mode, but despite no significant metabolic disturbance being demonstrated, concern must remain with the rise of IGF-1 levels to $+3.3$ SD, and unknown long-term consequences.

Jung et al. employed a prediction algorithm, the Cologne Growth-Prediction Model, for first year GH responsiveness. The predicted height velocity after 3 months' GH treatment can be calculated from HV response, pretreatment IGF-1 levels, bone age retardation and urinary deoxypyridinoline levels 1 month into treatment. If this value was below the predetermined level of 0.75 SDS, then the GH dosage regimen was doubled from the standard $35 \mu\text{g/kg/day}$. Only half of the study limb needed dose adjustments upwards, and although this approach produced a smaller growth increment, the authors argue this was not of major clinical relevance. Additionally, although the higher dosing regimen in both limbs increased IGF-1 levels, maximum levels of $+1.1$ SDS, only 4% required a GH dose reduction. This type of approach may herald a more economical and safe approach to improved therapeutic efficacy. However, we now have half a dozen prediction models, yet too many of them include parameters that are not readily available – urinary deoxypyridinoline levels in this report. We look forward for a model based on simple auxology and minimal laboratory workup.

Long-term follow-up and comparison between genotype and phenotype in 29 cases of complete androgen insensitivity syndrome

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J Urol 2008;180:1496–1501

Background: The aim of this study was to assess the safety of keeping gonads in place for spontaneous puberty in a consecutive cohort of patients with complete androgen insensitivity syndrome confirmed by genetic analysis as the diagnosis and management has dramatically changed over the last few decades, with earlier diagnosis and the development of molecular biology. Some patients maintaining wolffian and müllerian remnants may have subtle residual androgen activity. Variations of these features clearly exist among patients and may influence treatment. The need for vaginal surgery and gonadectomy was investigated on account of the potential risks of virilization at puberty and gonadal tumor development.

Methods: The authors reported the clinical outcome of 29 cases of complete androgen insensitivity syndrome managed by the same team from diagnosis (frequently in early childhood) to adulthood. They studied the genotype, phenotype, anatomy of the internal and external genitalia.

Results: All of the patients had a complete female phenotype. 19 different mutations (including 7 unreported) were found. Each family presented with a different mutation. No somatic mosaicism was detected. Vas deferens and epididymis were found in all types of mutations (missense, nonsense and frameshift). 23 patients were postpubertal at the time of reporting. Of those 19 with spontaneous pubertal development, no virilization was seen. Only 1 patient developed carcinoma in situ when the gonad was removed prophylactically once puberty was complete. Vaginal surgery was rarely necessary.

Conclusions: The authors recommend that removal of the gonads in the complete androgen insensitivity syndrome need only take place once spontaneous puberty is complete. The risk of virilization at puberty should be ruled out for each individual androgen receptor mutation before management decisions and genetic counseling are undertaken. Vaginal surgery is not necessary as first-line treatment.

Detailed long-term studies of relatively unselected cohorts combining genetic and clinical outcomes are rare, and that is why this report provides a valuable and unique insight into the management of females with CAIS. The general feeling of anxiety to remove the gonads at the earliest opportunity may have arisen from confusion with the clear association of dysgenetic gonads with the risk of gonadoblastoma. This has not been reported in CAIS. Carcinoma in situ and seminoma may occur, but mainly after 18 years of age, and carcinoma in situ was found in only 1 postpubertal patient in this cohort, hence the recommendation they make is to leave gonads in situ until after puberty has completed spontaneously, although the authors admitted this study did not look in detail at the psychological consequences of doing this. Benign testicular changes such as Sertoli adenomas and polar hamartomas were found more frequently in the postpubertal gonads. In the testes which were left, spermatid tubules tended to deteriorate in shape and germ cells disappeared progressively after 1 year of age. Inguinal hernia was the commonest form of presentation of childhood CAIS, none progressing beyond the inguinal ring. This was followed by prenatal diagnosis as the second most frequent where a mismatch between karyotype and ultrasonic phenotype was seen. This contrasts with the typical mode of presentation in late adolescence and adulthood of primary amenorrhea. Although the degree of wolffian duct remnants in 69% was very variable, there was no association with virilization (as in CAH) or genotype. Pubic or axillary hair development (if any) was not regarded as a sign of virilization, and was not associated with any particular genotype. Müllerian duct remnants were seen associated with the gonad in 38%, but complete uteri or fallopian tubes have never been reported in cases of CAIS. All of the patients had a completely normal female phenotype with a vagina of variable length. Androgen receptor mutations were identified in all patients, 17 cases occurring in 8 families, and there was only one de novo mutation. There was no association between anatomy and genotype.

Long-term GH treatment improves adult height in children with Noonan syndrome with and without mutations in protein tyrosine phosphatase, non-receptor type 11

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Eur J Endocrinol 2008;159:203–208

Background: Noonan syndrome (NS) is characterized by short stature, typical facial dysmorphology and mostly right-sided congenital heart defects. GH therapy in NS may produce short-term gains in height, but reports on the effect on adult height are scarce. This study aimed to determine the effect of long-term GH therapy in children with NS.

Methods: 29 children with the clinical diagnosis of NS from endocrinology departments in the Netherlands and Belgium were treated with GH until final height was reached. At the mean age of 11.0 years at the start of therapy, GH was administered subcutaneously at 50 µg/kg/day until growth velocity was 1 cm/6 months. Height was measured at 3-month intervals in the first year and at 6-month intervals thereafter until final height. 22 out of 27 tested children had a mutation in the protein tyrosine phosphatase, non-receptor type 11 gene (PTPN11 gene).

Results: At the start of treatment, median height SDS was –2.8 (–4.1 to –1.8) and 0.0 (–1.4 to +1.2), based on National Dutch/Belgian and Noonan standards respectively. GH therapy continued for 3.0–10.3 years (median 6.4 years), producing mean height gains of +1.3 SDS (+0.2 to +2.7) and +1.3 SDS (–0.6 to +2.4), compared with the National and Noonan standards respectively. In 22 children with a mutation in PTPN11 the mean gain for national standards was +1.3 SDS and not different from the mean height gain in the 5 children who did not show this mutation in PTPN11 of also +1.3 SDS ($p = 0.98$).

Conclusions: Long-term GH treatment in NS leads to attainment of adult height within the normal range in most patients (22/29). Safety monitoring revealed no concerns on carbohydrate metabolism or cardiovascular status.

This is the final report of a cohort study of pre- and peripubertal patients with NS, who did not have hypertrophic cardiomyopathy and whose height at referral was –2 SDS. Although this was not a randomized or controlled trial, the patients followed a carefully conducted protocol of a relatively high-dose GH, and this report of adult height must surely provide the best evidence of outcome. This in fact does represent the type of patient who would potentially be considered for GH therapy. The gain of +1.3 SDS represents about a 9.5 cm increase in boys and 9 cm in girls. Height gain after 4 years on treatment was maintained until adult height. The authors recommend that the use of Noonan-specific standards is a better predictor of height gain than bone age. This study provides the first report of adult height in long-term GH treatment where genetic analysis was performed. This study had a preponderance of children with PTPN11 mutations, thus it is not possible to state the magnitude of the effect of GH in children with *ras* and *SOS1* and *BRAF* mutations. However, PTPN11 and thus SHP-2 mutations may be associated with mild GH resistance on account of a postreceptor signaling defect, and that this may have a transient influence on GH treatment. More data on the outcome of GH treatment in children with other NS mutations are needed to explore this further.

High versus low dose of initial thyroid hormone replacement for congenital hypothyroidism

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Background: Congenital hypothyroidism (CHT) is one of the most common preventable causes of learning difficulties, affecting 1 in 4,000 infants. This systematic review aimed to determine the effects of high versus low dose of initial thyroid hormone replacement for CHT.

Methods: Randomized controlled trials were identified by searching The Cochrane Library, Medline and Embase. Randomized controlled clinical trials assessing the effects of high versus low dose of initial thyroid hormone replacement for CHT were chosen. Authors independently selected trials, assessed risk of bias and extracted data.

Results: The initial search identified 1,014 records which identified 13 publications for further examination. After screening the full text of the 13 selected papers, only one study evaluating 47 babies finally met the inclusion criteria. Using the same cohort at two different time periods, the study investigated the effects of high- versus low-dose thyroid hormone replacement in relation to (1) time taken to achieve euthyroid state and (2) neurodevelopmental outcome. The authors reported that a high dose is more effective at establishing free thyroxine concentrations in the normal range and also allows earlier normalization of thyroid-stimulating hormone compared with a lower dose. Intelligence quotient was significantly higher in children who received the high dose compared with the lower dose. No growth and adverse effects were reported.

Conclusions: Currently there is only one randomized controlled trial evaluating the effects of high versus low dose of initial thyroid hormone replacement for CHT. Current evidence is inadequate to confirm that a high dose is more beneficial than low dose as initial thyroid hormone replacement in the management of CHT.

Effect of high versus low initial doses of l-thyroxine for congenital hypothyroidism on thyroid function and somatic growth

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Background: The optimal dose of thyroxine (T_4) in congenital hypothyroidism (CH) during infancy is controversial. Higher doses lead to improvement in cognitive scores, but have been linked to later behavioral difficulties. The authors examined the effects of initial T_4 dose on somatic growth – a marker of overtreatment.

Methods: 314 CH children (214 girls, 100 boys) were analyzed according to initial daily dose of T_4 : group 1 (25 μ g, $n = 152$), group 2 (30–40 μ g, $n = 63$) and group 3 (50 μ g, $n = 99$). Thyroid function and weight, length and occipito-frontal head circumference (OFC) standard deviation score (SDS) were compared at 3, 6, 12, 18, 24 and 36 months of age. Linear growth SDS was compared between the three groups using a regression adjustment model. Thyroid function was compared at diagnosis (T_0), 7–21 days and after the start of treatment (T_1).

Results: At T_1 , median thyroid-stimulating hormone (TSH) for groups 1, 2 and 3 was 58, 29 and 4.1 mU/l, respectively ($p < 0.001$), group 3 values remaining significantly lower at 3 and 6 months. Median free T_4 (fT_4) was within or just above the reference range in all groups at T_1 , but 7.4% of group 1 had values <9 pmol/l compared with 5.1 and 0% for groups 2 and 3. At 3 months, weight, length and OFC SDS values were -0.39 , -0.35 , 0.09 ; -0.30 , -0.47 , 0.32 ; and -0.03 , -0.13 , 0.18 for groups 1, 2 and 3, respectively, reporting a relatively large OFC in these infants. Regression analysis revealed no significant difference in growth rate from baseline and 12 or 18 months of age, between the three groups.

Conclusions: A T_4 dose of 50 μ g daily at onset of disease normalizes thyroid function several months earlier than lower doses, with no evidence of somatic overgrowth between 3 months and 3 years.

These two papers were reviewed under the common endocrine disorder of congenital hypothyroidism (CHT). A Cochrane systematic review highlighted that only one randomized controlled trial was available to evaluate the effects of high- versus low-dose thyroxine for CHT. The authors concluded from this one trial that there was inadequate evidence to confirm that a high dose is more beneficial than low dose as initial thyroid hormone replacement in the management of CHT. The paper by Jones et al., on the other hand, used a different approach to explore the evidence for an initial higher dose regimen. They retrospectively analyzed 26 years' detailed data from a national database. Although no information on neurodevelopmental outcome was available, Jones et al. conclude that an initial thyroxine dose of 50 µg/day normalizes thyroid function several months earlier than lower doses with no evidence of somatic overgrowth between 3 months and 3 years.

The conflicting conclusions from these papers highlight that optimal initial management of CHT with high dose (50 µg/day) thyroid hormone remains controversial. This controversy remains largely on account of the paucity of well-conducted RCTs to definitively prove the point that high-dose treatment can achieve optimal intellectual development with no adverse sequelae. This contrasts with our current clinical understanding and practice, and underlines why it is important to gather evidence for therapeutic approaches in a systematic manner.

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