Evidence-Based Medicine in Pediatric Endocrinology

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As this is an evidence-based medicine chapter, by definition we aim for the integration of best research evidence with clinical expertise and patient values [1] and strive to apply this evidence to all our decisions in clinical practice in pediatric endocrinology. As before, we have included a selection of the best evidence-based medicine papers across the breadth of this specialty with the primary aim of informing and supporting you – the clinicians – to provide the best clinical care for your patients. In addition to this evidence, we refer you to the consensus statements and guidelines that ESPE and other endocrine societies have published over the past year. Although we have included rigorous studies on the metabolic outcome of growth hormone (GH) treatment, as much of the information on GH safety currently comes from preliminary cohort analyses where the evidence of potential risks is not yet of sufficient power, we have not discussed these, but refer you to presentations at the ESPE meeting itself. Reliable evidence is likely to be produced in subsequent years.

Mechanism of the year

Finally the evidence we have been waiting for – continuous glucose monitoring in clinical practice in pediatric diabetes

Effectiveness of continuous glucose monitoring in a clinical care environment: evidence from the Juvenile Diabetes Research Foundation continuous glucose monitoring (JDRF-CGM) trial

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Diabetes Care 2010;33:17–22.

Background: The authors aimed to determine whether continuous glucose monitoring (CGM) is effective in the management of type 1 diabetes when implemented in clinical practice.

Methods: A 6-month randomized controlled trial (RCT) was undertaken to evaluate CGM in children, adolescents, and adults with type 1 diabetes. CGM was commenced in patients with an outpatient training session, two follow-up phone calls, and outpatient visits at 1, 4, 13, and 26 weeks. The control group had a less intensive training and follow-up. Those with starting HbA1c $\geq 7.0\%$, the main aim was change in HbA1c at 6 months.

Results: The frequency of use of CGM decreased from 7.0 days/week in the first month in the > 25 -year-old group, 6.3 days/week in the 15- to 24-year-olds, and 6.8 days/week in the 8- to 14-year-olds to 6.5, 3.3, and 3.7 days/week at the end of the study period, respectively ($p < 0.001$ for all age groups). Those with a starting HbA1c $\geq 7.0\%$ demonstrated a reduction in HbA1c with CGM in all groups at 6 months ($p = 0.02$). Severe hypoglycemia decreased from 27.7 events per 100 person-years (in control group 6 months) to 15.0 events per 100 person-years in the 6-month follow-up CGM phase ($p = 0.08$).

Conclusions: Frequent use of CGM in a clinical care setting improves HbA1c and also reduces hypoglycemia. Sustained frequent use of CGM is less likely in children and adolescents.

Quality-of-life measures in children and adults with type 1 diabetes: Juvenile Diabetes Research Foundation Continuous Glucose Monitoring randomized trial

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Diabetes Care 2010;33:2175–77.

Background: The authors aimed to evaluate the impact of continuous glucose monitoring (CGM) on quality of life (QOL) in patients with type 1 diabetes.

Methods: Children and adults (n = 451) with type 1 diabetes were randomly assigned to CGM treatment or the control group. Diabetes and generic QOL questionnaires were completed at baseline and 26 weeks by all patients and parents of patients <18 years old. A CGM satisfaction scale was completed by the CGM group (patients and parents) at 26 weeks.

Results: After 26 weeks, QOL scores remained largely unchanged for both the treatment and the control group, although there was a slight difference favoring the adult CGM group on several subscales (p < 0.05). There was substantial satisfaction with CGM technology after 26 weeks among patients and parents.

Conclusions: Baseline QOL was high, and the measures showed little change with CGM use, but a high level of CGM satisfaction was reported.

Prolonged nocturnal hypoglycemia is common during 12 months of continuous glucose monitoring in children and adults with type 1 diabetes

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Background: To evaluate factors associated with nocturnal hypoglycemia and quantify the frequency of nocturnal hypoglycemia with continuous glucose monitoring (CGM) in children and adults with type 1 diabetes (participants in the Juvenile Diabetes Research Foundation CGM randomized clinical trial).

Methods: The authors analyzed 36,467 nights from 176 patients with > or =4 h of CGM glucose readings between 12 midnight and 6:00 a.m. The percentage of nocturnal hypoglycemia occurring was recorded for each patient (two consecutive CGM readings < or =60 mg/dl in 20 min). Baseline characteristics and clinical features were evaluated using a multivariate regression analysis.

Results: The study reported that nocturnal hypoglycemia occurred 8.5% of the time, with the median percentage of nocturnal hypoglycemia 7.4% per patient (interquartile range 3.7–12.1%). Hypoglycemia duration was > or =2 h on 23% of the nights when hypoglycemia was experienced. Multivariate analysis revealed that there was a higher incidence of nocturnal hypoglycemia with lower HbA1c levels (p < 0.001) and hypoglycemia recorded on one or more nights during baseline blinded CGM (p < 0.001). The hypoglycemia frequency was not associated with age or with mode of insulin delivery.

Conclusions: Nocturnal hypoglycemia is frequent and often prolonged in children and adults with type 1 diabetes. Patients with low HbA1c levels are at an increased risk. Blinded CGM over a 1-week period can also identify patients at greater risk for nocturnal hypoglycemia.

Evaluation of an algorithm to guide patients with type 1 diabetes treated with continuous subcutaneous insulin infusion on how to respond to real-time continuous glucose levels: a randomized controlled trial

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Diabetes Care 2010;33:1242–8.

Background: The authors evaluated algorithm-guided responses of insulin pump patients with type 1 diabetes (pumpDM1) using real-time continuous glucose monitoring (RT-CGM).

Methods: 60 pumpDM1 patients (aged 13–70 years, HbA1c < or =9.5%) were randomized in sex-, age- and HbA1c-matched pairs. Phase 1 was an open 16-week multicenter randomized controlled trial. Group A was treated with pump/RT-CGM with the algorithm, and group B was treated with pump/RT-CGM without the algorithm. The primary aim was the difference in time in target (4–10 mmol/l) glucose range on 6-day blinded CGM. Secondary aims were differences in HbA1c, low (< or =3.9 mmol/l) glucose CGM time, and glycemic variability. Phase 2 was a 16- to 32-week follow-up. Group A was returned to routine care, and group B used the algorithm. Glycemia parameters were unchanged. Comparisons were made between baseline and 16 and 32 weeks.

Results: In phase 1, there were 29/30 subjects left in group A and 28/30 subjects left in group B. There was no change in target glucose time between groups. In group A, HbA1c fell (mean 7.9% [95% CI 7.7–8.2 to 7.6% [7.2–8.0]; $p < 0.03$), but in group B there was no difference between groups (7.8% [7.5–8.1] to 7.7 [7.3–8.0]; NS). In group A, more patients achieved HbA1c < or =7% than patients in group B (2 of 29 to 14 of 29 vs. 4 of 28 to 7 of 28; $p = 0.015$). In phase 2, one participant was lost from each group. In group A, HbA1c returned to baseline with RT-CGM discontinuation but did not change in group B, who continued RT-CGM with addition of the algorithm.

Conclusions: Early but not late use of algorithm-guided responses in patients with DM1 using pump/RT-CGM did not increase the target glucose time but increased achievement of HbA1c < or =7%. After cessation of RT-CGM, HbA1c returned to baseline.

In the Evidence-Based Chapter in the *Yearbook of Pediatric Endocrinology 2009*, the authors highlighted that although continuous glucose monitoring (CGM) may be useful and valid in certain diabetes populations, its utility in clinical practice was still awaiting a large international prospective randomized control trial (RCT) [2]. Until this year these RCTs and evidence-based criteria were not available. The four papers chosen in this section collate the most clinical relevant papers by evidence-based criteria. Real-time (RT)-CGM has become more available, applicable and effective in everyday management of pediatric diabetes. It is no longer a research tool only reserved for complex and challenging cases. The CGM devices and sensors have evolved dramatically over the last 5–10 years. Today the newly released Medtronic Enlite sensor is shorter in length 10.5 mm (vs. 17 mm), smaller gauge needle 27 Ga (vs. 22 Ga) and more child friendly with the needle hidden from the child at all times. With the advent of the sensor-augmented pump (SAP), i.e. the pump and CGM speak to each other with real-time continuous glucose sensing (RT-CGM), together these technologies allow intensification of insulin therapy for all children and adolescents with type 1 diabetes. The four selected papers confirm that these new technologies are effective in reducing the glycated hemoglobin, recording the frequency and duration of nocturnal hypoglycemia and improving quality of life (QOL). In addition, we now have a specific algorithm that aids the patients' use of these technologies to further optimize their diabetes management. The first three papers summarize the new evidence provided by a large collaborative research group – the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. This group is leading the way at a global level with good scientific evidence-based results from large prospective international RCT on CGM in children, adolescents and adults with type 1 diabetes. The first paper by Beck et al. confirms the clinical effectiveness of CGM in the management of pediatric diabetes when implemented in clinical practice. The authors highlight that frequency of use decreased in all age groups from 7.0, 6.3 and 6.8 days/week to 6.5, 3.3 and 3.7 days/week in the adult (>25 years), adolescent (15–24 years) and pediatric age (8–14 years) groups respectively. However, frequency of use improved HbA1c and reduced hypoglycemic episodes. Another paper by Bergenstal et al. [3] in the *NEJM* reinforces this message and confirmed that in both children and adults with inadequately controlled DM1, SAP therapy resulted in significant improvement in HbA1c when compared with injection therapy (see Diabetes Chapter).

The second paper by Lawrence et al. looks at the impact of CGM on QOL in children with type 1 diabetes. The authors used generic and diabetes specific QOL questionnaires at baseline and after 6 months. They report that QOL remained unchanged after 26 weeks in treatment and controls, and that satisfaction was high with the CGM technology in patients and parents. The third paper by Beck et al. records the amount of nocturnal hypoglycemia assessed with CGM in adults and children with type 1 diabetes. These results are surprising both in frequency (8.5% of nights) and duration (>2 h on 23% of nights). Higher nocturnal hypoglycemia occurred in patients with low HbA1c and evidence of hypoglycemia on one or more nights of blinded CGM at baseline. Perhaps parental anxiety around hypoglycemia for their children with type 1 diabetes may in fact be evidence-based after all.

The fourth paper in this series by Jenkins et al. provides a new approach to using RT-CGM in pediatric diabetes. The authors assessed an algorithm-guided treatment using a SAP/RT-CGM. They conclude that the early use (but not late) of algorithms helped guide the patients' responses on SAP/RT-CGM and improved achievement of HbA1c <7%. In summary, the technologies now available to intensively manage pediatric diabetes have come a long way in 5–10 years. The future is brighter with huge advances in these technologies, which are effective in reducing HbA1c, recording unknown nocturnal hypoglycemia and improving QOL. Now these technologies are effective and evidence-based tools, it is important that we, as pediatric endocrinologists, promote their use where available.

New Paradigms

Metabolic outcome of GH treatment in prepubertal short children with and without classical GH deficiency

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Background: The metabolic outcome of growth hormone (GH) treatment in idiopathic short stature (ISS) has not been well studied, particularly as children with ISS may require higher GH doses than children with GH deficiency (GHD) for identical growth promotion so may be at increased risk of adverse events during treatment. This study employed individualized prediction models for estimation of GH responsiveness, which may have the advantage of narrowing the range of growth response, and reduce under- or overtreatment with GH.

Methods: The aim was to evaluate if individualized GH treatment could reduce the variance of the metabolic measures as shown for growth response and to compare changes in metabolic variables in children with ISS and GHD. Patients included 39 isolated GHD and 89 ISS short prepubertal children. They participated in a 2-year randomized trial of either individualized GH treatment with six different GH doses (range 17–100 µg/kg/day) or standard dose (43 µg/kg/day).

Results: There was a narrower variation for fasting insulin (–34.2%) and for homeostasis model assessment (HOMA) (–38.9%) after 2 years of individualized GH treatment in comparison with standard GH dose treatment. Both ISS and GHD groups showed similar metabolic changes. Increases in height SDS were correlated with changes in insulin-like growth factor I (IGF-I), leptin and body composition. Principal component analysis identified an anabolic and a lipolytic component. Anabolic variables (lean body mass SDS and IGF-I SDS) were similarly altered and correlated strongly with height SDS increases and GH dose, whereas lipolytic changes (fat mass SDS and leptin) were orientated differently from anabolic variables and showed no association. Regression analysis showed changes in lean body mass SDS and height SDS, but not fat mass, to be dependent on GH dose in ISS but to a lesser degree in GHD.

Conclusion: Individualized GH dosing during catch-up growth may reduce the variance in insulin and HOMA and produces equal metabolic responses in both GHD and ISS children.

Randomized GH trial with two different dosages in combination with a GnRH analog in short small for gestational age children: effects on metabolic profile and serum GH, IGF-1, and IGFBP3 levels

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Eur J Endocrinol 2010;162:887–95.

Background: The combination of GnRH analog (GnRHa) and GH treatments has been proposed to increase adult height in short small for gestational age (SGA) children. However, the effect on the metabolic profile and GH, IGF-1, and IGFBP3 levels is unknown. So this study aimed to assess fat mass and lean body mass SDS, percentage trunk fat, blood pressure (BP), insulin sensitivity (Si), β -cell function (disposition index, DI), lipid profile, and GH, IGF-1, and IGFBP3 levels throughout 2 years of combined treatment.

Methods: 41 pubertal short SGA children with a mean ($\pm$ SD) age of 12.1 ($\pm$ 1.0) years received 3.75 mg of leuprolide acetate depot subcutaneously every 4 weeks. They were randomly assigned to receive daily GH doses of 1 mg/m²/day (33 μ g/kg/day) (group A) or 2 mg/m²/day (67 μ g/kg/day) (group B).

Results: The percentage trunk fat increased in both groups, but to a lower extent in the high-dose group (group B). Lean body mass SDS increased only in group B. Both groups showed similar changes in BP, Si, DI, and lipids. Si significantly decreased, but DI remained unchanged. Lipids remained normal. GH and IGF-1 levels were significantly higher in group B.

Conclusion: Two years of GnRHa treatment combined with either 1 or 2 mg GH/m² per day does not adversely affect body composition and metabolic profile of short SGA children who are referred in early puberty. There was a dose-dependent effect on fat mass for height SDS, percentage trunk fat, lean body mass for height SDS, and GH and IGF-1 levels in favor of treatment with GnRHa and the higher GH dose of 2 mg/m²/day.

These two studies advance our understanding of how we can manage GH treatment more effectively and how to minimize adverse metabolic consequences whilst obtaining the best outcomes. Decker et al. reported a large open-label RCT of two GH regimens in short children with GHD or ISS. Dose selection was based on the predicted growth response and the predicted difference between current height and MPH SDS after 2 years of receiving a standard GH dose of 33 μ g/kg/day. The individualized GH dose was one of six doses within the range of 17–100 μ g/kg/day. They observed a narrower variation for fasting insulin and HOMA after 2 years of individualized GH treatment in comparison with standard GH dose treatment similar to the previous finding of a reduction in the variation of the growth response to target height after 2 years of individualized GH treatment. Principal component analysis, which is a powerful descriptive and data-reduction technique for multiple variables, a novel analytical approach in a clinical situation, was used to assess variables related to a complex system such as the metabolic network. This approach demonstrated clusters with high inter-correlations of anabolic variables (lean body mass, height, weight, IGF-I, IGFBP-3 and bone mineral content) with GH dose. The lipolytic cluster consisted of fat mass expressed in kg and SDS and leptin, and was separated from the anabolic cluster by an approximately 90° angle, indicating no correlation between these effects. The authors suggest that by adapting the GH dose, it is possible to take into account individual estimated GH sensitivity of each child and indirectly influence adverse metabolic outcomes such as the insulin resistance. However, the choice of dose was dependent upon measures of GH secretory capacity and auxological parameters, so the true effect of the GH dose on metabolic consequences may be partly obscured.

Van der Kay et al. explored metabolic changes associated with GH and GnRHa treatment in SGA children beginning at the start of puberty. Two fixed dose regimens were used: 33 and 67 μ g/kg/day, the latter higher than would currently be recommended on safety grounds. Although this randomized trial did not have a control group, the design allowed for the exploration of the metabolic effects of the two treatments independently. At the start of GnRHa treatment, lean body mass and height SDS were significantly lower than the population mean in both groups. During the study period, there was a significant GH dose effect on decrease of fat mass and increases in height SDS and lean body mass. The authors suggest that the high GH dose regimen counteracts the effect of simultaneous

treatment with a GnRHa, whereas lower dose treatment was insufficient to prevent children from gaining fat mass during GnRHa treatment. Although lipid parameter changes were similar between groups, the principal concern here is the effect on IGF-1. After 1 year of combined treatment, IGF-1 concentrations increased to values significantly higher than the population mean in both groups. IGF-1 concentrations were significantly higher in the high-dose group where 88.9% of the children had IGF-1 levels in the highest quintile and 27.8% above 2 SDS, compared with 43.8 and 6.3% of children in the lower treatment group respectively. These carefully designed studies both add much to our knowledge about the detailed metabolic consequences and interactions of GH treatment, with reassurances and warnings.

New hope

GH in combination with bisphosphonate treatment in osteogenesis imperfecta

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Eur J Endocrinol 2010;163:479–87.

Background: This was a 1-year open-label randomized controlled clinical trial to verify the effects of bisphosphonates (Bp) in combination with recombinant human GH (rhGH) in 30 prepubertal children (M:F = 14:16) with osteogenesis imperfecta (OI) (types I, IV, and III) being treated with neridronate. Outcome measures included improvement of bone mineral density (BMD), projected bone areas, growth velocity, and fracture risk.

Methods: The patients were observed for 12 months during standard neridronate treatment, then were randomized into two groups: 15 were treated for 12 months with rGH and neridronate (group Bp + rhGH) and 15 continued neridronate alone (group Bp). Outcome measures included auxological parameters, number of fractures, bone age (BA), bone metabolic parameters, and bone mass measurements at lumbar spine and radius by dual-energy X-ray absorptiometry.

Results: The mean variation in percentage of BMD at the lumbar spine (L2–L4), and at the distal and ultra-distal radius, and the projected area of lumbar spine increased significantly in group Bp + rhGH ($p < 0.05$). Growth velocity was significantly higher during rhGH treatment in group Bp + rhGH versus group Bp and versus pretreatment ($p < 0.05$), and there was no increase in BA advance or fracture risk rate. Patients with quantitative collagen synthesis defects had a higher, although not significant, response to rhGH in terms of growth velocity and BMD.

Conclusion: Combined rhGH and Bp treatment positively increases BMD at the lumbar spine and wrist and in the lumbar spine projected area, significantly increases the rate of linear growth velocity, with no BA advancement, but does not influence the peripheral fracture rate.

This is the first published RCT of GH treatment together with bisphosphonates in patients with osteogenesis imperfecta. The design allowed the direct comparison of the two arms for 1 year with bisphosphonate treatment alone before randomization permitted one limb to receive GH treatment. Employing a GH dose often used in skeletal abnormalities, 50 $\mu\text{g/kg/day}$, no excess IGF-1 concentrations were reported. Bisphosphonate treatment must now be recognized as standard treatment for children with osteogenesis imperfecta, and this study confirmed a major benefit of bisphosphonates in increasing BMD. The fact that 12 months' GH treatment produced a doubling of the BMD accrual at all sites, together with a significant increase in height velocity, is impressive. The bone age did not advance significantly as a result of GH treatment. There was no difference between groups for fracture occurrence, but as the authors state, time for follow-up was too short and the study underpowered to assess this factor accurately. So here we have confirmation of a major short-term benefit in the management of patients with these forms of osteogenesis imperfecta. Long-term studies of safety and efficacy are underway, until then, patients with osteogenesis imperfecta should receive GH as part of a clinical trial.

GnRH analog therapy in girls with early puberty is associated with the achievement of predicted final height but also with increased risk of polycystic ovary syndrome

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Eur J Endocrinol 2010;163:55–62.

Background: The aim of this study was to assess GnRH analog therapy (GnRHa) effectiveness on reaching adult stature and the risk of polycystic ovary syndrome (PCOS) in girls with early puberty. GnRHa has not been reported to have beneficial effects on adult stature in girls with early puberty. Additionally, an increased prevalence of PCOS has been described in girls treated for central precocious puberty. It is known that women with PCOS are at increased risk of cardiometabolic dysfunctions and infertility.

Methods: This was a longitudinal study from baseline to final height of 25 GnRHa-treated girls and 55 GnRHa who chose not to be treated, and who were consequently used as controls. Outcome measures included insulin resistance (IR; homeostasis model assessment of IR (HOMA-IR) and glucose-to-insulin ratio (G/I)), the effect of GnRHa on final height, and the prevalence of PCOS.

Results: In GnRHa-treated girls, no significant difference was found between predicted final height and final height, whereas baseline prediction significantly over predicted final height in untreated girls ($p = 0.0001$). At final height, GnRHa-treated girls showed higher HOMA-IR and lower G/I ($p = 0.03$ for both) as well as higher DHEAS and androstenedione levels ($p = 0.02$ and $p = 0.01$ respectively) compared with untreated girls. The prevalence of PCOS and hyperandrogenemia was significantly higher in GnRHa-treated adolescents than in untreated adolescents (36 and 14.5% respectively, $p = 0.04$; 56 and 23.6% respectively, $p = 0.01$). Finally, gonadotropin-suppressive therapy was significantly associated with a greater prevalence of PCOS during adolescence ($p = 0.03$).

Conclusion: In girls with early puberty, GnRHa therapy appears to permit achievement of predicted adult height. However, this treatment seems to act as an independent risk factor for the development of PCOS during adolescence.

The importance and difference of this paper is that it addresses the outcome of GnRHa treatment in girls with early puberty, in contrast to the findings of GnRHa treatment in girls with central precocious puberty where the evidence of the risk of developing PCOS is mixed (full review in the discussion section of the paper). Although, as the authors state, in this study, the control or observation group was comprised of those who refused GnRHa treatment, there was no difference between the groups at baseline. Its strength is that it has a complete and detailed follow-up program. The principal effect of GnRHa treatment was to delay menarche by 1.2 years to a mean age of 12.1 years. Adult height was similar in both groups (157.4 cm), but the predicted height at baseline had been higher in the control group meaning a potential mean loss of 2.9 cm growth overall. However, the observation that 36–40% of treated girls at final height at a mean age of 14.7 years had developed PCOS in contrast to 14.5–16.4% of untreated girls at 14.9 years by whichever criteria were used to define PCOS (Rotterdam 2003 or Androgen Excess Society 2006) is worrying. GnRHa treatment seemed to be an independent risk factor for the development of PCOS, although this could in part be linked with the weight gain associated with therapy and the inevitable consequence of worsening of insulin sensitivity as a consequence of the development of obesity. This warning makes it necessary, as the authors conclude, to select girls very carefully when considering treatment to delay early puberty and subsequently to monitor their progress. Consideration could be given, consequent on appropriate clinical trial data, to the consideration of metformin co-treatment if GnRHa is required (Ibanez et al., see below).

Triiodothyronine supplementation in infants and children undergoing cardiopulmonary bypass (TRICC): a multicenter placebo-controlled randomized trial: age analysis

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Background: Triiodothyronine levels decrease in infants and children after cardiopulmonary bypass. This study investigated if triiodothyronine (T_3) repletion is safe in this population and produces improvements in postoperative clinical outcome.

Methods: The TRICC study was a prospective, multicenter, double-blind, randomized, placebo-controlled trial in children younger than 2 years old undergoing heart surgery with cardiopulmonary bypass. Enrollment was stratified by surgical diagnosis. The primary outcome was time to extubation (TTE). Patients received intravenous T_3 as Triostat ($n = 98$) or placebo ($n = 95$). Cox proportional hazards were used to analyze data.

Results: There were no differences in adverse event rates, including arrhythmia. Overall, TTE was similar between groups. Prespecified analyses showed a significant interaction between age and treatment ($p = 0.0012$). For patients younger than 5 months, the hazard ratio (chance of extubation) for Triostat was 1.72. ($p = 0.0216$). Placebo median TTE was 98 h with 95% confidence interval (CI) of 71–142 compared to Triostat TTE at 55 h with CI of 44–92. TTE shortening corresponded to a reduction in inotropic agent use and improvement in cardiac function. For children 5 months of age, or older, Triostat produced a significant delay in median TTE: 16 h (CI 7–22) for placebo and 20 h (CI 16–45) for Triostat and (hazard ratio 0.60; $p = 0.0220$).

Conclusions: T_3 supplementation is safe. Analyses using age stratification indicate that T_3 supplementation provides clinical advantages in patients younger than 5 months and no benefit for those older than 5 months. [Clinical Trial Registration-URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00027417.]

Depression of thyroid hormone levels contributes to postoperative morbidity in adults who undergo cardiopulmonary bypass. T_3 levels also decrease after cardiac surgery in children and infants and are similarly associated with poor hemodynamic indices and therefore ultimately, poor clinical outcome. However, T_3 supplementation is not routinely used in this population, and, until the TRICC trial, had not been adequately investigated, not least due to fear surrounding possible resulting tachyarrhythmias. This prospective, multicenter, double-blind, randomized, placebo-controlled trial is very well designed, large and robustly addresses the many problems a study such as this can face. For example their complex stratification according to both underlying disease and overall risk is a particularly impressive and practical approach. In addition to recruiting equal numbers of children classified, as having 'high-risk' and 'low-risk' disease, similar numbers of children with various different underlying diagnoses were included in each arm of the study. Every attempt is also made to keep baseline characteristics and care standards equal between the two groups. The authors make a strong argument for their choices of primary outcomes. Time to extubation is a sensible, clinically relevant outcome and determining the rate of adverse events is of the utmost importance. The most important result from this paper is that T_3 supplementation in this population is safe. There were no differences in adverse events (including tachyarrhythmias) between the two groups. The other important finding from this paper is that age has a significant interaction with the effect of T_3 supplementation. Infants under 5 months of age had the largest benefit including a shorter time to extubation, a reduction in inotropic use and an improvement in cardiac function. The authors propose that this is largely because younger infants are intubated for longer and can therefore benefit not only from the short-term effects of T_3 on the cell membrane, but also possibly due to the genetic induction of protein translation occurring beyond these immediate effects. This definitely warrants

further investigation in this situation and in others where young infants require life-threatening interventions.

Important for clinical practice 1: These tarts are not sweet

Total adrenal volume but not testicular adrenal rest tumor volume is associated with hormonal control in patients with 21-hydroxylase deficiency

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Background: A high percentage of patients with 21-hydroxylase deficiency (21-OHD) have been shown to develop adrenal adenomas and, in males, testicular adrenal rest tumors (TARTs). So this cross-sectional controlled study aimed to investigate the correlation of adrenal masses and TARTs as well as factors stimulating tumor growth of orthotopic and ectopic adrenal tissue in 21-OHD.

Methods: 26 adult male patients with classic 21-OHD (15 salt wasting, 11 simple virilizing; age range 18–48 years) had a clinical evaluation of their hormonal control. Magnetic resonance imaging of the adrenals (26 of 26) and of the testes (18 of 26) was performed. Adrenal size and morphology were compared to 26 age-matched controls.

Results: Combined adrenal volume of 21-OHD patients was significantly higher (median 9.3 ml; range 3.2–124.5 ml) compared with the controls (median 7.4 ml; range 5.5–10.8 ml; $p = 0.005$). 42% of 21-OHD patients had an overall adrenal volume >11 ml, but this was not seen in the controls. Adrenal morphology was classified as normal without nodules in 27% of 21-OHD patients and 69% of controls. Ten of 18 patients had TARTs. The median volume was 3.3 ml (range 0.4–21.6 ml). Total adrenal volume and tumor size volume correlated positively with current parameters of hormonal control (androstenedione, morning 17-OHP in serum, pregnanetriol in 24-hour urine; $p < 0.001$ for each) but was not so with TARTs. Baseline ACTH was independent of adrenal and TART volume. There was no correlation of total adrenal or adrenal tumor size with TART volume.

Conclusion: This study provides indirect evidence that different factors regulate the growth of normally sited adrenal tissue and ectopic adrenal remnants in TARTs.

Testicular adrenal rest tumors in boys, adolescents and adult men with congenital adrenal hyperplasia may be associated with the CYP21A2 mutation

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Background: Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder associated with mutations in the CYP21A2 gene. The consequent impairment of the adrenal cortex function caused by the 21-hydroxylase deficiency accounts for 80–95% of CAH cases. Testicular adrenal rest tumors (TARTs) may be present in up to 95% of CAH adults and may already start to develop in childhood. The genotype subtype association with the development of TARTs has not been investigated previously.

Methods: This study compared clinical information in 49 male patients (age 2.6–40.3 years) with 21-hydroxylase deficiency CAH patients with information of their CYP21A2 genotype mutation. These were grouped according to the residual 21-hydroxylase activity: group Null (complete enzyme impair-

ment), group A (almost complete enzyme impairment), group B (severe enzyme impairment) and group C (partial impairment). TARTs were identified by testicular ultrasound examinations.

Results: TARTs were observed in 27 of 49 patients (55%). In the 23 patients younger than 18 years, TARTs were present in 11 (48%), the youngest patient being 7.5 years old. The presence of TARTs was associated with the CYP21A2 genotype. 27 of 37 patients (73%) with the most severe mutations (groups Null and A) had a TART, whereas none of 12 patients with the milder mutations (groups B and C) had TARTs.

Conclusion: TARTs were most frequently detected in patients with severe CYP21A2 mutations, and may develop in early childhood in such patients.

As pediatric endocrinologists we need to ensure long-term follow-up of our patients with appropriate handover of care. The importance of ensuring transitional care is highlighted, especially for CAH – see the paper by Arlt in the adrenal *Yearbook* chapter [4] – as many adults are not under follow-up. There are many adverse health outcomes in CAH when good surveillance is lacking. TARTs are common and a well-recognized but poorly understood consequence of poor metabolic control in CAH – or does their occurrence actually relate to the degree of control? Recent evidence from this longitudinal study in adolescent and adult males with genetically confirmed CAH have compared indices of hormonal control with the development of TARTs. Reisch et al. investigated 26 young adult CAH patients who had been continuously followed through childhood and compared findings with age-matched controls. Short-term measures of control correlated with adrenal gland volume, but not the development or size of TART, although TARTs were more common in males with the salt-wasting form of the disease. The conclusion was that different factors regulate the development of TARTs. This is where Mouritsen et al. begin to shed some light on this mystery with new evidence. The presence of TARTs was associated with the more severe genetic mutations in CAH, and even from 7.5 years of age in prepubertal boys. There was a suggestion of poorer control in this group, but perhaps, as the authors suggest, we now have the evidence for targeting a subset of patients with this condition to detect TART development at an early stage and then consider whether tightening control will really reduce potential testicular damage.

Important for clinical practice 2: the mystery of adrenal function unmasked at last?

The accuracy of the glucagon test compared to the insulin tolerance test in the diagnosis of adrenal insufficiency in young children with growth hormone deficiency

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J Clin Endocrinol Metab 2010;95:2132–9.

Background: The accuracy of the glucagon test in the diagnosis of central adrenal insufficiency in young children has not been definitively established yet, so this study aimed to investigate the diagnostic accuracy of the glucagon test as an alternative to the insulin tolerance test (ITT) in children under 6 years of age with confirmed GH deficiency.

Methods: This was a prospective study conducted in two Pediatric endocrinology centers of 48 children (median age 4.2 years) with GH deficiency confirmed (peak GH to ITT and arginine <275 nmol/l (10 µg/l) were enrolled. 24 had normal hypothalamic-pituitary anatomy, 7 had isolated anterior pituitary hypoplasia, and 17 had structural hypothalamic-pituitary abnormalities on magnetic resonance imaging. 12 subjects had central adrenal insufficiency as defined by a peak cortisol response of <550 nmol/l (20 µg/l) on the ITT. The glucagon stimulation test sampled for cortisol and glucose (time 0–180 min) after 30 µg/kg of glucagon IM.

Results: In the whole cohort, the mean peak cortisol after glucagon was similar to that obtained after the ITT (715 vs. 718 nmol/l; $p = 0.908$), but it was significantly reduced in patients with structural hypothalamic-pituitary abnormalities ($p < 0.001$). Receiver operating characteristic curve analysis showed that the best diagnostic accuracy from the glucagon test was by using a peak cortisol cutoff of 403 nmol/l (14.6 µg/dl) (sensitivity 66.67%; specificity 100%; area under the curve = 0.91; 95% confidence interval 0.82–0.99). Using this cutoff, 91.67% of the patients were correctly classified.

Conclusion: This study has demonstrated that glucagon is an accurate and safe diagnostic test of adrenal function in young children when adrenal insufficiency is suspected.

How often do we question the evidence base of our routine practice? How often do we wish we could provide the evidence base for what we do? In this latest paper, di Iorgi et al. systematically investigate the accuracy of the glucagon test in the diagnosis of central adrenal insufficiency. Although the ITT has been validated against a response to surgical stress and is considered the reference standard test for evaluating the integrity of the HPA, it is contraindicated in infants and young children, and in patients with cardiovascular disease or a history of seizures. This study reports for the first time the accuracy of the glucagon test in the diagnosis of central adrenal insufficiency in children with GHD who are younger than 6 years of age and indicates that this test can be reliable in this patient population. The mean cortisol peak after glucagon was, in fact, similar to that observed after ITT, and there was a significant correlation between cortisol response to glucagon and that to ITT. The overall prevalence of central adrenal insufficiency in our cohort based on ITT was 25% and was significantly greater in patients with an ectopic posterior pituitary (58.8%) than in those with anterior pituitary hypoplasia (14.3%) or with normal pituitary gland (4.2%). Receiver operating characteristic curve analysis indicated that a cortisol response to glucagon of <403 nmol/l (14.6 g/dl) strongly indicates central adrenal insufficiency in young children with GHD (assay-dependent). The authors conclude that there is now the evidence to suggest that testing with glucagon is a valid and safe alternative test for the evaluation of HPA function in young children [5].

Clinical trials – new treatment opportunities A good gut feeling for GH

A randomized controlled trial of growth hormone in active pediatric Crohn's disease

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J Pediatr Gastroenterol Nutr 2010;51:130–9.

Background: Growth hormone (GH) treatment may improve growth in Crohn's disease (CD). The effect on mucosal inflammation and reduction of symptoms is not known. The hypothesis of this study was that GH would improve both clinical and mucosal disease activity and stimulate linear growth in children with CD.

Methods: 20 patients ages 7–18 years receiving corticosteroids for active CD were randomized to begin GH at 75 µg/kg/day (group A), or continue corticosteroids alone (group B). Disease activity was assessed clinically and endoscopically after 12 weeks. Subsequently group B began GH at 12 weeks, and clinical disease activity was assessed after a further 12 weeks. Subjects who experienced a clinical response after 12 weeks of GH therapy continued treatment for an additional 52 weeks, and their growth was assessed.

Results: 65% of patients receiving GH achieved clinical remission, compared with 20% treated with corticosteroids alone ($p = 0.03$). Although endoscopic disease activity trended toward an improvement at week 12 in group A, this did not differ between the groups. 61% of week 12 GH responders maintained their clinical response through to week 64. Mean (95th confidence interval) height z score on

GH increased from -1.1 ($-1.6, -0.6$) to -0.4 ($-1, 0.2$), $p = 0.004$, during this 52-week extension phase. GH was well tolerated with no unexpected safety concerns.

Conclusion: GH in combination with corticosteroids therapy did not produce a reduction in mucosal inflammation, compared with corticosteroids alone. However, GH treatment was a safe and effective adjunct to corticosteroids for the management of clinical disease activity and growth failure in children with CD.

Several studies in recent years have shown an improvement in growth in children with inflammatory bowel disease with GH treatment. Is the apparent improvement in health also an effect of the GH treatment too? Denson et al. designed an elegant RCT to examine not only the growth-promoting effect of GH but also any effect on disease activity indices including quality of life, mucosal disease and the requirement for corticosteroid treatment, something that all subjects were receiving at study entry – a pointer to the homogeneity of the study arms. Corticosteroids as expected had a disease-ameliorating effect but after the initial 12-week GH treatment period, the percentage usage requirement significantly dropped, especially for budesonide. This effect was also seen once GH was started in the control group. GH treatment conferred a significant improvement in clinical disease activity indices, but no benefit on histological disease following colonic biopsy, although, as the authors' state, this may be due to the study being underpowered here. The dose of GH chosen was high ($75 \mu\text{g/kg/day}$), and notably higher than that currently recommended on grounds of safety. This high dose caused a significant elevation of IGF-1 to above $+2$ SD in both treatment groups. Although part of the proposed benefit of GH was explained by an inverse relationship between IGF-1 and interleukin-6 concentrations as a measure of inflammatory activity, the potential benefit using conventional doses of GH could not be ascertained. Quality of life measures also showed a small improvement over the course of GH treatment. This study breaks new ground in examining the wider effects of GH in an important area of pediatric and adolescent medicine and deserves further evaluation in this and in other gastrointestinal conditions such as short bowel syndromes, although the longer term benefits of GH need more extensive evaluation [6, 7].

New (uses for old) hormones

Early metformin therapy to delay menarche and augment height in girls with precocious pubarche

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Fertil Steril 2011;95:727–30.

Background: Low-birthweight (LBW) girls with precocious pubarche (PP) are at risk of an early menarche (<12 years), polycystic ovary syndrome (PCOS) and an adult stature below target level. Hyperinsulinemic insulin resistance is thought to be a key factor in the development of these problems. This study investigates the effects of early metformin treatment on menarche, height, and (PCOS) markers.

Methods: This open-label, single-center randomized study recruited 38 LBW-PP girls. At age 8 years, girls were randomly assigned to remain untreated or to receive metformin for 4 years. Both subgroups were followed without treatment until each girl was postmenarcheal. Age at menarche, height, weight, endocrine-metabolic state (fasting blood), body composition (by absorptiometry), abdominal fat (subcutaneous vs. visceral), and hepatic adiposity (by magnetic resonance imaging) were the main outcome measures.

Results: At last assessment, girls in each subgroup were on average 2 years beyond menarche; the mean growth velocity was <2 cm/year. Age at menarche was 11.4 ± 0.1 years in untreated girls and 12.5 ± 0.2 years in metformin-treated girls; the latter girls had more favorable levels of circulating insulin, androgens, and lipids and were taller and much leaner (with less visceral and hepatic fat).

Conclusion: Early metformin therapy (from age approximately 8–12 years) suffices to delay menarche; to reduce total, visceral, and hepatic adiposity; to augment postmenarcheal height, and to curb the endocrine-metabolic course of LBW-PP girls away from adolescent PCOS.

Metformin and placebo therapy both improve weight management and fasting insulin in obese insulin-resistant adolescents: a prospective, placebo-controlled, randomized study

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Background: This study aimed to study whether metformin reduces obesity, homeostasis model assessment for insulin resistance index (HOMA-IR), and the metabolic syndrome in obese European adolescents in addition to previous unsuccessful lifestyle intervention.

Methods: After 6 months of multi-professional lifestyle intervention, 70 out of 86 adolescents without improvement in HOMA-IR and body mass index (BMI) were randomized into either the metformin (2×500 mg/day, $n = 36$) or placebo ($n = 34$) group in addition to ongoing lifestyle intervention for another 6 months.

Results: Mean age was 13.8 years, BMI was 33.1 kg/m^2 , 65% were female, and 89% were Caucasians. During lifestyle intervention alone, HOMA-IR and BMI deteriorated significantly. In the subsequent medication period, HOMA-IR and fasting insulin improved similarly in the placebo and metformin groups (HOMA-IR decreased 73 vs. 54% respectively in metformin versus placebo; $p = 0.048$). BMI remained unchanged. The insulin sensitivity index improved in the metformin group only. High fasting insulin is correlated with a subsequent BMI increase irrespective of the medication. Metabolic syndrome risk parameters remained unchanged.

Conclusion: Obese adolescents' insulin sensitivity improved without weight change during placebo or metformin intervention in addition to lifestyle intervention. Most differences did not reach statistical significance, likely due to improved compliance with lifestyle intervention as a placebo effect. In addition, the metformin dose may have been too low in this study.

The use of metformin to improve insulin sensitivity and reduce BMI in young people has been reported to have a moderate beneficial effect on obesity outcomes, but researchers have called for further investigation in different populations [8]. Ibanez et al., in this open-label RCT, investigated metformin use in girls who, as happens in their population, were born low birth weight and have developed precocious pubarche. Hyperinsulinemic insulin resistance is thought to be a major driver of early menarche in this population and it is postulated that metformin use may modify this, resulting in a beneficial effect on adult height and body composition. A particular strength of this study is long (5–6 years) and complete follow-up. The open-labeled design is countered by the objectivity of most outcome measures and subjective outcome measures (including MRI calculated measures of adiposity) were assessed by blinded operators. Metformin use was found to have a significant effect, delaying puberty by a year on average, increasing height and decreasing adiposity. The authors conclude that metformin therapy in this situation holds potential but that further investigation in slightly different populations is necessary. In addition, further study will reveal if delayed puberty in this population reduces the risk of associated adult disease like PCOS, type 2 DM and cardiovascular disease, as speculated in this paper.

Wiegand et al. investigated the use of metformin in a highly selected group of obese adolescent patients. Patients who were not able to participate in a standard weight loss program (due to, for example, low educational level, dysfunctional family, or school problems) and who had unsuccessfully participated in a 6-month intensive lifestyle intervention program, were recruited. These patients were then randomized to receive either placebo or metformin in addition to continuing the lifestyle intervention. This randomized controlled trial failed to show significant differences between treatment and placebo groups, apart from a significant improvement in insulin sensitivity in the treatment group only. The reason for this appeared to be that starting medication (both for metformin and placebo) appeared to improve many outcomes compared with lifestyle intervention

alone. For example, appointment non-attendance rates decreased from 38% prior to randomization to 12% afterwards. HOMA-IR also improved after randomization in both groups and an increase in activity and a decrease in sedentary activities were reported regardless of treatment group. This placebo effect shows how important the belief in therapy can be as motivation for lifestyle changes in obese adolescents and in enhancing adhesion to a healthy lifestyle.

Intensive insulin therapy in severely burned pediatric patients: a prospective randomized trial

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Am J Respir Crit Care Med 2010;182:351–9.

Background: Mortality and morbidity in severely burned patients is increased by hyperglycemia and insulin resistance. Glycemic control appears essential to improve clinical outcomes. To date, no prospective randomized study has investigated whether intensive insulin therapy is associated with improved post-burn morbidity and mortality. This study aims to provide such evidence.

Methods: A total of 239 severely burned pediatric patients with burns over greater than 30% of their total body surface area were randomized (block randomization 1:3) to intensive insulin treatment ($n = 60$) or control ($n = 179$). Demographics, clinical outcomes, sepsis, glucose metabolism, organ function, and inflammatory, acute-phase, and hypermetabolic responses were measured in this population.

Results: Intensive insulin treatment significantly decreased the incidence of infections and sepsis compared with controls ($p < 0.05$). Mortality was 4% in the intensive insulin therapy group and 11% in the control group ($p = 0.14$). Intensive insulin therapy also improved organ function as indicated by improved serum markers, DENVER2 scores, and ultrasound ($p < 0.05$). Intensive insulin treatment dampened inflammatory and acute-phase responses by decreasing IL-6 and acute-phase proteins compared with controls ($p < 0.05$). Intensive insulin therapy alleviated post-burn insulin resistance and the vast catabolic response of the body ($p < 0.05$).

Conclusion: This prospective randomized clinical trial showed that intensive insulin therapy improves post-burn morbidity. [Clinical trial registered with www.clinicaltrials.gov (NCT00673309).]

Hyperglycemia is common in severely burned patients and is thought to be due to a combination of increased rate of glucose appearance and impaired tissue extraction of glucose. This has been shown to significantly increase the incidence of bacteremia and mortality [9–11]. This large, prospective, multicenter RCT includes a very detailed and comprehensive protocol in order to investigate the effect of tight glycemic control in children with severe burns. They consider and investigate many different effects of this treatment but concentrate on the most clinically important outcomes of sepsis and mortality. They show that tight glycemic control (maintaining glucose between 4.4 and 6.1 mmol/l) significantly improves the risk of sepsis, occurring in 8% of the treatment group compared to 23% in the control group (maintaining glucose between 7.7 and 10 mmol/l) ($p < 0.05$). They also showed a non-significant reduction in mortality of 4% in the treatment group, compared to 11% in the control group. This appears largely to be due to a reduction in the incidence of infections and a dampened acute-phase/inflammatory response. In addition, hepatic and renal function appears to be improved by intensive insulin therapy. Specific mechanisms are not explored by this study, however the authors speculate that insulin may affect immune system function and in addition, attenuate the inflammatory response. However, hypoglycemia was more common in the intensive insulin group (9% of patients in the control group compared to 26% in the treatment group). Given this risk and the continued uncertainty surrounding the ideal target, glucose for burned patients, the authors go on to recommend a target glucose level of 7.2 mmol/l with a maximum glucose level of 8.3 mmol/l.

Fear of hypoglycemia in parents of young children with type 1 diabetes: a systematic review

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BMC Pediatr 2010;10:50.

Background: Barnard et al. report since the Diabetes Control and Complications Trial (DCCT) showed that tighter control reduces complications of diabetes, there has been more emphasis on intensification of insulin in diabetes care. The authors report that children and families with type 1 diabetes (DM1) are afraid of hypoglycemia. Barnard et al. hypothesized that fear of hypoglycemia may take precedence over fear of long-term complications, and that certain behavior in order to reduce hypoglycemia may be result of poorer control in children with DM1. The aim of this review was to systematically review studies concerning the extent and consequences of fear of hypoglycemia in parents of children under 12 years of age with DM1, and interventions to reduce it.

Methods: MEDLINE, EMBASE, PsycINFO, The Cochrane Library, Web of Science, abstracts from the EASD, ADA and Diabetes UK, Current Controlled Trials, ClinicalTrials.gov, UK CRN data sources were reviewed.

Inclusions: Studies of any design relevant to the topic of parents of children under 12 years of age with DM1 were included. The key outcomes were the extent and impact of fear, hypoglycemia avoidance behavior in parents, the effect on diabetes control, and the impact of interventions to reduce this fear and hypoglycemia avoidance behavior.

Results: The authors reviewed eight articles from six studies that met the inclusion criteria. Selected studies were all cross sectional and of good quality. Parental fear of hypoglycemia, anxiety and depression were reported as common. There was a lack of evidence on behavior to avoid hypoglycemia, but suggestions that higher blood glucose was tolerated to avoid hypoglycemia. No studies reporting interventions to reduce parental fear of hypoglycemia were identified.

Conclusions: These dataset of evidence were limited. Parents of children with DM1 reported considerable fear of hypoglycemia, affecting both parental health and quality of life. Trials of interventions including a trial of structured education for parents of young children with DM1 to reduce parental anxiety and hypoglycemia avoidance behavior are warranted.

Interventions with adherence-promoting components in pediatric type 1 diabetes: meta-analysis of their impact on glycemic control

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Diabetes Care 2010;33:1658–64.

Background: In this review the authors undertake a meta-analysis on interventions with adherence-promoting components and document their impact on glycemic control.

Methods: 15 studies that met the following criteria were subjected to meta-analysis: (1) randomized, controlled trial, (2) sample included children aged <19 years, (3) children with type 1 diabetes (DM1), (4) reported results on glycemic control, and (5) reported use of *adherence- or self-management*.

Results: 997 children and young people with DM1 from 15 studies were studied. The mean effect size for pre- to posttreatment change for the intervention versus control group comparison was 0.11 (95% CI –0.01 to 0.23). There was a small effect providing a modest improvement in glycemic control. However, analysis for the pre- to posttreatment effects for the intervention group alone did show significant variability ($Q_{14} = 33.11$; $p < 0.05$). Multicomponent interventions, those that targeted emotional, social, or family processes that facilitate diabetes management, were more effective than direct interventions, i.e. a single behavioral process (e.g., more frequent blood glucose monitoring).

Conclusions: Interventions that focus on a single direct behavior and neglect emotional, social, and family processes are unlikely to have an impact on glycemic control. Multicomponent interventions in pediatric patients with DM1 showed more impact on HbA1c and warrant further research.

The systematic review by definition is an extensive literature review focused on a research question that aims to identify, appraise, select and synthesize all high-quality research evidence relevant to that question [12]. All four systematic reviews in this chapter draw from RCTs, large cohort studies, cross-sectional studies or large observational databases (KIGS), in doing so these systematic reviews answer the questions asked and provide updated evidence in pediatric endocrinology. The first two systematic reviews focus on parental anxieties associated with hypoglycemia and the lack of interventional studies in this area. In the paper by Barnard et al., parental fear of hypoglycemia, anxiety and depression of children with type 1 diabetes are found to be common. This is not surprising, however this review focuses on the Diabetes Control and Complications Trial (DCCT) [13] and hypothesizes that because of severe parental anxiety there are some suggestions that higher blood glucose levels are maintained in order to avoid hypoglycemia. This systematic review, although small with eight articles from six studies, does highlight the lack of interventional studies to reduce these parental anxieties. The authors also suggest that interventional studies including a structured educational program for young children with type 1 diabetes are warranted. The second systematic review using meta-analysis by Hood et al. merges very nicely with Barnard's paper. In this review the authors report that unifocused interventions have little impact on reducing HbA1c and parental anxieties, however a multicomponent interventional approach (targeting emotional, social and family processes) results in more effect reduction in HbA1c. This review includes 15 studies including 997 children and adolescents with type 1 diabetes.

Systematic review of the clinical effectiveness of Genotropin (somatropin) in children with short stature

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J Pediatr Endocrinol Metab 2010;23:535–51.

Background: The authors report that Genotropin (somatropin) is licensed for the treatment of children with growth hormone deficiency, Turner syndrome, Prader-Willi syndrome, chronic renal failure and small for gestational age children. In this systematic review, Loftus et al. evaluated the clinical efficacy and effectiveness of Genotropin in these conditions to inform a NICE Technology Appraisal of growth hormone for the treatment of growth failure in children.

Methods: Seven databases, including Medline and Embase, for English language studies were searched. Randomized controlled trials (RCTs) or observational studies investigating Genotropin in children were included.

Results: Loftus et al. report on 30 RCTs; only one reported final height data. Eleven observational studies reported final height and seven were based on the Pfizer International Growth Survey (KIGS).

Conclusions: The authors conclude from this systematic review that there is a paucity of long-term RCTs reporting final height data and other important qualitative outcomes. Observational data, like the KIGS database, remains important for guiding GH therapy prescribing.

Impact of growth hormone therapy on adult height of children with idiopathic short stature: systematic review

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BMJ 2011;342:c7157.

Background: The authors systematically determine the impact of growth hormone (GH) therapy on adult height of children with idiopathic short stature (ISS).

Methods: Cochrane Central Register of Controlled Trials, Medline, and articles were retrieved from bibliographic references of randomized and non-randomized controlled trials (1985–2010). Randomized and non-randomized controlled trials with height measurements for adults were selected. Inclusion criteria were initial short stature (defined as height >2 SD score below the mean), peak GH responses >10 $\mu\text{g/l}$, prepubertal stage, no previous GH therapy, and no other comorbidities. Adult height was defined as growth rate <1.5 cm/year or bone age of 15 years in females and 16 years in males.

Results: Three randomized controlled trials (115 children) met the inclusion criteria. The adult height of the GH-treated children was greater than controls by 0.65 SD score (~ 4 cm). The mean height gain in treated children was 1.2 SD score compared with 0.34 SD score in untreated group. A small difference of 1.2 cm in adult height was observed between the two GH dosing regimens. In the seven non-randomized controlled trials the adult height of the GH-treated group was higher than controls by 0.45 SD score (~ 3 cm).

Conclusions: GH therapy in children with ISS may be effective in partially reducing the deficit in height as adults, but the effectiveness is less than the average achieved in other conditions where GH is licensed. The individual response to GH therapy is highly variable, and further studies are warranted to identify the responders.

Loftus et al. undertook an important systematic review evaluating the efficacy and effectiveness of Genotropin to inform the technology appraisal review by the UK Government National Institute for Health and Clinical Excellence (NICE) in GH deficiency, Turner syndrome, Prader-Willi syndrome, chronic renal failure and children born SGA. The authors also highlight the important of large observational databases such as The Pfizer International Growth Database (KIGS). These datasets remain important sources of information on the use of GH, growth, safety and quality of life in children with short stature and maximize informed prescribing of GH in this scenario. They reported minor adverse events and where serious events were recorded, they were not reported to be related to GH therapy. Deodati and Cianfarani found that three randomized controlled trials (115 children) met the inclusion criteria in their systematic review of the assessment of the impact of GH therapy on adult height of children with idiopathic short stature (ISS). Adult height of GH-treated children exceeded controls by 0.65SD (4 cm), a value less than that reported in surveillance studies. The mean height gain in treated children was 1.2 SD compared with 0.34 SD in untreated group. The authors suggest that GH may be effective in partially reducing the deficit in height as adults, but the effectiveness is less than the average achieved in other conditions where GH is licensed. The individual response to GH therapy is highly variable, and further studies are warranted to identify the responders. Both these systematic reviews focus on the lack of final height data in children with various forms of GH deficiency and highlight that large observational databases such as KIGS remain important to inform decision-making; however further studies in all these areas are needed to confirm these quoted data.

Food for thought: food for growth

Effects of growth hormone and nutritional therapy in boys with constitutional growth delay: a randomized controlled trial

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J Pediatr 2010;158:427–32.

Background: This randomized, controlled trial aimed to examine whether supplemental nutrition augments the anabolic actions of growth hormone (GH) in boys with constitutional delay of growth and maturation (CDGM). The setting was an outpatient clinical research center.

Methods: 20 prepubertal boys (age 9.3 ± 1.3 years) with CDGM (height standard deviation score -2.0 ± 0.5 ; bone age delay 1.8 ± 0.8 years; body mass index standard deviation score -1.2 ± 1.0 ; peak stimulated GH 15.7 ± 7.7 $\mu\text{g/l}$), were randomized ($n = 10/\text{group}$) to 6 months of observation or daily nutri-

tional supplementation, followed by additional daily GH therapy (43 µg/kg/day) in all subjects for a further 12 months. Total energy expenditure (TEE), growth, hormones, and nutrition markers were compared using t tests and repeated measures of analyses of variance.

Results: Energy intake was increased at 6 months within the nutrition group ($p = 0.04$), but not in the observation group, whereas TEE was not statistically different within either group at 6 months. GH treatment resulted in a higher energy intake after 6 months, and increased TEE in the GH/nutrition group at 12 months ($p < 0.01$), but not in the GH group versus baseline. Height, weight, lean body mass, hormonal and nutrition markers increased comparably in both groups throughout the 18-month trial.

Conclusion: Boys with CDGM use energy at an accelerated rate, and this imbalance is not overcome with added nutrition. GH therapy increases growth comparably whether nutritional supplements are added or not in these patients.

'Functional food' for acceleration of growth in short children born small for gestational age

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J Pediatr Endocrinol Metab 2010;23:435–41.

Background: This RCT was designed to assess whether nutritional supplementation could stimulate growth in short children born small for gestational age (SGA) in comparison with conventional GH treatment.

Methods: Subjects included 54 short but otherwise healthy children (26 boys), 6.4 ± 1.8 years of age, born SGA. After a 6-month observation period the participants were randomly assigned to receive GH therapy (42 µg/kg/day) (GH), or a nutritional program (NUT) or to enter as controls (OBS). Patients in the nutritional program received 10 mg/day iron, 11 mg zinc 3 times a week and 10,000 IU/week of vitamin A. Height, weight, dietary intake and serum IGF-1 were measured every 3 months.

Results: Six months of nutritional supplement had a positive effect, inducing growth acceleration at a lower level than that seen in the GH-treated children, but significantly greater than noted in the observation group (OBS group 4.6 ± 1.3 cm/year; NUT group 7.9 ± 1.7 cm/year; GH group 9.1 ± 1.8 cm/year; $p < 0.001$).

Conclusion: Six months of supplementation with vitamin A, iron and zinc may induce growth acceleration in short children born SGA with subnormal nutrients but not as effectively as GH treatment alone.

So, should we worry about the nutritional status of our patients when we give GH treatment? Can extra nutrients improve the growth response, or even substitute for it? This year we have contrasting findings from two RCTs looking at these issues. Both studies involved a detailed look at food and energy intake in prepubertal children before and during a period of GH treatment with identical dosage regimens, but used different approaches to managing the supplementation. Han et al. explored giving a complete nutritional boost to 110% of the recommended daily allowance in boys with constitutional delay, whereas Zadik et al. supplemented SGA children with two micronutrients as laboratory and clinical evidence exists for the beneficial effect of zinc and vitamin A on growth, together with additional iron. Both studies compared the effect of extra nutrition versus a randomized control group, but Han et al. treated both groups subsequently with GH, Zadik et al. having three parallel arms, the control arm receiving dietetic advice only. The detail of design is important to understand the outcomes. Adding full nutritional supplementation significantly increased energy intake but had no effect on height or weight gain. Neither did the response to GH appear to be influenced by prescribed extra energy intake. However, in the SGA children, added micronutrients did appear to significantly increase height velocity without the requirement for additional energy intake. The response however was less than that in the GH-treated arm. There was not a GH plus supplementation arm. So what messages do these studies convey? The lack of effect of full nutritional supplementation could be explained by the fact that the subjects downregulated their own energy and food intake at other times during the day, so an energy homeostatic mechanism may be in operation during prepuberty, in contrast to the accelerated nutritional requirements in late puberty, especially in boys [14]. The effect of adding specific growth-associated micronutrients alone is impressive, and

although it is not yet clear whether attention to this level of detail will improve GH responsiveness, the overall message from both studies is that we should perhaps pay more attention to nutritional factors in short children, especially when a growth retardation process is implicated.

Follow-up on Yearbook 2010

The effect of oxandrolone on body proportions and body composition in growth hormone-treated girls with Turner syndrome

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Background: Untreated girls with Turner syndrome (TS) have short stature, short legs, relatively broad shoulders, a broad pelvis, low muscle mass and a high fat mass. This study aimed to assess the effect of the weak androgen oxandrolone (Ox) on body proportions and composition in growth hormone (GH)-treated girls with TS.

Methods: 133 patients were included in a randomized, placebo-controlled, double-blind study. Patients were treated with GH (1.33 mg/m² per day) from baseline, combined with placebo (Pl) or Ox in a low (0.03 mg/kg per day) or previously conventional (0.06 mg/kg per day) dose from the age of 8, and estrogens from the age of 12. Sitting height, biiliacal and biacromial distances compared with height (i.e. shape values), BMI, waist circumference, upper arm muscle area and sum of 4 skinfolds SD scores (SDS) were assessed half yearly.

Results: Compared with GH + Pl, adult shape values on GH + Ox tended to be higher for sitting height (Ox 0.03, $p = 0.2$; Ox 0.06, $p = 0.02$) and biacromial distance (Ox 0.03, $p = 0.2$; Ox 0.06, $p = 0.07$) and lower for biiliacal distance (Ox 0.03, $p = 0.004$; Ox 0.06, $p = 0.08$). Upper arm muscle area SDS increased more (Ox 0.03, $p < 0.001$; Ox 0.06, $p < 0.001$) than on GH + Pl while the sum of 4 skinfolds SDS tended to decrease more (Ox 0.03, $p = 0.2$; Ox 0.06, $p = 0.005$). The increase in waist circumference and BMI SDS was comparable between the dosage groups.

Conclusions: In GH-treated girls with TS, Ox 0.06 increases sitting height and tends to increase biacromial distance and decrease biiliacal distance, while Ox 0.03 significantly decreases biiliacal distance compared with height. Ox 0.06 reduces subcutaneous fat mass, and both Ox dosages increase muscle mass.

Effect of oxandrolone and timing of pubertal induction on final height in Turner's syndrome: randomized, double-blind, placebo-controlled trial

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Background: This study aimed to examine the effect of oxandrolone and the timing of pubertal induction on final height in girls with Turner's syndrome receiving a standard dose of growth hormone.

Methods: This was a randomized, double-blind, placebo-controlled trial set in 36 UK pediatric endocrinology departments. Girls with Turner's syndrome aged 7–13 years who were receiving recombinant growth hormone therapy 1.4 mg/m²/day (50 µg/kg/day) were recruited. Participants were randomized to oxandrolone (0.05 mg/kg/day, maximum 2.5 mg/day) or placebo from the age of 9 years. Those with evidence of ovarian failure at 12 years were further randomized to oral ethinylestradiol (year 1: 2 µg daily; year 2: 4 µg daily; year 3: 4 months each of 6, 8, and 10 µg daily) or placebo. Participants who received placebo and those recruited after the age of 12.25 years started ethinylestradiol at age 14. Final height was the main outcome measure.

Results: 106 participants were recruited, of whom 14 withdrew and 82/92 reached final height. Both oxandrolone and late pubertal induction increased final height: by 4.6 (95% confidence interval 1.9–

7.2) cm ($p = 0.001$, $n = 82$) for oxandrolone and 3.8 (0.0–7.5) cm ($p = 0.05$, $n = 48$) for late pubertal induction with ethinylestradiol. In the 48 children who were randomized twice, the effects on final height (compared with placebo and early induction of puberty) of oxandrolone alone, late induction alone, and oxandrolone + late induction were similar, averaging 7.1 (3.4–10.8) cm ($p < 0.001$). No cases of virilization were reported.

Conclusion: Oxandrolone had a positive effect on final height in girls with Turner's syndrome treated with growth hormone, as did late pubertal induction with ethinylestradiol at age 14 years. However, these effects were not additive, so using both had no advantage. Oxandrolone could, therefore, be offered as an alternative to late pubertal induction for increasing final height in Turner's syndrome. [Trial Registration Current Controlled Trials ISRCTN50343149.]

Menke et al. [15], reviewed in *Yearbook 2010* [16], reported the safety profile of the weak anabolic steroid oxandrolone in combination with growth hormone treatment in girls with Turner syndrome. They recommended the use of low-dose oxandrolone (0.03 mg/kg/day) over conventional dose (0.6 mg/kg/day) in combination with growth hormone to achieve a maximum benefit-to-risk ratio for increasing final height in such patients. In the past 12 months, knowledge in this area has been furthered by the publication of the three RCTs included in this section, all of which are well designed, well executed and provide a high level of evidence. Both the Menke and Gault papers suggest that the use of oxandrolone in combination with growth hormone can increase final height in girls with Turner syndrome. These two studies are elegant multicenter randomized controlled trials, both of relatively impressive size and each dealing with uncertainties well. In the current paper, Menke et al. go on to provide evidence that oxandrolone may produce favorable changes in body composition such as a reduction in subcutaneous fat and an increase in muscle mass. This is beneficial as girls with Turner syndrome tend to have a relatively high fat mass and reduced muscle mass [17]. Both studies also looked at the safety of oxandrolone. Menke reported virilization in 15 of 39 patients given a dose of 0.06 mg/kg/day, 7 of which considered the side effects serious enough to give up treatment and thus give up a potential increase in final height. In contrast, none of the 51 patients given 0.05 mg/kg/day in the Gault study reported signs of virilization, although 3 patients had adverse effects of acne, hypertension and abnormal liver function respectively. Potential explanations include different thresholds for symptom reporting between the two study populations, the slightly lower dose of 0.05 mg/kg/day or the maximum dose of 2.5 mg/day used in the Gault study. Delaying puberty to increase final adult height was found to be almost as effective as the use of oxandrolone by Gault et al. However, employing these two approaches together was not shown to have an additive effect and the authors recommend the use of oxandrolone in order to avoid potential adverse physiological and psychological consequences of delaying puberty.

Growth hormone plus childhood low-dose estrogen in Turner's syndrome

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Background: Short stature and ovarian failure are characteristic features of Turner syndrome. Although recombinant human growth hormone is commonly used to treat the short stature associated with this syndrome, a randomized, placebo-controlled trial is needed to document whether such treatment increases adult height. It is not known whether childhood estrogen replacement combined with growth hormone therapy provides additional benefit. This study investigated the independent and combined effects on adult height in patients with Turner syndrome of growth hormone and early, ultra-low-dose estrogen.

Methods: 149 girls, 5.0–12.5 years of age, were randomized in this double-blind, placebo-controlled trial, into four groups: double placebo (placebo injection + childhood oral placebo, $n = 39$), estrogen alone (placebo injection + childhood oral low-dose estrogen, $n = 40$), growth hormone alone (growth hormone injection + childhood oral placebo, $n = 35$), and growth hormone-estrogen (growth hormone injection + childhood oral low-dose estrogen, $n = 35$). The growth hormone dose was 100 $\mu\text{g/kg}$ three times per week. Doses of ethinylestradiol (or placebo) were adjusted according to age and pubertal

status. At 12.0 years of age all patients received escalating doses of ethinylestradiol. When adult height was reached, growth hormone injections were terminated.

Results: The mean standard deviation scores for adult height were -2.81 ± 0.85 , -3.39 ± 0.74 , -2.29 ± 1.10 , and -2.10 ± 1.02 for the double-placebo, estrogen-alone, growth hormone-alone, and growth hormone-estrogen groups, respectively ($p < 0.001$) (attained on average at 17 years of age after an average of 7.2 years in the study). Overall, growth hormone treatment increased adult height standard deviation score by 0.78 ± 0.13 (5.0 cm), compared to placebo ($p < 0.001$). Compared with growth hormone treatment alone, adult height was greater in the growth hormone-estrogen group by 0.32 ± 0.17 standard deviation score (2.1 cm) ($p = 0.059$). This suggests a modest synergy between childhood low-dose ethinylestradiol and growth hormone.

Conclusions: Growth hormone treatment increases adult height in patients with Turner syndrome. Combining childhood ultra-low-dose estrogen with growth hormone may improve growth and provide other potential benefits associated with early initiation of estrogen replacement. [Funded by the National Institute of Child Health and Human Development and Eli Lilly; ClinicalTrials.gov number, NCT00001221.]

This double-blind, placebo-controlled trial by Ross et al., spanning three decades, provides final confirmation that the use of growth hormone in girls with Turner syndrome can have a significant and positive effect on final adult height. The study was elegantly designed to include two randomizations of the 149 participants (growth hormone vs. placebo and low-dose childhood estrogen vs. placebo) and a 7-year follow-up period. Interestingly, this study also suggests a possible modest synergy between growth hormone and low-dose childhood estrogen. This data provides a challenge to the practice of delaying estrogen replacement until the mid-teenage years in girls with Turner syndrome (as was used by Gault et al. above). In summary, these three trials provide evidence that growth hormone is effective in increasing the final adult height of girls with Turner syndrome. In addition, there is evidence to consider one of three possible additional treatments: oxandrolone given at 9 years of age, low-dose childhood estrogen from 8 years of age, and finally, in contrast, the delay of pubertal induction until 14 years.

References

1. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS: Evidence-based medicine: what it is and what it isn't. *BMJ* 1996;312:71-72.
2. O'Riordan S, Butler G: Evidence-based medicine in pediatric endocrinology; in Carel JC, Hochberg Z (eds): *Yearbook of Pediatric Endocrinology*. Basel, Karger, 2009, pp 181-197.
3. Bergenstal RM, Tamborlane WV, Ahmann A, Buse JB, Dailey G, Davis SN, et al: Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. *N Engl J Med* 2010;363:311-320.
4. Arlt W, Willis DS, Wild SH, Krone N, Doherty EJ, Hahner S, et al: Health status of adults with congenital adrenal hyperplasia: a cohort study of 203 patients. *J Clin Endocrinol Metab* 2010;95:5110-5121.
5. Claahsen-van der Grinten HL, Otten BJ: Adrenal function: a gold standard test for adrenal insufficiency in children? *Nat Rev Endocrinol* 2010;6:605-606.
6. Goulet O, Dabbas-Tyan M, Talbotec C, Kapel N, Rosilio M, Souberbielle JC, et al: Effect of recombinant human growth hormone on intestinal absorption and body composition in children with short bowel syndrome. *JPEN J Parenter Enteral Nutr* 2010;34:513-520.
7. Wales PW, Nasr A, de Silva N, Yamada J: Human growth hormone and glutamine for patients with short bowel syndrome. *Cochrane Database Syst Rev* 2010(6):CD006321.
8. Park MH, Kinra S, Ward KJ, White B, Viner R: Metformin for obesity in children and adolescents: a systematic review. *Diabetes Care* 2009;32:817-822.
9. Gore DC, Chinkes D, Heggors J, Herndon DN, Wolf SE, Desai M: Association of hyperglycaemia with increased mortality after severe burn injury. *J Trauma* 2001;51:540-544.
10. Gore DC, Chinkes D, Hart DW, Wolf SE, Herndon DN, Sanford AP: Hyperglycemia exacerbates muscle protein catabolism in burn-injured patients. *Crit Care Med* 2002;30:2438-2442.
11. Hemmila MR, Taddonio M, Arbabi S, Maggio PM, Wahl WL: Intensive insulin therapy is associated with reduced infectious complications in burn patients. *Surgery* 2008;144:629-635.
12. Glasziou P: Centre for Evidence-Based Medicine. Oxford, University of Oxford, 2011 (available from <http://www.cebm.net/index>).
13. Shamooh H, Duffy H, Fleischer N, Engel S, Saenger P, Strelzyn M, et al: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977-986.
14. Shomaker LB, Tanofsky-Kraff M, Savastano DM, Kozlosky M, Columbo KM, Wolkoff LE, et al: Puberty and observed energy intake: boy, can they eat! *Am J Clin Nutr* 2010;92:123-129.
15. Menke LA, Sas T, de Muinck Keizer-Schrama SM, Zandwijken GR, de Ridder MA, Odink RJ, Jansen M, Delemarre-van de Waal HA, Stokvis-Brantsma WH, Waelkens JJ, Westerlaken C, Reeser HM, van Trotsenburg AS, Gevers EF, van Buuren S, Dejonckere PH, Hokken-Koelega AC, Otten BJ, Wit JM: Efficacy and safety of oxandrolone in growth hormone-treated girls with Turner syndrome. *J Clin Endocrinol Metab* 2010;95:1151-1160.

16. Butler G: Evidence-based medicine in pediatric endocrinology; in Carel JC, Hochberg Z (eds): Yearbook of Pediatric Endocrinology 2010. Basel, Karger, 2010, pp 189–205.
17. Gravholt CH, Hjerrild B, Mosekilde L, Hansen TK, Rasmussen LM, Frystyk J, Flyvbjerg A, Christiansen JS: Body composition is distinctly altered in Turner syndrome: relations to glucose metabolism, circulating adipokines, and endothelial adhesion molecules. *Eur J Endocrinol* 2006;155:583–592.