Evidence-Based Medicine in Pediatric Endocrinology

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Evidence-based pediatric endocrinology? How does one start to define it? Where are the boundaries and what does this term encompass? These are some of the challenges with this new chapter in the Yearbook. What about the typical evidence base hierarchy; does it really hold the truth about the quality and applicability of clinical research? Are all other forms of evidence really inferior to the classical double-blind randomized controlled clinical trial? Well, this chapter reflects a selection of what has been published in the past year in pediatric endocrinology, based on searches far and wide. Includes are classic randomized controlled trials in addition to well-conducted longitudinal studies where these provide the best evidence to solve a clinical conundrum. It has been more difficult deciding what to leave out rather than what to include. Overviews from drug company's databases and consensus statements (including those of ESPE) are widely consulted sources of evidence. Therefore, this chapter has concentrated on seeking out sources which we do not always come across. As the intention has been to aid decision-making in daily clinical practice, in deciding what topics to include and what not to include, the following parameter has been used: Is the subject likely to fall within the remit of a clinical pediatrician or pediatric endocrinologist? Is this something worthwhile knowing about? Is it a subject your colleagues from other disciplines might consult you about?

There are two points which come to the fore in this review: firstly the important marriage between basic science and therapeutic clinical practice which is only just beginning to flourish, for example GH responsiveness and genotyping, and the concepts revisited section where new and important clinical findings are emerging based on revisiting well-conducted studies of the previous generation, for example the apparently protective effect of childhood GH treatment on the development of cardiovascular problems in adult women with Turner syndrome. This all bodes very well for the future.

Mechanism of the year: genotype-therapeutic links in growth hormone treatment

The d3/fl-growth hormone (GH) receptor polymorphism does not influence the effect of GH treatment (66 µg/kg/day) or the spontaneous growth in short non-GH-deficient small-for-gestational-age children: results from a 2-year controlled prospective study in 170 Spanish patients

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J Clin Endocrinol Metab 2006;91:3281–3286

Background: The d3/fl-GH receptor polymorphism has been associated with increased GH responsiveness in short SGA and ISS French children, Turner syndrome in Germany and GH deficiency in Brazil, but not in SGA children in Germany nor in Italian children with GHD. This study aimed to look at GH responsiveness and spontaneous growth in SGA children in Spain.

Methods: This prospective randomized controlled trial was of 2 years' duration. 170 short (−2 SD) non-GHD SGA children (BW/BL < −2 SD), 84 boys mean age 8.0 years, and 86 girls mean age 7.4 years, were recruited from 30 Spanish hospitals. Centralized genotyping and assays of IGF-1/IGFBP-3 were performed. 86 subjects were randomized to receive GH (66 µg/kg/day) for 2 years.

Results: Similar GH responsiveness was seen during the first and second years of GH treatment irrespective of genotype. Total 2-year height gain was 18.5 ± 2.4 cm in d3/d3, 18.4 ± 2.6 cm in d3/fl, and

19.5 ± 2.3 cm in fl/fl. The genotype did not predict first year responsiveness. No differences in response were found between the subgroups which remained prepubertal or entered puberty. In the non-treated patients, similar height/height velocity changes were seen in each d3/fl GHR genotype subgroups.

Conclusions: In this study of SGA children, significant height increases were seen over 2 years of GH treatment, but were similar for each of the d3/fl GHR genotypes analyzed.

This large multicenter national study has sought not only to examine the effectiveness of GH in a defined population, but also to attempt to predict GH responsiveness and outcomes in subgroups of patients with SGA with the d3/fl GH receptor polymorphism. This study did not demonstrate differences between the genotypes analyzed. The rigorous approach using a multicenter randomized controlled trial with single-center scientific analysis has demonstrated how well a national cooperative approach can work. Why are their results different from other studies, however? Well, some authors studied different conditions, for example Turner syndrome, which can have other confounding factors. The dose of GH used in the present study was much higher than in the others, however. This throws up the possibility that there is a dose-response effect which may vary according to the genotype, but is overcome by saturation exposure to GH. This developing area of applied genetics will be very important for the direction of future therapeutic approaches.

New paradigms – using old treatments in new ways

Intermittent recombinant growth hormone treatment in short children born small for gestational age: 4-year results of a randomized trial of two different treatment regimens

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Horm Res 2006;66:118–123

Background: GH treatment for SGA children can increase height and height velocity, but the height velocity on standard treatment wanes in the second year. This randomized study explored the efficacy of two different discontinuous GH treatment regimens using a high GH dose schedule (67 µg/kg/day) over 4 years with the intention of avoiding this slow down in response to GH therapy.

Methods: This was a multicenter (11 centers in France) randomized open-label, parallel-group comparative study of 58 SGA children aged 2–5 years, all height ≤ -3 SDS and birth weight <10 th centile. Randomization was to two groups, either of alternating years' treatment, or two treatment years followed by 2 observation years. The principal outcome measure was total height gain.

Results: Height gain over 4 years was 1.4 ± 0.1 SDS in the alternating year treatment group, and 1.6 ± 0.2 SDS in the 2 years on/2 years off treatment group (NS). Height velocity increased during the treatment years and decreased during the observation years.

Conclusions: Significant 4-year growth gains were seen in both groups, but neither discontinuous regimen produced better growth than that which could be seen over 4 years with a continuous lower dosage regimen (33 µg/kg/day).

This well-designed randomized open-label, parallel-group comparative study of discontinuous GH regimens comparing alternating years treatment with the 2 years on/2 years off treatment was aimed at exploring ways of using GH therapy more efficiently in patients with SGA, and also to see whether the natural waning effect of response to treatment in second and subsequent years could be overcome by an intermittent GH regimen. Unfortunately no improvements in GH responsiveness were seen. The most important positive findings from this trial are that use of a discontinuous regimen is not detrimental to total growth gained and does not differ from continuous treatment, although an additional factor of course is the actual GH dosage itself [1]. Although continuous high-dose treatment produces the greatest long-term increases in height, absolute gains are not double the height gains on standard dose therapy. It is this factor, together with the still unknown very long-term

effects of high-dose GH treatment, which has been the basis of the European Medicines Agency (EMA) to recommend standard dose GH treatment for SGA patients. However, the evidence so far suggests that any observed metabolic changes associated with GH therapy reverse on stopping treatment. This is reassuring, and it paves the way for even more imaginative approaches to GH therapy, based on the knowledge of how children usually respond to treatment with an initial boost to growth, followed by the slowing of the height velocity. This pattern is remarkably similar across all different conditions.

New hope for health and fertility

Growth hormone treatment improves growth and clinical status in prepubertal children with cystic fibrosis: results of a multicenter randomized controlled trial

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J Clin Endocrinol Metab 2006;91:4925–4929

Background: GH treatment has been suggested as improving growth, weight, bone content, lung function and quality of life in prepubertal children with cystic fibrosis. This study consisted of a multicenter, randomized controlled crossover trial to examine the effect of GH.

Methods: 61 prepubertal children with height and weight <25th centile were randomized to receive GH or not in year 1, followed by a crossover in year 2. In addition to standard anthropometry, other measures included: quality of life (QoL) questionnaires, metabolic measures (blood glucose), nutritional assessment, lung function tests, bone density and recording of antibiotic usage and hospital admissions.

Results: Both groups were similar at baseline, but after 1 year, GH-treated patients (0.3 mg/kg/week) showed positive weight and height gain (irrespective of baseline measurements) together with improvements in bone density and QoL, and had fewer hospital admissions. No changes in lung function were seen. The same changes were shown in the GH-treated group after crossover. After GH treatment ceased, improvements noted were maintained.

Conclusions: This short-term trial of GH treatment has shown improved growth and weight gain and is associated with better physical and mental health. Benefits noted appear to be maintained for the year after treatment is stopped.

This is an important study, not only on account of its rigorous multicenter, randomized controlled crossover trial design, but as it explores effects of GH beyond the simple auxological into the realms of better physical and psychological wellbeing in children with cystic fibrosis where poor growth is a feature of this chronic condition. The improvements in growth and the wellbeing of the patients were both notable. The focus was on the shorter and lighter individuals (<25th centile) without adjusting for parental heights, but an equal improvement in growth was seen across the study group regardless, but this observation may not hold for a longer-term study as target height would need to be taken into account. Abnormal glucose tolerance was examined for by measuring random glucose in accord with US guidelines without abnormalities being seen, although it could be argued that this is insufficiently rigorous to examine for side effects of GH treatment on glucose metabolism. Bone mineralization increased, as did some measures of lung function, but these could be explained by the greater physical growth in the treated group. It was reassuring to see a statistical improvement in QoL and body image scores, but by far the most impressive outcome of this study is the decrease in the number of hospitalizations on account of better health, presumably due to the anticatabolic/anabolic actions of GH. Although GH is expensive, the authors argue that this is offset by the reduction of inpatient treatment costs and that the effects of GH are apparently maintained after cessation. This requires a health economic evaluation with longer-term data, but is impressive so far.

Testicular growth from birth to two years of age, and the effect of orchidopexy at age nine months: a randomized, controlled study

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Acta Paediatr 2006;95:318–324

Background: There is much debate over the benefits of early orchidopexy in the management of undescended testes. This is the first prospective randomized controlled trial in this field. Testicular growth was assessed by ultrasonography as a marker for the prediction of fertility potential.

Methods: Boys referred with congenital unilaterally palpable undescended testes were randomized at 6 months of age to surgical orchidopexy at 9 months of age ($n = 70$), or surgical treatment at 3 years of age ($n = 79$). The volume of each testis was measured at 3 weeks of age (or at referral) then at 2, 6, 12 months and annually until 5 years.

Results: Following orchidopexy, the operated (previously undescended) testes showed catch-up growth so that by 2 years of age the mean volume was significantly greater than the non-operated testes (0.49 vs. 0.36 ml, $p < 0.001$). The mean testicular growth ratio between the previously undescended and the scrotal testes in individual boys was higher at 2 years of age in the surgically treated versus untreated groups (0.84 vs. 0.63, $p < 0.001$).

Conclusions: Orchidopexy at 9 months of age is associated with catch-up growth of the operated testes by 2 years of age.

Undescended testis is a common clinical condition and a review of the existing literature by the authors in this paper highlights the lack of evidence base for the timing of orchidopexy. Concerns lie in two areas, namely risk of testicular cancer which is slightly higher, but principally on fertility outcomes as biopsies show reduction in germ cell and spermatogenesis in undescended testes. Testicular volume measured by ultrasound has previously been shown to equate with function, thus was used as the principal outcome measure for the prediction of fertility potential in this study. This large randomized controlled trial of appropriately simple design has already, in its first paper, demonstrated clear benefits of the early intervention with catch-up growth in the operated testis (although by 2 years of age this is not complete). The outcome of the later intervention is yet to be reported. This is part of a long-term longitudinal follow-up study which in due course on account of its design, should provide the definitive evidence base for this intervention.

New concerns – growth and asthma medication again

Long-term inhaled corticosteroids in preschool children at high risk for asthma

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N Engl J Med 2006;354:1985–1997

Background: This paper's primary aim was to determine whether inhaled corticosteroids for preschool children with a positive predictive index for asthma can modify the disease progression. The effects on growth were one of the secondary outcome measures of this study.

Methods: This was a multicenter, double-blind randomized, placebo-controlled parallel-group trial of 285 2- to 3-year-old children who either received inhaled fluticasone dipropionate 88 µg twice daily or masked placebo for 2 years, followed by a 1-year no intervention observation period for both groups. The primary outcome measure was the proportion of asthma-free days during this observation period.

Results: The study revealed no significant differences in proportion of episode-free days. This differed from during the treatment period where the steroid-receiving group had a lower number of exacerbations, less need of supplementary medication and more disease-free days. The fluticasone-treated group

grew 1.1 cm less over the 24-month treatment period ($p < 0.001$), but exhibited a small degree of catch-up during the observation year, so that at the end of the trial the mean reduction in height was 0.7 cm compared with the controls (total 3-year growth 19.2 ± 2.2 vs. 19.9 ± 2.2 cm, $p = 0.008$).

Conclusions: The primary intention of the trial was to investigate the disease-modifying effect of inhaled corticosteroids. This could not be demonstrated during an observation year following 2 years of active intervention. The findings do not provide evidence for a disease-modifying effect of inhaled corticosteroids. Two years of treatment leaves a significant deficit in growth which is only partly restored 1 year later when treatment is withdrawn.

Much has been written about growth and asthma, and whether growth deficits arise from the condition itself or from treatments such as inhaled corticosteroids. The discussion about the relationship between chronic childhood diseases, their treatment and growth continues, and the evidence here from a large multicenter, double-blind randomized, placebo-controlled parallel-group trial on the effect of inhaled steroids for asthma on growth is important, and important for two reasons: firstly, that as pediatricians, a frequently prescribed treatment for a common condition such as asthma is and remains suitable for control of symptoms only, and has no effect on altering the long-term disease process, and secondly, inappropriate use of an apparently innocuous treatment may have prolonged growth-restrictive effects, even though the overall effect is small and is controversial [2]. Height velocity was lower in the treated group (6.6 ± 1.0 cm/year) compared with the placebo group (7.3 ± 1.0 cm/year), but catch-up in the third observation year (6.4 ± 0.90 vs. 7.0 ± 0.8 cm/year in the controls) was insufficient to restore the height loss. Children in the inhaled corticosteroid group's average height centile was 51.5 ± 29.2 after treatment, recovering to centile 54.4 ± 27.9 during the observation period compared with centile 56.4 ± 26.9 in the controls. Although there were no significant differences in mean centile position between the groups, the SD in the treated group was broader. This statistical observation, together with the slightly lower mean height centile position of the treated patients, would produce, in absolute terms, a greater number of children in the lower centile bands in whom concerns over their growth may be expressed. This could be one explanation why we would see more referrals for short stature in children with asthma on inhaled corticosteroids and one reason why we as pediatric endocrinologists are involved in the asthma treatment debate.

Concepts revisited – good clinical science today is the foundation for the future

Aortic distensibility and dimensions and the effects of growth hormone treatment in the Turner syndrome

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Background: Turner syndrome (TS) is associated with cardiovascular malformations, one of which is aortic dilatation, which although idiopathic, may be associated within increases in aortic size and distensibility. This study aimed to investigate the biophysical aspects and size of the aorta in TS.

Methods: 38 girls with TS who had previously been included in a randomized trial of different GH doses were included, and on this occasion an additional control group of 27 women aged 21 ± 2 years was recruited. The TS girls had been started at a mean age of 12 ± 2 years on either 0.045, 0.067 or 0.09 mg/kg/day. All had cardiac MRI imaging ± 6 months after stopping GH determining aortic dimensions and distensibility in four areas: (1) the ascending aorta, (2) the descending aorta, (3) at the level of the diaphragm, and (4) the abdominal aorta.

Results: TS girls demonstrated larger aortic dimensions at all sites except within the abdomen (level 4), and tended to have reduced distensibility at the level of the diaphragm. TS patients in the lowest GH dosage group had larger aortic diameters at the diaphragm and above (levels 1–3) and reduced abdominal aortic distensibility. In patients in the two higher GH dose groups, measurements did not differ from the controls.

Conclusions: The severity of cardiac and aortic abnormalities seems to be inversely related to the dose of GH used. This would suggest larger doses of GH are beneficial to cardiac health.

The longer-term surveillance for side effects of GH treatment continues, especially when high-dose regimens are used and in conditions such as TS with known cardiovascular morbidities. The outcome of different doses of GH on the cardiovascular system in TS patients has revealed some interesting results. An important feature of this study is that this extension was possible on account of careful design and recording of clinical data in the initial randomized controlled trial. Additional investigation of outcomes together with the recruitment of an additional control group has extended the observations still further. The finding of a potentially positive benefit to high-dose GH preventing cardiovascular degeneration in TS is novel. It is encouraging therefore that sometimes we get unexpected positive benefits from treatment as in this study where the higher doses of GH seem to be beneficial. Careful monitoring of clinical practice must be done to seek to ensure that no harm is done by treatments offered, and the lack of a harmful effect of GH had been confirmed by a retrospective cross-sectional volunteer study of TS girls receiving conventional GH treatment (0.03–0.05 mg/kg/day) or no treatment by the US National Institute for Health [3]. It's back to the laboratory bench to sort this one out.

Reproductive outcome in patients treated and not treated for idiopathic early puberty: long-term results of a randomized trial in adults

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J Pediatr 2006;149:532–536

Background: This study was conceived as outcome follow-up to assess reproductive outcome in girls who had previously received triptorelin treatment for early puberty.

Methods: 22 girls and 18 controls who had participated in 1991 in a randomized controlled trial to assess efficacy and outcomes of triptorelin treatment were recalled at a mean age of 20 years, and underwent physical examination, pelvic ultrasound and endocrine evaluation in comparison with a new control group of 22 age-matched controls.

Results: All three groups showed no significant changes in reproductive hormone levels, ultrasound results including ovarian volume and menstrual histories. The untreated group of early puberty girls showed slightly but non-significantly larger ovaries. Sexual activity was greater in those initially presenting with early puberty whether treated (76%) or not (72%) compared with the current controls (59%).

Conclusions: Triptorelin treatment for early puberty seems to have no long-term adverse effect on reproductive functioning.

This randomized controlled trial reported the effects of GnRH analogue treatment in girls with early normal treatment 15 years ago and demonstrated that there was no additional height advantage gained by this treatment, despite altering the tempo of puberty. The longer-term outcomes of suppressing puberty, especially on fertility, had yet to be determined at that stage. Although we may be more circumspect nowadays about treatment of early normal, as opposed to pathological precocious puberty, it is reassuring to know that triptorelin treatment in girls presenting with early puberty has no long-term adverse sequelae, nor does there seem to be a link with polycystic ovaries which had been reported previously. An early onset of puberty, whether or not progress is delayed with GnRH analogues, was associated with higher levels of sexual activity in early adulthood. The methodology of this paper deserves a comment. The initial randomized controlled trial was of good quality design. This permitted a follow-up study, which with the recruitment of a new control group has led to the current conclusions.

Bilateral anorchia in infancy: occurrence of micropenis and the effect of testosterone treatment

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Background: Bilateral anorchia in infancy is rare; the etiology and its timing remains unclear. This study aimed to review clinical and histological findings and compare these with the growth of the penis in response to testosterone treatment.

Methods: This was a French multicenter retrospective study collecting clinical and histological data on 55 boys with congenital bilateral anorchia born between 1975 and 2004. The patients were divided into two groups depending on the absence (29) or presence (26) of a palpable intrascrotal or inguinal mass at first examination.

Results: 24 boys (46%) had micropenis, equal numbers in each group. Testosterone treatment produced a gain of penis length of 1.9 ± 1.3 SDS with no response in 6 patients. Histology of removed tissue showed absent testicular structures except in 3 where a hemorrhagic testis was found, possibly as a result of torsion during descent.

Conclusions: As half of the patients with congenital anorchia in this study had micropenis, but with normal male sex differentiation, this suggests that testicular damage occurs during the second half of gestation. The majority of boys responded to exogenous testosterone. Although this is a condition of heterogeneous etiology, boys with congenital anorchia are likely to have had functionally normal testes before their disappearance, although some may have an intrinsic endocrine disorder.

This was a longitudinal retrospective case study analyzing the clinical and histological findings in boys with bilateral anorchia and the response to testosterone treatment on penis length, and merits inclusion in this chapter as it represents the best way of gathering good clinical evidence in rare conditions. Data were gathered over a 30-year period, beyond the feasibility of most prospective clinical studies, but were of sufficient detail for retrospective analysis having been managed in designated pediatric endocrine units as they included histological confirmation of anorchia or testicular torsion. Evidence from this type of study is more reassuring than ground-breaking, nevertheless, with such large case series, patterns emerge. Although the majority of cases of anorchia seem to arise as a result of a testicular 'accident', a significant proportion did not show good androgen responsiveness. This suggests either a failure of testosterone secretion following on from sex differentiation, or else a degree of partial androgen resistance. Here's where prospective longitudinal studies may be of help.

Insulin pumps in pediatric routine care improve long-term metabolic control without increasing the risk of hypoglycemia

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Background: This paper is the first 5-year pure longitudinal report of a non-randomized population-based study evaluating continuous subcutaneous insulin infusion pumps in routine care. The baseline was a detailed cross-sectional study in the first year.

Methods: 27/89 patients aged 7–21 years were transferred to insulin pumps compared with conventional treatment of 4–6 injections/day. Pump treatment was generally started to improve control when HbA1c $>8.5\%$ (HbA1c 8.9 ± 1.0 vs. $8.2 \pm 1.6\%$, $p = 0.04$), often due to diabetes duration >2 years. Reports of HbA1c change and frequency of adverse events were studied.

Results: In the first year using pumps, insulin dosage was lower (0.9 ± 0.1 vs. 1.0 ± 0.2 U/kg/day, $p = 0.002$). The incidence of severe hypoglycemia was lower with pump therapy (11.1 vs. 40.3/100 patient-years, NS).

and no pump patients experienced severe hypoglycemia with unconsciousness or seizures. No admissions were seen in either group for ketoacidosis. Over the 5 years, for the patients with poor control as the main indication for starting with pump therapy, mean HbA1c fell from 9.5 to 8.9% after 1 year ($p = 0.019$), 8.6% in year 2 ($p = 0.017$), 8.6% in year 3 ($p = 0.012$), and then rose to 8.7% in year 4 ($p = 0.062$), and 8.9% in year 5 ($p = 0.28$). Six pump patients had ketoacidosis (4.7/100 patient-years).

Conclusions: The authors found some long-term lowering of HbA1c in a poorly controlled pediatric population even though the initial fall was not maintained. Pump therapy was associated with a decreased frequency of severe hypoglycemia and a low risk of ketoacidosis.

Use of insulin pumps in children with diabetes may make emotions run high, so although this is not a randomized trial, it is the first objective report of 5-year longitudinal outcomes in children and adolescents using pump therapy in a single center. Five-year reductions in HbA1c of 0.6% in the poorly controlled group and of 0.2% in all patients seemed poor in comparison with the much greater initial fall, but may need to be evaluated in comparison with lifestyle convenience and a lower reported incidence of severe complications, even though there is a higher administrative cost. The debate continues.

Clinical trials, new treatments: 1 – new wine, old skins

Median nerve conduction velocity and central conduction time measured with somatosensory-evoked potentials in thyroxine-treated infants with Down syndrome

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Pediatrics 2006;118:e825–e832

Background: Down syndrome is a common cause of developmental delay, with a predisposition to autoimmune thyroid disease. Plasma T_4 levels are usually lower in neonates with Down's. This study was conducted to ascertain whether supplementation could improve the developmental outcome in this condition using median nerve conduction velocity and central conduction time measured by somatosensory-evoked potentials which have established associations with developmental variability.

Methods: A double-blind randomized controlled trial was carried out in a single center over 4 years. Neonates with Down syndrome received either T_4 ($n = 99$) or placebo ($n = 97$) treatment for 2 years. Dosages were adjusted to keep T_4 levels in the high normal range and TSH in the normal range. Outcome measures were nerve conduction velocity and somatosensory-evoked potential recording changes ascertained at age 24 months.

Results: Peripheral nerve conduction velocity and central conduction time did not show any significant differences between the 81 T_4 -treated and 84 placebo-treated subjects (nerve conduction velocity 51.0 vs. 50.1 m/s; central conduction time 8.83 vs. 8.73 ms).

Conclusions: Supplementation of Down syndrome infants with T_4 to 'normalize' levels was not associated with improvement in nerve conduction velocity and somatosensory-evoked potentials. Therefore it is likely that the impaired nerve conduction in Down syndrome is due to alternative explanations. No adverse effects were seen suggesting that high-normal T_4 levels are not harmful to nerve maturation.

Nothing ventured, nothing gained. Down syndrome is associated with developmental delay and lesser degrees of thyroid activity. The working hypothesis was that supplementation with T_4 to normalize levels would lessen the degree of developmental delay by accelerating nerve maturation. Although this study produced negative results, they are conclusively negative on account of the quality of the study design, rigorous methodology and large sample size, and the use of a reproducible methodology which had previously been shown to accurately reflect developmental variation. Although a causal association between mild hypothyroxinemia and developmental delay cannot be ruled out [4], a treatment protocol similar to that used in true congenital hypothyroidism was not successful in accelerating neurological maturation in this condition.

The effects of oxandrolone and exercise on muscle mass and function in children with severe burns

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Pediatrics 2007;119:e109–e116

Background: A structured exercise programme is standard treatment in the rehabilitation of children with severe burns to prevent muscle wasting and to improve lean body mass. This study hypothesized that the combination of the anabolic steroid oxandrolone together with the exercise programme would be superior in accelerating muscle strength and lean mass accrual, thus accelerating rehabilitation.

Methods: 51 children with severe burns (>40% total body surface area) were entered into a four-way randomized placebo-controlled trial receiving oxandrolone alone (0.1 mg/kg/day); oxandrolone + exercise; placebo alone, and placebo + exercise. Oxandrolone was started at discharge for 1 year. The exercise programme started at 6 months after the burn injury and ran for 12 weeks. Assessments at 6 and 9 months included muscle strength, lean body mass assessments by DEXA, cardiopulmonary capacity, and serum hormones.

Results: Body weight increased significantly in the oxandrolone + exercise group (14%) compared with the other subgroups (2.5–8.6%). Lean body mass increased in all three active intervention groups (mostly in the oxandrolone + exercise group) in contrast with a small reduction in the placebo group showing that children are still in a catabolic state 6 months after severe burns. Peak cardiopulmonary capacity improved in both exercise groups. Oxandrolone alone produced the most significant increase in IGF-1 levels, whereas both groups with an exercise component showed equal increments in IGFBP-3.

Conclusions: Oxandrolone in addition to a planned exercise training programme improves rehabilitation in severely burned patients.

This study has demonstrated the positive benefit from adding oxandrolone to an active rehabilitation programme aiding recovery in children who had suffered severe burn injuries in whom a continued catabolic state is the norm without intervention. The mechanism of action is still not clear for this enigmatic hormone treatment. Although significant increases in IGF-1 were seen (greater even without the exercise component, interestingly), attempts to reproduce the anabolic effect in a similar study using GH alone were unsuccessful [5]. The answer may arise from its direct anabolic effect on muscle mass, hence increased strength and lean body mass, although this paper does not address the mechanisms in any more detail. This effect, however, is similar to that seen in studies of oxandrolone in AIDS/HIV wasting and catabolic states given together with active rehabilitation. One useful practice point relates to economic costings. Exercise programmes such as used here are very resource-dependent and thus expensive, and therefore may not be available in all localities. Oxandrolone, on the other hand, is cheap, and if available on its own can produce as good an improvement in muscle mass and strength as the exercise programme. If only we knew how it worked!

Clinical trials, new treatments: 2 – pediatric endocrinology reaching outwards

Randomised, double-blind trial of oxytocin nasal spray in mothers expressing breast milk for preterm infants

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Arch Dis Child Fetal Neonatal Ed 2006;91:F169–F174

Background: Oxytocin had previously been advocated for initiating and increasing human lactation as breast milk conveys advantages, especially in sick preterm infants. Whether with current early feeding practices would maternal oxytocin treatment improve milk production.

Methods: Both the total amount and pattern of milk production were measured following a double-blind randomized controlled trial of oxytocin nasal spray (100 µl/dose) for the first 5 postnatal days prior to

milk expression using a portable electric pump. The study power was calculated to detect >1 SD difference between groups.

Results: 27 mothers received oxytocin spray compared with 24 controls. The total milk production was greater in the first 2 days with oxytocin (analysis of variance $p < 0.001$) but then patterns of milk production converged although eventually placebo-treated mothers overtook oxytocin-treated mothers, producing more milk by weight (though not significantly more). Neither the milk production rate, parity, nor milk content differed between groups.

Conclusions: Although there was an early improvement in breast milk weight produced during the first 2 days, the use of oxytocin did not produce overall benefits to lactation stimulation. Breastfeeding support as experienced by the mothers in the control group of this trial may also have a positive benefit on lactation.

This paper of classic double-blind randomized controlled trial design has helped to clarify further some of the functions of the mysterious hormone oxytocin and whether it has any influence on the time to establish lactation and whether it can increase total milk production. Although there may be some improvement of efficiency of breast milk expression with additional oxytocin, there is no evidence for the augmentation of milk production, suggesting this is more dependent on other factors such as prolactin secretion and as yet other undetermined facets of exocrine breast gland secretory function.

Sleep hygiene and melatonin treatment for children and adolescents with ADHD and initial insomnia

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J Am Acad Child Adolesc Psychiatry 2006;45:512–519

Background: Children with attention deficit hyperactivity disorder (ADHD) may show disordered patterns of sleep as part of their general behavioral disturbance. This study aimed to evaluate the efficacy of both sleep hygiene interventions and melatonin treatment in ADHD children.

Methods: 27 children aged 6–14 years with initial insomnia (sleep delay >60 min) were given advice and practical help with sleep hygiene improvement. Those who failed to respond were entered into a double-blind crossover randomized controlled trial of melatonin 5 mg or placebo for 10 days each followed by a 5-day washout period. The whole trial lasted for 90 days. The principal outcome measure was time from putting to bed to sleep onset recorded by the parents.

Results: Behavioral modification advice on sleep hygiene was successful in 5 cases only reducing time to sleep onset <60 min, with an overall effect size of 0.67. The addition of melatonin relative to placebo reduced initial insomnia by 16 min. These interventions in combination increased the effect size to 1.7 over the full 90-day trial period, with a mean decrease of initial insomnia of 60 min. ADHD symptoms did not demonstrate any beneficial effect as a result of improved sleep patterns.

Conclusions: The combination of sleep hygiene advice and melatonin is safe and effective intervention in the management of abnormal sleep patterns in children with ADHD.

Although the subject of this double-blind crossover randomized controlled trial to evaluate the efficacy of sleep hygiene and melatonin treatment for initial insomnia in children with ADHD is on the borderline of pediatric endocrine practice, it demonstrates how it is possible to plan a successful project combining a behavioral and an endocrine intervention using a robust study design. It looked specifically at one behavioral facet, namely delayed sleep onset, and so the results are not generalizable to other sleep problems, and it does not explore the effect of melatonin alone, although one could argue that this design accurately reflects a standard approach in clinical practice. Although melatonin is pivotal in defining the reproductive cycle in most mammals, its true role in human endocrine function is still unclear, and even in the control of sleep onset is not of greater importance than behavioral interventions.

Effects of calcium supplementation on bone density in healthy children: meta-analysis of randomized controlled trials

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BMJ 2006;333:775

Background: The development of osteoporosis later in life is a major public health problem, so preventative interventions are important. This paper describes a meta-analysis of studies of calcium supplementation in children to determine whether if any benefit persists after treatment stops or whether the effect is modified by any other factors.

Methods: Two reviewers independently searched electronic databases, conference proceedings and contacted authors for unpublished results. Studies included were of calcium supplementation in healthy children of at least 3 months and had bone outcome measures given as standardized mean differences as an endpoint to the study after a minimum of 6 months' follow-up.

Results: 19 studies met the selection criteria (2,859 children participants). No changes in bone density were seen at the femoral neck or lumbar spine with calcium supplementation. A small positive effect on total body bone mineral content (standardized mean difference 0.14; 95% CI 0.01–0.27) and upper limb bone mineral density (standardized mean difference 0.14; 95% CI 0.04–0.24) was identified. Negative factors were sex, pubertal stage, ethnicity, physical activity levels or baseline calcium intake.

Conclusions: Although outcome effects were non-significantly greater in females than males, and slightly more so in the upper limb, there is insufficient evidence to suggest that routine calcium supplementation improves bone density enough to reduce fracture risk later on in life to a degree of major public health importance.

Although bone density is much studied, only 19 randomized controlled trials of calcium supplementation in children with a view to prevent osteoporosis risk out of a total of 233 references were of sufficient quality of evidence to be considered in this systematic review. Additionally, with the known difficulties in adjusting bone density for body size, the authors conducted a sub-analysis comparing reports where this was done or not, but there were no differences found which would alter the overall conclusions. Calcium needed to be given as an active treatment supplement (300–1,200 mg/day) and not as dairy products to qualify for inclusion. Although the authors report a negative conclusion, maximum length of follow-up was only 7 years and equating this with absolute fracture risk is problematical. However, as an overall positive effect could be detected in the upper limbs (perhaps surprisingly) upholding the rationale behind additional calcium intake, the conclusions of the meta-analysis were upheld and called into question the public health benefits of routine calcium supplementation. What this study does not address is supplementation in children with low calcium intakes and other possible ways of increasing bone density through better fruit and vegetable intake and vitamin D supplementation.

Food for thought – diet and exercise, so don't think for too long!

Diet and sex hormones in boys: findings from the dietary intervention study in children

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Background: Adults who diet may show alterations in sex hormone levels, but little is known what happens in puberty. This study is ancillary to the Dietary Intervention Study in Children which is a multi-center randomized controlled trial aimed at lowering cholesterol by dietary intervention in children.

Methods: 354 healthy 8- to 10-year-old boys with elevated low-density lipoprotein were randomized to a trial diet of 28% energy from total fat (<8% from unsaturated fat and cholesterol, 75 mg/1,000 kcal) and were followed up for median 7.1 years. Outcome measures were non-SHBG-bound testosterone, total testosterone, dihydrotestosterone, androstenedione, estradiol, estrone, SHBG and Tanner puberty stage.

Results: Longitudinal analysis did not show differences in any clinical or biochemical parameter over the study period between the randomized groups.

Conclusions: When a dietary intervention which uses modest total fat, saturated fat and energy intake restriction is undertaken, no clinical or sex-hormone changes are seen in adolescent boys.

Although this was primarily conceived as a dietary intervention study in children with raised lipid levels, this randomized controlled trial also allowed the possibility of observing the effect of varying the energy intake on pubertal onset and progression. The study group before randomization was identified as having elevated low-density lipoprotein so it is not a true fully-representative population study. The trial was terminated prematurely on account of no treatment effect being observed. Nevertheless, some useful conclusions can be drawn. Boys of increased BMI (+0.86 to +1.06 SDS at baseline) did not differ from population norms or between study groups in the onset or progress through puberty. The inference is that neither modest degrees of overnutrition nor attempts to restrict this are associated with disturbances to the timing of the puberty control mechanism. However, as the trial was unsuccessful and neither lipid nor BMI reductions were seen, either more restrictive dietary parameters or a different approach should be considered, and it would be very interesting to study what degree of energy intake decrement would affect the tempo of puberty in today's overnourished adolescents.

Early determinants of physical activity in adolescence: prospective birth cohort study

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BMJ 2006;332:1002–1007

Background: The benefits of physical activity on physical and mental health are well established, but the early social, behavioral and anthropometric variables on adolescent physical activity are unclear and the influence of 'programming' needs clarification.

Methods: 4,453 adolescents aged 10–12 years participating in the 1993 longitudinal prospective birth cohort study from Pelotas in Southern Brazil. Study measures included detailed data on levels of physical activity: sedentary classified as <300 min of physical activity/week (outside of school physical education classes).

Results: Sedentary lifestyle prevalence was 58.2% (95% CI 56.7–59.7), associated risk factors being female sex, higher maternal education and family income at birth, and lower birth order. Longitudinal measures of weight gain, or prevalence of overweight at 1 or 4 years of age, did not significantly predict adolescent physical activity levels. Sedentary lifestyle at age 10–12 years was inversely related to income and maternal reports of physical activity levels at age 4 years.

Conclusions: Factors affecting adolescent sedentary lifestyles are not programmed by infant physiological factors. Longitudinal follow-up of physical activity suggests that both genetic factors and early habit formation may be important as there was a positive association between higher birth order and greater activity in childhood and adolescence. Weight gain, whether in infancy or childhood, did not correlate with adolescent activity levels.

Physical activity to prevent obesity in young children: cluster randomised controlled trial

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BMJ 2006;333:1041

Background: Childhood obesity is rising in prevalence, with an earlier onset. This study was designed to assess whether an enhanced physical activity programme would reduce BMI in preschool children.

Methods: This was a cluster randomized controlled single-blind trial lasting 12 months taking place in 36 nurseries in Glasgow involving 545 children, mean age 4.2 years. The programme consisted of enhanced physical activity of three 30-minute sessions over 24 weeks, backed up by a home health education initiative to reduce sedentary behavior by encouraging play. Outcomes were BMI and evaluation of sedentary behavior by accelerometry and movement skills.

Results: This particular intervention produced no significant changes in BMI at 6 and 12 months, or on measures of physical or sedentary behavior. However, children participating in the programme performed significantly better in tests of movement skills ($p = 0.0027$) with adjustment for sex and baseline performance.

Conclusions: This trial showed a positive effect on improvement of motor skills with training, but no differences in overall activity levels or reduction in BMI.

Large-scale, well planned and executed longitudinal studies produce high-quality evidence for observing population changes and correlating with disease risk. Testing individual hypotheses can be done by well-planned large-scale interventional studies, but the important message here is that there must be some evidence that the proposed intervention is effective before conducting large-scale research. This is where pilot studies can be so helpful. Factors determining the onset of obesity in early childhood may have important environmental etiologies which need to be understood before successful interventions can be instigated. Active lifestyles are associated with improved cardiovascular health. Although socioeconomic factors such as higher family income and maternal education levels were predictive of lower adolescent physical activity levels, the lack of an association of early weight gain by 4 years of age with adolescent activity levels as in the paper by Hallal et al. are important and controversial findings. If promotion of an active lifestyle is desirable, then this study sends the message that it needs to start early in life, as supported by the finding of higher child and adolescent activity levels in bigger families. This study throws down the gauntlet to challenge the notion that early weight gain is a risk factor for adult metabolic and cardiovascular disease [6]. If this is really the case, have we been 'Barker'ing up the wrong tree with the current generation thus far? The starting early with a high activity lifestyle hypothesis was put to the test in the paper by Reilly et al. which showed that using a cluster randomized trial of an enhanced physical activity programme in the preschool age group improved motor skill development, but had no overall effect on changing lifestyles or on sedentary behavior. The lack of effect on BMI (as the principal outcome measure) may have arisen from using an insufficiently rigorous exercise programme, and the lack of change in sedentary behavior was explained by the home intervention being purely educational rather than interventional. Alternatively, it could be argued that BMI per se is not the best measure of obesity in the young. This issue is clearly much more complicated than first realized and improved outcomes are going to have to depend on much more proactive family interventions, but when do we step over the line in restriction of personal liberty and where does the responsibility for this obesity problem lie?

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