Evidence-Based Medicine in Pediatric Endocrinology

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'True science is that which has penetrated into the senses through experience and silenced the tongue of disputers, and which does not feed those who investigate it with dreams, but proceeds from the basis of primary truths and established principles successively and by true sequence to the end....'

Leonardo Da Vinci: Thoughts on Science

in: Thoughts on Art and Life, ed. Lewis Einstein, transl. Maurice Baring

Boston/MA, Merrymount Press, 1906, p. 144

Important for clinical practice

Recombinant growth hormone therapy for cystic fibrosis in children and young adults

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Background: Nutritional supplementation does not improve growth optimally in children and adolescents with cystic fibrosis (CF). Therefore, recombinant GH (rGH) therapy has been studied as a potential intervention. The authors carried out a Cochrane review of the effectiveness and safety of rGH therapy to improve lung function, quality of life and the clinical status of children and young adults with CF. The authors examined randomized and quasi-RCTs of all GH preparations compared to either no treatment, placebo, or each other for any dose, route or duration, in children or young adults (<25 years) diagnosed with CF (by sweat test or genetic testing).

Methods: The authors comprehensively searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's Trials Register, endocrine journals and meeting proceedings. Two authors independently screened papers, extracted trial details and assessed their risk of bias.

Results: Four controlled trials comprising 161 participants were included. In each the risk of bias was unclear. Whilst there was improvement in height for all comparisons, improvements in weight and lean body mass were reported only in the comparison of standard dose rGH versus no treatment. There was moderate improvement in percent predicted functional vital capacity comparing standard dose rGH and no treatment. Little evidence was found for improvement in quality of life (QoL). Improved fasting blood glucose levels were found comparing rGH to placebo only. Exercise capacity improved in participants receiving standard dose rGH versus no treatment, but not for any other comparison. There was insufficient evidence to determine any changes in hospitalization, antibiotic use or significant adverse effects.

Conclusions: Whilst rGH therapy appears effective in improving intermediate outcomes in height, weight and lean body mass compared with no treatment, and a measure of pulmonary function showed moderate improvement, no significant changes in QoL, clinical status or side effects were observed. Long-term, well-designed RCTs of rGH therapy in patients with cystic fibrosis are still required in order to properly evaluate the routine use of GH therapy in CF patients.

Historically some 40% of infants with CF were below the 5th percentile for weight and length at diagnosis with some subsequent catch-up growth. Even with the introduction of newborn screening, with failure to thrive less likely to be seen, suboptimal growth remains a problem. The childhood growth rate generally follows a normal pattern at about -0.5 SD for the general population [1] but by adolescence (and despite care in specialist centers) nutritional and growth impairment with pubertal delay tend to be severe, with delayed and impaired adult height attainment [2]. Although individuals with CF show normal spontaneous and stimulated growth hormone (GH) levels, they have low levels of insulin like growth factor-1 (IGF-1) and binding proteins (IGFBP-3) indicating a relative GH insensitivity. Therefore, rGH treatment for CF patients could improve growth and adult height but, importantly, its anabolic effects might also improve pulmonary function and outcomes in CF patients (who are not GH-deficient). Current evidence confirms modest short-term (6–12 months) improvements in height, weight, height and weight velocity and lean body mass. There are too few data as to whether this translates into better pulmonary outcomes, reduced morbidity or improved QoL. Larger studies with detailed evaluation of benefits, adverse effects and a cost-benefit analysis are necessary. Currently there is insufficient evidence to conclude that rGH therapy has clinically significant benefits in CF patients.

Future studies should be designed and powered to evaluate hospitalization, QoL, mortality, glucose metabolism and other adverse effects that are not best determined by randomized controlled trials (RCTs). The use of standardized outcome measures in future studies can aid in making results generalizable and for cost-benefit analysis. Longer durations of therapy and follow-up (e.g. surveillance databases) would enable adverse events such as SCFE (see p. 190), CF-related diabetes mellitus or a tendency to malignancy to be determined. Studies should include glucose tolerance tests, as HbA_{1c} is not an accurate measure of impaired glucose tolerance in CF patients. Rigorous and complete reporting of data needs to conform to the Consolidated Standards of Reporting Trials (CONSORT) statement (www.consortstatement.org/) which would facilitate appraisal and interpretation of results, allow judgements to be made regarding the risk of study bias and about the overall evidence quality. Studies in which the reported methodology is unclear tend to produce more biased estimates of treatment effects.

Systematic reviews are, themselves, not automatically free from bias. These authors made every attempt to limit bias in the review process by ensuring a comprehensive search for potentially eligible studies (including translating non-English language studies and contacting the original authors to clarify study details or to resolve ambiguities).

Interestingly a previous 'systematic review' of GH therapy in CF patients [3] used a narrower search strategy and graded all the included studies as 'low risk of bias' despite details of randomization, allocation concealment, blinding of participants and outcome assessors being unavailable for most. Additionally, the retrospective and observational studies included, whilst providing information on various clinical variables, do not provide reliable high-level evidence for the efficacy of the interventions considered.

The authors helpfully provide a plain language summary of their conclusions so that their implications can be readily understood by the general public. Such knowledge amongst patients and self-help groups is important in the development, acceptability and thus implementation of evidence-based clinical treatment guidelines (whether pro or con).

A population-based study of risk factors for severe hypoglycaemia in a contemporary cohort of childhood-onset type 1 diabetes

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Background: Severe hypoglycaemia has historically been a barrier to optimizing glycaemic control. This observational study, involving a cohort of children and adolescents with type 1 diabetes, examined the incidence rates and risk factors associated with severe hypoglycaemia.

Methods: Young people, ≤ 18 years of age, with type 1 diabetes in Western Australia, were identified from a population-based register. Comprehensive data from 3 monthly clinic visits were prospectively recorded. A severe hypoglycaemic event was defined as coma or convulsion associated with hypoglycaemia. The authors assessed as risk factors for severe hypoglycaemia: age, sex, duration of diabetes, glycaemic control, insulin therapy, socioeconomic status and calendar year.

Results: 841 episodes of severe hypoglycaemia were observed from the follow-up data in 1,770 patients from 2000 to 2011. No difference was found between age groups in the risk of severe hypoglycaemia, nor was there an increased severe hypoglycaemia risk association between target HbA_{1c} (<53 mmol/mol) compared with those within the cohort average HbA_{1c} band (64–75 mmol/mol). There was a reduced risk of severe hypoglycaemia for those subjects aged 12–18 years on insulin pump therapy compared to their peers on injection regimens.

Conclusion: The authors conclude that, within their population-based sample of youth with type 1 diabetes, there has been a change of pattern in the incidence of severe hypoglycaemia with current diabetes management.

Whereas all diabetes teams strive to achieve an optimal HbA_{1c} for their patients, by delivering a full diabetes education package, they recognize the parental fear of hypoglycaemia [4]. Importantly the authors report a decrease in the rates of severe hypoglycaemia (which was clearly defined) over the 12 years of this study. Young age (<6 years old) is no longer a risk factor for severe hypoglycaemia, regardless of insulin regimen. This is a key message to be shared and allows a standard target HbA_{1c} value for children of all ages.

Another major finding is that of a weaker relationship between good glycaemic control and the frequency of severe hypoglycaemic episodes. Recognition is made of the change in insulin regimens over the study period with increasing use of basal and bolus analogues and insulin pump therapy (CSII): by 2011, 26.5% patients were using CSII. Despite the changes in insulin therapy there was no significant change over the 12-year study period in cohort mean HbA_{1c}.

An observational study can only comment on observed associations and not causative factors. There was no difference in severe hypoglycaemia between those receiving MDI (three or more injections/day) and those on twice-daily insulin regimens. Therefore, one must consider other factors, which may have influenced a reduction in severe hypoglycaemia, e.g. improved education. However, CSII therapy is associated with a reduced risk of severe hypoglycaemia in adolescents when compared with insulin injection therapy in this study.

This study gives significant encouragement to all involved in improving glycaemic control in youth with T1D by identifying the reduction in risk of severe hypoglycaemia with modern therapies.

Long-term outcome of insulin pump therapy in children with type 1 diabetes assessed in a large population-based case-control study

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Diabetologia 2013;56:2392–2400

Background: This case-controlled study reviewed the long-term outcome of insulin pump therapy on: glycaemic control, BMI, severe hypoglycaemia rate, and DKA (diabetic ketoacidosis).

Methods: Prospective data were collected on both pump patients and their case-controlled peers managed by insulin injections. Subjects attending the same tertiary paediatric hospital were matched for age, duration of diabetes and HbA_{1c} at pump start.

Results: 345 pump patients (mean age 11.4 years, duration of diabetes at pump start 4.1 years) and matched controls were followed up for a mean of 3.5 (±2.5) years. An improvement in HbA_{1c} in pump patients of 6.6 mmol/mol was sustained for the 7-year follow-up period. Pump therapy also halved the events of severe hypoglycaemia to 7.2 events/100 patient-years, as well as significantly reducing the rate of DKA.

Conclusion: The authors state that this is the longest and largest paediatric insulin pump study. They conclude that insulin pump therapy provides a prolonged improvement in HbA_{1c} and reduces the rate of severe hypoglycaemia and DKA.

This 7-year observational study involving 1,160 patient-years of follow-up data supports the argument that pump therapy can lead to a sustained improvement in glycaemic control. An initial improvement in HbA_{1c} following pump start is well recognized but debate continues over the long-term benefits.

At the time of pump start there was no difference between the two cohorts for HbA_{1c} or DKA admission rate but in the year prior to pump start, the pump cohort had a statistically higher rate of severe

hypoglycaemia (coma or convulsion associated with hypoglycaemia), which may have prompted the switch to pump therapy. Whereas the authors acknowledge the intensive training pre-pump start and the impact that this may have had on glycaemic control, the sustained improvement throughout the 7-year follow-up is noteworthy. In contrast, the injection cohort had a steady increase in HbA_{1c} over time (1.1 mmol/mol per year).

Interestingly, in pump patients, those with higher HbA_{1c} at pump start (≤ 69.4 mmol/mol) had the greatest reduction in HbA_{1c}; each age group had an improved HbA_{1c} at sequential time points, the insulin dose was lower and there was no difference between the groups in BMI z-score. DKA admission rate for pump patients was half that of those using injections.

Overall the authors have identified a sustained benefit from pump therapy in optimizing HbA_{1c} with a reduction in both the rates of severe hypoglycaemia and DKA. The finding that those pump starters with 'poorer' glycaemic control had the greatest reduction in HbA_{1c}, which was then sustained, helps in decision-making regarding suitability for pump start.

24-Month use of once-weekly GH, LB03002, in prepubertal children with GH deficiency

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Background: Sustained-release GH (SR-GH) formulations may help treatment compliance and persistence in GH-deficient patients. The authors carried out a phase III, 12-month, multinational, randomized, open-label, comparator controlled trial with a 12-month uncontrolled extension to evaluate the efficacy and safety of LB03002, a SR-GH formulation for once-weekly administration in prepubertal GH treatment-naïve GH-deficient children (mean age 7.8 years).

Methods: Once-weekly LB03002 (n = 91) or daily rGH (n = 87) for 1 year was followed by once-weekly LB03002 for all patients for another year (LB03002 throughout, n = 87; switched to LB03002, n = 80). Both formulations were administered subcutaneously. Height, height velocity (HV), IGF-1, GH antibodies, and adverse events were assessed. Primary analysis was non-inferiority of LB03002 versus daily GH at 1 year by covariance analysis.

Results: Mean $\pm$ SD HV during year 1 was 11.63 ± 2.60 cm/year with LB03002 and 11.97 ± 3.09 cm/year with daily GH, with increases from baseline of 8.94 ± 2.91 and 9.04 ± 3.19 cm/year, respectively. Mean HV remained above baseline in year 2 8.33 ± 1.92 cm/year in the LB03002 throughout group, and 7.28 ± 2.34 cm/year in the switched to LB03002 group. Injection site reactions occurred more frequently in LB03002-treated patients but were considered mild to moderate in >90% of cases.

Conclusions: The growth response to once-weekly LB03002 in GH-deficient children is comparable to that with daily GH, attaining expected growth rates over 24 months. The authors conclude that once-weekly LB03002 is a strong candidate for long-term GH replacement in GH-deficient children.

GH administration has changed over the last 50 years from three times weekly intramuscular injections to daily subcutaneous injections, with greater efficacy and reduced (albeit more frequent) discomfort. However, concordance with GH therapy has remained problematic. This study of patients from 31 study centers in the USA, Europe, Egypt, India and South America randomized 91 GH-naïve patients to receive LB03002 at a once-weekly dose of 0.5 mg/kg body weight, and 89 to receive GH at a daily dose of 0.03 mg/kg (0.21 mg/kg/week). Randomization was stratified by age (<7 and >7 years) and gender. The primary outcome was height velocity at the end of the 12-month comparative treatment period using an analysis of covariance (ANCOVA) model with fixed effects for treatment, age group, gender, and region and adjusted for baseline HV and baseline height. The primary hypothesis tested was the non-inferiority of LB03002 compared to daily GH for height velocity.

Perhaps inevitably, this is a pharma-sponsored study. The authors acknowledge financial support from Biopartners GmbH, Switzerland, and LG Life Sciences Ltd, South Korea. Additionally, five authors are employees of either company and the senior author received consultancy fees from both companies. These issues are discussed further in our commentary on the paper by Bes-Rastrollo et al. immediately below.

The relative bioavailability of LB03002 in children is <80% compared to daily GH and the exposure pattern with SR-GH differs. The weekly dose of LB03002 was based on a previous dose-ranging study as is approximately 2.4-fold higher than the weekly equivalent of daily GH. Recombinant LB03002 is chemically and structurally identical to endogenous GH. Although around 40% of children taking LB03002 developed GH antibodies at least once over the 2-year trial period, their levels and lack of clinical consequences were similar to those seen with daily GH, with no apparent effect on efficacy and safety. Injection site reactions (notably swelling) were more frequent in those on LB03002, perhaps due to formulation differences and, in particular, the larger volume of injection. These reactions were considered mild in >90% and their frequency diminished with continued administration. Overall there were no unexpected safety issues.

With this and similar formulations, longer experience with and assessment of clinical- and cost-effectiveness are necessary, particularly with regard to safety, before any potential benefits of less frequent injections with, perhaps, greater treatment concordance, can be realized. Adverse effects from new drugs or formulations, unless very dramatic, are unlikely to be detected by short-term randomized controlled trials that are powered to assess efficacy. Observational studies and long-term surveillance through large clinical databases are important sources of such evidence.

(Not) new concerns: Quis custodiet ipsos custodes?*

Financial conflicts of interest and reporting bias regarding the association between sugar-sweetened beverages and weight gain: a systematic review of systematic reviews

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Background: Can the financial interests of pharma or other commercial organizations bias the conclusions of industry-sponsored scientific research? The authors examined whether such funding or the disclosure of potential conflicts of interest influenced the results of systematic reviews (SRs) conducted in the field of sugar-sweetened beverages (SSBs) and weight gain/obesity.

Methods: PubMed, Cochrane Library and Scopus databases were searched for relevant SRs. Further SRs were identified from relevant reference lists and reviews. Two researchers blinded to authors' financial conflicts of interest and stated sources of funding, independently extracted the SR conclusions. Agreement between the researchers was 93.3%. Disagreement was resolved through a third researcher's assessment to reach a consensus. SRs were divided into those that concluded a positive association between SSB consumption and weight gain/obesity versus those that did not. A further researcher classified the SRs according to the authors' financial conflicts of interest (whether explicitly stated or not) or declared sources of funding (affiliation or financial disclosure by an author demonstrating a link with the food industry).

Results: 17 out of 405 potentially eligible reviews were included (reporting 18 conclusions). 12 SRs included adults and children/adolescents, 4 only children/adolescents, and 1 only adults. Six SRs declared potential conflicts of interest with industry: 11 declared none or did not report any potential conflicts. 10 of 12 conclusions (83.3%) from SRs without reported conflicts of interest were that SSB consumption was a potential risk factor for weight gain. However, 5 of 6 conclusions from SRs with some reported conflict of interest with the food industry (83.3%) concluded that the evidence was insufficient. Reviews with conflicts of interest were five times more likely to conclude no positive association than those without conflicts (relative risk 5.0, 95% CI 1.3–19.3).

Conclusions: Financial conflicts of interest (whether or not made explicit by authors) may bias conclusions from SRs on SSB consumption and weight gain or obesity.

Systematic reviews (SRs) use predefined criteria to identify relevant research to answer a specific scientific question. They should, in theory, provide both a comprehensive summary of the literature and a synthesis of the strength of the evidence available, in order to robustly inform healthcare and pub-

lic health recommendations. However, SRs may be susceptible to bias, including from authors' conflicts of interest (declared or undeclared), which can undermine their reliability. This paper reports a 'SR of SRs' and is important in demonstrating that SRs with financial conflicts of interest with food or drink companies are more likely to conclude that there is no positive association between sugar-sweetened beverages (SSB) consumption and weight gain than reviews with no conflicts of interest. Whether there is or not a causal link between SSB intake and excessive weight gain/obesity cannot be answered in this way. It is, at least theoretically, possible that scientists, supposedly in a 'pure' search for evidence, knowledge and 'truth', could be prejudiced by their preexisting attitudes to SSBs. However, the interests of the food industry or pharmaceutical companies (to promote sales of their products) differ greatly from those of most independent researchers and there is increasing evidence of bias in the conclusions of some industry-sponsored research (not only in the field of healthcare). For example, reports of pharma-sponsored drug trials may emphasize positive results and 'bury' negative findings or side effects within the report or omit them altogether. Furthermore, recent RCTs support the positive association between SSB consumption and overweight/obesity.

What conclusions can we draw? At the very least, this important study highlights possible inaccuracies in research funded by the food and drink industry. Unfortunately in health research, and paediatric endocrinology research in particular, we are often dependent on pharma support and this situation is unlikely to change soon. Given that, in some research areas, industry sponsorship and support is almost inevitable, clear principles need to be agreed before such support is accepted. At a minimum, sponsors must provide signed agreements that they will not block the publication of any results, nor influence their interpretation or conclusions. Declarations of authors' conflicts of interests should be mandatory, comprehensive and explicitly reported. Healthcare professionals and the public need reassurance that the research underpinning healthcare-related decisions is as unbiased and scientifically reliable as possible.

For a discussion of potential bias by professional and public perceptions and expectations on mammography screening programs, see the paper by Biller-Andorno and Jüni in this volume (p. 225).

**Quis custodiet ipsos custodes? (Latin) – literally 'Who will guard the guards themselves?' or 'Who watches the watchmen?'*

Review – with a different perspective

Much paediatric endocrine clinical practice involves multidisciplinary work with colleagues in other specialties. We draw attention to a review authored by such specialists:

Slipped capital femoral epiphysis and its association with endocrine, metabolic and chronic diseases: a systematic review of the literature

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J Child Orthop 2013;7:213–223

Background: What is the nature of the association between chronic endocrine and systemic conditions and slipped capital femoral epiphysis (SCFE)? Is SCFE predisposed by rapid growth, for example during puberty or in response to growth hormone (GH) therapy? Its pathogenesis and mechanism of development at a cellular level are still unclear.

Methods: The authors carried out a systematic review of published studies of endocrine, morphological and cellular abnormalities of the physis in children with SCFE. They further looked for studies of the effects of endocrinopathies associated with SCFE, particularly hormonal signalling, receptor expression and extracellular matrix (ECM) composition. 689 references were examined and 56 papers were suitable for inclusion.

Results: Inflammation, acidosis and/or malnutrition associated with chronic diseases influence the growth hormone-insulin-like growth factor 1 (GH-IGF-1) axis. The pubertal growth spurt followed by

cessation of growth (with gonadal axis activation and GH-IGF-1 axis augmentation) also increase the risk of developing SCFE. The risk of SCFE and avascular necrosis in children with chronic renal insufficiency, renal osteodystrophy or growth hormone therapy remains equivocal.

Conclusions: SCFE is probably a multifactorial event during adolescence when height and weight increase dramatically with recrudescence of the (previously relatively quiescent) hypothalamo-pituitary-gonadal axis of childhood. There are currently no tests to predict high-risk subjects.

Histological study of biopsy tissue obtained during surgery for SCFE show significant histological differences to the normal physis, in columnar organization and in the extracellular matrix. Such non-specific changes also occur in various endocrine and metabolic disorders and could be adaptive rather than causal. The GH-IGF-1 axis is a major growth regulator during childhood and adolescence. At puberty, oestrogens also regulate linear growth in both sexes via direct (local IGF-1) and indirect effects on the physis. Low oestrogen levels stimulate chondrocyte growth in the proliferative zone and augment skeletal growth via the GH-IGF-1 axis. Prolonged high oestrogen levels inhibit hypertrophic zone clonal expansion and cell proliferation, induce hypertrophic chondrocytes apoptosis and stimulate osteoblast invasion, resulting in epiphyseal fusion.

The vulnerability of the physis during the pubertal growth spurt is greater with increased time and load (increasing body weight). Thus SCFE is more common in children with delayed puberty and obesity. Higher leptin levels also increase the width of the proliferative zone, as is seen in SCFE. No specific relationship between endogenous or exogenous glucocorticoids and SCFE has been demonstrated. The observed seasonal variation in its incidence could reflect lower vitamin D levels.

The endocrine evaluation of patients with SCFE is generally unrewarding and extensive screening is inappropriate. There are no large prospective population-based studies available to determine whether short-term hormonal changes precede SCFE development. Children with overt endocrinopathies (such as hyper- and hypothyroidism, hyperparathyroidism, hypogonadal states and hypopituitarism) may be at greater risk of SCFE. Thyroid function should be investigated if SCFE is bilateral.

There is no high-quality evidence that GH deficiency or prolonged primary hypothyroidism predispose to SCFE, which typically occurs during rapid 'catch-up' growth. It would, therefore, seem appropriate to test for endocrine abnormalities (particularly of the thyroid and GH axes) in prepubertal children, if there is short stature, or if there is a bilateral problem.

Concepts revis(it)ed

The effect of vitamin D supplementation on skeletal, vascular, or cancer outcomes: a trial sequential meta-analysis

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Lancet Diabetes Endocrinol 2014;2:307–320

Background: Vitamin D supplementation is a hot topic, maybe a 'cure-all', and there are widespread calls for its routine supplementation in adults and children. Such claims are based on observed associations between vitamin D insufficiency with many health disorders (not just of bone). How strong is the evidence base? Would further trials help?

Methods: The authors performed a trial sequential meta-analysis of existing RCTs of vitamin D supplements, with or without calcium, to determine the potential value of further trials to expand the evidence base in relation to prevention of myocardial infarction or ischaemic heart disease, stroke or cerebrovascular disease, cancer, total fracture, hip fracture, and mortality. They chose a risk reduction threshold of 5% for mortality and 15% for other endpoints.

Results: Vitamin D supplementation with or without calcium does not alter the relative risk by 15% or more for myocardial infarction or ischaemic heart disease (9 trials in 48,647 patients), stroke or cerebrovascular disease (8 trials in 46,431 patients), cancer (7 trials in 48,167 patients), and total fracture (22 trials in 76,497 patients). Similarly, supplementation of vitamin D alone does not reduce hip fracture by 15% or more (12 trials in 27,834 patients). Although vitamin D plus calcium reduces hip frac-

ture in institutionalized individuals (2 trials in 3,853 patients) it does not alter the relative risk of hip fracture by 15% or more in community-dwelling individuals (7 trials in 46,237 patients). It remains unclear whether vitamin D with or without calcium reduces the risk of death (38 trials in 81,173).

Conclusions: The authors conclude that vitamin D supplementation with or without calcium does not reduce skeletal or non-skeletal outcomes in unselected community-dwelling individuals by more than 15%. Future trials with similar designs are unlikely to alter these conclusions.

Observational studies often report that vitamin D insufficiency is associated with a multiplicity of disorders ranging through fractures, ischaemic heart disease, cerebrovascular disease and cancer. This has led to calls for widespread vitamin D supplementation. Is this a fad or a fallacy? The more cautious suggest that such recommendations should not be implemented without further evidence, and they call for additional RCTs of vitamin D supplementation with non-skeletal endpoints as primary outcomes. In fact, as these authors demonstrate, several RCTs have already reported the efficacy of vitamin D supplementation on these outcomes, often as secondary endpoints, and several meta-analyses have been performed.

Future trials would be evaluated in the context of existing data. The authors modeled the changing precision in efficacy as trials are reported, and the likely influence of future data on those already available. They used a 'trial sequential meta-analysis' to define the point at which a body of evidence is sufficiently large and consistent to render further trials superfluous and thus unjustified ethically and economically. This 'futility analysis' is analogous to the termination of a clinical trial when an interim analysis indicates that further data collection is highly unlikely to alter the interim result.

Importantly, the funding source for this analysis was the Health Research Council of New Zealand (and not pharma) so there was no potential conflict whether in the study design or conduct, or in data collection, management, preparation or approval. The authors conclude that there is already sufficient evidence that vitamin D supplements (in unselected adults living in the community) does not substantially prevent a wide range of outcomes. Investigators and funding bodies should be aware of the likely futility of undertaking similar trials.

Can these data be extrapolated to vitamin D supplementation in children? It certainly behooves us all to ensure that limited healthcare and research budgets are spent effectively. Unnecessary research distracts much needed funding from important questions and funding for effective and cost-effective drugs. Importantly, it also constitutes patient abuse.

Postnatal ovarian activation has effects in estrogen target tissues in infant girls

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Background: Although the postnatal gonadotrophin surge resulting from transient pituitary activation is known to be more robust in preterm than term infants and is associated with testicular activity in boys, its relevance in girls is less well understood. The authors aimed to evaluate changes in oestrogen target tissues associated with postnatal pituitary-ovarian activation in full-term (FT) and preterm (PT) infants.

Methods: Urinary estradiol (E_2) was measured in 29 FT and 34 PT girls by mass spectrometry between the age of 1 week (D7) and 6 months (M1–M6). Levels in girls were compared to those in a comparable cohort of boys (29 FT, 33 PT) in order to assess the contribution of ovarian E_2 to urinary E_2 levels. Simultaneous changes in estrogen target tissues (mammary glands in both sexes, and uterus and vulvar epithelium in girls) were assessed.

Results: Median urinary E_2 levels increased after D7 only in girls. Mammary gland diameter was greater in girls than boys from M4 onwards in FT ($p < 0.001$) and from M2 in PT infants ($p < 0.0001$). E_2 levels increased at term in PT girls, and were then higher than in FT girls ($p < 0.0001$). Urinary E_2 levels in PT girls were positively associated with mammary gland and uterine growth.

Conclusions: These data confirm that gonadal steroidogenesis activates during the postnatal gonadotropin surge in girls and demonstrate that the consequent elevation in E_2 levels does affect target tissues. Postnatal activation of the pituitary-ovarian axis is relevant to normal female reproductive development.

This is the first longitudinal study to confirm an increase in postnatal E₂ levels in girls (previous studies over the last 30 years have been cross-sectional or mixed longitudinal). It is also the first to demonstrate that increasing endogenous E₂ secretion in PT girls results in target tissue changes, suggesting an early priming role for female reproductive organ development. In contrast to infant boys, in whom testosterone levels peak during the early months of life, in infant girls E₂ levels were found to fluctuate, perhaps reflecting maturation and atrophy of ovarian follicles.

Studies in infants with premature thelarche would be of interest: inhibin B as well as FSH levels are high [5], potentially exerting effects both at pituitary level, on FSH independently of the gonadotroph GnRH receptor, and at gonadal level by paracrine regulation [6].

Whilst the definitive importance of estrogens in early development is still unclear, given that estrogen receptors are widely expressed in the fetus, these and others' data suggest that estrogen is probably important for the maturation of many organs including the brain, and that the PT infant, deprived of these effects, could suffer long-term consequences as a result. The authors speculate that the better infancy outcome of PT girls compared to boys could reflect postnatal E₂ production.

No evidence of an increase in early infant mortality from congenital adrenal hyperplasia in the absence of screening

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Background: Congenital adrenal hyperplasia (CAH) is not included in the current UK newborn screening programme. The authors hypothesized that, due to the non-specific nature of symptoms, a proportion of males affected by salt-wasting (SW) CAH die in infancy prior to diagnosis.

Methods: 17 α -Hydroxyprogesterone (17-OHP) levels were determined from stored newborn screening bloodspot samples in deceased infants (n = 1,198), born in the North West of England in 1994–2006, who had died by 6 months age, a neonatal reference group (full-term n = 100; preterm n = 100) and a CAH-positive control group. A newborn bloodspot sample collected preceding diagnosis was available in 29/61 CAH patients. SW CAH was identified in 18/29 patients (16 males and 2 females). In the deceased group, samples with raised 17-OHP levels underwent analysis for 8 common mutations in the 21-hydroxylase gene (CYP21A2).

Results: In the deceased group, mean (maximum) blood spot 17-OHP in nmol/l was as follows. Deceased full-term n = 279, 6 (107); deceased premature n = 365, 28 (251); deceased unknown gestational age n = 553, 13 (>394). In the SW-positive control group, the lowest 17-OHP level was 179 nmol/l and 14 had levels above the highest standard (>268 to >420 nmol/l). Mutation analyses was performed in all samples in the deceased group with 17-OHP results >179 nmol/l (n = 6), and in an additional 13 samples. No mutations were found.

Conclusion: These findings do not suggest that the absence of screening leads to early infant mortality from CAH.

Screening to identify apparently healthy individuals at high risk of a disease is an integral part of public health. Implementation of a new screening programme requires rigorous assessment of evidence against internationally recognized criteria, hand in hand with thorough economic evaluation. Newborn screening for CAH, based on analysis of 17-OHP, is currently undertaken in many developed countries, but not in the UK (although this is currently under review). The main rationale for screening is that early diagnosis and treatment can prevent the mortality and morbidity associated with salt-losing crises. This may be particularly important in boys, whose physical appearance at birth is normal, whereas ambiguous genitalia at birth in girls hopefully alerts prompt diagnosis. This concept was supported by the authors' observation of a female preponderance of CAH in their clinic population, possibly because affected boys were more likely to die without a diagnosis being made.

This population-based cohort study compared bloodspot 17-OHP concentrations in newborn screening samples from the following groups: neonates who subsequently died by 6 months of age (deceased group), healthy full-term and preterm neonates (reference group) and from neonates with known CYP21A2 deficiency (positive control group). They found 17-OHP levels of 179 nmol/l or greater in the SW-positive control group. Mutation analyses of all samples from the deceased group

with levels in excess of 179 nmol/l, followed by analyses of a further 13 samples, did not identify any mutations.

This paper is important because the findings, contrary to expectations, do not provide evidence that in an unscreened population male infants with SW CAH die before diagnosis. This questions the utility of universal screening for CAH. However, as discussed in our 2013 *Yearbook* chapter, we should remember that well-being and not just survival, is important. Therefore, CAH screening programs should be evaluated in terms of both mortality and morbidity reduction.

Interestingly, another study of newborn screening for late-presenting CAH found that in an unscreened UK population around 30 children aged 1–15 years are diagnosed annually with CAH [7]. Those authors postulated that newborn screening and early treatment could potentially prevent later adverse impacts on health and quality of life. However, this comes with the important caveat that we must approach screening with caution as it may also detect children with CAH who are asymptomatic, in whom the benefits of treatment remains uncertain and may cause more harm than good.

Mechanisms of disease: diabetes and the brain

Patients with type 1 diabetes exhibit altered cerebral metabolism during hypoglycaemia

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Background: Hypoglycemic episodes occur frequently in patients with type 1 diabetes mellitus (T1DM). This study aimed to determine the effect of hypoglycemia on cerebral glucose metabolism in T1DM.

Methods: Hyperinsulinemic euglycemic and hypoglycemic glucose clamps using [^{1-13}C]glucose infusion were used to increase plasma ^{13}C enrichment. ^{13}C magnetic resonance spectroscopy measured, in vivo, incorporation of the ^{13}C label into different metabolites. The tricarboxylic acid cycle flux (V_{TCA}) was subsequently calculated using a one-compartment metabolic model.

Results: In patients with T1DM, cerebral glucose metabolism as indicated by V_{TCA} was not significantly different under hypoglycemia compared with euglycemia. V_{TCA} was inversely related to HbA_{1c} and was ~45% higher under hypoglycemic conditions compared to a previous study of healthy subjects.

Conclusions: These results suggest that moderate hypoglycemia may be better tolerated by the brains of patients with T1DM compared to those of subjects without diabetes.

Cerebral hyperemia measured with near infrared spectroscopy during treatment of diabetic ketoacidosis in children

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Background: Mild cerebral edema occurs commonly in diabetic ketoacidosis (DKA) in children. Subtle memory deficits are described in such patients. The pathophysiology is poorly understood but may involve increased cerebral blood flow with treatment. Near infrared spectroscopy (NIRS) can be used to detect cerebral hyperemia.

Methods: NIRS was used to evaluate the timing of onset and duration of cerebral hyperemia during DKA in children. Patients with DKA (19 episodes) were randomized to receive intravenous fluid using either a rapid or slower treatment regimen. NIRS measured rSO_2 during DKA treatment, from the time of informed consent until transfer out of critical care.

Results: In 17 of 19 DKA episodes, rSO_2 values were above the normal range. These elevated rSO_2 values could be detected as early as the second hour and could still be detected up to 27 h after commencing DKA treatment. There was no significant difference in hourly mean rSO_2 levels between the two fluid treatment groups.

Conclusions: DKA treatment in children is associated with elevated rSO_2 values consistent with cerebral hyperemia, but were unaffected by slower versus more rapid intravenous rehydration.

Neurological dysfunction is a recognized complication of both extremes of blood glucose control in patients with type 1 diabetes mellitus. Whilst recurrent hypoglycaemia may result in impaired cognitive function, it has been reported that deficits in memory may occur in children who have experienced DKA [8]. The mechanisms that lead to these neurological deficits are poorly understood. These two studies investigate brain metabolism and blood flow in patients with hypoglycaemia and DKA respectively. Importantly the DKA study also assesses the consequences of intravenous fluid regimen during treatment on cerebral blood flow in patients with DKA.

Cerebral metabolism was similar in patients under euglycaemic and hypoglycaemic conditions. Healthy individuals had a lower V_{TCA} during hypoglycaemia than that of patients. Interestingly, the same pattern was observed under euglycaemic conditions; however an extreme outlier may have prevented this from reaching significance. This highlights the importance of sample size as a larger study would likely have resolved this question. Caution should also be exercised as the two datasets were obtained from separate studies and subtle differences may have impacted their comparability. Overall the study points to potential adaptations that may occur in the brains of patients with type 1 diabetes as a response to recurrent hypoglycaemia.

Glaser et al. found that rSO_2 levels were elevated during DKA treatment, indicating cerebral hyperemia. No significant differences were seen between the two fluid replacement regimens despite variation in the pattern of change during the course of treatment. Interestingly, both fluid replacement regimens included use of fluid boluses. Recent guidelines have resulted in fluid boluses being administered less frequently, typically only in patients presenting with shock [9]. There were also partial replacements of urinary losses in the rapid fluid replacement group which is also in contrast to recent guidelines. It is conceivable that even slower fluid replacement with fewer fluid boluses may reduce cerebral hyperaemia. Conducting studies in patients with severe illness is challenging and may require deviation from published guidelines for both practical and safety reasons.

Food for thought: 'healthy obese' or 'unhealthy lean'?

Are metabolically healthy overweight and obesity benign conditions? A systematic review and meta-analysis

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Background: There has been interest in a unique subgroup of overweight and obese individuals who display normal metabolic features, whilst normal-weight individuals with adverse metabolic status have also been described. Whether a metabolic phenotype can modify the morbidity and mortality associated with higher body mass index (BMI) is unknown. The authors aimed to determine the effect of metabolic status on all-cause mortality and cardiovascular events in normal-weight, overweight, and obese persons.

Methods: Meta-analysis included studies of all-cause mortality or cardiovascular events (or both) and clinical characteristics of 6 patient groups, according to BMI category and metabolic status, as defined by the presence or absence of components of the metabolic syndrome. Metabolically healthy people of normal weight made up the reference group.

Results: Eight studies were included ($n = 61,386$; 3,988 events). When studies with ≥ 10 years' follow-up were considered, metabolically healthy obese individuals were at higher risk (relative risk 1.24; 95% CI 1.02–1.55) for events compared to metabolically healthy normal-weight individuals. All metabolically unhealthy groups had similarly elevated risks: normal weight (3.14; CI 2.36–3.93), overweight (2.70; CI 2.08–3.30), and obese (2.65; CI 2.18–3.12). The duration of exposure was not described in the present studies and could partially affect the estimates.

Conclusions: Obese persons are at higher risk for adverse long-term outcomes even in the absence of metabolic abnormalities when compared to metabolically healthy normal-weight individuals. These results suggest that there is no healthy pattern of increased weight.

The relationship between obesity, metabolic health and subsequent morbidity/mortality is a matter of some debate. Some large-scale studies suggest that whilst obese individuals have a higher mortality risk than normal-weight individuals, conversely overweight individuals may have lower risks [10]. Studies of the influence of metabolic health in these subgroups have led to conflicting results. As a result the concept of 'healthy obesity' is still controversial.

The present systematic review and meta-analysis on mortality and cardiovascular events according to BMI and metabolic status found that metabolically unhealthy individuals had a higher risk of adverse events regardless of their weight status. The study demonstrates the importance of long-term follow-up when studying outcomes such as cardiovascular events and all-cause mortality, as the differences in event rate between metabolically healthy obese versus metabolically healthy normal-weight groups was apparent only after a minimum follow-up of 10 years. This could explain why other studies with shorter follow-up report different findings that support the concept of 'healthy obesity'. The heterogeneous mix of individuals with different metabolic phenotypes must also be considered. Indeed, given that the metabolically unhealthy normal-weight group had similar risk compared with the metabolically unhealthy obese and overweight group, this may define an 'unhealthy lean' group who have the most severe metabolic phenotype. Definitions of metabolically healthy must be clear. The present study defines patients with less than two risk factors as healthy; however, these patients are likely to have higher risk of events than those with no risk factors. The debate surrounding 'benign obesity' rages on.

Food for thought: global priorities

The double scandal of insulin

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Background: This editorial summarizes and emphasizes important concepts and lessons which need to be learnt if we, as a global community, truly wish to provide the greatest good to the greatest number of patients with diabetes mellitus worldwide.

The St Vincent (1989) and ISPAD Declarations (1993) highlighted the aspirations to make insulin available to all children and adolescents with diabetes and ensure that they are provided with skilled care and social, economic and emotional support. 20 years ago, in an international textbook of paediatric and adolescent diabetes where the Declarations were reproduced, we commented 'How is this to be done in the context of dwindling health resources in many "developed" countries, let alone in parts of the world ... where insulin itself is unavailable?' [11].

Twenty years on, these authors paint a gloomy picture of the lack of progress and highlight lessons still to be learned. They cite and highlight research from countries including Kyrgyzstan, Mali, Mozambique, Nicaragua, Vietnam and Zambia which demonstrate that diabetes care requires more than just insulin availability – ongoing problems include lack of access to syringes, diagnostic and monitoring tools, and a dearth of healthcare facilities and workers with appropriate skills. War and political corruption are also important factors in many countries. Nevertheless, we should all be ashamed that, worldwide, the commonest cause of mortality in children with diabetes is lack of access to insulin.

The authors emphasize that access to insulin and poor health outcomes are not just problems for low-income countries. In the USA insulin discontinuation was the leading precipitating cause of diabetic ketoacidosis in adults in an inner city setting, in whom 27% reported lack of money to buy

insulin and 5% made their insulin supplies last longer by using smaller doses. Similar problems have arisen in Europe during the current financial crisis.

There is now overwhelming evidence that mortality and health is less dependent on the overall wealth of the population but more dependent on how evenly wealth is distributed: the more equally wealth is distributed the better the health of that society [12]. The data are comprehensively set out in Richard Wilkinson's and Kate Pickett's book 'The Spirit Level. Why Equality Is Better for Everyone' [13]; see also <http://www.equalitytrust.org.uk>.

It is salutary, therefore, to realize that insulin sales in the USA for 2011 totalled USD 8.3 billion, an increase of 14.9% in 1 year. The authors highlight several reasons for this: the cost of insulin is increasing (three international companies dominate the insulin market with limited competition and no major generic producers), and more patients with type 2 diabetes mellitus are being treated with insulin. However, most importantly, the (ab)use of analogue insulins has escalated far beyond that recommended in national or international guidelines. This is true not only in resource-rich countries but also in the poorest: Kyrgyzstan spends about USD 140 per capita on healthcare (about 43-fold less than the USA), yet there the prescription of analogue insulin (8.5 times as expensive as human insulin) costs the Ministry of Health the equivalent of healthcare spending for 5,000 individuals.

The authors conclude that we live in a world where resources are wasted on products that show only small benefits – most systematic reviews of analogue insulins find them (especially the long-acting analogues) to be of marginal advantage compared to human insulin and many studies are open-label pharma-funded comparisons. They also highlight a disconnect between clinical practice, treatment guidelines and scientific evidence, particularly for type 2 diabetes.

We live in globalized world. In 'Promoting Excellence in the Care of Pediatric Endocrine Diseases in the Developing World' [14], the authors discuss how the healthcare needs of the child with an endocrine disorder may be tackled by developing sustainable programs for education and research, and thus improved health outcomes.

Clinical guidelines developed in, and intended for, wealthy (although grossly unevenly wealthy) nations inevitably influence clinical practice in settings where resources are comparatively minimal. Optimal healthcare solutions need to be adapted to their national, societal and local contexts. The diabetes and broader pediatric endocrinology communities (including doctors, patients and their carers, pharma and governments) have a responsibility to support the proper use of scarce resources so that no one suffers from lack of access to insulin or the misuse of limited healthcare budgets.

References

1. Morison S, Dodge JA, Cole TJ, et al: Height and weight in cystic fibrosis: a cross-sectional study. UK Cystic Fibrosis Survey Management Committee. *Arch Dis Child* 1997;77:497–500.
2. Lucidi V, Alghisi F, Raia V, et al: Growth assessment of paediatric patients with CF comparing different auxologic indicators: a multicentre Italian study. *J Pediatr Gastroenterol Nutr* 2009;49:335–342.
3. Phung OJ, Coleman CI, Baker EL, et al: Effectiveness of recombinant human growth hormone (rhGH) in the treatment of patients with cystic fibrosis. Rockville/MD, Agency for Healthcare Research and Quality (US), 2010 Oct. Report No. 11-EHC003-EF.
4. Barnard K, Thomas S, Royle P, et al: Fear of hypoglycaemia in parents of young children with type 1 diabetes: a systematic review. *BMC Pediatr* 2010;10:50.
5. Crofton PM, Evans AEM, Wardhaugh B, et al: Evidence for increased ovarian follicular activity in girls with premature thelarche. *Clin Endocrinol (Oxf)* 2005;62:205–209.
6. Crofton PM, Evans AEM, Groome NP, et al: Dimeric inhibins in girls from birth to adulthood: relationship with age, pubertal stage, follicle-stimulating hormone and oestradiol. *Clin Endocrinol (Oxf)* 2002;56:223–230.
7. Knowles RL, Khalid JM, Oerton JM, et al: Late presentation of congenital adrenal hyperplasia in older children: findings from national paediatric surveillance. *Arch Dis Child* 2014;99:30–34.
8. Ghetti S, Lee J, Holpatrick C, DeMaster D, et al: Diabetic ketoacidosis and memory impairment in children with type 1 diabetes. *J Paediatr* 2010;156:109–114.
9. Wolfsdorf J, Craig ME, Daneman D, et al: Diabetic ketoacidosis in children and adolescents with diabetes. *Pediatr Diabetes* 2009;10(suppl 12):118–133.
10. Flegal KM, Kit BK, Orpana H, et al: Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA* 2013;309:71–82.
11. Kelnar CJH (ed): Preface in *Childhood and Adolescent Diabetes*. London, Chapman & Hall Medical, 1994.
12. Wilkinson RG: Income distribution and life expectancy. *BMJ* 1992;304:165–168 and Editor's Choice, 'The Big Idea'. *BMJ* 1996;312:0.
13. Wilkinson RG, Pickett K: *The Spirit Level. Why Equality Is Better for Everyone*. London, Penguin Books, 2010.
14. Zacharin M, Chanoine JP, Cassorla F, et al: Promoting excellence in the care of pediatric endocrine diseases in the developing world. *Pediatrics* 2013;131:e573.