Evidence-Based Medicine in Pediatric Endocrinology

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The purpose of this chapter is twofold: (1) to examine some key evidence-based papers in pediatric endocrinology published in the last year, and (2) to highlight aspects of the importance and limitations of evidence-based medicine as applied to research in children and adolescents and their health implications.

Concepts revis(it)ed To screen or not to screen? – That is the question

Population screening to identify unrecognized disease in individuals without signs or symptoms is relevant to a number of areas of pediatric endocrinology. This important public health service, like other aspects of healthcare, is under increasing pressure to show that current or potential screening practice satisfies effectiveness and cost-effectiveness criteria.

One hundred years of congenital adrenal hyperplasia in Sweden: a retrospective, population-based cohort study

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Background: The authors aimed to assess the effect of historical medical improvements in managing patients with congenital adrenal hyperplasia (CAH) and of neonatal screening in Sweden.

Methods: Data sources including the registry at the Swedish national screening laboratory were used to identify patients with CAH for this retrospective, population-based cohort study. The authors collected data from 2010/2011. They also identified patients via the neonatal screening program, late diagnosed patients reported to the laboratory, and patients who underwent genetic analysis or known to the authors through clinical contacts.

Results: 606 patients with the disorder born between 1915 and 2011 were identified. The *CYP21A2* genotype was known in 490 patients (81%). The female-to-male ratio was 1.25 in the whole cohort, but close to 1 in patients detected by screening. There was a sharp increase in diagnoses in the 1960s and 1970s. After the introduction of neonatal screening (1986), the proportion of patients with the salt-wasting form increased in both sexes, from 114 (47%) of 242 individuals between 1950 and 1985 to 165 (57%) of 292 individuals between 1986 and 2011 ($p = 0.038$). 5–10 children were missed annually before 1970.

Conclusion: The authors found that, contrary to current belief, boys and girls with salt-wasting CAH were equally missed clinically. Screening improved detection of the salt-wasting form in both sexes, saving lives in girls as well as boys. The non-classic form was diagnosed more often in females, explaining the female preponderance in this cohort.

Using a national screening registry containing virtually 100 years of data, the authors assessed the impacts of treatment advances and of screening. It has been assumed that CAH screening is important for detecting simple virilizing and salt-wasting males because ambiguous genitalia found at birth lead

to a diagnosis in females and anticipation of salt-wasting. Whilst CAH screening is adopted in many 'developed' countries, screening programs can have a high proportion of false positives, leading to parental anxiety and extra healthcare costs. CAH screening programs should be evaluated in terms of both mortality and morbidity reduction. Well-being, not just survival, is important: there remain many surgical and psychological issues in relation to treatment timing, efficacy, compliance, etc.

This paper is important because the authors find that, contrary to received wisdom, girls with salt-wasting CAH are missed clinically as often as boys despite a highly developed healthcare system; screening also improved detection in girls. Apparent increases in incidence over time reflected improvements in diagnosis and treatment, increased awareness of diagnosis from healthcare improvements and the development of pediatric endocrinology as a specialty.

Earlier detection of salt-wasting through screening means that both sexes escape negative effects (potentially from neonatal hyponatremia/hyperkalemia/hypoglycemia/acidosis) at this important window for brain development. Healthcare benefits are maximized by integrating molecular genetics with development of specialized care and a healthcare system that collects universal data. This has been shown to be beneficial even in a 'developing' country, such as Cuba [1].

Given its increasing incidence and prevalence in the child and adolescent population, is it effective/cost-effective to screen children for dysglycemia or type 2 diabetes mellitus (T2DM)?

Cost-effectiveness of screening strategies for identifying pediatric diabetes mellitus and dysglycemia

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Background: A cost-effectiveness analysis of screening strategies to identify children with type 2 diabetes mellitus and dysglycemia.

Methods: 2.5 million children aged 10–17 years were identified as part of a one-time US screening program. Effectiveness (proportion of cases identified), total costs (direct and indirect), and efficiency (cost per case identified) of each screening strategy was determined.

Results: 500 and 400,000 US adolescents had diabetes and dysglycemia, respectively. The screening cost per diabetes case was extremely high (USD 312,000–831,000) because of its low prevalence. Screening costs for dysglycemia were more reasonable: 2-hour oral glucose tolerance test (100% effectiveness; USD 390 per case), 1-hour glucose challenge test (63% effectiveness; USD 571), random glucose test (55% effectiveness; USD 498), or a hemoglobin A_{1c} (HbA_{1c}) threshold of 5.5% (45% effectiveness; USD 763). HbA_{1c} thresholds of 5.7 and 6.5% were least effective and least efficient (ranges 7–32% and USD 938–3,370) of all strategies evaluated. Disease prevalence was a major driver of cost-effectiveness.

Conclusions: The extremely high cost per case for T2DM is because of its low prevalence in the pediatric population. Screening could become more cost-effective with dysglycemia as the outcome.

The American Diabetes Association (ADA) formulated the first screening guidelines for T2DM in children in 2000 in response to the US obesity 'epidemic' [2]. At that time, empirical screening efficacy and costs data were unavailable and recommendations based on expert opinion.

In the last 13 years, T2DM in adolescents and children has become an increasing problem, particularly in developed countries and in association with obesity; nevertheless the overall burden in children is still low compared with adults. Since disease prevalence is a major determinant of cost-effectiveness it is no surprise that the authors find an extremely high cost per case of screening for T2DM in adolescents regardless of test type. Although the authors did not explicitly calculate costs per quality adjusted life-year (QALY), one must agree with them that screening for T2DM in children 'may not fall into the cost-effective range'!

Whilst early identification and treatment of adults with pre-diabetes is effective and cost-effective for reducing diabetes rates, it is unclear whether these conclusions could be extrapolated to the pediatric population – the benefits of early detection of dysglycemia in children are currently unknown and there is accelerated progression of disease in adolescence. Are any dysglycemia screening tests

simple, safe, precise, validated and practical? Limitations of the preferred strategy, the 2-hour fasting glucose tolerance test, are considerable. Despite guidelines [3] recommending exclusive use of HbA_{1c} for diagnosing childhood pre-diabetes and diabetes, HbA_{1c} thresholds are the least preferred strategy because of highest cost per case and proportion of cases missed – this has important policy implications. Total costs, efficiency (cost per case), and effectiveness (proportion of cases identified) of screening at-risk individuals are important criteria for determining optimal screening policy. These data highlight important tradeoffs to consider for the pediatric population.

New hope?

T2DM: are any interventions effective in reducing (risk factors for) morbidity?

If screening for T2DM is not currently effective or cost-effective, how effective are lifestyle (e.g. exercise) or drug (e.g. metformin) interventions? Indeed, are all types of exercise all they are cracked up to be? (See the Casazza paper discussed below!) In fact, why exercise if you can simply sleep more to reduce your BMI?

Effects of exercise on sRAGE levels and cardiometabolic risk factors in patients with type 2 diabetes: a randomized controlled trial

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Background: T2DM is associated with low levels of systemic inflammation markers, e.g. soluble receptor for advanced glycation end-products (sRAGE).

Methods: The effects of exercise on sRAGE and its association with diverse cardiometabolic risk factors and indicators of atherosclerosis in patients with T2DM were examined in 75 patients with T2DM randomized into control and aerobic exercise groups (60 min at moderate intensity, 5 times/week for 12 weeks). sRAGE, energy expenditure, dietary energy intake, cardiorespiratory fitness, inflammatory markers, visceral fat area, pulse-wave velocity, and flow-mediated dilatation were evaluated.

Results: Baseline sRAGE concentrations were independently associated with age, glycated hemoglobin, glucose, triglyceride, and high-density lipoprotein cholesterol levels ($R^2 = 0.244$). 12 weeks of exercise training significantly decreased body weight, waist circumference, blood pressure, glycated hemoglobin, apolipoprotein B, and free fatty acid levels. Cardiorespiratory fitness, body fat percentage and visceral fat area all significantly improved in the exercise group; sRAGE levels were increased and high-sensitivity C-reactive protein (CRP) levels decreased in the exercise group. Change in sRAGE level negatively correlated with CRP ($r = -0.27$; $p = 0.019$).

Conclusions: sRAGE levels increase and other cardiometabolic risk factors improve with aerobic exercise in patients with T2DM.

Increased risk of atherosclerosis in patients with T2DM is well established, as is the concept of reduction of cardiometabolic risk by increasing exercise. However, the mechanisms by which exercise might induce beneficial effects are less frequently studied. Accumulation of advanced glycation end products (AGE) and changes in receptor (RAGE) numbers are implicated in atherosclerosis development in T2DM by activating pro-atherogenic factors. The soluble form of sRAGE has also been shown to inhibit atherosclerosis in a diabetic mouse model.

This randomized controlled trial (RCT) investigates the effect of an exercise intervention on sRAGE levels in adults with T2DM. The 12-week exercise intervention resulted in an increase in sRAGE levels compared to controls, and improvement in established cardiometabolic risk factors. Interestingly, there was a significant reduction in BMI in both the exercise intervention and control groups, which was associated with a reduction in daily energy intake. The inflammatory marker CRP was reduced in the exercise group and inversely correlated with sRAGE levels.

Whether interventions, such as increasing exercise, can be replaced by therapies targeted towards signaling pathways, such as AGE, remains to be determined. Additionally, the long-term impact of increased exercise on sRAGE levels and applicability to the pediatric/adolescent population needs evaluation. Perhaps an appropriate and adequate sleep pattern can also help?

Sleep duration and adolescent obesity

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Background: Reduced sleep time has been associated with adolescent obesity. The authors sought to determine if sleep duration was associated with BMI distribution changes in adolescents (age 14–18 years).

Methods: Subjects (ninth grade, $n = 1,390$) recruited from suburban high schools in Philadelphia were followed up 6 monthly for 4 years. Height, weight and hours of sleep were self-reported and BMIs calculated. BMI percentiles were modeled as dependent variables; study wave and sleep were the main predictors.

Results: BMI increased from age 14 to 18, with largest increases observed at the 90th BMI percentile. Each additional hour of sleep was associated with decreases in BMI across all BMI percentiles with the association strongest at the upper BMI distribution tail. Increasing sleep from 7.5 to 10.0 h/day at age 18 predicted a reduction in the proportion of adolescents with a BMI >25 kg/m² by 4%.

Conclusions: More sleep was associated with non-uniform changes in BMI distribution in adolescence. Increasing sleep in this age group, especially those in the upper half of the BMI distribution, could help prevent overweight and obesity.

This study of over 1,000 Philadelphia-area high school students suggests that fewer hours of sleep are associated with greater increases in adolescent BMI for participants between 14 and 18 years of age. The strength of the association between sleep and BMI was weaker at the lower tail of BMI distribution, compared to the upper; each additional hour of sleep was associated with only a slight reduction in BMI (0.07 kg/m²) at the 10th BMI percentile compared with 0.17 kg/m² at the 50th and 0.28 kg/m² at the 90th.

The relationship between sleep duration and BMI remained after adjusting for time spent in front of computer/television screens and being physically active. The authors suggest that increasing sleep duration to 10 h/day, especially for those in the upper half of the BMI distribution, could help reduce the prevalence of adolescent obesity – a 4% reduction would translate to ~500,000 fewer overweight adolescents in the USA.

Unfortunately, various circadian rhythms are reset in adolescence. Melatonin is produced later at night in adolescents than in children or adults, which may explain why teenagers seem to be getting up and going ‘out on the town’ when the rest of us are getting ready for bed. As with other interventions in obesity, applying knowledge to changing lifestyle will be difficult. Adolescents who naturally go to sleep at 4 a.m. still have to get up early for school. How likely is it that an education policy, such as delaying the start of the school day based on the evidence that this could help reduce obesity in adolescents, will be applied in practice?

Metformin in obese children and adolescents: the MOCA trial

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Background: Childhood obesity is increasingly associated with T2DM. The risk for T2DM in adult obese non-diabetic patients is reduced by metformin, but evidence in obese children and adolescents is inconclusive.

Methods: This prospective, randomized, double-blind, placebo-controlled study in six UK pediatric endocrine centers evaluated the effect of metformin on BMI-standard deviation score (SDS), metabolic risk factors and adipokines. 151 obese subjects (aged 8–18 years, mean 13.7 (SD 2.3), 67.5% girls) with

hyperinsulinemia and/or impaired fasting glucose or impaired glucose tolerance (metformin 74, placebo 77) took part. 65.6% were postpubertal and 23.8% British-Asian or Afro-Caribbean. Mean BMI-SDS was +3.4 (SD 0.5). Patients were randomized to receive metformin 1 g in the morning/500 mg in the evening or placebo; BMI-SDS was calculated at 6 months. Secondary outcomes included insulin and glucose levels from oral glucose tolerance tests, alanine aminotransferase (ALT), and adiponectin to leptin ratio (ALR) at 3 and 6 months.

Results: Metformin significantly reduced BMI-SDS compared with placebo at 6 months (mean difference -0.1 SD (95% CI -0.18 to -0.02), $p = 0.02$). Significant improvements at 3 months were found in the metformin group: fasting glucose, -0.16 mmol/l (-0.31 to -0.00), $p = 0.047$; ALT, 19% (5–36%), $p = 0.008$, and ALR, 32% (4–67%), $p = 0.02$.

Conclusions: The authors concluded that metformin therapy has a beneficial treatment effect over placebo for BMI-SDS, fasting glucose, ALT, and ALR ratio at 3 months, with changes in BMI-SDS sustained at 6 months.

There is a dearth of high-quality studies in this area (for a systematic review and meta-analysis, see Bouza et al. [4]) and the present study illustrates some of the difficulties involved including issues with recruitment and high dropout rates. Clinicians should be wary of basing interventions on outcomes that are statistically significant but are of doubtful clinical significance.

How relevant is it to extrapolate these data to clinical practice, whether in primary or secondary care settings? BMI reduction is not the most appropriate primary outcome measure in studies such as this and a BMI-SDS reduction of 0.1 vs. placebo at 6 months is not clinically relevant. Nor (in our view) is a barely statistically significant improvement in a mean fasting glucose of 0.16 mmol/l or the changes in ALT and ALR at 3 months (only).

The prevalence of T2DM in children and adolescents is increasing, but is still low in Western Europe. T1DM is still the major workload for most pediatricians. One 'holy grail' in T1DM management is closing the loop with an artificial pancreas – this has been evaluated in a diabetes camp setting [5] and this paper is evaluated by the current *Yearbook* chapter on Type 1 Diabetes by Marcovecchio and Chiarelli. Demonstrating effectiveness in a hospital setting is very different from applying this complex and expensive technology to 'real life' outside the hospital. Additionally, median values for individual overnight glucose levels, whilst statistically significant, are not necessarily of clinical significance (as already discussed).

Important for clinical practice

Morbidity in important pediatric endocrine disorders – glucocorticoids and related issues

Whilst CAH screening is widely considered effective and cost-effective (see above paper by Gidlöf et al.), it is not yet universally adopted, for example in the UK. Improvements in CAH management have also reduced morbidity and mortality. However, available management strategies are still suboptimal; side effects from chronic glucocorticoid (GC) treatment, suboptimal treatment regimens and poor patient concordance remain major concerns.

Clinical characteristics of a cohort of 244 patients with congenital adrenal hyperplasia

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Background: Suboptimal treatment regimens and chronic GC therapy both contribute to long-term complications in CAH.

Methods: The authors describe clinical characteristics in a large cohort of CAH patients (pediatric and adult) in a cross-sectional, natural history study of 244 CAH patients (183 classical, 61 non-classical

(NC)). Outcomes studied included height SDS, obesity, blood pressure, insulin resistance, metabolic syndrome, bone mineral density (BMD), hirsutism (females), and testicular adrenal rests (TART).

Results: The majority studied, regardless of treatment regimen, had elevated or suppressed androgens. Mean adult height SDS was -1.0 ± 1.1 for classic vs. -0.4 ± 0.9 for NC patients ($p = 0.015$). Approximately one-third of patients were obese. Raised BP was more common in classical CAH patients ($p \leq 0.01$); pediatric hypertension was associated with suppressed plasma renin activity ($p = 0.001$). Insulin resistance was more common in classical CAH children (27%) and adults (38% classical, 20% NC); 18% of adults had metabolic syndrome. Low vitamin D and reduced BMD were common in adults, as were hirsutism in women and TART in classical CAH males (33% boys, 44% men).

Conclusions: Using current treatment regimens, adverse outcomes are still common in CAH. Children with classical CAH should have BP and plasma renin activity measured. Osteoporosis prophylaxis and TART screening should begin during childhood.

This study recruited CAH patients from a variety of sources, including self-referral from a national CAH support group. Therefore, self-selection of highly motivated families may have resulted in recruitment bias. Only 5% of patients were physician-referred. 170 of the 244 patients recruited were 'children' (0.6–17 years). Various important outcomes were studied, but unfortunately not fertility. The population was geographically heterogeneous. Only one (baseline) evaluation was carried out and the authors were unable to estimate long-term GC exposure.

Although the study is just a 'snapshot' of CAH management, it highlights the limitations of currently available therapies (e.g. a GC dose that achieves adequate androgen suppression may be associated with GC-related side effects). It also suggests limited competence in those managing CAH (especially as those self-referring are likely to be more highly motivated and, perhaps, better controlled than typical clinic patients). Although the authors recommend that the minimum GC dose compatible with appropriately assessed growth and endocrine parameters should be used, this is not easy to achieve in practice. They argue for routine measurement of BP and plasma renin activity, but the reliability of these measures in an outpatient setting is controversial. They recommend osteoporosis prophylaxis (exercise, calcium, vitamin D) and DEXA scans for bone health assessment. Importantly, screening ultrasound for testicular adrenal rests should start in childhood. The authors' long-term longitudinal study that aims to elucidate hormone-mediated and disease-specific phenotypic characterizations will be important in strengthening the evidence base behind such statements.

As with (e.g.) diabetes (see above) or managing SGA children (see below), pediatric endocrinologists need to be aware of the potential health problems that they 'bequeath' with their patients to adult colleagues. Whilst the morbidity associated with GC excess in treating of CAH is considerable, there are other much more common groups of patients where such side effects are underrecognized.

Hypothalamic-pituitary-adrenal axis suppression in asthmatic school children

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Background: It is thought that suppression of the hypothalamic-pituitary-adrenal axis (HPAS) when treating children with corticosteroids is rare. The authors studied the prevalence of and predictive factors for various degrees of HPAS.

Methods: 143 asthmatic children were studied and clinical features of HPAS, doses, adherence, asthma score, and lung function were evaluated. Overnight metyrapone tests were performed if morning cortisol was >83 nmol/l. Correlations were calculated between 3 post-metyrapone outcomes and each continuous variable, and a logistic regression model for HPAS developed.

Results: Hypocortisolemia was found in 6.1% (1.8–10.5), hypothalamic-pituitary suppression (HPS) in 22.2% (14.5–29.9), adrenal suppression in 32.3% (23.7–40.9), HPAS in 16.3% (9.3–23.3), and any hypothalamic-pituitary-adrenal axis dysfunction in 65.1% (56.5–72.9). Nasal steroids (NS) dose/ m^2 was positively associated with HPAS (OR 3.7, 95% CI 1.1–13.6). Daily inhaled corticosteroids (ICSs) + NS dose/ m^2 predicted HPAS ($p = 0.038$). Forced expiratory volume in 1 s (FEV_1)/forced vital capacity

(FVC) <80% was associated with HPAS (OR 4.1, 95% CI 1.0–14.8). Daily ICS + NS/m² dose was correlated with the post-metyrapone ACTH ($r = -0.29$, $p < 0.001$). BMI ($p = 0.048$) and percent adherence to ICS ($p < 0.001$) and NS ($p = 0.002$) were predictive of radical post-metyrapone ACTH ($R^2 = 0.176$). *Conclusions:* Two-thirds of children on corticosteroids may have hypothalamic-pituitary-adrenal axis dysfunction. In one-third, central recovers before adrenal function. NS use, BMI, and adherence to ICS and NS are all predictive of HPAS.

The authors make an important distinction between adrenal gland suppression and (more common) hypothalamic-pituitary-adrenal axis suppression (HPAS). Although there are difficulties with determining appropriate tests and defining age- and assay-appropriate normal ranges and cut-offs for adrenal function (there are few appropriate studies and data extrapolated from adults), the metyrapone test is ideally suited to distinguish between the various levels of suppression of the HPA axis. The authors find that HPAS may occur at low GC doses (equal to the daily cortisol production rate) and, especially, with concomitant nasal steroids. Low FEV₁/FVC, but not cumulative GC doses, may be independently predictive. Children on NS with poor adherence or obesity may be less prone to adrenal crisis.

Whilst the authors recommend that every asthmatic child with a low BMI treated with both inhaled and intranasal GCs and adherent to therapy should have HPA function assessed, this raises significant practical healthcare issues. Close liaison between pediatric endocrinologists and our respiratory colleagues is important in identifying and managing children at risk. Nevertheless, issues around selecting patients for evaluation, determining which tests should be used, their interpretation, and how those at risk should be managed, are not straightforward.

Important for clinical practice **Advantages of national databases and research –** **pediatric reference ranges and SGA interventions**

The need for appropriately derived and applied pediatric reference ranges is highlighted in the following paper in relation to the interpretation of thyroid function tests.

Serum thyroid hormone levels in healthy children from birth to adulthood and in short children born small for gestational age

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Background: Detecting pediatric thyroid dysfunction is dependent on age-appropriate reference ranges for thyroid hormones (TH). There are no data on TH and peripheral metabolism in short children born small for gestational age (SGA) before and during GH treatment.

Methods: The authors derived pediatric TH reference ranges (in 512 healthy children, 225 females, 0–18 years) and used these to evaluate thyroid function in short SGA children and adolescents, during therapy with GH, and with GnRH analogue (GnRHa) puberty postponement. Free T₄ (FT₄), TSH, total T₄, T₃, rT₃, and T₄-binding globulin were determined. In 125 short SGA children (62 females, mean age 11.3 years), THs were analyzed before and after 2 years of GH treatment and additional GnRHa.

Results: Postnatal thyroid reference ranges were wide and subsequent patterns age-specific, comparable in boys and girls. FT₄ and T₄ levels were similar in short untreated SGA children and the reference population, but T₃-, rT₃-, and T₄-binding globulin levels were significantly higher. During puberty and during GH treatment, FT₄ and rT₃ significantly decreased, whereas T₃ increased.

Conclusions: Puberty and GH therapy both induced changes in peripheral thyroid metabolism compared to appropriate reference data, resulting in more biologically active T₃ at the expense of less (inactive) rT₃, perhaps mediated by IGF-I. GH treatment alters peripheral thyroid metabolism but does not cause thyroid dysfunction.

Clinical practice and research in pediatric endocrinology rely crucially on appropriate age-related reference ranges for hormone levels (ideally locally derived). This study establishes these for TH. Wide variation in T_4 and TSH at birth is demonstrated, with a sharp decline and narrowing of the ranges at day 4, coinciding with the standard age for congenital hypothyroidism screening. The study also investigated TH levels in patients born SGA with or without GH therapy. T_3 levels were above the reference range in untreated SGA patients. Puberty was associated with lower FT_4 and higher T_3 than prepuberty, whilst puberty suppression led to the reverse pattern, consistent with prepubertal levels. Interestingly, in patients treated with GH and GnRHa, FT_4 decreased and T_3 increased – as in puberty. Increased levels of active compared to inactive TH during puberty and with GH may contribute to increased growth in these situations. The authors suggest that the fall in T_4 is due to altered peripheral metabolism of TH rather than changes in TH production from the gland. They conclude that GH treatment of SGA children does not result in thyroid dysfunction. This requires validation in a larger cohort of patients, but may have implications for thyroid function screening in SGA patients on GH. The relationship between the peripheral metabolism of TH and the GH-IGF-1 axis requires further investigation.

These authors have also investigated broader issues in relation to the use of GH therapy in SGA children [6] (see the current *Yearbook* chapter on Growth and Growth Factors by Cianfarani). They conclude that ‘high-dose’ GH starting peripubertally may result in statistically (and possibly clinically) positive effects in terms of adult height, and the concurrent use of GnRHa therapy to delay puberty in those shortest at puberty onset may be similarly ‘beneficial’. However, there are important potential implications for the use of high-dose GH: e.g. high IGF-1 levels and cancer, and metabolic risk are poorly evaluated in RCTs designed to evaluate efficacy. Such studies are generally poor at determining adverse outcomes due to a lack of power and inadequate follow-up periods (see below).

Food for thought

Fatalism (in both senses of the word). What is predetermined and what can be influenced by prevention and intervention healthcare strategies?

Is obesity risk predetermined or can we do something about it? Are we predisposing and contributing to an obesity ‘epidemic’ by our feeding practices in the newborn? What are the considerations in the SGA baby born at term, compared to the preterm SGA or appropriate for gestational age (AGA) baby? What is the importance for metabolic risk of spontaneous or GH treatment-related ‘catch-up’ growth in height and weight in the SGA child?

Polygenic risk, rapid childhood growth, and the development of obesity: evidence from a four-decade longitudinal study

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Background: This study used findings of genome-wide association studies (GWAS) to investigate the influence of genomic loci on obesity development.

Methods: 1,037 male and female subjects were studied as part of a 38-year prospective longitudinal study of a representative birth cohort. Genetic risk was assessed using a multilocus genetic risk score, composed of single-nucleotide polymorphisms, identified in GWAS of obesity-related phenotypes. The authors collected parent BMI data when subjects were 11 years of age. BMI curves, obesity developmental phenotypes, and adult obesity outcomes were defined from anthropometric assessments at birth and at 12 personal follow-up interviews until 38 years of age.

Results: Chronic adulthood obesity was more common in those with higher genetic risk scores. Genetic risk first manifested as rapid growth during early childhood, but was unrelated to birth weight (BW).

Postnatally, children at higher genetic risk gained weight more rapidly and reached adiposity rebound earlier and at a higher BMI. These developmental phenotypes also predicted adult obesity, accounting for about half the genetic effect on adult obesity risk. Genetic associations with growth were independent of family history (FH), suggesting that the genetic risk score could provide additional information.

Conclusions: Genetic variation linked with obesity risk operates, in part, through accelerating growth in the early years after birth. Prevention strategies should be targeted towards the early childhood years.

It is well established that there are polygenic influences on height amongst those of normal stature [7]. The same applies to obesity with GWAS enabling identification of multiple single nucleotide polymorphisms (SNPs) associated with BMI.

Whether information regarding obesity risk additional to that gleaned from FH can be obtained from analysis of a panel of genetic loci has not previously been investigated. This study used information from published GWAS studies of BMI, obesity, weight and waist circumference in European populations to establish a panel of 32 SNPs, which they applied as part of a genetic risk score (GRS). The GRS was compared to a FH score for obesity based on the parental BMI when the children were 11 years of age. Obesity and growth were assessed using a variety of measures. Developmental phenotypes were assessed to determine the timing of obesity development.

A higher GRS predicted a higher BMI, not manifest at birth but evident by 3 years of age – so the first year is likely to be of critical importance (see below). This weight gain contributes significantly to genetic risk for obesity in the teenage years, but not in the third or fourth decade. The authors found a similar association between GRS and adiposity rebound (the nadir of the BMI curve in childhood) with subsequent childhood obesity. Genetic risk also provided independent obesity risk information beyond that gained from FH alone.

The study identifies developmental phenotypes useful for determining where intervention may be required. The contribution of individual genetic influences is usually small except in well-described clinical syndromes [7]. Clinically, the key issue is whether additional information provided by GWAS and other similar approaches should result in changes to patient management.

A number of recent studies have attempted to evaluate the role of weight in early life as a key risk factor for obesity.

Birth weight and long-term overweight risk: systematic review and a meta-analysis including 643,902 persons from 66 studies and 26 countries globally

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Background: BW, a critical indicator of prenatal developmental conditions, may be related to long-term overweight risk. The authors tested this assumption by comprehensive systematic review and meta-analysis.

Methods: Literature searches using Medline and Embase identified 66 studies (from 26 countries and 5 continents, encompassing 643,902 persons aged 1–75 years), investigating the relationship between BW and later risk of overweight.

Results: A linear positive relationship was found between BW and later overweight risk ($p < 0.001$). Low BW (LBW, $< 2,500$ g) was associated with a decreased subsequent risk of overweight (OR 0.67, 95% CI 0.59–0.76). High BW ($> 4,000$ g) was associated with increased overweight risk (OR 1.66, 95% CI 1.55–1.77). The authors estimate a doubling of long-term overweight risk in high compared to normal BW subjects (OR 1.96, 95% CI 1.43–2.67).

Conclusions: LBW is associated with a decreased long-term risk of overweight. In contrast, high BW predisposes to later overweight. A promising strategy for reducing overweight globally could be prevention of in-utero overnutrition, for example by avoiding maternal overnutrition, overweight and/or diabetes during pregnancy.

It has been shown that rapid infancy growth is associated with higher BMI and the metabolic syndrome [8]. However, it is increasingly clear that fetal growth is also predictive of later BMI. This study

investigates the long-term risk of overweight based on BW. Given the increasing evidence of early developmental origins of components of the metabolic syndrome, the direction and strength of the relationship between BW and future overweight risk was sought. This extensive meta-analysis demonstrated a positive relationship between BW and subsequent overweight in the majority of studies (89%). A large number of potential confounders had no effect on the results.

The increased risk of overweight in those born >4,000 g suggests that overweight may, in part, be preventable by interventions aimed at controlling excessive fetal weight gain. This is successful in infants of diabetic mothers when pregnancy nutritional and metabolic management is optimized. Results from LBW subjects are intriguing given evidence of risk for metabolic syndrome components and, indeed, overweight/obesity in LBW babies. There was a higher risk of overweight in adulthood in LBW subjects compared to those assessed before 18 years (OR 0.97, 95% CI 0.79–1.20) but this does not indicate an increased overweight risk compared to those born >2,500 g. There remains the possibility of a latency period in developing overweight in the LBW group.

In addition, fetal growth rate may be as important as weight at any given age in future obesity development. Growth from second trimester to birth has been shown to be important for subsequent BMI risk at 3 years of age [9]. Similar results have been demonstrated in babies born preterm in whom rapid weight gain from birth is associated with determinants of cardiovascular disease in adulthood [10].

Care must be taken when recommendations are made based on these studies: association does not prove causality and avoiding rapid weight gain before 3 months corrected age may be inappropriate. Indeed the authors point out that feeding babies nutrition-enriched diet produces conflicting results in terms of body composition and that restriction of nutrition may have significant adverse effects, particularly in preterm babies.

Thought for food Obesity and its health consequences

Obesity and its health consequences are the greatest lifestyle challenge to the health of populations in 'developed countries' – malnutrition remains by far the bigger global health issue. Numerous, more or less evidence-based, 'obesity guidelines' have been produced for use in a variety of health-care settings, e.g. for the USA [11, 12] and in Europe, e.g. from NICE (for England and Wales) [13] and SIGN (for Scotland) [14]. Strongest evidence behind recommendations is not necessarily available in areas of healthcare where implementation would provide the greatest impact on individual and public health. Obesity prevention and management is one area where evidence is possibly less robust, but likely clinical impact and health gain from implementation of recommendations informed by such evidence can still be immense. Are there any preventative or management interventions or strategies in childhood/adolescent obesity that work?

Effects of intervention programs on child and adolescent BMI: a meta-analysis study

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Background: The efficacy of school-based and after-school intervention programs on the BMIs of children and adolescents was assessed by meta-analysis.

Methods: 52 studies (n = 28,236) published between 2000 and 2011 were analyzed.

Results: Overall intervention effect size was 0.068 ($p < 0.001$) and similar for both school ($r = 0.069$) and after-school ($r = 0.065$) intervention. Programs in children aged between 15 and 19 years were most effective ($r = 0.133$) as were mixed gender intervention programs. Effect size was higher in interventions lasting 1 year ($r = 0.095$), targeting both physical activity and nutritional education ($r = 0.148$), and if 3–5 sessions of physical activity per week were included ($r = 0.080$). Parental involvement also increased effect size.

Conclusions: The intervention programs had a positive but weak overall effect size ($r = 0.068$) in preventing and decreasing childhood obesity. This effect was higher in older children, with physical activity and nutritional education combined, with parental participation and with 1-year duration.

Effectiveness of lifestyle interventions in child obesity: systematic review with meta-analysis

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Pediatrics 2012;130:e1647–1671

Background: The authors examined the effects of dietary lifestyle interventions on cardiometabolic outcomes in overweight/obese children and reviewed these systematically.

Methods: Data were obtained from 7 databases by two independent reviewers. Eligibility criteria included RCT, participants overweight/obese and ≤ 18 years, comparing lifestyle interventions to no treatment/wait-list controls, usual care, or written education materials. Studies were critically appraised by two reviewers using established criteria.

Results: 38 eligible studies were identified: 33 had complete data for meta-analysis on weight change, 15 reported serum lipids, fasting insulin, or BP. Lifestyle interventions resulted in significant weight loss compared with no-treatment controls: BMI (-1.25 kg/m^2 , 95% CI -2.18 to -0.32); BMI z score (-0.10 , 95% CI -0.18 to -0.02). Compared to usual care, lifestyle interventions resulted in significant immediate (-1.30 kg/m^2 , 95% CI -1.58 to -1.03) and posttreatment effects (-0.92 kg/m^2 , 95% CI -1.31 to -0.54) on BMI up to 1 year from baseline. Lifestyle interventions led to significant improvements in low-density lipoprotein cholesterol (-0.30 mmol/L , 95% CI -0.45 to -0.15), triglycerides (-0.15 mmol/L , 95% CI -0.24 to -0.07), fasting insulin (-55.1 pmol/L , 95% CI -71.2 to -39.1) and BP up to 1 year from baseline.

Conclusions: Improvements in weight and cardiometabolic outcomes may be achieved with lifestyle interventions. However, the optimal length, intensity, and long-term effectiveness of lifestyle interventions require further study.

Vasques et al. demonstrate that the effectiveness of interventions to reduce obesity may depend on several factors, many of which are not directly related to the intervention regimen itself. Their conclusion that parental influence is important for the success of an intervention is reinforced by another recent meta-analysis by Neimeier et al. in 2012 [15]. Unfortunately, many of the studies included did not compare an intervention with or without parental involvement, i.e. there was no internal control group. Perhaps most concerning is that many effect magnitudes were low, for example in relation to BMI reduction in those with optional parental involvement compared to none.

A separate meta-analysis has calculated that the overall effect of an intervention encouraging physical activity may only be equivalent to 4 min of extra walking or running a day [16]. Whether such effects are clinically relevant as opposed to statistically significant is an important issue.

Whilst these papers suggest that interventions may not be very effective and may result in low magnitude changes in BMI, the meta-analysis by Ho et al. suggests that the effects on BMI might be somewhat greater. The interventions in their review specifically included a dietary intervention with or without a physical activity component (19/38 studies). The majority of the studies demonstrated an improvement in weight loss in terms of BMI (1.25 kg/m^2) with the intervention, with some studies (those involving more intensive regimens) resulting in much larger effects. Longer interventions (as discussed previously) also resulted in more weight loss, in some cases sustained beyond the intervention period. In addition, 13 of the 38 studies reported at least 1 positive cardiometabolic outcome, 5 studies showed a modest positive effect on lipid profile, and 4 studies demonstrated a reduction in fasting insulin.

Overall such studies indicate that the success of interventions may depend in part on parental participation, longer duration and inclusion of both dietary and exercise components. The use of meta-analysis to estimate a combined effect by pooling data from a group of 'similar' available trials is extremely valuable. However, as in this situation, this can be problematical if the individual study designs are too dissimilar to be confident that a combined estimate will accurately reflect the evidence presented and conclusions drawn.

Concepts revised

Children are not mini-adults; adolescents are neither grown-up children nor immature adults

The adolescent patient has special needs. The process of maturing from childhood to adulthood is complex for young people, their carers and health-providers. Young people move from a model where healthcare decisions are made by parents and others acting in their 'best interests' to systems where they are expected and encouraged to do more for themselves. There are issues about how best to recognize developing autonomy, the appropriate development of services and facilities and the best use of limited resources.

Many recommendations as to how healthcare should be delivered to young people are based on experience rather than evidence – further research is required but small patient numbers and heterogeneity between patient groups make this difficult to acquire.

The diagnosis of growth hormone (GH) insufficiency in adolescence can be particularly problematical as can ensuring concordance with and optimizing GH therapy.

The challenge of growth hormone deficiency diagnosis and treatment during the transition from puberty into adulthood

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Front Endocrinol (Lausanne) 2013;4:34

Background: Replacement GH therapy in children with childhood-onset GH deficiency (GHD) is successful. It both normalizes height during childhood, results in an adult height within the target range and also has beneficial effects on body composition and metabolism through adult life. The authors define the transition phase as the period from mid- to late teens until 6–7 years after the achievement of adult height.

Methods: The authors critically reviewed evidence on best management of transition patients to ensure the correct diagnosis and establish an appropriate therapeutic regimen.

Results: The authors emphasize the importance of the transition phase as a crucial time for reassessing children's GH secretion and deciding whether GH therapy should be continued throughout life.

Conclusions: Evidence-based guidelines for the diagnosis and treatment of GH-deficient children during transition are lacking.

In addition to important effects on childhood and pubertal growth, GH plays a key role in regulating body composition and metabolism. GH deficiency in adulthood is associated with reduced lean body mass and bone mineral density (BMD), increased visceral adiposity, abnormal lipid profile, decreased muscle strength, increased cardiovascular risk, and impaired quality of life. As the authors rightly comment, diagnosing permanent GHD is crucial for selecting patients who need lifelong GH therapy and should be based on a comprehensive clinical, anthropometric, biochemical, endocrine, and neuroradiological approach.

However, endogenous GH secretory patterns relate to the stage of puberty. GH test cut-off values also vary with the stimulation test(s) and laboratory assay used, and are often applied arbitrarily and unthinkingly. The authors state that the GH dose in adolescence should be tailored to meet individual requirements for optimizing growth, body composition, bone mineralization, and metabolic homeostasis, but there is no agreement about which surrogate markers for these outcomes are most relevant or how they should be applied. In particular, there is no clear evidence base for GH dosing in severely GH-insufficient adolescents in the transition to adulthood or during continuing bone mass acquisition to its peak in the mid-20 years.

It is unclear whether GH exposure during late adolescence is critical to improved longer-term cardiovascular and related metabolic outcomes. Optimizing potential therapeutic benefits must also be balanced against risks of unforeseen harm due to unnecessary or excessive treatment. A comprehensive assessment of the health economics and quality of life aspects of GH therapy in young people is also required.

New concerns

Does size matter? Height, sexual health and fertility – important issues for many adolescents of both sexes

Adolescent girls are commonly referred to pediatric endocrinologists, whether with growth disorders (short or tall), puberty delay or menstrual irregularities or discomfort (see below).

Too many treatments in pediatrics are introduced without proper evaluation of their efficacy and, particularly, their safety. One example is the treatment of tall girls in childhood on the basis of an 'excessive' predicted adult height, often following pressure to treat from tall mothers worried about their normal daughters' heights. Historically, extremely high doses of estrogen were used.

Fertility of tall girls treated with high-dose estrogen, a dose-response relationship

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J Clin Endocrinol Metab 2012;97:3107–3114

Background: High-dose estrogen therapy in tall adolescent girls has been commonly used to reduce final height, although resulting infertility has been reported.

Methods: The authors report a retrospective cohort study of 125 tall women aged 20–42 years. 52 had been treated with 100 µg/day and 43 with 200 µg/day of ethinyl estradiol (EE) in adolescence. The effect of estrogen dose on fertility outcome including time to first pregnancy, treatment for infertility, and live birth rate was assessed.

Results: Of untreated women, 80% conceived within 1 year vs. 69% of women treated with 100 µg/day EE and 59% of women treated with 200 µg/day EE. A significant trend for time to pregnancy with increasing estrogen dose was demonstrated (log-rank trend test, $p = 0.01$). Compared with untreated women, fertility was reduced in women treated with both 100 µg/day EE (hazard ratio 0.42, 95% CI 0.19–0.95) and 200 µg/day EE (hazard ratio 0.30, 95% CI 0.13–0.72), with a significant trend in the incidence of treatment for infertility with increased estrogen dose ($p = 0.04$). In women treated with 200 µg/day EE there was a reduced chance of achieving at least one live birth, in contrast to women treated with 100 µg/day EE.

Conclusions: The authors report a dose-response relationship between fertility in later life and estrogen dose used for the treatment of tall stature in adolescent girls.

For a clinician to make a balanced judgment as to whether to prescribe a drug for a particular indication in a particular child, information is needed about both efficacy and safety and, because of the nature of most clinical trials, efficacy data are much more quickly and readily available. RCTs to determine the efficacy, but more importantly, safety of the extremely high doses of estrogen used in this context were never carried out. Deleterious effects on fertility were first reported in 2004 [17]. Women treated with high-dose estrogen in adolescence show signs of primary ovarian insufficiency with concomitant early follicle pool depletion.

This paper reports experience in relation to girls treated between 1979 and 1999. Compared with those untreated, tall women treated with high-dose estrogen had increased time to pregnancy and more fertility problems. For the first time, the association between estrogen treatment and infertility is shown to be dose-dependent within an extremely high range (higher than that used in oral contraceptives). Women treated with 200 µg/day EE had significantly reduced chances of achieving at least one live birth, one-third with involuntary childlessness for a median of 25 months. Due to the small sample size it is unclear whether women treated with 100 µg/day EE are also at risk. The authors discuss possible mechanisms by which high-dose estrogen may result in infertility: serum IGF-I levels are reduced during high-dose estrogen treatment, probably in a dose-dependent manner and IGF-1 may promote fertility by limiting recruitment of primordial follicles into the growing pool, thus conserving the resting pool.

Such treatment raises important issues about both the nature of 'informed' consent when dealing with children and adolescents and their parents, and the parental pressure which can be brought to bear on clinicians to prescribe for 'cosmetic' reasons in various contexts. It behooves investigators of

new or untried therapies to take all steps possible to identify potential or actual adverse outcomes that will not be identified during RCT efficacy studies (see also Barajas-Nava below).

Menstrual disorders are common reasons for referral of adolescent girls to the pediatric endocrinologist, but there is a paucity of evidence-based data on which to base treatments. Where evidence-based recommendations are unavailable, important information can still be gleaned from 'eminence-based' reviews based on wide clinical experience supported by available relevant medical literature data. One advantage of such a review is that, as with properly constituted consensus conferences, it can highlight areas where data are currently lacking and areas for future study.

Menstrual disorders in adolescents: review of current practice

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Horm Res Paediatr 2012;78:135–143

Background: Although serious pathology is rare, menstrual disorders are common in adolescent girls.

Methods: The authors performed a review of current practices in the clinical management of menstrual disorders.

Results: Periods can be irregular, heavy and/or painful, especially in the first few years following menarche. Management of girls with additional medical problems and learning difficulties are also discussed.

Conclusions: Many treatments are safe to use in adolescents, but evidence regarding their efficacy is extrapolated from adult studies.

The authors' conclusion highlights a problem relevant to many areas of pediatric endocrinology where relevant studies have not been, and are unlikely to be, carried out on infants, children of different ages and adolescents, for practical reasons of rarity, recruitment, consent, cost, etc. This may particularly apply to common but seldom life-threatening conditions that impact particularly on difficult-to-assess outcomes such as lifestyle and quality of life.

Whilst one adolescent girl in four has menstrual dysfunction affecting activities and school attendance, few robust efficacy data are available for clinicians managing this complex area of gynecology. Evidence of safety is also extrapolated from adult studies. The use of the combined oral contraceptive pill is associated with increased *relative* risks of venous thromboembolism and breast cancer in adults. However, as the baseline risk of serious pathology is lower in adolescents, it can be assumed (but without direct evidence) that the *absolute* risk associated with these treatments may actually be lower in this younger patient group.

Male reproductive health is also an under-researched area. How important is cryptorchidism for subsequent fertility and does size (of the testes!) matter?

Boys with undescended testes: endocrine, volumetric and morphometric studies on testicular function before and after orchidopexy at nine months or three years of age

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J Clin Endocrinol Metab 2012;97:4588–4595

Background: The appropriate timing of surgery to correct cryptorchidism is unclear.

Methods: The authors compared outcomes (germ and Sertoli cell numbers, serum inhibin B, FSH, LH, and testosterone) following surgery to correct congenital cryptorchidism performed at 9 months versus 3 years of age in an RCT involving 213 biopsies taken at orchidopexy.

Results: Germ and Sertoli cell numbers and testicular volume (TV) at 9 months were significantly larger than at 3 years. Intra-abdominal testes showed greatest germ cell depletion at 3 years. TV correlated with germ and Sertoli cell numbers, however LH, FSH, testosterone and inhibin B in the first 6 months of life did not predict cell numbers at 9 or 36 months.

Conclusion: Orchidopexy at 9 months is more beneficial for testicular development than surgery at 3 years. TV reflected germ cell numbers in early childhood; endocrine parameters did not predict testis cellular structure.

Cryptorchidism is a common reproductive abnormality with increased risk of adult testicular cancer and infertility, yet optimal management remains unclear. Surgery timing is an important management consideration. Previous studies indicated benefits of early (in the first year) versus later orchidopexy. However, no RCTs of early versus late intervention have been performed. This large cohort of cryptorchid patients, identified in the neonatal period, was randomly assigned at the age of 6 months to orchidopexy at 9 months or 3 years.

It is generally accepted that testicular volume is an indicator of spermatogenic potential – size reflecting potential function. These authors had previously reported that surgery at 9 months results in larger testicular volumes at ages 2, 3 and 4 years compared with surgery at 3 years of age [18]. They now investigated levels of gonadotrophins, testosterone and inhibin B over the first 4 years of life in the same cohort. Ultrasound was also performed and biopsies were obtained at surgery. Germ cell numbers in the 'late' orchidopexy group were extremely low, particularly in intra-abdominal testes, suggesting that more severe germ cell loss occurs if testes are not brought down into the scrotum. Measurement of hormones at 0–3 weeks did not predict spontaneous descent or Sertoli/germ cell counts.

The study could not determine whether germ and Sertoli cell depletion at 3 years in the late group also occurs by 3 years in the early intervention group as no further biopsies were taken from the latter. However, this cohort is available for future assessment of fertility and testicular cancer risk.

Important for clinical practice: *primum non nocere*

Identification and description of randomized controlled trials and systematic reviews on patient safety published in medical journals

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J Patient Saf 2013;9:79–86

Background: To identify randomized controlled trials (RCTs) and systematic reviews (SRs) relating to patient safety.

Methods: The authors hand searched 12 English language medical journals and searched Medline for articles relating to patient safety to identify RCTs and SRs published between 1973 and 2010 inclusive.

Results: 131 RCTs and 127 SRs addressed interventions relating to patient safety but many had significant methodological deficiencies. The types of incidents related to patient safety that were included most often in RCTs involved the clinical process, and for SRs, those related to resources/organizational management.

Conclusions: Few RCTs and SRs on patient safety are published in specialized journals. Knowing the content of RCTs and SRs published on patient safety can better target future research.

Few RCTs and SRs across the whole field of healthcare relate to patient safety issues; furthermore, Medline searches fail to identify all that are relevant. Observational studies and large clinical databases are important potential sources of additional information.

How does this relate to pediatric endocrinology? One example dates from 1978, 20 years after pituitary GH was introduced to treat children with GH deficiency. Then, Tanner [19] was still able to state that 'very occasionally antibodies develop to the injected (growth) hormone and cancel out the effects of treatment; otherwise side effects are practically unknown'. Yet within a further 7 years there were the first reports linking pituitary-extract GH therapy with Creutzfeldt-Jacob disease.

It is in this context that 'postmarketing surveillance' databases find their main justification. Even in rare conditions, patient-years of treatment documented can be considerable. Keeping such databases active would allow continuing targeting of specific research questions relating, for example, to adults treated with GH in childhood and/or adolescence only, where there may be no other reported data.

In Scotland, the Patient Safety Alliance (<http://www.patientsafetyalliance.scot.nhs.uk>), a strategic alliance of key partners (Scottish Government Health Department, NHS Scotland, Royal Colleges and other professional bodies, 'experts' and patients) has been set up to implement and evaluate interventions demonstrated to reduce harms, with integrated arrangements nationally, regionally and locally. Its impact remains to be seen – and evaluated!

Finally ... old wives' tales and other stories – separating fact from fiction (not just) in obesity

Myths, presumptions and facts about obesity

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Background: Many beliefs about obesity persist in the absence of supporting scientific evidence (presumptions); some persist despite contradicting evidence (myths). Their dissemination results in uninformed policy-making decisions, inappropriate clinical and public health recommendations and unsuitable research resource allocation, thus distracting from truly evidence-based information.

Methods: Obesity-related myths and presumptions were identified, reviewed, and classified using internet searches of popular media and scientific literature. The authors also examined facts well supported by evidence, especially those that have practical implications for public health, policy, or clinical recommendations.

Results: Seven obesity-related myths related to effects of small sustained increases in energy intake/expenditure, establishment of realistic weight-loss goals, rapid weight loss, weight-loss readiness, physical-education classes, breastfeeding, and energy expended during sexual activity; six presumptions related to eating breakfast regularly, early childhood experiences, eating fruit and vegetables, weight cycling, snacking, and the human-made environment.

Nine evidence-supported facts relevant for sound public health policy formulation or clinical recommendations were identified.

Conclusions: False (scientifically unsupported) beliefs about obesity are pervasive in both scientific literature and the popular press.

Obesity attracts many hypotheses regarding causation, prevention and treatment. Many become engrained in society by propagation in the media and by the general public (especially via the internet). Testing such hypotheses using well-designed RCTs is important for developing effective interventions and public health policies.

Presumptions discussed include emphases on eating breakfast, fruit and vegetables and cutting out snacks, none of which have been proven. Small, sustained changes in energy intake/expenditure do lead to modest weight reduction and, importantly, may prevent persistent weight gain. However the concept which forms the basis of much clinical obesity management, that they result in large, long-term weight reduction is untrue, perhaps due to ensuing compensatory changes in energy requirements as a result of changes in body mass. Analogously, after bariatric surgery, patients remain obese although substantial weight is lost: a new 'set point' is established despite a continued reduced calorie intake.

Several other myths are discussed, including the importance of being 'ready' to lose weight, setting 'realistic' goals and losing weight gradually. Unfortunately, substantial energy is *not* expended in typical sexual activity between two adults: in reality, the authors calculate that a man in his early to mid-30s expends about 21 kcal during sexual intercourse, with an incremental benefit compared to just watching television instead, of only around 14 kcal!

The paper also discusses the high level of confirmation bias in this area, i.e. failing to seek data that will refute concepts already intuitively accepted. Politicians are notorious for introducing unpiloted

and unevaluated interventions in many areas of healthcare not least in obesity prevention and management. Facts for which there is good evidence include: heritability is not destiny, parental involvement in environmental change is important, such change can promote weight loss and exercise helps to reduce the health-damaging effects of obesity even in the absence of weight loss. Finally, there is evidence for the effective use of pharmaceutical and surgical approaches in selected cases.

Summary

One of the aims of evidence-based medicine is to distinguish ‘fact from fiction’. Facts are propositions backed by sufficient evidence to be considered empirically proven. Bill Silverman, doyen of American neonatologists, looked back in 2003 at the age of 86, on ‘important’ therapies which had been introduced in the care of newborn babies within his professional lifetime [20]. Of 25 therapies, he concluded that 4 had led to improved practice, 12 had misled practitioners and researchers into fruitless byways, and 9 had led to disastrous adverse clinical outcomes.

Rigorously and transparently developed guidelines are designed to help practitioners assimilate, evaluate and implement ever-increasing evidence and opinion on best practice. However, there remains a challenge to demonstrate (rather than assume) that evidence-based medicine as a whole and, specifically, guideline development, can improve both the process and outcome of medical care [21].

Healthcare organization can significantly impact on guideline uptake and implementation. Policies and practice do not inevitably flow from research evidence and guidelines. The strongest evidence behind recommendations is not necessarily in areas where implementation would provide greatest impact on improvements in individual and public health. We need to think carefully about the important, clinically relevant outcomes for patients (not necessarily those easiest to assay or assess) and to distinguish between clinically and statistically relevant outcomes.

A clinician must synthesize complex information in contexts of imperfect knowledge. Evidence-based medicine is important in defining and underpinning the *science* on which a diagnosis, the prescribing of a drug or another intervention may be appropriate. The *art* of medicine still requires breadth of knowledge and experience to enable best clinical judgment against a background of risk and uncertainty.

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