Editor's Choice

Ken Ong and Ze'ev Hochberg

Optimizing therapy Fluid resuscitation in severe infection

Mortality after fluid bolus in African children with severe infection

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Background: The study aimed to establish the role of fluid resuscitation in children with shock and life-threatening infections in resource-limited settings.

Methods: The authors randomized children with severe febrile illness and impaired perfusion to receive boluses of 20–40 ml/kg body weight of 5% albumin solution (albumin-bolus group) or 0.9% saline solution (saline-bolus group) or no bolus (control group) on admission to a hospital in Uganda, Kenya, or Tanzania (stratum A); children with severe hypotension were randomized to one of the bolus groups only (stratum B). All children received appropriate antimicrobial treatment, intravenous maintenance fluids, and supportive care, according to guidelines. Children with malnutrition or gastroenteritis were excluded. The primary endpoint was 48-hour mortality.

Results: Recruitment was halted after 3,141 of the projected 3,600 children in stratum A were enrolled. Malaria status (57% overall) and clinical severity were similar across groups. The 48-hour mortality was 10.6% (111 of 1,050 children), 10.5% (110 of 1,047 children), and 7.3% (76 of 1,044 children) in the albumin-bolus, saline-bolus, and control groups, respectively (relative risk for saline bolus vs. control, 1.44; 95% CI 1.09–1.90; $p = 0.01$; albumin bolus vs. saline bolus, 1.01; 0.78–1.29; $p = 0.96$; any bolus vs. control, 1.45; 1.13–1.86; $p = 0.003$). Regarding secondary outcomes, the 4-week mortality was 12.2, 12.0, and 8.7% in the three groups, respectively ($p = 0.004$ for any bolus vs. control). Neurologic sequelae occurred in 2.2, 1.9, and 2.0% in the respective groups ($p = 0.92$), and pulmonary edema or increased intracranial pressure occurred in 2.6, 2.2, and 1.7% ($p = 0.17$), respectively. In stratum B, 69% of the children (9 of 13) in the albumin-bolus group and 56% (9 of 16) in the saline-bolus group died ($p = 0.45$). The results did not differ between centers or across subgroups by severity of shock, malaria, coma, sepsis, acidosis, or severe anemia status.

Conclusions: Fluid boluses significantly increased 48-hour mortality in critically ill children with impaired perfusion in these resource-limited settings in Africa.

This paper, describing the Fluid Expansion as Supportive Therapy (FEAST) study, won the *BMJ* 2012 Paper of the Year award. The World Health Organization recommends reserving fluid resuscitation for children with advanced shock (characterized by a delayed capillary refill time of more than 3 s, weak and fast pulse, and cold extremities) in poor-resource settings, such as sub-Saharan Africa, in which intensive care facilities are rarely available. These trial findings clearly show that earlier use of fluid resuscitation in such settings is not beneficial. The trial was discontinued early, on the recommendations of its data and safety monitoring committee, as both bolus therapy groups showed increased 48-hour mortality in the absence of features of fluid overload. The authors speculate that the vasoconstrictor response in shock may confer protection by reducing perfusion to nonvital tissues and that rapid reversal with fluid resuscitation is deleterious. Other possible adverse consequences of fluid boluses include reperfusion injury, subclinical effects on pulmonary compliance, myocardial function, or intracranial pressure. In these settings, and possibly in others, fluid bolus therapy should be reserved for children with clear signs of hypotension.

Effect of a dietary portfolio of cholesterol-lowering foods given at two levels of intensity of dietary advice on serum lipids in hyperlipidemia: a randomized controlled trial

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Background: Combining foods with recognized cholesterol-lowering properties (dietary portfolio) effectively lowers serum cholesterol under metabolically controlled conditions. This study aimed to assess the effect of a dietary portfolio administered at two levels of intensity on change in low-density lipoprotein cholesterol (LDL-C) among participants following self-selected diets.

Methods: This parallel-design trial randomized 351 participants with hyperlipidemia from four participating academic centers across Canada (Quebec City, Toronto, Winnipeg, and Vancouver) to one of three treatments lasting 6 months. Those on 'control diet' received advice for 6 months on a low-saturated fat diet. The 'routine dietary portfolio' group received counseling at two clinic visits over 6 months on dietary incorporation of plant sterols, soy protein, viscous fibers, and nuts. The 'intensive dietary portfolio' group received the same counseling at seven clinic visits over 6 months. The primary outcome was % change in serum LDL-C.

Results: In the modified intention-to-treat analysis ($n = 345$), the overall attrition rate did not differ between treatments (18% for intensive dietary portfolio, 23% for routine dietary portfolio, and 26% for control; Fisher exact test, $p = 0.33$). The % LDL-C changes were -13.8% (95% CI -17.2 to -10.3% ; $p < 0.001$) for the intensive dietary portfolio; -13.1% (-16.7 to -9.5% ; $p < 0.001$) for the routine dietary portfolio, and -3.0% (95% CI -6.1 to 0.1% ; $p = 0.06$) for the control diet. Among participants randomized to one of the dietary portfolio interventions, % reduction in LDL-C on the dietary portfolio was associated with dietary adherence ($r = -0.34$, $n = 157$, $p < 0.001$).

Conclusions: A dietary portfolio was more effective than low-saturated fat dietary advice in lowering LDL-C during 6 months of follow-up.

While there is increasing evidence to start using statins in children and adolescents with familial hypercholesterolemia, such very long-term treatments should only be given after a period of optimal dietary management, which usually involves advice to follow a low-saturated fat diet, whole-grain cereals, and plenty of fruits and vegetables. This clinical trial now shows that such typical dietary advice may have little effect on reducing LDL-C levels. Mean LDL-C at baseline in these participants was 171 mg/dl (4.4 mmol/l) and reduced by only -8 mg/dl (0.2 mmol/l) in those given routine low-saturated fat dietary advice. In contrast, average reductions in LDL-C were -26 mg/dl (-0.67 mmol/l) and -24 mg/dl (-0.62 mmol/l) in the intensive and routine dietary portfolio groups, which is around half of that observed with statins. Of note, all three diets were vegetarian, were weight-maintaining, and participants in all three arms showed equal mild weight loss, by on average of 1.5 kg over 6 months. These findings should encourage the incorporation of foods with active cholesterol-lowering properties, such as plant sterols (e.g. plant sterol ester-enriched margarines), viscous fibers (oats, barley, and psyllium), soy (soy milk, tofu, and soy meat analogues), and nuts (including tree nuts and peanuts).

The pendrin anion exchanger gene is transcriptionally regulated by uroguanylin: a novel enterorenal link

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Background: The pendrin/SLC26A4 $\text{Cl}^-/\text{HCO}_3^-$ exchanger, encoded by the PDS gene, is expressed in cortical collecting duct (CCD) non-A intercalated cells. Pendrin is essential for CCD bicarbonate secretion and is also involved in NaCl balance and blood pressure regulation. The intestinal peptide uroguanylin (UGN) is produced in response to oral salt load and can function as an ‘intestinal natriuretic hormone’. This study aimed to investigate whether UGN modulates pendrin activity and to explore the underlying molecular mechanisms.

Results: Injection of UGN into mice resulted in decreased pendrin mRNA and protein expression in the kidney. UGN decreased endogenous pendrin mRNA levels in HEK293 cells. A 4.2-kb human PDS (hPDS) promoter sequence and consecutive 5' deletion products were cloned into luciferase reporter vectors and transiently transfected into HEK293 cells. Exposure of transfected cells to UGN decreased hPDS promoter activity. This UGN-induced effect on the hPDS promoter occurred within a 52-bp region encompassing a single heat-shock element (HSE). The effect of UGN on the promoter was abolished when the HSE located between nt –1119 and –1115 was absent or was mutated. Furthermore, treatment of HEK293 cells with heat-shock factor 1 (HSF1) small interfering RNA (siRNA) reversed the UGN-induced decrease in endogenous PDS mRNA level. In conclusion, pendrin-mediated $\text{Cl}^-/\text{HCO}_3^-$ exchange in the renal tubule may be regulated transcriptionally by the peptide hormone UGN. UGN exerts its inhibitory activity on the hPDS promoter likely via HSF1 action at a defined HSE site.

Conclusions: These data define a novel signaling pathway involved in the enterorenal axis controlling electrolyte and water homeostasis.

We were not aware of an ‘entero-renal axis’. Here is an ancient dilemma: eating salt results in renal salt wasting even before intestinal salt is absorbed. How does the kidney know that salt was taken? It turns out that the intestinal peptide uroguanylin (UGN) is produced in response to oral salt load, travels to the kidneys and within minutes exerts its function as an ‘intestinal natriuretic hormone’. UGN signaling involves an enhancing promoter activity of the pendrin gene PDS. We are familiar with pendrin mutations in the deafness-goiter syndrome Pendred. Yet pendrin is also expressed in the distal renal tubule where it exerts $\text{Cl}^-/\text{HCO}_3^-$ exchange and responds the UGN by salt wasting.

A new cause of hypercalcemia

Genetic defect in CYP24A1, the vitamin D 24-hydroxylase gene, in a patient with severe infantile hypercalcemia

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Background: Idiopathic infantile hypercalcemia (IIH) is a disorder, the genetic etiology and physiological basis of which are not well understood. The objective of the study was to describe the underlying physiology and genetic cause of hypercalcemia in an infant with severe IIH and to extend these genetic findings into an additional cohort of children with IIH.

Methods: This was an inpatient study of a single patient with consanguineous parents at an academic medical center with follow-up in a specialty clinic cohort. The patient population was 1 patient with

severe IIH for gene discovery and physiological testing and 27 patients with idiopathic infantile hypercalcemia in the replication cohort. Interventions included a calcium isotopic absorption study as well as homozygosity mapping and whole-exome sequencing in a single patient followed up by gene sequencing in the replication cohort. Fractional absorption of calcium and genetic variants causing hypercalcemia were measured.

Results: Intestinal calcium absorption was extremely elevated (~90%). A rare homozygous deletion in the CYP24A1 gene was found, leading to the loss of a single highly conserved amino acid. In vivo functional studies confirmed decreased 24-hydroxylase activity because the subject had undetectable levels of 24,25-dihydroxyvitamin D. No coding variants in CYP24A1 were found in the 27 additional patients with IIH.

Conclusions: The study confirms that CYP24A1 plays a causal role in some but not all cases of IIH via markedly increased intestinal absorption of calcium, suggesting that genetic diagnosis could be helpful in a subset of IIH patients. This case demonstrates the power of an unbiased, genome-wide approach accompanied by informative physiological studies to provide new insights into human biology.

This year we learnt of a novel mechanism of hypercalcemia by loss of function of the vitamin D 24-hydroxylase enzyme, leading to defective detoxification mechanism of 1,25(OH)₂D to 1,24,25(OH)₂D₃. Similar reports were made by two other authors [1–3]. Interestingly, the severity of the hypercalcemia in the infants decreased or corrected with age. Despite the several reports from three groups in a single year, this is not a common mechanism for hypercalcemia. Those of you who can measure 1,24(OH)₂D can easily diagnose these rare cases.

A new double AKT AKT1 and AKT2

A mosaic-activating mutation in AKT1 associated with the Proteus syndrome

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N Engl J Med 2011;365:611–619

Background: The Proteus syndrome is characterized by the overgrowth of skin, connective tissue, brain, and other tissues, and is hypothesized to be caused by somatic mosaicism.

Methods: Exome sequencing was performed on DNA from biopsy samples obtained from patients with the Proteus syndrome. DNA sequences were compared between affected and unaffected tissues from the same patients. Findings were confirmed and extended, using a custom restriction-enzyme assay, by analyzing further DNA in 158 samples from 29 Proteus syndrome patients. Activation of the AKT protein in affected tissues was assayed using phosphorylation-specific antibodies on Western blots.

Results: 26 out of 29 patients with the Proteus syndrome had a somatic activating mutation (c.49G→A, p.Glu17Lys) in the oncogene AKT1, encoding the AKT1 kinase, an enzyme known to mediate processes such as cell proliferation and apoptosis. Tissues and cell lines from patients harbored admixtures of mutant alleles that ranged from 1% to approximately 50%. Mutant cell lines showed greater AKT phosphorylation than did control cell lines. A pair of single-cell clones that were established from the same starting culture and differed with respect to their mutation status had different levels of AKT phosphorylation.

Conclusions: The Proteus syndrome is caused by a somatic activating mutation in AKT1. These findings prove the hypothesis of somatic mosaicism and implicate activation of the PI3K-AKT pathway in overgrowth and tumor susceptibility in humans.

An activating mutation of AKT2 and human hypoglycemia

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Science 2011;334:474

Background and Methods: Pathological fasting hypoglycemia in humans is usually explained by excessive circulating insulin or insulin-like molecules or by inborn errors of metabolism impairing liver glucose production. The authors studied 3 unrelated children with unexplained, recurrent, and severe fasting hypoglycemia. One child also displayed asymmetrical growth.

Results: All 3 patients were found to carry the same de novo mutation, p.Glu17Lys, in the serine/threonine kinase AKT2, in 2 cases as heterozygotes and in 1 case in mosaic form. In heterologous cells, the mutant AKT2 was constitutively recruited to the plasma membrane, leading to insulin-independent activation of downstream signaling.

Conclusions: These findings show that constitutive, cell-autonomous activation of insulin signaling pathways causes severe fasting hypoglycemia with suppression of ketone bodies and branched chain amino acids in the absence of detectable circulating insulin levels.

I strongly encourage clinicians to read these two fascinating reports, which demonstrate the power of whole-exome sequencing to understand the basis of human disease and reveal new insights into human biology. Both insulin and insulin-like growth factor-1 (IGF-1) signal on the phosphoinositide 3-kinase (PI3K)/AKT/mTOR pathway, leading to activation of downstream metabolic and somatic pathways. The contrast between the largely metabolic phenotype of patients with germline or mosaic-activating mutations in AKT2 (Hussain et al.) and the marked somatic overgrowth due to mosaic-activating mutations in AKT1 (Lindhurst et al.) illustrates the distinct functions of AKT1 and AKT2 in humans.

New mechanisms Steroid sensitivity

Genome-wide association between GLCCI1 and response to glucocorticoid therapy in asthma

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Background: The response to treatment for asthma is characterized by wide interindividual variability. A substantial number of patients show no response. The authors hypothesized that a genome-wide association study (GWAS) would reveal novel pharmacogenetic determinants of the response to inhaled glucocorticoids.

Methods: The authors performed a family-based GWAS of 534,290 single-nucleotide polymorphisms (SNPs) and selected a small number of statistically powerful variants for association with changes in lung function in response to inhaled glucocorticoids. A significant, replicated association was found, and its functional effects were characterized.

Results: A significant pharmacogenetic association at SNP rs37972, in the glucocorticoid-induced transcript 1 gene (GLCCI1), was replicated in four independent populations totaling 935 persons ($p = 0.0007$). rs37972 is in complete linkage disequilibrium with SNP rs37973 and both SNPs were associated with decrements in GLCCI1 expression. In isolated cell systems, rs37973 was associated with decreased luciferase reporter activity. Pooled data from treatment trials indicate reduced lung function in response

to inhaled glucocorticoids in subjects with the variant allele ($p = 0.0007$). Overall, the mean ($\pm$ SE) increase in forced expiratory volume in 1 s in the treated subjects who were homozygous for the rs37973 variant was only about one third of that seen in similarly treated subjects who were homozygous for the wild-type allele (3.2 ± 1.6 vs. $9.4 \pm 1.1\%$), and their risk of a poor response was higher (OR 2.36; 95% CI 1.27–4.41). This genotype accounted for 6.6% of inhaled glucocorticoid response variability.

Conclusions: A functional GLCCI1 variant was associated with substantial decrements in the response to inhaled glucocorticoids in patients with asthma.

We all see patients with variable responses to glucocorticoid therapy resulting in either poor responses to treatment, variable risk of side effects, or both. This landmark study sheds light on the underlying genetic basis of interindividual differences in glucocorticoid sensitivity. GLCCI1 expression is enhanced by glucocorticoids, and the degree of induced GLCCI1 expression in B-cell lines was associated with the clinical response to inhaled glucocorticoids in the same subjects. The authors therefore surmise that patients with rs37972 and rs37973 variants have diminished clinical responses to inhaled glucocorticoids, due to reduced GLCCI1 expression and consequently reduced inflammatory-cell apoptosis, a key mechanism through which glucocorticoids resolve lymphocytic and eosinophilic inflammation in asthma. Notably, GLCCI1 is expressed in lung cells and immune cells, which raises the strong possibility of tissue-specific steroid-sensitivity – patients with rs37972 and rs37973 variants who require higher steroid doses for asthma control may yet remain highly susceptible to glucocorticoid-induced adrenal suppression or growth-plate suppression.

New treatments TSHR antagonists

Complete inhibition of rhTSH-, Graves' disease IgG-, and M22-induced cAMP production in differentiated orbital fibroblasts by a low-molecular-weight TSHR antagonist

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Background: Autoimmune stimulation of the TSH receptor (TSHR) on orbital fibroblasts (OF) is a proposed mechanism underlying Graves' ophthalmopathy.

Methods: In cultured and differentiated OF from patients with severe Graves' ophthalmopathy undergoing orbital decompression surgery, the authors tested whether a novel low-molecular-weight (LMW) TSHR antagonist Org-274179-0 inhibits cAMP production induced by rhTSH, Graves' disease IgG (GD-IgG), or M22 (a potent human monoclonal TSHR stimulating antibody).

Results: cAMP production increased after incubation either with 10 mU/ml rhTSH (3-fold; ≤ 0.05), 1 mg/ml GD-IgG (2-fold; ≤ 0.05), or 500 ng/ml M22 (5-fold; ≤ 0.05). Incubation with the LMW TSHR antagonist dose dependently inhibited rhTSH, GD-IgG as well as the M22-induced cAMP production at nanomolar concentrations; complete blockade was affected at 10^{-6} M.

Conclusions: These findings suggest that the production of cAMP, stimulated by the Graves' disease antibodies GD-IgG and M22, is exclusively mediated via the TSHR.

LMW TSHR antagonists have been proposed as possible future therapeutic agents for Graves' hyperthyroidism, and particularly for Graves' ophthalmopathy for which there are limited treatment modalities. The TSH receptor (TSHR) is expressed on fibroblasts in orbital adipose/connective tissue and in extraocular muscles of patients, and the authors hypothesized that these receptors are an important target of autoimmunity. The new compound, Org-274179-0, appears to be far more potent than previously tested TSHR antagonists. Future studies are needed to test whether Org-274179-0 inhibits the production of glycosaminoglycan by the orbital tissues.

Intranasal insulin suppresses food intake via enhancement of brain energy levels in humans

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Diabetes 2012 (E-pub ahead of print)

Background: Cerebral insulin exerts anorexic effects in humans and animals through yet unknown mechanisms. Insulin facilitates glucose uptake by most tissues of the body and thereby promotes intracellular energy supply. Therefore, the authors hypothesized that intranasal insulin reduces food consumption by enhancing neuroenergetic levels.

Methods: In a double-blind, placebo-controlled, cross-over study, 15 healthy men (BMI 22.2 ± 0.37 kg/m²) aged 22–28 years were given intranasal insulin 40 IU or placebo after an overnight fast. Cerebral energy metabolism was measured by ³¹P magnetic resonance spectroscopy. At 100 min after the intranasal spray, participants consumed an ad libitum test buffet.

Results: Intranasal insulin increased brain energy (i.e. adenosine triphosphate and phosphocreatine levels). In the placebo arm, cerebral energy content correlated inversely with subsequent calorie intake. Moreover, the degree of rise in brain energy following intranasal insulin correlated with the subsequent reduction in calorie consumption.

Conclusions: The brain appears to regulate food intake behavior dependent on its current energetic status. Intranasal insulin seems a promising future treatment option in obesity to increase cerebral energy homeostasis and reduce free-choice food intake.

Effect of intranasal insulin on cognitive function: a systematic review

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J Clin Endocrinol Metab 2012;97:366–376

Background: Epidemiological and mechanistic studies suggest that insulin may influence cognitive function. The authors systematically reviewed clinical trials that tested the potential effects of intranasal insulin administration on cognitive functions.

Methods: Interventional studies published in English measuring changes in cognitive functions in response to intranasal insulin were included.

Results: Eight studies (328 participants) were included. Seven studies included healthy subjects' response to intranasal insulin, and three evaluated the cognitive effect among patients with. Among healthy people (7 studies), Cohen's effect size calculations suggest that only 160 IU/day intranasal insulin induced potential beneficial effects. Among patients with minimal cognitive impairment or overt Alzheimer's disease, only lower doses of insulin were assessed, and 20 IU revealed potential beneficial effects on cognitive functions. No significant side effects of intranasal insulin administration were reported.

Conclusions: The current limited clinical experience suggests potential beneficial cognitive effects of intranasal insulin. Analyses provide clinical considerations for future research aimed at elucidating whether intranasal insulin may be used to improve cognitive functions.

Intranasal insulin has been shown to induce immune tolerance to insulin in adults with established type 1 diabetes, and its efficacy to prevent diabetes is currently being tested in the Intranasal Insulin Trial (INIT II), in Australia and New Zealand.

These fascinating studies describe other potential future roles for intranasal insulin, a route of administration that is known to increase cerebrospinal fluid insulin levels and therefore achieve central actions, but without altering peripheral circulating insulin levels. A physiological postprandial rise in brain insulin may act as a relevant satiety signal and giving intranasal before meals to reduce meal calorie consumption, as studied by Jauch-Chara et al., or enhancing the meal-related signal by post-

prandial administration to reduce postmeal snacking, may both be considered as future therapeutic strategies.

Other central actions of insulin include neuronal maintenance and neurogenesis and this could explain why adult diabetic patients have faster rates of decline in cognitive function, and higher risk of dementia. In their systematic review, Shemesh et al. describe that much more evidence is needed to be able to robustly evaluate the potential therapeutic role for intranasal insulin to prevent or reverse cognitive decline.

New tests β -Cell death

Detection of β -cell death in diabetes using differentially methylated circulating DNA

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Background: In diabetes mellitus, β -cell destruction is largely silent and can be detected only after significant loss of insulin secretion capacity.

Methods and Results: The authors developed a method for detecting β -cell death in vivo by amplifying and measuring the proportion of insulin 1 gene DNA from β cells in mouse serum. By using primers that are specific for DNA methylation patterns in β cells, circulating copies of β -cell-derived demethylated DNA were detected in serum of mice by quantitative PCR. Accordingly, there was a detectable increase of β -cell-derived DNA after induction of diabetes with streptozotocin and during development of diabetes in nonobese diabetic mice. The authors extended the use of this assay to measure β -cell-derived insulin DNA in human tissues and serum. Higher levels of demethylated insulin gene DNA were found in patients with new-onset type 1 diabetes compared with age-matched control subjects.

Conclusions: This novel method provides a noninvasive approach to detect β -cell death in vivo that may be used to track the progression of diabetes and guide its treatment.

It is estimated that over 90% of the β cell has already been silently destroyed by the time the patient presents with type 1 diabetes, which is probably far too late for successful preservation of β -cell function. These authors developed a novel method to identify and quantify circulating DNA that is released specifically from β cells when they die. A key role for genomic methylation is to control tissue-specific gene expression; as insulin is secreted exclusively by the pancreas, the authors correctly hypothesized that β -cell insulin gene DNA would have its own unique methylation pattern. The next challenge to overcome was to design an assay to detect these tiny amounts of DNA using methylation-sensitive primers. The authors discuss the many potential uses of such an assay, both for the prediction and monitoring of disease and interventions such as transplantation, and also for studying β -cell turnover during growth and development.

Bariatric surgery versus intensive medical therapy in obese patients with diabetes

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Background: Observational studies have shown improved glycemic control in patients with type 2 diabetes mellitus (T2DM) after bariatric surgery.

Methods: This nonblinded, single-center trial randomized 150 obese patients with uncontrolled T2DM (mean age 49 ± 8 years, 66% women) to intensive medical therapy alone, or medical therapy plus Roux-en-Y gastric bypass or sleeve gastrectomy. At baseline, mean glycated hemoglobin level (HbA_{1c}) was $9.2 \pm 1.5\%$. The primary endpoint was HbA_{1c} of 6.0% or less 12 months after treatment.

Results: 93% completed 12 months of follow-up. The proportion of patients with the primary endpoint was 12% (5 of 41) in the medical-therapy group, 42% (21 of 50) in the gastric-bypass group ($p = 0.002$), and 37% (18 of 49) in the sleeve-gastrectomy group ($p = 0.008$). Glycemic control improved in all three groups, with a mean HbA_{1c} $7.5 \pm 1.8\%$ in the medical-therapy group, $6.4 \pm 0.9\%$ in the gastric-bypass group ($p < 0.001$), and $6.6 \pm 1.0\%$ in the sleeve-gastrectomy group ($p = 0.003$). Weight loss was greater in the gastric-bypass group and sleeve-gastrectomy group (-29.4 ± 9.0 and -25.1 ± 8.5 kg, respectively) than in the medical-therapy group (-5.4 ± 8.0 kg) ($p < 0.001$ for both comparisons). The use of drugs to lower glucose, lipid, and blood-pressure levels decreased significantly in both surgical groups and increased in the intensive medical therapy group. Four patients required reoperation. There were no deaths or life-threatening complications.

Conclusions: In obese patients with uncontrolled T2DM, 12 months of medical therapy plus bariatric surgery was more effective than medical therapy alone to achieve glycemic control. Follow-up is needed to assess the durability of these results.

Bariatric surgery versus conventional medical therapy for type 2 diabetes

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Background: Roux-en-Y gastric bypass and biliopancreatic diversion can markedly ameliorate diabetes in morbidly obese patients, often resulting in diabetes remission.

Methods: This nonblinded, single-center trial, randomized 60 obese ($BMI \geq 35$) patients (ages 30–60 years) with diabetes duration >5 years and glycated hemoglobin level (HbA_{1c}) of 7.0% or more, to conventional medical therapy or either gastric bypass or biliopancreatic diversion. At baseline, mean glycated hemoglobin level (HbA_{1c}) was $8.65 \pm 1.45\%$. The primary endpoint was diabetes remission at 2 years (defined as fasting glucose <100 mg/dl (5.6 mmol/l) and $HbA_{1c} <6.5\%$ in the absence of pharmacologic therapy).

Results: At 2 years, diabetes remission had occurred in no patients in the medical-therapy group, 75% in the gastric-bypass group, and 95% in the biliopancreatic-diversion group ($p < 0.001$ for both comparisons). Age, sex, baseline BMI, duration of diabetes, and weight changes did not predict diabetes remission at 2 years or improvement in glycemia at 1 and 3 months. Glycemic control improved in all three groups; at 2 years mean HbA_{1c} was $7.69 \pm 0.57\%$ in the medical-therapy group, $6.35 \pm 1.42\%$ in the gastric-bypass group ($p < 0.001$), and $4.95 \pm 0.49\%$ in the biliopancreatic-diversion group. Two patients required reoperation, 1 for incisional hernia and 1 for intestinal obstruction. There were no deaths.

Conclusions: In severely obese patients with T2DM, bariatric surgery resulted in better glucose control than medical therapy. Preoperative BMI and weight loss did not predict the improvement in hyperglycemia after these procedures.

Is bariatric surgery no longer the last resort for obese adults with T2DM? These two trials report remarkable benefits of surgery on glycemic control and indeed very high rates of remission of T2DM in severely obese adults. It should be noted that both trials assessed highly invasive forms of surgery, rather than gastric banding, they were underpowered to robustly assess the risks of complications and side effects of treatment, and disappointingly using available baseline criteria they were unable to identify who would benefit the most. We should always take a cautious approach in translating new therapies from adults to children and adolescents, however the recently reported failure of conventional oral medication for T2DM in the latter group (see paper by the TODAY Study Group in the chapter 'Type 2 Diabetes, Metabolic Syndrome and Lipids') will increase the pressure to find effective alternative treatments.

Environmental concerns Chemical obesity

Urinary bisphenol A (BPA) concentration associates with obesity and insulin resistance

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Background: Bisphenol A (BPA) is one of the world's highest-volume chemicals in use today. Previous studies have suggested BPA disturbs body weight regulation and promotes obesity and insulin resistance. But epidemiological data in humans were limited.

Methods: To determine whether BPA associates with obesity and insulin resistance, the authors examined a cross-sectional study of 3,390 adults aged 40 years or older, in Songnan Community, Baoshan District, Shanghai, China. Questionnaire, clinical and biochemical measurements, and urinary BPA concentration were determined. Overweight was defined as a BMI of 24–28 kg/m² and obesity as a BMI of 28 kg/m² or higher. Abdominal obesity was defined as waist circumference at least 90 cm for men and 85 cm for women. Insulin resistance was defined using the index of homeostasis model assessment.

Results: Those in the highest quartile of BPA had the highest prevalence of obesity (OR 1.50; 95% CI 1.15–1.97), abdominal obesity (OR 1.28; 95% CI 1.03–1.60), and insulin resistance (OR 1.37; 95% CI 1.06–1.77). Among participants with a BMI <24 kg/m², compared with the lowest quartile, the highest quartile of BPA increased the prevalence of insulin resistance by 94% (OR 1.94; 95% CI 1.20–3.14), but this association was not observed in those with a BMI of 24 kg/m² or higher.

Conclusions: BPA was positively associated with obesity, abdominal obesity, and insulin resistance in middle-aged and elderly Chinese adults.

You would think that after a decade of scientific offense, bisphenol A (BPA) would disappear from our environmental, but it remains one of the world's highest-volume chemicals in use today. Among other untoward effects, BPA promotes obesity by its effects on adipocyte differentiation, lipid accumulation, insulin resistance, glucose transport, and adiponectin secretion (NHANES 2003–2004 and 2005–2006). The association is now confirmed: urinary BPA was associated with generalized obesity, abdominal obesity, and insulin resistance in middle-aged and elderly adult Chinese. Also this year, canned soup consumption increased urinary bisphenol [4].

Fig. 1. Pathways to androgen synthesis in 21-hydroxylase deficiency.

A new chapter in steroid metabolism Infants take the backdoor

Increased activation of the alternative 'backdoor' pathway in patients with 21-hydroxylase deficiency: evidence from urinary steroid hormone analysis

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Background: 17-Hydroxypregesterone (17-OHP) can be converted to dihydrotestosterone (DHT) via an alternative 'backdoor' route that bypasses the conventional intermediates androstenedione and testosterone. In this backdoor pathway, 17-OHP is converted to 5 α -pregnane-3 α ,17 α -diol-20-one (pdol), which is an excellent substrate for the 17,20-lyase activity of CYP17A1 to produce androsterone.

Methods: To obtain evidence for the presence of the backdoor pathway in patients with 21-hydroxylase deficiency (21-OHD), the authors compared urinary steroid hormone profiles determined by gas chromatography-mass spectrometry of 142 untreated 21-OHD patients (age range 1 day to 25.4 years; 51 males) with 138 control subjects. The activity of the backdoor pathway was assessed using the ratios of the urinary concentrations of pdol to those of the metabolites of the classic Δ^4 and Δ^5 pathways. In contrast to etiocholanolone, which originates almost exclusively from the classic pathways, androsterone may be derived additionally from the backdoor pathway. Therefore, the androsterone to etiocholanolone ratio can be used as an indicator for the presence of the backdoor pathway.

Results: Untreated 21-OHD subjects showed increased urinary ratios of pdol to the Δ^4 and Δ^5 pathway metabolites and a higher androsterone to etiocholanolone ratio.

Conclusions: The elevated ratios of pdol to the Δ^4 and Δ^5 pathway metabolites as well as the higher androsterone to etiocholanolone ratio in patients with 21-OHD indicate postnatal activity of the backdoor pathway with maximum activity during early infancy. These data provide new insights into the pathophysiology of androgen biosynthesis in 21-OHD.

This article was accompanied by an eye-opening editorial in *JCEM* [5]. In the presence of a block in 21-hydroxylation, 17-hydroxyprogesterone (17-OHP) accumulates. Textbooks claim that 17-OHP is the precursor for androstenedione, which was regarded as being an androgen as well as being a precursor of testosterone and DHT; the latter being the critical androgen for in utero virilization. Only that the human 17,20-lyase can hardly convert 17-OHP to androstenedione – the so-called Δ^4 pathway. Androstenedione is normally a product of DHEA through the Δ^5 pathway (fig. 1), yet the fetal adrenal normally produces abundant DHEA which converts to estriol in the placenta, defending the female fetus from virilization. This enigma is now solved with the demonstration of the ‘backdoor pathway’ – a new chapter to be learnt in steroid metabolism. They show that total flux to androgens through the classical Δ^4 and Δ^5 pathways is not elevated in 21-OHD children until after the first year of life, whereas 17OH-allopregnanolone (or Pdiol) is drastically elevated. Pdiol provides the entrance to the ‘backdoor pathway’, ultimately producing the nonaromatizable DHT as the source of virilization in utero and until age one. This solves another enigma: it is now appreciated that estrogens, not androgens advance bone age; why is it then that children with CAH rarely advance their bone ages during the first year of life? The answer lies in the nonaromatizable nature of DHT, the end-product of the backdoor pathway.

Stressful puberty

Individual differences in boys’ and girls’ timing and tempo of puberty: modeling development with nonlinear growth models

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Context: Pubertal development is a nonlinear process progressing from prepubescent beginnings through biological, physical, and psychological changes to full sexual maturity.

Aim: To tether theoretical concepts of puberty with sophisticated longitudinal, analytical models capable of articulating pubertal development more accurately, the authors used nonlinear mixed-effects models to describe both the timing and tempo of pubertal development in the sample of 364 white boys and 373 white girls measured across 6 years as part of the National Institute of Child Health and Human Development Study of Early Child Care and Youth Development. Individual differences in timing and tempo were extracted with models of logistic growth.

Outcomes: Differential relations emerged for how boys’ and girls’ timing and tempo of development were related to physical characteristics (body mass index, height, and weight) and psychological outcomes (internalizing problems, externalizing problems, and risky sexual behavior). Timing and tempo are associated in boys but not girls. Pubertal timing and tempo are particularly important for predicting psychological outcomes in girls but only sparsely related to boys’ psychological outcomes.

Conclusions: Results highlight the importance of considering the nonlinear nature of puberty and expand the repertoire of possibilities for examining important aspects of how and when pubertal processes contribute to development.

Reported early family environment covaries with menarcheal age as a function of polymorphic variation in estrogen receptor- α

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Context: Age at menarche, a sentinel index of pubertal maturation, was examined in relation to early family relationships (conflict, cohesion) and polymorphic variation in the gene encoding estrogen receptor- α (ESR1) in a midlife sample of 455 European-American women.

Outcomes: Consistent with prior literature, women who reported being raised in families characterized by close interpersonal relationships and little conflict tended to reach menarche at a later age than participants reared in families lacking cohesion and prone to discord. Moreover, this association was moderated by ESR1 variation, such that quality of the family environment covaried positively with menarcheal age among participants homozygous for minor alleles of the two ESR1 polymorphisms studied here (rs9304799, rs2234693), but not among women of other ESR1 genotypes. In addition, (a) family relationship variables were unrelated to ESR1 variation, and (b) genotype-dependent effects of childhood environment on age at menarche could not be accounted for by personality traits elsewhere shown to explain heritable variation in reported family conflict and cohesion.

Conclusions: These findings are consistent with theories of differential susceptibility to environmental influence, as well as the more specific hypothesis (by Belsky) that girls differ genetically in their sensitivity to rearing effects on pubertal maturation.

The attachment theory claims that growing in an insecure environment during the transition from infancy to childhood and from childhood to juvenility programs a person to an insecure reproductive strategy: early puberty, multiple sexual partners, early fecundity, and many offspring from several partners. Such individuals will also provide insecure attachment for their many offspring [6]. In a previous study from the same database, Belsky et al. showed that individuals who had been insecure as infants initiated and completed pubertal development earlier and had an earlier age of menarche compared with individuals who had been secure infants, even after accounting for age of menarche in the infants' mothers [7]. A second genetic possibility is suggested by accumulating evidence of gene-environment interaction, in which DNA polymorphisms have been found to modify environmental influences on behavioral phenotypes as childhood temperament, early cognitive abilities, juvenile and adult antisocial behavior, and depression. Recently, common polymorphisms of the ESR1 gene have been associated with menarche ages of adolescent girls in Greece [8]. The present article shows that the quality of the family environment covaried positively with menarche age among subjects homozygous for minor alleles of the two ESR1 polymorphisms, but not among women of other ESR1 genotypes. The family relationship variables were unrelated to ESR1 variation. To what extent do these observations reflect an interaction of genetic and environmental variation? Genotype-dependent associations of early family environment with menarche age in the present study could conceivably entail interactive effects involving other genes, strictly environmental factors (gene-environment interaction), or both.

Psychosocial risk and correlates of early menarche in Mexican-American girls

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Context: Mexican-American girls have one of the fastest rates of decline in age at menarche.

Aim: To study the role of psychosocial factors on age at menarche in this population.

Methods: Using data from a longitudinal cohort of Mexican-American girls from the Houston, Texas, metropolitan area recruited in 2005, the authors investigated associations between family life and socioeconomic environment and age at menarche in 523 girls.

Outcomes: After adjusting for maternal age at menarche, daughter's age, and body mass index at baseline, perception of family life environment as conflict-prone was significantly associated with an earlier age at menarche (<11 years). Additionally, there was a 2-fold higher risk (OR 2.22; 95% CI 1.12, 4.40) of early menarche among daughters of mothers who were single parents compared with those who were not. Furthermore, girls who matured early had a 2.5-fold increased risk (OR 2.69; 95% CI 1.04, 6.96) of experimenting with cigarettes compared with those who had an average-to-late age at menarche (≥11 years).

Conclusion: This study provides important information regarding the role of family life environment and single parenting on age at menarche in Mexican-Americans. Awareness of the impact of the family life environment and fathers' absence during the early years should be emphasized when addressing early age at menarche across cultures.

This study adds to the previous two: caregiving behaviors of parents are predictive indicators of the security of their environment. The biological rationale is that in stressful conditions, parenting becomes less sensitive; the child experiences psychosocial stress and adaptively responds in an adaptive reproductive strategy. This article provides important information regarding the role of family life environment and single parenting on the timing and duration of puberty. When addressing a child, be aware of the impact of the family life environment and fathers' absence during the early years.

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