
Marco A. Rivarola y Alicia Belgorosky
Servicio de Endocrinología, Hospital de Pediatria Garrahan, Buenos Aires, Argentina

As announced by the President of ESPE, Dr. Raimo Voutilainen, a quarter of a century elapsed since ESPE had its last Meeting in Finland. The theme of the present ESPE Meeting is “Prevention of endocrine disorders and their long-term sequelae”. Although few endocrine diseases can currently be prevented, clarification and understanding of the molecular basis of these diseases will create possibilities for prevention. Extreme prematurity, intrauterine growth restriction, and obesity are examples of originally non-endocrine conditions leading to endocrine or metabolic problems which could be prevented. Early diagnosis and careful treatment of classic endocrine diseases will reduce their long-term sequelae. The activities directed to clinical practitioners, as well as clinical and basic researchers, included 9 Plenary Lectures, 13 Symposia, 12 Sessions of 6 Oral Free Communications each (total 76), 3 Sessions of Poster Presentations (total 742 communications), 6 Satellite Symposia, 4 ESPE Working Group Sessions, 1 Workshop, 2 Year Book Presentation Sessions, 2 Research Methodology Sessions and 6 Meet the Expert Sessions.

As in previous years, the ESPE annual meeting is the most important international event of the year in the field of Pediatric Endocrinology.

Summaries and comments of some of the presentations follow:

PLENARY LECTURES
Summaries and comments on most Plenary Lectures follow:

Endocannabinoid system in endocrine regulation and energy balance
*Ubero Pagotto*
Alma Mater University of Bologna, Endocrinology Unit, Bologna, Italy.

Recently, the endocannabinoid system has emerged as a highly relevant topic in the scientific community. Many different regulatory actions have been attributed to endocannabinoids, and their involvement in several pathophysiological conditions is under intense scrutiny. Cannabinoid receptors, named CB1 receptor and CB2 receptor, participate in the physiological modulation of many central and peripheral functions, in particular the endocannabinoid system is supposed to play an important role in the first phases of life. The system is implicated in the embryonic implantation and in the in neural development. Moreover, endocannabinoids are pivotal in the initiation of suckling in the newborn (where activation of the CB1 receptors in the neonatal brain is critical for survival). Similarly in adults, the endocannabinoid system has been
described to play a crucial role in controlling appetite, food intake and energy balance as recently documented by an increasing number of publications. The endocannabinoid system modulates rewarding properties of food by acting at specific mesolimbic areas in the brain. In the hypothalamus, CB1 receptor and endocannabinoids are integrated components of the networks controlling appetite and food intake. Interestingly, the endocannabinoid system was recently shown to control several metabolic functions by acting on peripheral tissues, such as adipocytes, hepatocytes, the gastrointestinal tract, the skeletal muscles and the endocrine pancreas. The general relevance of the system is further strengthened by the notion that endocannabinoid activation is known to modulate all the endocrine hypothalamic-peripheral endocrine axes. An increasing amount of data highlights the role of the system in the stress response by influencing the hypothalamic-pituitary-adrenal axis and in the control of the reproduction by modifying gonadotropin release, fertility and sexual behavior.

Can fetal programming after intrauterine growth restriction be reversed postnatally?
Peter Gluckman1; Alan Beedle1; Mark Vickers1; Mark Hanson2; Karen Lillycrop2; Graham Burdge2
1, Liggins Institute, University of Auckland, Auckland, New Zealand 2, Institute for Developmental Sciences, University of Southampton, Southampton, United Kingdom

It is now clear that developmental programming is an adaptive phenomenon underpinned by epigenetic switches which become maladaptive because of a mismatch between the environment inducing the epigenetic changes and that the organism subsequently experiences. Evidence of this is provided for example by studies in the rat subjected to maternal under-nutrition. Particularly if placed on a high-fat diet after weaning these animals develop obesity, hyperinsulinemia and hyperphagia and have reduced activity in an open field. These changes are associated with specific epigenetic and expression changes; for example in hepatic genes associated with the HPA axis and metabolic regulation. The mismatch model implies that if the animals are given a false cue while still in the window of plasticity, then that cue will have later consequences. They have used leptin as a false signal of relative adiposity in maternally undernourished neonatal rats and shown that these rats even when put on a high fat diet do not develop any evidence of the metabolic phenotype. Importantly the long-term epigenetic and expression changes in the liver are prevented. This demonstrates that developmental programming can be reversed and that reversal involves epigenetic processes. The global scope of the reversal effects of leptin suggests actions on core processes underpinning programming rather than on a particular effector component of the pathway. These studies have implications not only for understanding the biology of programming, but have the potential to lead to novel strategies for detection and intervention.

Fetal origins of polycystic ovary syndrome
Stephen Franks
Imperial College London, Institute of Reproductive & Developmental Biology, London, United Kingdom

Polycystic ovary syndrome (PCOS) frequently presents during adolescence and is the commonest cause of menstrual irregularity and hirsutism. The characteristic endocrine
abnormalities include hypersecretion of androgens and LH. Metabolic dysfunction is also a feature of many young women with PCOS. Hyperinsulinemia and insulin resistance, which can be regarded as an exaggeration of the normal metabolic changes that occur during puberty, are further amplified by obesity. It is of concern that adults with symptoms of PCOS who have the most unfavourable metabolic profile are those who were obese as children. The aetiology of PCOS is uncertain but there is evidence for a primary abnormality of ovarian androgen production which is manifest at puberty but may have its origins in childhood or even during fetal development. We have recently proposed that polycystic ovary syndrome has its origin in fetal life. This hypothesis is based on data from animal models (Rhesus monkey or sheep that have been exposed prenatally to high doses of androgen) and is supported by clinical studies. It is suggested that, in human females, exposure to excess androgen, at any stage from fetal development of the ovary to the onset of puberty, leads to many of the characteristic features of PCOS, including abnormalities of LH secretion and insulin resistance. It is likely that, in humans with PCOS, the development of the PCOS phenotype results primarily from a genetic predisposition for the fetal ovary to hypersecrete androgen. At present, it is unclear whether the maternal environment directly influences the development of PCOS in the offspring. Maternal androgen excess is unlikely to affect the fetus, because the placenta presents an effective barrier, but metabolic disturbances during pregnancy could affect development of the syndrome in the fetus. In postnatal life the natural history of PCOS can be further modified by factors affecting insulin secretion and/or action, most importantly, nutrition.

**Hypothalamic-pituitary-adrenal function and glucocorticoid treatment in extremely premature newborns**

*Kristi Waterberg*

University of New Mexico, Pediatrics, Albuquerque, United States

Accumulating evidence supports the existence of a relative adrenal insufficiency in some extremely premature newborns, which has been linked to adverse clinical outcomes including cardiovascular dysfunction and shock, chronic lung disease (bronchopulmonary dysplasia, BPD), and death. A review of fetal development provides a physiologic basis for the above findings, including both immaturity and endocrine changes during transition to extra-uterine life. Relative adrenal insufficiency in this population has been difficult to define in part because normal values and responses to ACTH have not been established in this population. When 145 extremely low birth weight infants were tested with 1mcg/kg ACTH at 3 weeks of age, the 10th percentile of response was 17mcg/dl (569 nmol/L). A response less than that was associated with increased length of hospital stay and increased incidence of BPD. Randomized clinical trials have tested hydrocortisone (HC) at various doses to treat hypotension or to prevent BPD. Additionally, short and long term outcome data are available from an observational study of hydrocortisone for extubation of premature infants. HC treatment of hypotension results in improved blood pressure. Early treatment with HC for prevention of BPD did not improve outcome; however, in infants exposed to prenatal inflammation, treatment resulted in decreased mortality and decreased BPD. The trial was stopped due to an increased incidence of spontaneous GI perforation, likely related to interaction with early indomethacin therapy. Long term outcomes showed no increase in cerebral palsy, a complication of dexamethasone therapy, and no increase in neurodevelopmental impairment. HC-treated infants had some evidence of neurodevelopmental benefit: fewer treated patients had a Mental...
Developmental Index <70 (2 SD below mean) and more showed awareness of object permanence, an early measure of prefrontal cortex and hippocampal development. These data support further clinical trials of HC in this population.

Mechanism of Osteoclastic Bone Resorption
Patrick Ross
St. Louis, MO, United States

Physiological bone turnover can be divided into 2 temporal phases: modeling, which occurs during development (a topic not addressed in this conference) and remodeling, a lifelong process involving tissue renewal. Remodeling starts with removal by osteoclasts of matrix, a mixture of insoluble proteins in which type I collagen is predominant (>90%) and a poorly crystalline, chemically modified hydroxyapatite. Following resorption, osteoblasts are recruited to the site, where they secrete and mineralize new matrix. Until about age 30–35 bone replacement exceeds or equals removal, thus increasing or maintaining bone mass; thereafter, bone mass decreases, reflecting the predominance of osteoclast activity.

The osteoclast is generated by differentiation and fusion of precursors of the monocyte/macrophage lineage, giving rise to a polykaryon with unique cellular and molecular properties. Two cytokines mediate basal osteoclastogenesis, receptor activator of NF-kappa B ligand (RANKL) and M-CSF, also called CSF-1. Both proteins, produced by marrow stromal cells and their derivative osteoblasts, are membrane bound, and thus differentiation of osteoclasts requires direct interaction of these nonhematopoietic, bone-residing cells with osteoclast precursors. The discovery RANKL was preceded by identification of its physiological inhibitor osteoprotegerine (OPG), to which it binds with high affinity. M-CSF regulates many aspects of myeloid precursors and mature osteoclasts, including proliferation and/or survival, differentiation, and the cytoskeletal rearrangements required for efficient bone resorption. A combination of biochemistry and genetics helps to explain how osteoclasts resorb bone. The capacity of osteoclasts to isolate the enclosed area between themselves and the underlying bone is at the heart of their function. The acidic pH (~4.5) decalcifies the tissue, exposing the organic matrix to degradation by lysosomal-derived proteases, particularly cathepsin K. The fact that dysfunction of the proton pump, Cl– channel, or cathepsin K results in human diseases of excess bone mass, namely osteopetrosis or pyknodysostosis, attests to their critical role in osteoclast function.

This model of bone degradation requires close apposition between the osteoclast and bone, a role provided by integrins in the form of αβ heterodimers. Integrin activation mediates both cellular adhesion and transmembrane signaling. Important downstream transducers include the proto-oncogene c-src, important for membrane ruffling and osteoclast migration, and Rac and Rho, members of a small subfamily of the small GTPase superfamily that are central to remodeling of the actin cytoskeleton in many cell types and play a similar role in osteoclastic bone resorption. It is now clear that bisphosphonates block bone resorption by inhibiting membrane targeting of a number of small GTPases.

Regulators of osteoclast function include small molecules and proteins. The steroid hormone 1,25(OH)2D3 plays a major role in regulating calcium and phosphate homeostasis. Deficiency of the hormone increases bone loss by altering the RANKL/OPG ratio secondary to hypocalcemia and resulting in hyperparathyroidism. In
contrast, high levels of the steroid directly stimulate mesenchymal cell expression of RANKL and suppresses that of OPG as well as suppress the proosteoclastogenic hormone PTH. Both endogenous glucocorticoids and their synthetic analogs, which continue to be a mainstay of immunosuppressive therapy, have major impacts on bone biology because of severe osteoporosis arising from decreased bone formation and resorption (low-turnover osteoporosis). The majority of the evidence focuses on the osteoblast as the prime target, with glucocorticoids increasing apoptosis of these bone-forming cells. However, human studies document a rapid initial decrease in bone resorption, suggesting that the osteoclast and/or its precursors may also be impacted by the steroid via an ill-defined mechanism.

Proteins. In addition to M-CSF and RANKL, several proteins play important roles in osteoclast biology. OPG, an endogenous RANKL inhibitor, is secreted by mesenchymal cells both basally and in response to other regulatory signals, including cytokines and bone-targeting steroids. Importantly, postmenopausal women exhibit higher levels of RANKL on their bone marrow stroma, and treatment with estrogen reverses this outcome. Several observations indicate that circulating OPG modulates the bone-resorptive activity of RANKL and suggest that the RANKL/OPG ratio in serum will become a clinically important index.

Osteoblasts are specialized fibroblasts that secrete and calcify a specific matrix. Their lineage specification from mesenchymal stems cells is regulated by a plethora of signals. A range of cytokines modulate osteoblast differentiation, including bone matrix–derived TGF-β, bone morphogenic protein 2 (BMP-2), BMP-4, and BMP-7, and their inhibitors noggin, chordin, gremlin, and sclerostin, the last identified by positional cloning of families with increased bone mass. Similarly, numerous hormones impact osteoblast function positively including IGF-1, PTH, PTH-related protein (PTHrP), 1,25(OH)2D3, leptin, glucocorticoids, the Notch pathway, and members of the leukemia inhibitory factor/IL-6 family. The osteoblast’s best-characterized intracellular signaling pathway is the p42/44 MAPK system. Osteoblasts ligate existing matrix via β1 integrins, forming a monolayer that is linked by cadherins. Once active, the cells secrete a matrix containing type I collagen and smaller but significant amounts of osteocalcin, matrix gla protein, osteopontin, bone sialoprotein, many minor components, and, importantly, growth factors such as BMPs and TGF-β. Key ectoproteins, including progressive ankylosis gene (ANK) and tissue nonspecific alkaline phosphatase (TNAP), export pyrophosphate generated intracellularly and cleave this small-molecule inhibitor of calcification, respectively. In contrast to their proapoptotic role in osteoclasts, bisphosphonates increase osteoblast lifespan and perhaps function.

Lymphangiogenesis in Development and Human Disease

Kari Alitalo1; Collaborators2
1Haartman Institute and Biomedicum Helsinki, Molecular/Cancer Biology Laboratory, Helsinki, Finland; 2Ludwig Institute for Cancer Research, University of Helsinki, Helsinki, Finland

Angiogenesis and permeability of blood vessels are regulated by vascular endothelial growth factor (VEGF) via its two receptors VEGFR-1 and VEGFR-2. The VEGFR-3 receptor does not bind VEGF and its expression becomes restricted mainly to lymphatic endothelia during development. We have found that homozygous VEGFR-3 targeted mice die around midgestation due to failure of cardiovascular development. We have also purified and cloned the VEGFR-3 ligand, VEGF-C. Transgenic mice expressing VEGFC show evidence of lymphangiogenesis and VEGF-C knockout mice have
defective lymphatic vessels. The proteolytically processed form of VEGFC binds also to VEGFR-2 and is angiogenic. VEGF-D is closely related to VEGF-C, similarly processed and binds to the same receptors. Thus VEGFC and VEGF-D appear to be both angiogenic and lymphangiogenic growth factors. VEGF-C overexpression led to lymphangiogenesis and growth of the draining lymphatic vessels, intralymphatic tumor growth and lymph node metastasis in several tumor models. Furthermore, soluble VEGFR-3, which blocked embryonic lymphangiogenesis, also blocked lymphatic metastasis in breast and lung cancer models. These results together with recent clinical cancer studies suggest that paracrine signal transduction between tumor cells and the lymphatic endothelium may be involved in lymphatic metastasis of human cancers.

**Award Session 2 (Henning Andersen Prizes - Clinical)** SF1 mutations are a frequent cause in 46,XY patients with ambiguous genitalia due to impaired testicular androgen synthesis without adrenal insufficiency

* Birgit Köhler1; Lin Lin2; Vanessa Schröder3; Heike Biebermann3; Peter Heidemann4; Peter Wieacker5; Olaf Hior t6; Annet te Grüters1; John Achermann7

1 Charite, Children’s Hospital, Pediatric Endocrinology, Berlin, Germany; 2 University College London, UCL Institute of Child Health, London, United Kingdom; 3 Charite, Institute of Experimental Pediatric Endocrinology, Berlin, Germany; 4 Kinderklinik, Augsburg, Germany; 5 Otto von Guericke Universität Magdeburg, Institute of Human Genetics, Magdeburg, Germany; 6 Universität zu Lübeck, Pediatric Endocrinology, Lübeck, Germany; 7 University College London, UCL Institute of Child Health, London, Germany

Steroidogenic factor 1 (SF1/Ad4BP, NR5A1) is a transcription factor that plays a key role in the development and function of the gonad and adrenal glands. Although initial reports of SF1 mutations were in 46,XY individuals with gonadal dysgenesis and adrenal failure, haploinsufficiency of SF1 has recently been reported in seven patients with gonadal dysgenesis/impaired androgenization without adrenal failure. They sequenced the SF1 gene in 98 patients with 46,XY disorders of sex development (DSD). In this cohort, 46 patients had severe underandrogenization and 52 had hypospadias. They found 8 novel heterozygous SF1 mutations: E7X, C33S, R84H, Y138X, 4 bp ins (exon 4)/G146A, and 1bp ins (exon 7) in patients with severe underandrogenization (6/46) and Q107X and a splice-site mutation in intron 3 in patients with hypospadias (2/52). The missense mutations (C33S, R84H, Y138X) showed impaired DNA-binding and transactivation of different SF1 target genes in vitro. The patient with the mutation 4 bp ins (exon4)/G146A had streak gonads; all other patients had normal testicular architecture. All 8 patients had low testosterone levels at diagnosis. Adrenal function is normal in all individuals to date. SF1 mutations are a frequent cause of severe underandrogenization due to mild testicular dysgenesis and impaired androgen synthesis in 46,XY individuals with normal adrenal insufficiency. Furthermore, SF1 mutations should be considered in patients with hypospadias and low testosterone levels. This study confirms that human testis development and function is more sensitive to gene dosage effects than adrenal function, and analysis of SF1 should be added in the diagnostic work-up of 46,XY patients with ambiguous genitalia and low testosterone. Our data have a significant clinical impact in directing management and counselling of the individual and their family appropriately. Moreover, adrenal function in patients with SF1 mutations should be monitored regularly, as it might deteriorate in later life.
Generalized glucocorticoid resistance is a rare condition characterized by partial, target-tissue insensitivity to glucocorticoids. Compensatory elevations in circulating ACTH concentrations lead to increased secretion of cortisol and adrenal steroids with mineralocorticoid and/or androgenic activity, but no clinical evidence of hypercortisolism. The molecular basis of generalized glucocorticoid resistance has been ascribed to mutations in the human glucocorticoid receptor (hGR) gene, which impair glucocorticoid signal transduction, thereby altering tissue sensitivity to glucocorticoids. We have identified 6 out of the 10 hGR mutations described so far and have systematically investigated the molecular mechanisms through which various natural hGR mutants affect glucocorticoid signal transduction. Mutations within the ligand-binding domain (LBD) of the receptor have been shown to affect mostly the affinity of the receptor for ligand and the interaction of the receptor with the p160 coactivators, while the mutation identified in the DNA-binding domain of the receptor (R477H) impaired its ability to bind to DNA. Localization of the described mutations in the crystal structure of hGRα LBD suggests that two mutations (I559 and V571A) are located within Helix (H) 5, while four (V729I, F737L, I747M and L773P) are located within or close to H11 and H12. Upon ligand-binding, the receptor undergoes major conformational changes, which alter the position of H11 and H12 and generate an interaction surface that allows coactivators to bind to the LBD. The fact that most hGR mutations are clustered around H5, H11 and H12 indicates that these helices play an important role in glucocorticoid-signal transduction. The study of the functional defects of natural hGR mutants sheds light to the mechanisms of hGR action, and highlights the importance of integrated cellular and molecular signaling mechanisms for maintaining homeostasis and preserving normal physiology.

SYMPOSIAS

S3-16. CRYPTOCHIDISM

Genetic and endocrine regulation of testicular descent
Hughes, Ieuan
United Kingdom

The sitting of the bipotential, sexually unimorphic gonad at the urogenital ridge cements a long route map for the testis determined gonad to reach its final destination in the scrotum. Intuitively, an abnormal testis determining gene will cause gonadal dysgenesis and invariably testis maldescent. The normal descends in two phases: an 8 week transabdominal phase in early pregnancy, followed by an inguinoscrotal phase in the last 12 weeks of pregnancy. The interphase hiatus in activity is not explained. The testis
is initially anchored cranially and caudally by ligaments upon which hormone action initiates the first phase of descent. The testis is released for descent by testosterone-induced regression of the cranial suspensory ligament while a Leydig cell-produced peptide counterpart, insulin-like hormone 3 (INSL3), causes swelling of the caudal ligament (gubernaculum) to firmly anchor the testis towards the direction of the inguinal canal. Androgens are not critical for this phase as evidenced by transabdominal descent of the testis in hypogonadotrophic hypogonadism and androgen insensitivity syndromes. Disruption of Ins3 in mice leading to cryptorchidism is more illustrative of its crucial role in rodent testis descent compared with mutation studies of this ligand (and its receptor, LGR-8) in humans with undescended testes. Normal androgen signalling is key to directing final descent of the testis via the gubernaculum. Androgen-induced activation of the androgen receptor is the trophic mechanism whereby the neurotransmitter, calcitonin gene-related peptide (CGRP), is released from the genitofemoral nerve to act as a chemoattractant for the developing gubernaculum tip. It follows that any defect in fetal androgen production or action during the latter part of gestation will be associated with testis maldescent. Unrelated to genetic mechanisms per se, the apparent geographical differences in cryptorchidism incidence of environmental origin are likely to be through exogenous chemical disruption of androgen synthesis.

Hormones or knives: review of results after hormonal and surgical treatment

Hutson, John
Australia

Hormone treatment for cryptorchidism has been used in a range of different guises for over 50 years. The results of controlled trials, however, have not shown a significant improvement except in a small percentage of cases. Likewise, surgical treatment has had relatively poor long-term results. Why is this so?

Recent advances in understanding testicular descent now allow us to explain the apparent failures of previous treatment strategies based on three insights. First, the complexity of mechanical events in testicular descent had been underestimated. Secondly, the postnatal development of the germ cells was unknown, as the testis was thought to be in “suspended animation” biologically until puberty. Finally, the recognition of acquired cryptorchidism as a separate entity has meant previous follow-up studies probably contained heterogeneous groups. Either one or both testes fail to migrate to the base of the scrotum. Cryptorchidism affects 4% to 5% of full-term and 9% to 30% of premature males at birth. The undescended testis can be non-palpable or found in any position along its usual line of descent: inguinal, suprascrotal, high scrotal. However, approximately 80% will be located in the inguinal region, just outside the inguinal canal. We now have most of the evidence to plan rational treatment strategies, which at present means early surgery at 6-12 months of age for congenital cryptorchidism and screening of 5-10 years olds for acquired cryptorchidism. The preferred means of investigation and subsequent surgical intervention are dependent on the position of the cryptorchid testis. Risks associated with cryptorchidism include infertility and malignancy. The aim of appropriate management is to minimize these, and any other, associated complications.

What is the optimal age for treatment?

Ritzen, Martin; Kollin, Claude; Karpe, Bengt; Hesser, Ulf
Karolinska Institutet, Woman and Child Health, Stockholm, Sweden
There is general consensus that undescended testes should be brought down into the scrotum during childhood, in order to improve future spermatogenesis and make detection of tumours easier. The remaining questions concern how and when this should be done. A recent Nordic consensus conference concluded that surgery (orchiopexy) rather than hormonal treatment is to be preferred (Ritzén et al, Acta Paediatrica, June 2007). Histopathological studies show that retained testes have fewer spermatogonia per tubule than scrotal ones from age 2 years and onwards. Based on these observations early surgery has been advocated. However, follow-up studies proving better outcome after surgery in infancy have been lacking. In adulthood, mean sperm counts are lower in the formerly cryptorchid than in normal men. Few reports are available that focus on the effect of age at surgery on future spermatogenesis. In a retrospective analysis, sperm count within normal limits was found in 76% of men that had been operated between 10 months and 3 years of age, but only 26% in those operated between age 4 and 14 years. These findings are supported by several animal studies demonstrating that earlier intervention preserves spermatogenesis and fertility. We recently completed the only controlled prospective study where boys with undescended testes were randomised to early or later surgery. The results were clear: Surgery at age 9 months resulted in significantly larger testicular volume (mesured with ultrasonography) at age 4 years compared to surgery at 3 years of age. Since testicular volume generally reflects the activity of spermatogenesis, these results suggest that early surgery is to be preferred in order to preserve as much spermatogenesis as possible.

S5. Mayor Advances in Paediatric Endocrinology. Clinical Research

Neonatal onset of autosomal recessive familial neurohypophyseal diabetes insipidus (FNDI)

Abulibdeh, Abdulsalam1; Levy, Floris1; White, Perrin2; Korner, Mira1; Zangen, David1

Hadassah Hebrew University Medical Center, Division of Pediatric Endocrinology, Jerusalem, Israel; Southwestern Medical Center, Division of Pediatric Endocrinology, Dallas, United States; Live Sciences Institution Hebrew University, The Center for Genomic Technologies, Jerusalem, Israel.

1Israel;
2United States

FNDI is usually an autosomal dominant disorder, presenting in childhood (1-6 years of age) with polyuria and polydipsia. It is mostly caused by mutations in the neurophysin II (NP II) moiety of the AVP-NPII prohormone resulting in arginine vasopressin (AVP) deficiency. The mutations probably impair prohormone processing leading to gradual destruction of AVP secreting cells. Only one family with autosomal recessive mutation (P26L) for FNDI has been described with clinical presentation only at 2-8 years of age with unremarkable infantile medical record. Clinical Data: We studied 3 Palestinian cousins, and their 6 asymptomatic parents presenting with FNDI in the neonatal period. Their neonatal presentation included failure to thrive, vomiting, diarrhea, irritability, hypotonia & fever. Blood sodium ranged from 154-163mmol/L, blood osmolality was over 320mOsm/kg & while urine osmolality remained between 73-229mOsm/kg. They were easily responsive to ddAVP. Head MRI's at 2 months of age revealed no posterior pituitary bright spot.

Molecular Data: Allelic homozygosity at the AVP-NPII gene was tested using
Chromosome 20 microsatellite markers – D20S906, D20S842, D20S193. All 3 patients were homozygous for these markers flanking the AVP-NPII gene while their parents were heterozygous indicating a recessive mode of inheritance. Sequencing exon 1 of AVP-NPII gene revealed a C301-T homozygous mutation in the patients resulting in proline to leucine (P26L) substitution at the seventh amino acid residue of the hormone moiety of the AVP-NPII prohormone.

**Conclusion:** This is the first description of an autosomal recessive FNDI presenting in the neonatal period. This unusual early clinical and imaging (MRI) presentation raises doubts on the concept of a slow gradual destruction of AVP secreting neurons as the pathophysiological mechanism for FNDI. In spite of no known consanguinity with the only other family described with autosomal recessive FNDI and P26L mutation we are currently studying the possibility of a founder effect and other mechanisms for the early clinical presentation.

**FGF8 is a key ligand for FGFR1 in GnRH ontogeny: evidence from a human disease model**

Raivio, Taneli¹; Cole, Lindsay W.¹; Hayes, Frances J.¹; Seminara, Stephanie¹; Plummer, Lacey¹; Hughes, Virginia¹; Dwyer, Andrew¹; Quinton, Richard²; Pearce, Simon H.²; Hall, Janet¹; Crowley, William F.¹; Mohammadi, Mosadî; Pitteloud, Nelly¹

A longstanding biologic question in the FGF field is the delineation of the physiological FGF(s) for each of the seven principal FGFRs. **FGFR1** mutations underlie idiopathic hypogonadotropic hypogonadism (IHH) with (Kallmann syndrome; KS) or without anosmia (normosmic IHH; nIHH) indicating a critical role of **FGFR1** in GnRH neuron ontogeny. To date, no specific ligand for **FGFR1** in the GnRH neurons has been identified. However, both Fgfr1 (conditional knock-out) and Fgf8 (hypomorphic) deficient mice exhibit defective nasal cavity and olfactory bulb development. Furthermore, a specific **FGFR1** mutation (L342S) found in a KS patient exhibits decreased binding of FGF8. We therefore hypothesized that FGF8 is a key ligand for **FGFR1** in the etiology of IHH. Probands with KS (n=100), nIHH (n=100), or adult-onset IHH (AHH; n=10) were screened for **FGF8**. Phenotypes were assessed in detail in the probands and family members. FGF8 mutants were mapped to the crystal structure of FGF8-FGFR; in vitro studies are underway. One homozygous (F40L) and 5 heterozygous **FGF8** mutations (H14N, P26L, K100E, R127G, T229M) were identified in 6 unrelated probands (3 men and 3 women) (2 KS, 3 nIHH, and 1 AHH). **FGF8** mutations underlie varying degrees of GnRH deficiency; associated phenotypes included cleft lip/ palate, and osteoporosis. Two subjects also carried a heterozygous **FGFR1** mutation, which could explain some of the variable expressivity. Structural analyses predict mutant FGF8 proteins to have decreased biological activity. In conclusion: 1) Heterozygous mutations in **FGF8**, either alone or in combination with other gene defects, can underlie nIHH/KS or AHH; 2) Mutations in both the ligand (**FGF8**) and receptor (**FGFR1**) lead to similar reproductive and non-reproductive phenotypes; 3) FGF8 is a key ligand for FGFR1 in GnRH neuronal ontogeny.
Severe growth hormone insensitivity in siblings due to a Stat5b gene defect is associated with two distinct immune disorders

Camacho-Hubner, Cecilia¹; Cale, Catherine M¹; Rosenthal, Mark¹; Woo, Patricia¹; Hwa, Vivian²; Rosenfeld, Ron¹; Klein, Nigel¹; Savage, Martin O¹

William Harvey Research Institute, QMUL, Endocrinology, London, United Kingdom; Great Ormond Street Hospital, Immunology, London, United Kingdom; Royal Bronton Hospital, Pediatrics, London, United Kingdom; Great Ormond Street Hospital, Rheumatology, London, United Kingdom; Oregon Health and Science University, Pediatrics, Oregon, United States; Great Ormond Street Hospital, Infectious Diseases and Immunology, London, United Kingdom

¹United Kingdom; ²United States

Growth Hormone Insensitivity (GHI) is characterized by severe short stature, high serum GH, very low serum IGF-I and IGFBP-3 levels and is classically associated with genetic defects of the GH receptor (GHR). We report two sisters from a consanguineous family from Kuwait, with clinical and biochemical features of GHI, due to a novel homozygous splice site mutation in exon 13 of the STAT5b gene, which encodes for part of the Linker domain in the STAT5b protein in both children. The parents, who are of normal height (mother 160.2, father 167.7 cm), were heterozygous for the mutation.

Patient 1, a 5 year old with a Ht SDS -5.81 was diagnosed with juvenile idiopathic arthritis (JIA) at the age 2.1 yr and Patient 2: a 6.3 yr old with a Ht SDS: -5.6 was diagnosed at the age of 5 yr with lymphocytic interstitial pneumonitis type I LD lung disease confirmed by lung biopsy. The facial features of both patients were suggestive of mild GHI syndrome; patient 2 had in addition marked clubbing. Biochemical investigations indicated basal serum GH of 53 and 17 mU/L (patient 1 and 2, respectively) and normal GHBP levels, whereas serum IGF-I, IGFBP-3 and ALS were all extremely low. Immunological studies of Patient 2 demonstrated normal T, B and NK cell numbers, but very few naïve T cells for the child's age. Functional studies of lymphocytes demonstrated poor tyrosine phosphorylation of STAT5 in response to IL2 stimulation. Currently both children are on treatment as follows: Patient 1 receives methotrexate, predinosolone, ibuprofen and cimetidine and Patient 2 receives prednisolone, azathiaprine, hydroxycloroquine and pulmicort. The possible contribution of the mutation to the immune dysfunction found in these patients with either JIA or Interstitial Pneumonitis remains unclear. This is the first report of familial GHI due to a novel STAT5b mutation associated with two distinct immune disorders.

S11. Report on Recent Consensus Meeting

Continuous insulin infusion treatment in the pediatric age group – consensus meeting

Phillip, Moshe¹; Battelino, Tadej²; Rodriguez, Henry³; Danne, Thomas⁴; Kaufman, Francine³

Schneider Children’s Medical Center of Israel, National Center for Chilhood Diabetes, Petah Tikva, Israel; University Childrens’s Hospital, Department of Pediatric Endocrinology, Ljubljana, Slovenia; James Whitcomb Riley Hospital for Children, Section of Pediatric Endocrinology, IUSM, Indianapolis, United States; Kinderkrankenhaus auf der bult, Diabeteszentrum für Kinder und Jugendliche,
Children with Diabetes, their families and physicians still face the challenge of controlling blood glucose levels close to the normal range in order to delay or prevent long-term microvascular and macrovascular complications, to minimize the risk of severe hypoglycemic episodes and to improve quality of life. Continuous subcutaneous insulin infusion (CSII) therapy, which is the most physiologic method of insulin delivery currently available, provides a treatment option that can aid in achieving these goals. However, diabetes care practitioners are still debating as to whether CSII has advantages over multiple daily injections (MDI) in achieving these targets in young patients.

In order to address these issues, 25 expert physicians from various countries in the world convened in Berlin in April 2006 and discussed the various aspects of treating young patients with diabetes with insulin pumps. CSII offers the possibility of more flexibility and more precise insulin delivery than MDI, thus may be associated with improved glycemic control, decreased extremes of glycemic excursion, reduced frequency of severe hypoglycemia and improved QOL.

The timing of pump initiation remains an important consideration for the family and health-care team in optimizing the likelihood of successful implementation and outcomes.

Minimizing risks of CSII entails the same interventions that promote safety in all patients with Type 1 diabetes (T1DM) including proper education, frequent blood glucose monitoring, attention to diet and exercise and the maintenance of communication with a diabetes team.

The recommendations of the consensus meeting were that all pediatric patients with T1DM are potential candidates for CSII. To optimize the advantages of CSII, the basal-bolus mode and the selection of the insulin pump with its disposable equipment have to be tailored for every patient. Connection of the CSII with a real-time glucose sensor can serve as a step toward development of the future artificial pancreas.

S12. Pancreatic Beta Cell: Birth, Death and Dysfunction

Identification of therapeutic targets for the prevention of beta cell death in type 1 diabetes

Université Libre de Bruxelles, Laboratory of Experimental Medicine, Brussels, Belgium.

Eizirik, Decio L.

Belgium

Accumulating evidence indicates that beta cells die by apoptosis in T1D. Apoptosis is an active, gene directed process. We are utilizing microarray analysis to clarify the pattern of gene expression in rat beta-cells and in human islets exposed to the pro-apoptotic cytokines interleukin-1b (IL-1b) + interferon-g (IFN-g) and to diabetogenic viruses. Beta-cells respond to cytokine-mediated damage by triggering genes involved in defense/repair and endoplasmic reticulum stress, by decreasing their most differentiated functions and their capacity for growth and regeneration, and by inducing
expression of diverse cytokines and chemokines. Several of these effects of cytokines depend on the activation of the transcription factors NF-kB and STAT-1, and by blocking these transcription factors we prevented cytokine-induced rat beta-cell death. Subsequent experiments, combining NF-kB blocking and microarray analysis and "in vivo" interference with NF-kB activation, suggested that NF-kB functions as a "master switch" of IL-1 effects on beta-cells, controlling diverse networks of transcription factors and effector genes that contribute to induction of endoplasmic reticulum stress and beta-cell apoptosis. STAT-1 plays a similar role for IFN-g-induced genes. This hypothesis was further investigated by time course and cluster analysis of gene expression in cytokine-treated insulin-producing INS-1 cells, and by “in silico” and molecular biology analysis of the promoter regions of genes located in different clusters. Based on these data we are presently constructing a "Beta Cell Gene Expression Bank", which is already accessible at http://t1dbase.org/cgi-bin/enter_bcgb.cgi. By combining functional studies with microarray analysis, performed with or without targeted perturbations of the system, we hope to eventually understand the complex mechanisms regulating the cytokine-induced beta-cell "decision" to undergo apoptosis and the downstream mechanisms of beta-cell death. This approach is already pointing to novel approaches to prevent beta-cell death in early T1D.

**Could beta-cell regeneration be a therapeutic option for the treatment of insulin deficiency?**

Bonner-Weir, Susan
Joslin Diabetes Center, Harvard Medical School, Section of Islet Transplantation and Cell biology, Boston, United States.
United States

It is now appreciated that diabetes mellitus, whether type 1, type 2 or MODY, results from a mass of insulin producing beta cells that is inadequate to maintain normoglycemia. Beta cell replacement by transplantation has been successful in correcting this inadequacy but is functionally transient and necessitates immunosuppression against allograft rejection and also autoimmunity in the case of type 1 diabetes. Additionally the available tissue for replacement therapy is insufficient. An alternative therapeutic option would be if beta cell regeneration could be accomplished within the pancreas. Experimental rodent models provide evidence that replication of pre-existing beta cells as well as differentiation of new beta cells from progenitors contribute to the normal, compensatory, and regenerative growth in both rats and mice. However, without a reliable method for non-invasive imaging of the beta cell mass in humans, we can only make extrapolations based on animal studies and in vitro studies on human pancreatic tissue. Treatment with GLP-1 receptor agonists or DPPIV inhibitors have been shown to increase rodent beta cell mass by both mechanisms and also perhaps by limiting cell death. The combination of EGF and gastrin has also been used in rodents to stimulate increased beta cell mass and has been one of the few strategies that have been documented to increase beta cell mass in recent onset diabetic NOD mice. Using the human pancreatic digests remaining after islet isolation, we and others have shown that human pancreatic epithelial cells can be expanded in vitro and differentiated into islet tissue with some further increase of islet tissue obtained with GLP1 receptor agonists/DPPIV inhibitors or EGF/gastrin. The question is whether such approaches will have similar results in vivo in humans. Both of these approaches are in clinical trials currently.
Deregulation of insulin secretion in infantile hyperinsulinism: in vitro studies
Henquin, Jean-Claude
University of Louvain, Faculty of Medicine, Unit of Endocrinology and Metabolism, Brussels, Belgium

In normal pancreatic β-cells, the insulin secretory rate is precisely adjusted to blood glucose levels by two hierarchical mechanisms. A triggering pathway relies on ATP-sensitive K channels (KATP) to transduce changes in β-cell glucose metabolism into changes in membrane potential, thereby controlling the rise in cytosolic [Ca\(^{2+}\)] that serves to trigger exocytosis of insulin granules. Independently of this action on KATP channels, glucose also turns on a metabolic amplifying pathway (distinct from the neurohormonal amplification) that augments the amount of insulin released without further increasing cytosolic [Ca\(^{2+}\)]. It will be shown that both pathways, initially identified in rodent islets, also operate in human β-cells, and the characteristics of in vitro insulin secretion by isolated islets from normal infants will be described. Inactivating mutations of either of the two subunits of KATP channels (Sulfonylurea Receptor 1 or Kir6.2) cause sustained depolarization of β-cells, resulting in a glucose-independent elevation of cytosolic [Ca\(^{2+}\)] and excessive insulin secretion. Such mutations account for about 50% of cases of congenital hyperinsulinaemic hypoglycaemia. The pathology of the disease may involve all β-cells of the pancreas (diffuse forms) or be limited to a zone of adenomatous hyperplasia (J. Rahier, Brussels). The abnormalities of insulin secretion by β-cells from infants whose pancreas was partly resected (C. Fekete, Paris) to treat this form of congenital hyperinsulinism have been studied in vitro. Comparisons will be made between focal lesions and the adjacent normal pancreas, and with the diffuse pathology. (Dis)similarities with insulin secretion from 2 week-old mouse islets lacking KATP channels will be pointed out, raising the hypothesis that, unlike the mice, the infants are hypoglycaemic because the amplifying pathway does not function well in their abnormal β-cells.


Definition and risk of morbid obesity and insulin resistance
Frelut, Marie-Laure
Saint Vincent de Paul Hospital, Ap-HP
Margency
France

Morbid obesity is not defined so far in a satisfactory manner either in adults or in children. The reason why a definition seems to be required is that these patients deserve special support or medical cares. Because the complications linked to obesity are only roughly proportional to its duration or degree and cover a wide range of fields, various criteria need to be examined: anthropometric thresholds, existence of a severe complication or of multiple comorbidities. BMI is highly correlated to fat mass but using body composition techniques shows a 20% difference in fat mass at similar severe obesity levels. Since body composition varies markedly with growth and sexual differentiation in all children, including the obese ones, plotting the centiles equivalent to 40 kg/m\(^2\) at the age of 18 on existing
charts would be a useful indicator. Insulin resistance, metabolic disturbances and other comorbidities have genetic determinants, so that prevalence rates differ markedly at similar BMIs and among populations with different ethnic backgrounds. In Europe only mild differences were detected when comparing the prevalence of the metabolic syndrome in adolescents of 5 countries despite different BMIs (France, Greece, Hungary, Italy, Poland, in press). In contrast with data from other continents, type 2 diabetes is still rare even in very obese subjects (personal data). Other severe comorbidities, such as sleep apnoea or slipped capita femora, are not yet taken into account. Using the sole best identified metabolic criteria would lead to an excess indication of drugs targeting insulin resistance while the impact of other complications requiring other kinds of treatments would be neglected. We therefore suggest that a scoring system should be developed that would take into account various criteria in addition to BMI. The ideal goal to achieve would be to define a whole therapeutic strategy by merging actual risk and prognosis factors.

The HPA axis: a forever young player in the development and maintenance of obesity

Pagotto, Uberto; Pasquali, Renato
S. Orsola-Malpighi, Internal Medicine and Gastroenterology and CRBA, Bologna Italy

Steroids are known to act as important players in the regulation of adipose tissue metabolism, with relevant differences according to its distribution. Alterations of the hypothalamic-pituitary-adrenal (HPA) axis may profoundly affect adipose tissue morphology and function. The central obesity phenotype and syndromes of endogenous or exogenous hypercortisolism share several similarities, including all features of the metabolic syndrome; a hypothetical role of glucocorticoid excess in the pathophysiology of the central obesity phenotype has therefore been hypothesized. Human studies have clearly shown that in the presence of central obesity the activity of the HPA axis is increased and the catecholaminergic system is overactivated, particularly in women. An androgen imbalance is also present, with low testosterone levels in male obesity, and a condition of functional hyperandrogenism in female obesity, particularly in the presence of the central phenotype. Unfortunately, no single available marker, particularly in the basal state, has the power to detect subtle alterations of the HPA axis in these conditions. Increased cortical production in obesity may also depend on peripheral mechanisms. Higher numbers of glucocorticoid receptors have been demonstrated in visceral than in subcutaneous adipocytes, which favours an increase in intracellular cortisol action in the visceral fat. In addition, alterations of the activity of two enzyme systems, such as impaired activity of the 11β-hydroxysteroid dehydrogenase type 1 (11βHSD-1), which reactivates cortisol from inactive cortisone in the liver and the adipose tissue, and enhanced activity of the 5α-reductase, which metabolizes cortisol to its tetrahydroderivates, have been described in patients with central adiposity. The potential importance of this system has been emphasized by studies demonstrating that transgenic mice overexpressing 11βHSD-1 selectively in the adipose tissue have increased levels of corticosterone and develop visceral obesity and all features of the metabolic syndrome and insulin resistance, whereas those lacking 11βHSD-1 appear to be protected from these alterations. Therefore, both neuroendocrine hyperactivity of the HPA axis as well as peripheral cortisol production can be associated with central obesity and may therefore may have some relevance in the pathophysiology of this disorder.
The global epidemic of childhood obesity is ever-increasing. Weight gain obeys the First Law of Thermodynamics, which states that energy can neither be created nor destroyed, just shifted around. In human terms, it is usually stated: “If you eat it, you better burn it, or you’re going to store it”. It is therefore assumed by the laity that obesity is a behavior. This places the onus on the patient, as the perpetrator of “gluttony and sloth”. However, studies show that obese children have a quality of life akin to those on cancer chemotherapy. How could, and why would, any child choose to be obese? Indeed, all behaviors have biochemical underpinnings.

To understand the biochemical contributions to behavior, one may look at experiments of nature that change behavior. Children who develop brain tumors are normal weight at diagnosis, but many become massively obese after treatment. Caloric intake goes up, and energy expenditure goes down. Diet and exercise are ineffective in ameliorating the obesity. This is termed “hypothalamic obesity”, due to damage to the hypothalamus, the brain area which regulates energy balance. Normally, leptin, a hormone produced by fat cells, tells the hypothalamus about peripheral energy stores. These children can’t see the leptin signal due to hypothalamic damage, thus their brain thinks they are starved. This leads to an oversecretion of the pancreatic hormone insulin, which shunts energy (in the form of glucose and lipids) into adipose tissue for storage. Treatment of these children with a medication called octreotide, which suppresses pancreatic insulin secretion, reduces weight, reduces caloric intake, and increases spontaneous physical activity and quality of life in these patients.

Does insulin play a role in garden-variety obesity? High insulin levels is characteristic of adult obesity. In two adult studies, we found a small group (20%) of obese adults who also oversecreted insulin, like the children, and who responded to octreotide treatment with weight loss, the cessation of carbohydrate craving and intake, and increased physical activity and quality of life. We also showed that in these patients, energy expenditure went up after treatment, and this correlated with the degree of insulin suppression. Thus, the oversecretion of insulin was interfering with the leptin signal at the hypothalamus, creating the “gluttony and sloth” that these patients evidenced. By lowering insulin, the brain can now see the leptin signal, and the patient can reduce caloric intake and increase energy expenditure voluntarily.

Insulin also plays a role in another area, the Nucleus Accumbens, or the “reward center” of the brain. This is the same area that opiates and nicotine influence to promote addiction. Both of these compounds increase the secretion and levels of dopamine, a neurochemical that promotes reward. Rat data shows that in the low-insulin state (characteristic of leanness), insulin decreases dopamine, which turns off reward. This is part of the satiety mechanism that follows the meal. However, in the obese and high-insulin state (characteristic of obesity), the brain becomes tolerant of the insulin signal, thus dopamine increases, and reward is fostered. This promotes excessive and frequent eating; again promoting obesity.

Our data, and those of others, offer a different interpretation of the First Law of Thermodynamics: “If you store it, and you expect to burn it, then you’re going to have to eat it”. In this paradigm, there is an obligate energy storage, weight gain, and ingestive drive set up by the high insulin. This can be attacked by various methods of
insulin reduction; i.e. energy restriction, foods that limit insulin secretion (e.g. the low glycemic index diet), increased physical activity, and medications that lower insulin levels, such as octreotide and metformin. Our data help establish the notion that “behavior is really biochemistry”. Targeted approaches of environmental manipulation to influence these biochemical pathways should ultimately be successful in altering these behaviors and impacting on the global obesity epidemic.

**Surgical treatment of childhood obesity**
Dahlgren, Jovanna; Marild, Stafan
Institute for Clinical Sciences, GP-GRC, Department of Pediatrics, GU Sweden

Over the last decades a large amount of studies have reported results on surgery treatment of morbid obese adults. Laparoscopic vertical banded gastroplasty (VBG) and gastric bypass (GB) are the two bariatric procedures recommended today. A review of the literature shows that surgical time and hospital stay is often significantly longer in VBG versus GB, early and late complication rate is often higher. Moreover, GB is found to have significantly better weight loss years after surgery. Recently, several reports are published showing a similar in-hospital complication rate in adolescents but a significantly shorter length of hospital stay and no mortality. The majority of youngsters show substantial weight loss and improvement in their quality of life. Several randomised studies performed at our surgery unit comparing VBG and GB in adults showed that the latter patients had significantly greater reduction of weight (50% versus 75% of excess body weight), waist circumference and sagittal diameter one year after surgery. A better result was also shown with DEXA and CT measurement with a larger reduction of body fat. Those treated with GB had significantly larger decreased of spontaneously proportion of dietary fat postoperatively. However, the two methods were comparable in terms of operative safety and postoperative recovery. We have studied a group of 17-18 year old adolescents with morbid obesity that underwent GB. Mean preoperative BMI was x and mean postoperative BMI after 12 months follow-up was y. These youngsters were found to have less postoperative complications than adults. Bariatric surgery is safe, satisfactory and efficient in weight reduction in morbid obese adolescents, but is not recommended in prepubertal children as data on long-term outcome is lacking. The rate of complications is decreased in larger bariatric centres, which emphasizes the importance of units with a single team with large experience of this type of surgery.

**WG3. ESPE Turner Syndrome Working Group – Puberty Induction and Hormonal Replacement Therapy.**

**Serum estrogens in normal girls from early life to puberty. Implications for estrogen therapy in Turners Syndrome girls**
Norjavaara, Ensio; Ankarberg-Lindgren, Carina
Institute of Clinical Sciences Sahlgrenska Academy, Department of Pediatrics, Goteborg, Sweden; The Queen Silvia children’s hospital, Goteborg. Sweden

Accurate measurements of 17β-estradiol are important in clinical settings of pubertal disorders and hormone replacement therapy among children. An extraction
immunoassay is needed to achieve high functional sensitivity and reliable quantification of low 17β-estradiol concentrations in serum from prepubertal girls. The analytical sensitivity and functional sensitivity for our in-house method is 4 pmol/L and 6 pmol/L. The method includes a diethyl ether extraction before RIA (modified Spectria Estradiol Radioimmunoassay).

During puberty in girls, serum estradiol demonstrate a diurnal rhythm up to one year post menarche, with high levels in the morning (06.00-10.00 h) and low levels during the evening and early night (22.00-02.00 h). We present morning (10.00 h) and night levels (2200-0200 h) of 17β-estradiol concentrations in serum from healthy girls, prepuberty and during puberty; before menarche; for guidance of sex hormone replacement therapy in girls with Turner Syndrome.

<table>
<thead>
<tr>
<th>Pubertal stage</th>
<th>n</th>
<th>Age (mean)</th>
<th>17β-estradiol pmol/L (95% confidence interval for the median)</th>
<th>17β-estradiol pmol/L (95% confidence interval for the median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 – 5 years before breast development</td>
<td>7</td>
<td>9.4</td>
<td>&lt; 4 – 9</td>
<td>&lt; 4 – 9</td>
</tr>
<tr>
<td>0 – 2 years before breast development</td>
<td>10</td>
<td>11.0</td>
<td>7 - 16</td>
<td>&lt; 4 – 8</td>
</tr>
<tr>
<td>Tanner breast stage 2</td>
<td>18</td>
<td>11.8</td>
<td>12 - 45</td>
<td>4 – 14</td>
</tr>
<tr>
<td>Tanner breast stage 3-4 before menarche</td>
<td>17</td>
<td>12.8</td>
<td>75 - 131</td>
<td>20 – 43</td>
</tr>
</tbody>
</table>

**Effects of percutaneous estrogen gel for induction of puberty in girls with Turner syndrome**

Piippo, Sáila
Helsinki University Hospital, Pediatrics, Helsinki.
Finland

Patients with hypergonadotropic hypogonadism have significantly elevated gonadotropin levels due to ovarian failure. Turner syndrome (TS), with 46 XO karyotype, is the single most common cause of primary ovarian failure. The aim of pubertal induction in hypogonadic girls is to achieve psychological development similar to that in natural puberty. We investigated the use of percutaneous estradiol (E2) gel for induction of puberty in twenty-three girls with Turner syndrome. The initial percutaneous daily dose of 0.5 mg of estradiol ended as 1,5 mg in the fifth year. The starting dose of 0.1 mg of E2 equalled to 0.13 mg of estradiol valerate or 0.04 mg of conjugated equine estradiol. The efficacy of the treatment was monitored by measuring height, weight, skeletal age, pubertal status and serum hormone levels and gynecological ultrasonographic examinations throughout the study. Mean serum E2 concentrations increased from 22.2 pmol/l at baseline to 162,2 pmol/l as mean FSH levels decreased from 77.4 to 19.2 IU/l after five years. There were no significant differences between GH users and non GH users as regards height-SDS, weight SDS; bone age acceleration and adult height. The steady increase of mean E2 concentrations proves the efficacy of percutaneous E2 therapy. E2 concentrations show great variation, and gonadotropin levels and measurements of uterine growth are most useful in
measuring the efficacy of the estradiol treatment. With estradiol gel it is possible to tailor individual pubertal induction in hypogonadic subjects. The use of percutaneous estradiol gel provides a safe, individual and well-accepted treatment for the induction of puberty in hypogonadic girls. In our study the development of secondary sexual characteristics, and uterine growth proceeded gradually mimicking the natural puberty. The regimen of very low starting dose and slow gradual increase of the dose did not have a negative effect on final height. With gel the estrogen dose can easily be individually tailored to mimic the natural pubertal development.

**Androgen replacement therapy in Turner syndrome**

Zuckerman-Levin, Nehema

Haifa

Israel

Gonadal insufficiency is present in most women with Turner syndrome (TS), and estrogen replacement therapy (ERT) is given routinely. However, gonadal dysgenesis in adolescents and adults with TS is also associated with reduced androgen levels of up to fifty percent of controls. ERT reduces androgen levels further. Morbidity associated with TS such as bone fragility, metabolic changes, sexual problems and unique neurocognitive profile is partly related to androgen insufficiency. Androgen replacement therapy (ART) has been used with substantial success in medical conditions with low ovarian or adrenal secretion of androgens, such as postmenopausal women and adrenal insufficiency, though recent clinical practice guidelines suggested that it remains investigational. Our pilot trial of ART in adult TS patients showed an improved bone mineral density, particularly in cortical sites such as the femur, pelvis and legs. ART increased lean body mass and decreased fat mass, reduced total cholesterol, triglycerides, LDL but also HDL cholesterol. ART effect on cognition demonstrated improved attention, reaction time and recognition of new learned verbal information. Moreover, TS patients reported improved QOL, including general health, well-being, coping with stressful events and sexual desire. ART was safe with no overt virilization or drug-related side effects. Results of this pilot study suggest that androgen deficiency plays a role in some aspects of the Turner syndrome phenotype, and these aspects improve with ART.

**Quality of life/Psychosocial functioning after growth hormone therapy and induced puberty in women with Turner syndrome**

Carel, Jean Claude


France

Pediatric management of patients with Turner syndrome focuses on height, frequently resulting in a delay of pubertal induction. The influence of pubertal management on psychosocial adjustment and sex life has not been evaluated in Turner syndrome patients. We evaluated the determinants of self-esteem, social adjustment and initiation of sex life in patients with Turner syndrome, particularly those related to pubertal management in the StaTur study, based on a population registry of growth hormone-treated patients. 566 young adult women with Turner syndrome, aged 22.6±2.6 yr, range 18.3/31.2 participated in the study.
We used the Coopersmith’s Self-Esteem Inventory (SEI), Social Adjustment Scale Self-Report (SAS-SR) and asked questions on sexual experience and extensive data on pediatric management.
Low self-esteem was associated with otological involvement and limited sexual experience. Low social adjustment was associated with lower paternal socioprofessional class and an absence of sexual experience. Late age at first kiss or date was associated with cardiac involvement and a lack of spontaneous pubertal development. Age at first sexual intercourse was related to age at puberty and to paternal socioprofessional class. Delayed induction of puberty had a long lasting effect on sex life. Height and height gain due to growth hormone treatment had no effect on outcomes.
We conclude that puberty should be induced at a physiologically appropriate age in patients with Turner syndrome, to optimize self-esteem, social adjustment and initiation of the patient’s sex life. Therapeutic interventions altering normal pubertal development in other groups of patients should be reconsidered in light of these findings.