ESPE Working Groups

WG1-48 ESPE Bone and Growth Plate Working Group

Impact of chronic diseases on growth plate cartilage

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Growth disorders are commonly observed in children with chronic diseases. It is likely that these disorders are mediated by a combination of factors, including the disease process and its treatment with drugs such as glucocorticoids. Insufficient caloric or protein intake may also contribute to the growth impairment often seen in chronically ill patients. Furthermore, cytokines produced by inflamed tissues may also suppress growth. These factors commonly affect the growth hormone (GH)-insulin-like growth factor I (IGF-I)-axis, which is crucial for promoting linear growth at the level of the growth plate. Recent advances in our knowledge of the effects of glucocorticoids and proinflammatory cytokines on the growth plate have led to an improved understanding of the biological rationale for the use of growth-promoting therapy in children with chronic inflammatory disease and concurrent growth retardation. Both glucocorticoids and proinflammatory cytokines can adversely affect a number of components of growth plate chondrogenesis, and these effects can be ameliorated by raising local IGF-I exposure and/or blocking cytokine activity. However, this intervention often does not lead to complete normalization of the growth plate. In children with chronic inflammation, the cornerstone of improving growth remains the judicious use of glucocorticoids while ensuring effective control of the disease process.

WG1-49 ESPE Bone and Growth Plate Working Group

Idiopathic infantile hypercalcemia and CYP24A1

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Background: Vitamin D supplementation during infancy to prevent rickets is one of the most effective prophylactic measures in medicine. Despite a broad margin between prophylactic and toxic doses, an increased incidence of idiopathic infantile hypercalcemia (IIH) was observed in the 1950s during a period of high vitamin D supplementation in Great Britain.
Objective and hypotheses: IIH is characterized by severe hypercalcemia, vomiting, dehydration, and nephrocalcinosis. The laboratory evaluation reveals a suppressed PTH and inadequately high 1,25(OH)2-VitD3 levels.
Methods: In a cohort of familial cases with IIH and suspected autosomal recessive inheritance, we performed an extended candidate gene approach to identify the causative genetic defect. Identified mutations in the vitamin D–metabolizing enzyme CYP24A1 were evaluated with the use of a mammalian expression system.
Results: We identified homozygous or compound-heterozygous mutations in the CYP24A1 gene encoding Vitamin D-24-hydroxylase responsible for the inactivation of 1,25(OH)2-VitD3. CYP24A1 mutations were not only identified in IIH patients given regular 500 IU vitamin D daily, but also in a second cohort of patients from German Democratic Republic who presented during infancy with suspected vitamin D intoxication after receiving a bolus prophylaxis of 600.000 IU VitD2 in the late 1980s. The functional analysis of the mutant CYP24A1 enzyme in a mammalian overexpression system revealed a lack of 24-hydroxylated vitamin D metabolites after incubation with radioactively labeled 1,25(OH)2-VitD3 indicating a complete loss-of-function.
Conclusions: In conclusion, we not only highlight the role of CYP24A1 mutations as causative for IIH but identify a genetic risk factor for the development of a serious adverse effect of generally advocated vitamin D prophylaxis.

WG1-50 ESPE Bone and Growth Plate Working Group

Unusual presentations of mutations affecting type I collagen processing

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Background: Most cases of osteogenesis imperfecta are caused by mutations affecting the structure of the type I collagen genes, COL1A1 or COL1A2. The most common types of these mutations cause glycine substitutions or exon splicing abnormalities.
Objective and hypotheses: Mutations that affect processing of procollagen to collagen or the X or Y position of the collagen helical Gly-X-Y triplets will have distinctive phenotypes.
Methods: Probands with unusual forms of OI were investigated by sequencing their collagen genes and studying the mechanism by which they affected bone disease.
Results: We found distinctive phenotypes for all three groups of patients. Patients with X or Y position mutations had kinking of the collagen helix, leading to register shift propagated to the amino terminal end of the helix. This shift in register delayed N-terminal process and caused OI/EDS. Patients with mutations in the 90 residues adjacent to the procollagen N-terminal cleavage site have destabilized the collagen anchor region. This unwinds the cleavage site, which can no longer be processed because the enzyme requires the proper tertiary configuration. the resulting pN-collagen is incorporated into fibrils, leading to mechanical instability, early and rapidly progressive scoliosis and severe hyperextensibility of both large and small joints.Finally, retention of the C-propeptide of collagen, whether by mutations in the collagen substrate or mutations in the cleavage enzyme, lead to the paradoxical high bone mass forms of OI.
Conclusions: Mutations affecting processing of the N-or C-terminal propeptides of type I collagen or of non-glycine positions in the triple helix, have distinctive phenotypes.

WG1-51 ESPE Bone and Growth Plate Working Group

Osteopetrosis and high bone mass diseases

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Increased bone mass can be a diagnostic challenge for the clinicians. Radiographically, osteocondensation can present as osteosclerosis (trabecular bone thickening) or hyperostosis (cortical bone thickening). Bone turnover markers, bone density by DEXA and radionuclide bone scans are tools frequently used to make a diagnosis among acquired, iatrogenic and genetic conditions. Once secondary causes are excluded the clinician faces a relatively long list

of hereditary conditions. Despite recent improvement in identification of underlying molecular mechanisms, direct radiography is still the most practical tool in everyday practice.
This lecture aims to give an overview on the molecular findings in osteocondensation phenotypes, providing clinical and radiographic clues on diagnosis and management of high bone mass disorders with special emphasis on osteopetrosis.

WG1-52 ESPE Bone and Growth Plate Working Group

Osteopetrosis type II due to a CLCN7 mutation

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Disorders of high bone mass in children may present to clinicians with clinical symptoms eg fractures or alternatively may be a coincidental finding when dense bones are identified on X-ray. The index patient was a 9 year old girl who presented with a fractured neck of femur who was noted to have dense bones on X-ray with thickened cortices and narrow medullary cavities. She was previously well with no family history of note. She had a normal full blood count and film with no evidence of bone marrow compression. She also had normal vision and hearing making it unlikely that she had autosomal recessive infantile osteopetrosis. Lumbar spine bone density showed a Z-score of + 8.1. Additional X-rays showed increased density of the skull base and the spine with a "rugger jersey" appearance suggestive of autosomal dominant osteopetrosis Type II (Albers-Schonberg Disease). Genetic analysis of the CLCN7 gene on Chromosome 16p13.3 that codes for the chloride channel in the osteoclast showed a heterozygous missense mutation in exon 19 confirming the diagnosis. She has remained well with no further fractures or complications after ten years of follow up. Investigation of the bone density of her parents identified that her mother who was asymptomatic also had a high lumbar spine bone density and was also identified as having a mutation of the CLCN7 gene. Her grandmother who had a bone density scan to exclude osteoporosis was also identified as having a high bone density and is likely to have the same condition. Although ADO Type II is often described as a benign condition a large series of 42 patients identified that 27% developed osteoarthritis of the hips, 11% mandibular osteomyelitis and 16% cranial nerve compression.

WG1-53 ESPE Bone and Growth Plate Working Group

Van Buchem disease (hyperostosis corticalis generalisata) in pediatric patients

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Background: Hyperostosis corticalis generalisata, an autosomal recessive disease, is characterized by progressive bone overgrowth, causing narrowing of the neuroforamina in the skull base and consequently cranial neuropathies.
Objective and hypotheses: The objective is to obtain a better understanding of the underlying molecular mechanisms of van Buchem disease in order to lead to a preventive treatment in the future.
Methods: Neurological examination was performed and additionally a head computerized tomography (CT) scan, measurement of bone mineral density, evaluation of biochemical markers of bone turnover and DNA analysis.
Results: We present three pediatric patients with recurrent facial neuropathy which had started before the age of three years. All patients came from the same isolated village. Head CT scan revealed thickened calvarium, skull base and mandible with narrowing of facial nerve canals. Bone mineral density of lumbar spine and total body was markedly increased. Biochemical markers of bone turnover were increased. The diagnosis was confirmed by DNA analysis showing a homozygous deletion of the area downstream the SOST gene on chromosome 17q12-q21, described in van Buchem disease. The presence of this deletion most likely suppresses SOST gene expression. The SOST gene encodes sclerostin, normally produced by osteocytes, which antagonizes bone formation. Mutations in the SOST gene cause the disease sclerosteosis, a disorder with similar clinical features described in patients from South Africa. Continuous treatment with corticosteroid has been described to be beneficial in an adult patient with van Buchem disease. Glucocorticoid treatment during an exacerbation may inhibit the excessive bone formation in pediatric patients.
Conclusions: Facial nerve palsy may be the presenting symptom of hyperostosis corticalis generalisata (van Buchem disease) in pediatric patients. The excessive bone formation is caused by a lack of sclerostin.

WG1-54 ESPE Bone and Growth Plate Working Group

Pycnodysostosis with cathepsin K mutations

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Pycnodysostosis is a rare, autosomal recessive disease characterized by Pycnodysostosis is a rare, autosomal recessive disease characterized by osteosclerosis, short stature, acroosteolysis of the distal phalanges, bone fragility, clavicular dysplasia, and skull deformities with delayed closure of the sutures. The disease is caused by a deficiency of the cysteine protease, cathepsin K, located at 1q21, which is responsible for degradation of collagen type I and other bone proteins.
Most common presentations of the patients with pycnodysostosis to pediatric endocrinology clinics are short stature and/or frequent fractures. In our clinic, genetically proven 9 patients with pycnodysostosis from 6 families were followed for 2 to 8 years. All of the index cases were presented with short stature and, progressive loss of height SDS at follow-up was a common feature. Fractures of cranial bones, clavicles, long bones of lower extremity were noted in 7 of the 9 patients. Widely open anterior fontanel with delayed closure was noted, as far as 11 years of age. One of the patient with delayed fontanel fusion had intracranial hemorrhage after mild trauma.
Acroosteolysis and osteosclerosis with dysmorphic features led to the diagnosis in all cases. X-rays revealed increased bone density with almost complete obliteration of medullary cavity, batman sign and sandwich vertebrae appearance. Fundus examination revealed papilledema in one patient, needed one decompression surgery of optic nerve and then, surgery for craniosynostosis for continuing papilledema.
All of the patients had the symptoms of obstructive sleep apnea and, adenoidectomy had been performed in 6.
The detailed clinical and laboratory data with x-rays will be presented at the meeting.

WG2-55 The 5th ESPE DSD Working Group Meeting

A holistic perspective on DSD

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The Chicago Consensus on DSD was a turning point in recognising that a truly holistic approach was required to improve management for families with DSD. Never before in the recent history of medicine has such a revolution taken place to axe a set of perjorative terms to be replaced with a forward-looking medical lexicon now in common usage across the whole spectrum of DSD-related work. Diagnosis is a prerequisite for optimal management. DSD has hitherto posed problems in this repsect, particularly in XY DSD. Targetted genetic studies based on detailed phenotyping are paying dividends in disorders associated with complete resistance to androgens and in defects of androgen biosynthesis, with high specifity and sensitivity. Even gonadal dysgenesis is becoming ‚less idiopathic' with the recognition that NR5A1 mutations are pleiotropic in their manifestation. The phenotype of possible partial androgen unresponsiveness continues to pose an unhelpful diagnostic conundrum in the majority of cases. The hype from the current explosion in whole genome sequencing may, as a cautionary note, promise a false dawn.
The scientific advances are equalled in measure by a momentum whereby DSD management is expected to be multi-disciplinary. It is now characterised by a tempered approach to surgery, formulation of planned age-related conduct of disclosure, widespread constructive discussion of ethical issues and positive engagement with family support groups. Worldwide recognition of, and funding initiatives for, rare diseases and coupled with DSD registries promises a major boost for DSD research. Holism is a philosophical concept that denotes ‚wholes' as being greater than the sum of their parts. Nowhere in medicine is this approach more applicable than in DSD management.

WG2-56 The 5th ESPE DSD Working Group Meeting

New methods for investigating DSD

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Background: Disorders of Sex Development (DSDs) are congenital conditions in which development of chromosomal, gonadal or anatomical sex is atypical. The cause of these problems is most often a breakdown of the complex network of gene regulation responsible for proper development of testes or ovaries in the embryo. Most DSD patients have an unknown etiology and cannot be given an accurate diagnosis.
Objective: To develop a rapid, accurate, cheap, high volume approach to identify the underlying genetic defect in patients with DSD.
Methods: We have used targeted massively parallel sequencing (MPS) of 80 known or putative DSD genes, in 96 patients in parallel. The number of genes analysed is flexible and can be up to 300. Any patients that are negative for a mutation from this screen are subsequently analysed by microarrays to look for large genomic rearrangements (CNVs). If patients are still negative they undergo whole exome sequencing. Eventually we anticipate moving to whole genome sequencing as this become more affordable. This will enable us to extract different datasets as required. Key to the success of these approaches is strong bioinformatics support and new algorithms to enable rapid identification of disease causing genes from the overwhelming wealth of genomics information.
Results: Data on DSD patients who have been subjected to targeted MPS, CNV arrays, exome or whole genome sequencing will be presented.
Conclusions: The tremendous power of massively parallel sequencing approaches is leading to a revolution in the diagnosis of DSD conditions.

WG2-57 The 5th ESPE DSD Working Group Meeting

New genes for DSD: CGH microarray disorders of the Müllerian ducts in females

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Background: Anomalies of the female genital tract cause infertility or sterility. The frequency of fusion defects of Müllerian ducts is about 0.4%. They can occur as isolated anomalies or parts of syndromes. Mayer-Rokitansky-Küster-Hauser syndrome (MRKH) is a congenital anomaly of the female genital tract characterized by agenesis of the upper vagina and rudimentary or absent uterus. The external genitalia are normal and the karyotype is 46,XX. A variety of different defects, especially renal anomalies, can be associated.
Objective, hypothesis and methods: To date in most of the cases the cause of MRKH remains unclear. Therefore, we performed array-CGH analysis in a group of 108 MRKH patients by using high-resolution Agilent oligonucleotide arrays. Furthermore, we performed sequential analysis of candidate genes.
Results: We could delineate three definitively relevant regions (1q21.1, 17q12 and 22q11.21) and suggest that LHX1 is a candidate gene for MRKH. Sequential analysis of LHX1 und HNF1B gene, being located in candidate region 17q12, revealed in one MRKH patient a missense mutation in the LHX1 gene.
Conclusions: Our findings suggest that different chromosomal regions are associated with MRKH.

WG2-58 The 5th ESPE DSD Working Group Meeting

Update on the International DSD Registry

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Background and objectives: Effective research into understanding the aetiology of Disorders of Sex Development (DSD), as well as long-term outcome of these rare conditions, requires multicentre collaboration across national boundaries and across multiple clinical and research disciplines. Between 2008 and 2011, the DSD Registry was at the heart of the EuroDSD collaboration for supporting the sharing of data. The Registry adheres to the highest standards of data governance and security and has attracted much interest internationally and has changed from a European initiative to an international activity and can support projects other than those in the EuroDSD collaboration.
Results: In May 2012, there were 1033 cases added by registered users from 18 centres in 13 countries across 3 continents. A further 25 centres and 10 countries have registered as users (without cases) covering all 6 habitable continents. The age of presentation ranges from <1 month to 53 years, with a median age of presentation of 10 years. The median year of birth is 1995 (range 1927-2011). The commonest disorder type is disorders of androgen action (305) followed by disorders of gonadal development (237). The majority of cases had a 46XY karyotype (748), followed by a 46XX karyotype (187). Around 59% (609) cases in the Registry have a female sex and 41% (424) have a male sex. There are 19 males with 46XX karyotype and 405 females with 46XY karyotype on the Register. Associated malformations were present in 25% (255) cases. In addition to clinical data, biological samples are available in 40% (410) cases.
Conclusions: The I-DSD Registry is open to new researchers and clinical contributors and interested parties can register to use the Registry at www.i-dsd.org. In case of queries please contact the I-DSD Project Manager, Jillian Bryce (Jillian.Bryce@glasgow.ac.uk). *The IDSD project is funded by MRC (G1100236)*

WG2-59 The 5th ESPE DSD Working Group Meeting

Update on the ESPE e-learning module

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The aim of the ESPE elearning webportal (www.espe-elearning.org) is to provide entrance to an interactive learning environment for an up-to-date program on DSD including normal development, patho-physiological mechanisms, diagnostic and therapeutic interventions, psychological counseling and outcome. Target groups are medical students, residents, fellows, specialists, consultants, and teachers around the world. The portal is developed in the English language with two levels of learning: a. basal (medical student): the focus is the understanding of the normal development and its patho-physiology with clinical and social implications. b. advanced (post-doc, etc): the fellow is additionally invited to analyze and diagnose disorders, to solve problems, to appraise scientific evidence and to communicate with professionals, patients and parents. Following an intensive phase of construction the web-portal has gone live the fall of 2010. The main emphasis is on expanding data entry, i.e text for chapters and case descriptions. Authors have been invited to contribute content. Based on results of a pilot study evaluating content and user experience of a set of chapters and cases in the current portal recommendations for further improvement have been formulated. It is the intention to develop functionalities for scoring of questions and to develop formative assessment of competencies of students and portal users making use of a forum functionality. Moreover a pilot on e-consultation is underway.

WG2-60 The 5th ESPE DSD Working Group Meeting

2012 working party on DSD: Evaluation report

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Background: Advances in understanding the genetic control of sexual determination and differentiation, improvements in diagnostic testing and surgical genital repair, and the controversies inherent to clinical management were the most compelling factors that led to the organization of the 2012 Working Party on the 'Disorders of Sex Development' (DSD) Evaluation.
Objectives: The aims of this Meeting were to acknowledge and discuss the most important issues in the management of patients with DSD, to explore the development of objective datasets that can describe phenotype at presentation and in the long-term, and to explore how a web-based portal can help global research and clinical practice.
Methods and results: Topics discussed were as follows: 1) The evaluation of the undervirilized genital tubercle, including how to describe the undervirilized genital tubercle, who are the patients that need to be evaluated and how, when and how to assess tissue responsiveness to hormones, the long-term ef-

fects of androgen stimulation and the the outcome of genital reconstruction in adulthood; 2) 46,XX DSD: Evaluation of the virilized genital tubercle, including how to describe the virilized genitalia, the preferred prenatal diagnosis and management, the prenatal treatment in patients with Congenital Adrenal Hyperplasia (CAH), and the long-term outcome of 46,XX patients with CAH raised as females or males; 3) Gender assignment, including gender assignment and long-term monitoring, the role of surgery from the perspective of an Endocrinologist, Urologist, Gynecologist and Child Psychologist, and the role of patient support groups in comprehensive care of patients and families coping with DSDs; 4) The dysgenetic gonads, including how to identify and treat them; and 5) Lessons to learn from Euro DSD, including the outcome of a web-based registry and an outline of future research programs.
Conclusions: The development of a Professional Network for DSD is of fundamental importance for the long-term management of these patients.

WG2-61 The 5th ESPE DSD Working Group Meeting

The future of a European reference network (ERN) on DSD

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European reference networks (ERNs) for Rare Diseases are collaborative networks between Centres of Expertise (CoE) within Europe. Currently, member states of the EU are urged to designate national CoEs for Rare Diseases according to the recommendations of the EU Committee of Experts on Rare Diseases (EUCERD). Once this is established, ERNs are financed after October 2012 in the context of the 3rd Health Programme of the EU. The added value of ERNs to the EU is particularly high for rare diseases, because of the rarity of the conditions, implied both by the limited number of patients and the scarcity of expertise within a single country. Gathering expertise at the European level is therefore paramount in order to ensure access to accurate information, appropriate and timely diagnosis and high quality care for rare diseases patients (see EUCERD report on ERNs 2011). DSD constitute a group of rare to very rare conditions with atypical development of the urogenital and often the reproductive systems. The development of an information network that facilitates the development of standards for highly specialised multidisciplinary care and promotes education of health professionals and empowers parents and patients is of great strategic relevance. An ERN for DSD will lead to increased visibility of research in DSD and will improve public engagement as well as participation in patient centred research. It will connect the established CoEs for DSD and promote both diagnostic procedures as well as management. In the long run, an ERN for DSD will improve health outcomes of patients and their families considerably.

WG3-62 ESPE Obesity Working Group

Obesity, adipocyte inflammation and vitamin D

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The balance between energy intake and energy utilization plays a major role in the maintenance of a stable body weight. As is well known, obesity results when the energy consumed exceeds the energy utilized. The Vitamin D Receptor (VDR) is a member of the nuclear receptor superfamily whose ligand is 1,25-dihydroxyvitamin D (VitD). VitD has numerous activities which are not related to calcium metabolism, such as the regulation of adipocyte differentiation, in that it inhibits differentiation of the NIH3T3-L1 preadipocytes implicating a role for the VDR in the regulation of energy metabolism in vivo. VDR-null mutant mice are lean and resistant to high fat diet-induced obesity, in part due to the up-regulation of uncoupling proteins UCP-2 and UCP-3 in adipose tissue. Also a direct role of the VDR in the regulation of beta-oxidation and lipolysis in the adipose tissue has been implicated.
Childhood obesity is associated with increased oxidative stress and low-grade systemic inflammation. In aP2-agouti transgenic mice, a high-calcium diet was able to inhibit the expression of pro-inflammatory factors TNF-a and IL-6 in visceral fat and to stimulate the expression of the anti-inflammatory factor IL-15 and the adipokine, adiponectin. Also, clinical studies in obese adults have shown that a higher consumption of dairy calcium is associated with successful weight loss.
Growing evidence suggests that VitD has immunoregulatory effects and adipose tissue could be a target for its action. Preadipocytes, one of the major cell types in adipose tissue, are actively involved in inflammatory processes. Recent studies in human preadipocytes have shown that VitD decreases the production of monocyte chemoattractant proteint-1 (MCP-1) and other pro-inflammatory mediators by preadipocytes and reduces monocyte migration. Thus, VitD may protect against adipose tissue inflammation by disrupting the deleterious cycle of macrophage recruitment observed in obesity.

WG3-63 ESPE Obesity Working Group

Deletion of Fas in adipocytes as a potential therapeutic intervention for adipose tissue inflammation and hepatic manifestations of obesity

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A new link is proposed between the membrane receptor Fas (known for its mediation of apoptosis) and insulin sensitivity of fat tissue. Independently of apoptosis, adipocyte Fas is shown to be required for adipose tissue inflammation during high fat diet, and to contribute to hepatic steatosis and hepatic insulin resistance. Moreover, Fas expression and protein levels were increased in obese adults suffering from type 2 diabetes. Thus, Fas may constitute a potential new therapeutic target in the treatment of insulin resistance and type 2 diabetes.

WG3-64 ESPE Obesity Working Group

Gut-brain communication as a target for diabetes prevention and therapy

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Abstract text has not been submitted.

WG3-65 ESPE Obesity Working Group

Restoration of euglycemia in morbidly obese patients with NIDDM following bariatric surgery

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Bariatric procedures are divided into restrictive, malabsorptive and hybrid procedures, the latter combining gastric restriction and malabsorption. Restrictive procedures, such as gastric banding (GB) and sleeve gastrectomy (SG) reduce gastric volume. Malabsorptive procedures include the biliopancreatic diversion (BPD). Hybrid operations include Roux-en-Y gastric bypass (RYGB) and BPD with duodenal switch (BPD-DS). The long term diabetes remission rate following bariatric surgery is approximately 78% overall, 95% after BPD/DS, 80% after RYGB and SG and 57% after GB. Several mechanisms have been proposed as an explanation for diabetes remission. Bariatric operations result in attenuated appetite despite reduced calorie intake in people, and some procedures increase energy expenditure in animals after weight loss. Insulin sensitivity is greatly enhanced after the operation due to caloric restriction, negative energy balance and weight loss. Insulin sensitivity increases more than expected from weight loss. Reduction of lipotoxicity, a condition related to dysregulated fatty acid flux and the deposition of lipid metabolites in tissues and also changes in adipocytokine secretion enhance further insulin sensitivity. Bariatric surgery induces rapid improvement of hyperglycemia, reduction in hepatic insulin resistance, and improved insulin secretion, and changes in food preferences. Substantial reductions in lipotoxic and glucotoxic effects and decreased inflammation achieved quickly after bariatric surgery result in better â-cell function. Glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) show exaggerated responses after RYGB, BPD/DS and SG. GLP-1 has a strong incretin effect while both GLP-1 and PYY promote satiety and decrease food intake. Ghrelin levels decrease after SG and change slightly after RYGB or BPD, so that the levels are lower postop-

eratively compared to normal weight controls and this might also contribute to decreased appetite and improved glucose homeostasis since ghrelin exerts negative effects on insulin secretion and action.

WG4-66 ESPE Paediatric and Adolescent Gynaecology Working Group: Sexual Precocity in Girls: a Growing Problem

Pubertal development in girls: a worldwide changing trend

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Abstract has not been submitted.

WG4-67 ESPE Paediatric and Adolescent Gynaecology Working Group: Sexual Precocity in Girls: a Growing Problem

Precocious pubarche: significance for subsequent gonadal function

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Precocious pubarche (PP) in girls refers to the appearance of pubic hair before age 8 yr in the absence of signs of gonadal activity. It is most commonly caused by precocious adrenarche, i.e., the earlier rise in adrenal androgen production. Typically, girls with PP are taller than their peers and have moderately advanced bone age at diagnosis.

The reported prevalence of PP differs among populations and may be partly explained by genetic variation in androgen sensitivity. Increased body weight may also trigger the early onset of adrenal secretion and subsequent PP.

PP has been traditionally considered a benign entity. Long-term follow-up of PP girls has diclosed that this is indeed so in girls with a normal birth weight (BW) and a normal or high-normal body mass index at diagnosis. In those patients, bone age advancement is usually not associated with an early puberty or with a reduced adult height. In contrast, in non-obese PP girls with low BW followed by excessive postnatal catch-up in weight, puberty tends to start earlier and to have a faster course, so that final height may be below target. These girls present already in prepuberty markers of the metabolic syndrome, including increased visceral fat, serum triglycerides, insulin and leptin and lower levels of adiponectin and SHBG, and are at higher risk of developing PCOS in adolescence. The same sequence may occur in obese girls, regardless of BW.

In non-obese, low-BW PP girls (who are thus at high risk for PCOS), treatment with metformin across late prepuberty and puberty is associated with a delay of menarche (by ~ 1 yr), with an increment of adult stature (by ~4 cm), with postpubertal reductions in visceral, hepatic and total-body adiposity and also with a reduction in the prevalence of PCOS (5% vs 47% by NIH or AES criteria).

In conclusion, the pubertal course of many girls with PP will be essentially normal. Metformin therapy can be considered in PP girls at relatively high risk for developing PCOS, for example, in girls with central adiposity and low SHBG after a low BW.

WG4-68 ESPE Paediatric and Adolescent Gynaecology Working Group: Sexual Precocity in Girls: a Growing Problem

Precocious pubertal development: early-normal variants vs progressive variants

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Precocious pubertal development is generally defined as the appearance of secondary sex characteristics before the age of 8 years in girls and before the age of 9 years in boys. In girls, a spectrum of presentations has been found among girls with premature sexual development. These presentations range from rapidly progressive central precocious puberty, in which pubertal development is highly accelerated, to the non or slowly progressive or transient forms of precocious puberty, characterized by stabilization or slow progression, or even regression of pubertal signs. The non or slowly progressive or transient forms are usually benign and require no treatment, while rapidly progressive central precocious puberty may require further evaluation and gonadotropin-releasing hormone analog (GnRH-a) suppressive therapy. Early recognition of the rapidly progressive form is important, but in many cases, it is difficult to diagnose. The distinction is usually based on clinical, biochemical and imaging parameters. The advantages and disadvantages of these tools will be discussed.

WG4-69 ESPE Paediatric and Adolescent Gynaecology Working Group: Sexual Precocity in Girls: a Growing Problem

Prevalence of hyperandrogenism in adolescent girls previously treated for central precocious puberty and followed for at least two years beyond menarche

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Adolescent hyperandrogenism should be considered in the presence of clinical and/or biochemical signs of hyperandrogenism, irregular menses or oligoamenorrhea, and/or polycystic ovaries two years after menarche. A high risk of developing hyperandrogenism and/or polycystic ovary syndrome (PCOS) has been hypothesized in girls with previous idiopathic central precocious puberty (ICCP). An analysis of the literature reveals that the prevalence of reproductive dysfunction after discontinuation of gonadotropin-releasing hormone analog (GnRHa) treatment ranges between 1 and 50% in girls with ICPP. The key issue is to determine whether an underlying neuroendocrine dysfunction, such as abnormal LH pulse frequency, can explain the association between ICPP and hyperandrogenism/PCOS. This raises several questions: 1. Are some cases of ICPP the consequence of a primary increase in GnRH pulsatility? 2. Is the development of PCOS in ICPP more than a coincidence? 3. Is there a PCOS subtype arising from primary neuroendocrine hyperactivation in early childhood? In this ESPE – PAG – Working Group-Collaborative Project, we plan to: 1. Identify cases of ICPP with exaggerated adrenarche for follow-up. 2. Perform a longitudinal study of the diurnal LH rhythm in ICPP before and after discontinuation of GnRHa treatment. 3. Analyze the long-term reproductive outcome of adolescent girls with ICPP, such as menstrual disorders, clinical and biological hyperandrogenism, and ovarian morphology.

WG4-70 ESPE Paediatric and Adolescent Gynaecology Working Group: Sexual Precocity in Girls: a Growing Problem

Perinatal endocrine disruption of female pubertal timing and early causal interaction with nutrition

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Endocrine disrupting chemicals (EDCs) could affect pubertal timing through both short term and delayed effects resulting from exposure in perinatal life. This latter condition is consistent with the concept of fetal origin of health and disease that accounts for several implications: 1) Along that concept, early events disturb homeostasis as a whole process and could account for associated disorders of the control of energy balance and reproduction; 2) IUGR that is featured as a central component in that concept could result from different primary causes including altered nutrition and exposure to EDCs; 3) Linking perinatal exposure to EDCs and disorders of human puberty is challenging due to diversity of EDCs acting as mixtures and due to time lag between evidence of exposure and occurrence of the resulting disorders. Therefore, animal models exposed to a single EDC are required. We studied the effects of neonatal 5-day exposure to diethylstilbestrol (DES), a banned highly potent synthetic estrogen used as a reference EDC and bisphenol A (BPA), an estrogenic EDC currently widespread in human environment. These two EDCs are demonstrated or suspected to be involved in both reproductive and metabolic disorders. Preliminary data indicate that the dose of EDC is critical for the effects on timing of pubertal development that could be advanced or delayed. Evidence of neuroendocrine mechanisms comes from prematurely

accelerated pulsatile GnRH secretion, reduction in kisspeptin transcripts and reduction in sensitivity of GnRH secretion to stimulatory leptin effects possibly involving reduced expression of leptin receptors. The latter finding is similarly caused by moderate prenatal food restriction. It is concluded that early temporary exposure to DES or BPA can account for long term effects including alteration of pubertal timing with involvement of neuroendocrine mechanisms. These effects however are not consistent with unequivocally precocious maturation, the level of exposure being critical for the changes in pubertal timing.

WG4-71 ESPE Paediatric and Adolescent Gynaecology Working Group: Sexual Precocity in Girls: a Growing Problem

Precocious puberty: endocrine-metabolic and gynecological outcomes

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Abstract text has not been submitted.

WG4-72 ESPE Paediatric and Adolescent Gynaecology Working Group: Sexual Precocity in Girls: a Growing Problem

Peripheral precocious puberty: a difficult diagnosis and treatment

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Peripheral precocious puberty is much less common than central precocious puberty. In girls, peripheral precocious puberty may be associated with exposure to external sources of estrogen, environmental induced disorders as well as ovarian cysts and tumors.
In this presentation we will focus on our practical experience as a medical and surgical team in the diagnosis and treatment of girls with peripheral puberty related to Mc Cune Albright syndrome and granulosa cell tumors. We will discuss signs and circumstances of diagnosis in 11 cases of precocious puberty due to Mc Cune Albright syndrome, managed by our team from 1988 to 2006. Some of those girls were treated with aromatase inhibitors and/or with cyproterone acetate. Two children were treated with kystectomy without ovariectomy, with success. We will also analyze the data of 10 cases of granulosa cell tumors diagnosed and treated by our team between 1995 and 2006. Peripheral precocious puberty in girls remains a challenge for its diagnosis and treatment strategy.

WG5-73 ESPE Turner Syndrome Working Group: Talking about Turner Syndrome

Talking about Turner syndrome

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Having a daughter or be carriers of Turner syndrome is a condition that causes many troubles during life. How you communicate the diagnosis is very important for what will be thought later, how the family will live, how can accept and overcome this grief. We believe that as we speak in a clinic and a family of a condition is very important, the freedom of speech also means freedom of thinking, and this is the way you will accept a diagnosis of rare disease. Overcome the difficulties associated with this diagnosis means having looked at the problem in its different facets. For this reason the title 'Talking about Turner syndrome' was chosen for the ESPE Turner Syndrome Working Group Meeting of Leipzig 2012. Opening the meeting the geneticist will discuss the communication of the diagnosis of ST during pregnancy, when a child can't be seen, but only imagined. This will be followed by a talk about the difficulty of communicating the presence of a Y-chromosome mosaicism. A psychologist will present the painful wound of infertility with its potential harmful relationship with femininity. The results of a questionnaire sent to all members ESPE about the communication of the diagnosis of TS will be reported. A space will be reserved to TS support groups. We will hear the voice and point of view of support groups, valuable opportunity to understand the perspective of the subjects which we seek to care and to reflect on how best to talk about the pain of life that even in many people not detract from the ability to give full meaning to their history and enjoy life.

WG5-74 ESPE Turner Syndrome Working Group: Talking about Turner Syndrome

Explaining the Turner syndrome karyotype to parents during pregnancy

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Background: Genetic counseling aiming at communicating to parents a prenatal test result is a complex issue, due to the disbelief of an unexpected result, the difficulty to understand a rare disease and the clinical variability associated with a specific test result.
Objective and hypotheses: These points must be considered when explaining to parents the results of a prenatal investigation pointing to the possibility that the fetus is affected by Turner syndrome (TS).
Methods: Increased nuchal translucency on ultrasound (US) indicates an enhanced likelihood of TS, although it can be associated with other aneuploidies. This diagnosis is more likely in the presence of cystic hygroma, with poly- or oligo-hydramnios, growth retardation, cardiac and renal defects, and brachycephaly.
Results: Abnormal triple/quadruple maternal serum screening can suggest TS and prompts karyotype confirmation. A notable exception is the prenatal detection of 45,X/46,XY mosaic, which in the 95% of cases results in a normal 46,XY male newborn. However, US confirmation of male external genitalia in the fetus is mandatory. Non-mosaic 45,X fetuses with cystic hygroma/lymphedema are very often spontaneously discharged. The TS phenotype in the 45,X mosaics is broader and less severe than reported in the textbooks.
Conclusions: Prenatal information should consider these facets and highlight that only a minority of these mosaics will develop TS. Accordingly, the word "syndrome" should not be emphasized; other definitions, as ovarian dysgenesis or amenorrhea or premature ovarian failure with short stature should be privileged. Subsequent information should be communicated lining up the statements in order of importance, emphasizing that intelligence scores are in the normal range in most of these individuals. The potentially associated cardiovascular defects, short stature, ovarian failure and their management should be fully discussed. The final part of communication should include the assessment of the parents' reproductive risks in future pregnancies.

WG5-75 ESPE Turner Syndrome Working Group: Talking about Turner Syndrome

Gonadectomy in Turner syndrome with Y-chromosome mosaicism: Who, why and when?

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The increased risk for the development of Type II germ cell tumors (GCT) is well established in a subset of patients with Disorders of Sex Development, including 45,X/46,XY mosaicism. This knowledge has led to the common practice of prophylactic gonadectomy in Turner syndrome (TS) girls in whom Y chromosomal material is detected.
Older series report incidence rates for tumor development as high as 30%. However, these data suffer from methodological limitations and have been questioned recently. In recent years, major progress has been made in our understanding of the pathophysiology of these tumors, their incidence and related risk factors. Not the Y chromosome itself, but the Gonadoblastoma Region on Y (GBY) predicts if someone is at increased risk for GCT develop-

ment. GCT typically develop in poorly differentiated gonadal tissue, containing germ cells that are blocked in their normal maturational program. The clinical phenotype of 45,X/46,XY individuals is highly variable, including phenotypical males, phenotypical females, and children born with ambiguous genitalia. The clinical phenotype mirrors to a certain degree the gonadal phenotype, and therefore it has been postulated that a thorough clinical description can be helpful in estimating tumor risk.
Additional research in larger patient series is mandatory to confirm these data. Insight in the different aspects related to GCT development, in combination with future perspectives of gonadal function (e.g. hormone production) determine the rationale for gonadectomy on an individualized basis.

WG5-76 ESPE Turner Syndrome Working Group: Talking about Turner Syndrome

Communicating a diagnosis of rare disease involving possible infertility: femininity and TS (German TS support group psychologist)

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A diagnosis like TS can potentially undermine the self-esteem and feeling of femininity in the patients and as well be disturbing and unsettling for parents. This lecture will be focused on the factors which psychologically strengthen a feeling of self-esteem and femininity in females with TS and reassure parents. It will discuss how those can be made use of and communicated by doctors and family.
Even though there is no one "recipe" on how to communicate a diagnosis or aspects of it, there is much doctors and family can do to help the girls or woman with TS cope. Apart from general communication psychology, two dissertations from Germany (D. Dörrholt) and Australia (K. Mills) have been focused on such factors and will be shortly presented. One of the major factors appears to be a feeling of being accepted and supported by the family and treated according to age, not height.

WG5-77 ESPE Turner Syndrome Working Group: Talking about Turner Syndrome

Results of an ESPE questionnaire about communicating the diagnosis of Turner syndrome

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Background: To inform a patient and her family about the diagnosis of Turner syndrome (TS) is a delicate matter, because of the psychological impact, even in later life. Little is known about the practical approach the pediatric endocrinologists mostly confronted with this task have in communicating this difficult message.
Objective and hypotheses: The aim of this study was to find out more about how and when pediatric endocrinologists communicate the diagnosis of TS to the patient and her family.
Methods: A questionnaire with 15 questions about the communication of TS was developed and sent to all ESPE members. We asked questions about referral to other health workers, collaboration with the local TS support group, additional material use (e.g. drawings, booklets), and the time dedicated for such consultation. Questions about the setting (parents alone or whole family, extra – female-colleague or other health professional) at different ages of the patient (school age/adolescence) were asked in order to get insight in different practices.
Regarding early diagnosis, we asked whether the pediatric endocrinologist had been asked to help inform future parents in case of prenatal diagnosis. In addition, we asked when and how to discuss the TS diagnosis in patients diagnosed at birth. Questions about handling parents who refuse their daughter to be informed and parents (and patients) not accepting the diagnosis were asked as well. The topic of informing patients who need to undergo a gonadectomy in case of 45X/46XY mosaicism was also investigated.
Conclusions: By collecting the different experiences of the pediatric endocrinologists regarding the communication of TS diagnosis, the conditions to communicate this message can be optimised and the psychological acceptance of this condition can be improved from the very beginning. The reflection on the collaboration with other health care workers and the TS support group is important to improve this goal.

WG5-78 ESPE Turner Syndrome Working Group: Talking about Turner Syndrome

Experience of TS support group about communication of diagnosis

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Although a lot of change has happened in how parents and girls/women with TS are informed over the last decades, some problems and questions still remain for all families and females with TS. And they are still answered very differently in each unique case – in each family and in each doctor's office:
1. When do we tell our daughter/the patient what?
2. How much information must kindergarten / school have?
3. In what way and how much do I as a girl/women with TS tell other about it?
From my experience and frequent exchange with group leaders, younger women with TS on the average are more self-assured and more independent. They feel more comfortable asking about all different aspects of TS. But there are exceptions and great differences in how girls and women are being informed and how families communicate about TS.