PO1-224 Bone

Osteoporosis-pseudoglioma syndrome - a rare cause of primary osteoporosis in children

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We report a Pakistani boy with osteoporosis pseudoglioma syndrome (OPPG), not diagnosed until age 14 years. Although congenitally blind with developmental delay, the only early diagnostic suggestion was Norrie disease, an X-linked recessive condition consistent with the consultand having a similarly affected older brother. From 12 years of age he sustained 7 fragility fractures, including neck of femur, ankles and wrists. DEXA scanning (Lunar Prodigy) identified severe osteoporosis with Bone Mineral Density (BMD) 0.610 g/cm2, z score — 5.6. Multiple fractures, low BMD and ocular abnormalities suggested OPPG. Genetic studies showed the patient was homozygous for a putative novel homozygous missense mutation in exon 10 of the Low Density Lipoprotein Receptor 5 (LRP5) gene. Bisphosphonate treatment was recommended and pamidronate infusions commenced. No further fractures have occurred. Repeat DEXA scan shows BMD 0.778 g/cm2, 27.5% increase from baseline, z score -3.2. The parents are consanguineous and the consultand's 23 year-old brother suffered blindness, glaucoma in infancy, severe developmental delay, and has had several fractures. He was homozygous for the same LRP5 mutation, and both parents heterozygous.
Bone density scans show the brother has severe osteoporosis (z score -5.0) and the parents have low BMD (z scores: father -2.5, mother -2.0). OPPG is an autosomal recessive condition due to mutations inactivating the LRP5 gene. LRP5 is expressed in a variety of tissues including osteoblasts and alters bone formation via the Wnt signalling pathway. Haploinsufficiency also interferes with normal bone formation, as illustrated in this family where carrier parents have low BMD. OPPG was diagnosed in this family following multiple fractures in late adolescence in the two brothers. Early diagnosis facilitates enhanced bone health and minimisation of additional morbidity through appropriate investigation and management of osteoporosis. OPPG should be considered in patients with congenital blindness, particularly in the context of any fractures.

PO1-225 Bone

Novel mutations in cathepsin K gene in Turkish patients with pycnodysostosis

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Pycnodysostosis is a rare, autosomal recessive disease characterized by osteosclerosis, short stature, acro-osteolysis of the distal phalanges, bone fragility, clavicular dysplasia, skull deformities and delayed closure of sutures.
The disease is caused by a deficiency of the cysteine protease cathepsin K located at 1q21 (CTSK), which is responsible for degradation of collagen type I and other bone proteins. More than 10 mutations described in CTSK as a cause of pycnodysostosis. Here we describe 3 different novel mutations in 4 cases from 3 families.
A 6.5-yr-old girl and her 11 mo-old sister and two unrelated females (5 and 3 yrs old) were presented with short stature. All patients were product of consanguineous marriages. The diagnosis of pycnodysostosis in all patients was made on the basis of dysmorphic features and, osteosclerosis and osteolysis of distal phalanges on X-rays. Three of the patients also had large fontanels at the time of diagnosis.
Primers for amplification of CTSK by PCR were designed as exons 2-4 and 6-7 together and exons 5 and 8 alone and their flanking splice sites. PCR products were visualized on 2% agarose gels to rule out large deletion and insertions. The amplified PCR products for CTSK were purified and sequenced with direct sequencing of the DNA Cycle sequencing System (ABI Prism kit). We defined two different missense mutations (M1I and I249T) and one large insertion mutation (repeating sequences) in the CTSK. M1I mutation was detected in translational initiation codon at exon 2 caused by changing of G residue of ATG to A (ATA). I249T mutation was located at exon 6 and this mutation was created by changing of the first U residue of AUU to C to make ACU encoding threonine amino acid. Insertion mutation was located at exon 8 and part of intron region of CTSK and this mutation may be caused by recombination. All mutations described are novel mutations.

PO1-226 Bone

Oncogenic osteomalacia associated with a giant cell tumor and detected by F-18 fluorodeoxyglucose PET/CT SCAN

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Oncogenic osteomalacia tumor is a rare disorder characterized by severe hypophosphoremia, hyperphosphaturia, and osteomalacia, mimicking X-linked or autosomal-dominant hereditary hypophosphatemic rickets and mostly related to tumors of benign mesenchymal origin. To date, there is no standard method for detecting oncogenic osteomalacia tumors. The whole body bone scintigraphy and magnetic resonance imaging (MRI) are often non-contributory. Recently, some oncogenic osteomalacia tumors have been successfully detected by 111 IN-pentetreotide or octreotide scintigraphy, however, the true-positive rate of octreotide in the detection of these tumors is not known. Here we report a case of oncogenic osteomalacia. Either a whole body bone scintigraphy or 111 IN-pentetreotide scintigraphy did not reveal any underlying disease. However F-18 FDG PET showed accumulation in the region of left humeral head, and a small tumor (1.5X1.6 cm2) was detected by MRI examination. The tumor was surgically removed, and turned out to be a giant cell tumor. By removal of the tumor, either the symptoms or the laboratory data were improved significantly.

PO1-227 Bone

Bisphosphonate in the treatment of a child with McCune-Albright syndrome

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McCune-Albright Syndrome comprises of precocious puberty, multiple endocrinopathies and polyostotic fibrous dysplasia. Later is characterizes with recurrent bone fractures, poor healing. The use of bisphosphonates has been reported to decrease the incidence of bone fractures in the adult patients with fibrous dysplasias. We report our experience of the bisphosphonate use in a 12-year-old boy who was diagnosed with McCune-Albright syndrome. Initially this boy presented with a short stature, recurrent bone fractures, multiple cafe-au-lait spots and macroorchidism. The laboratory findings revealed normal calcium and vitamin D levels, with elevated alkaline phosphatase, N-Telopeptide, Urine Cross-linked Collagen and PTH and low phosphorus levels. Peripheral blood leukocyte DNA analysis was non-confirmatory for an activating Gs alpha subunit mutation. However PCR-based DNA analysis of a bone tissue specimen was positive for an activating mutation of arginine 201 in the Gs alpha protein, a substitution for cysteine. Radiographic findings of both hands were consistent with polyostotic fibrous dysplasia. To alleviate pain level and bone fracture rate Palmidronate therapy at 0.5 mg/kg/dose once a month has been initiated. Within first 3 month of the therapy with palmidronate Urine Cross-linked Collagen level decreased from 7011 to 5264 (nM BCE/mM Cr). An assessment of the pain revealed significant decrease of the pain score. The boy also reported a significant improvement in ambulation and less pain associated with walking. Pt denies any side effects associated with his monthly Plamidronate infusions. Thus, Palmidronate use in children with McCune Albright Syndrome can improve their quality of life by attenuation of pain and reducing the incidence of bone fracture.

PO1-228 Bone

Calcitonin therapy in cherubism

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Cherubism is a rare fibro-osseous disease of the jaw with an autosomal dominant inheritance. The mutation for Cherubism is identified in the SH3BP2 gene. Bilateral multilocular cystic expansion of the maxilla and mandibula are observed. Three patients with Cherubism were treated with calcitonin during one year. Calcitonin inhibits bone resorption.
A male and a female patient, both 15 years, old and a girl of 7 years old, were treated with daily subcutaneous injections of 100 IU calcitonin. The first weeks orally clemastine was added to reduce the side effect of nausea. Before start of treatment and after 1 year a 3-dimensional CT scan of the skull was performed and bone mineral density of the lumbar spine and total body were assessed with dual energy X-ray absorptiometry. Biochemical bone parameters were evaluated every 6 months.
After 1 year of treatment the cystic lesions of the mandibula had considerably decreased in size in both patients of 15 yrs. The young girl improved clinically but has yet not been treated for one year. The treatment was tolerated well and clemastine was stopped after a few weeks. Bone mineral density did not change significantly. Serum amino-terminal propeptide of type I collagen decreased in both adolescent patients, the other biochemical bone parameters, calcium and phosphate remained stable.
Calcitonin treatment seems to be effective in reducing the cystic lesions in the jaw in patients with Cherubism.

PO2-229 Calcium, PTH and Vitamin D

CYP27B1 gene mutations in two rickets patients with 1α-hydoxylase deficiency

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1α-hydroxylase deficiency, also known as vitamin D dependant rickets type I (VDDRI - MIM 609506), is an autosomal recessive disorder due to deficiency of the enzyme 25-hydroxyvitamin D_3-1α-hydroxylase (*CYP27B1*), which is involved in the synthesis of the active vitamin D ($1,25[OH]_2D_3$). The enzyme catalyzes the second hydroxylation step of vitamin D, which converts 25-$(OH)D_3$ to $1,25\text{-}(OH)_2D_3$. The absence of such conversion leads to the failure of vitamin-D utilization and this causes the development of rickets in the affected patients. We report the mutation screening of 1α-hydroxylase gene (*CYP27B1*) in two patients, aged 9 and 12 months with clinical signs of rickets at presentation. They were from two different families.
Their biochemical and hormonal profiles are shown in the table below. We used published primers to amplify all *CYP27B1* nine exons and used a combination of SSCP and heteroduplex analysis for the mutation screening of all exons. We discovered that both patients were compound heterozygotes for mutations in *CYP27B1* gene. Patient 1 had c.281_283delTCG (exon 2) and c.1319_1325dupCCCACCC (exon 8 - MIM 609506.0008) mutations, while patient 2 had c.281_283delTCG (exon 2) and p.[R389H + 397V] (exon 7) mutations. Of the four sequence alterations, two are novel mutations – p.397V (c.1191G>A) and c.281_283delTCG (exon 2). Using splicing analysis software, we noted that the silent mutation c.1191G>A (p.397V) would create a novel splice donor site, which could potentially affect *CYP27B1* mRNA transcript maturation.
The published p.R389H (MIM 609506.0012) mutation had already been reported to be pathogenic by other group. The c.281_283delTCG mutation would result to the loss of amino acid residue-94 (Valine).

Parameter	Serum Ca	Serum Phosphorus	Alkaline Phosphatase	PTH	25 $(OH)D_3$	1,25-OH_2D_3
Normal values	2.2 - 2.6 mmol/L	0.8-1.5 mmol/L	50-450 IU/L	0.7-5.6 pmol/L	60-160 nmol/L	50-150 pmol/L
Patient 1	1.94	0.9	2245	34.9	24.5	40
Patient 2	1.7	1.1	2200	88.9	48.1	15

PO2-230 Calcium, PTH and Vitamin D

Mutational analysis in 59 patients with X-linked hypophosphatemic rickets

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X-linked hypophosphatemic rickets (XLH) is characterized by hypophosphatemia, rickets, and impaired growth. Despite oral phosphate and 1,25-dihydroxyvitamin D3 treatment, many patients have suboptimal growth.
The aim of this study was to perform mutational analysis in patients with XLH and compare the available clinical data according to the type of mutation.
We analysed DNA of 59 patients from 45 families with XLH with a SSCP-gel screening and a subsequent sequencing of the suspicious regions of the Phex gene.
We also collected comprehensive clinical and laboratory data of 29 of these patients and compared the different types of mutations according to their clinical outcome using the Mann-Whitney-U-test (SSPS13.0).
We found 33 different Phex gene mutations in 45 families. Only 17 of these are known mutations and have been described earlier and only 57% were hereditary cases. We found 67% replacements, 20% deletions and 13% insertions. 45% were stop mutations, 22% missense, 24% frameshift and 9% splice site mutations. Comparing the last available height SDS data, showing a H-SDS in patients with stop mutations of -2,72 and missense mutations of -1,89 (p 0,19), frameshift mutations of -2,24 and splice site mutations of -1,17.
In the 29 patients with comprehensive clinical data there seems to be a tendency towards poorer growth in patients with stop mutations than with missense mutations of the PHEX-gene. However, growth and outcome of these patients may depend on further factors that need to be elucidated in the future.

PO2-231 Calcium, PTH and Vitamin D

Radiological score in malnourished and well-nourished children with active rickets

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Nutritional rickets and malnutrition are common problems in Turkey and many other developing countries. We planned to evaluate radiological parameters in malnourished and well-nourished children with active rickets and to investigate the responce to vitamin D treatment.
The study population consisted of 99 children with rickets (73 molnourished and 26 well-nourished) aged 3-30 months. The patients were treated with single dose of 300 000 IU of vitamin D intramuscularly and oral calcium, in addition to nutritional rehabilitation in malnourished children. Radiographic evaluation was performed by using x-ray of wrist and knee. Radiographic scoring method defined by Thacher et al. was used for the assessment of the severity of the nutritional rickets.
The mean radiological scores of both groups were similar ($p>0.05$). The mean radiological score at the beginning of the treatment improved from 5.3 to 2.6 after four weeks of treatment and to 1.0 after 12 weeks. The initial radiographic scores of rickets correlated with serum ALP concentrations. We observed that radiological healing delayed in rachitic children with severe radiological finding of rickets. We found that 300 000 IU vitamin D of therapy was effective for all patients with rickets also in malnourished children.

PO2-232 Calcium, PTH and Vitamin D

High prevalence of vitamin D deficiency in newborns of high-risk mothers

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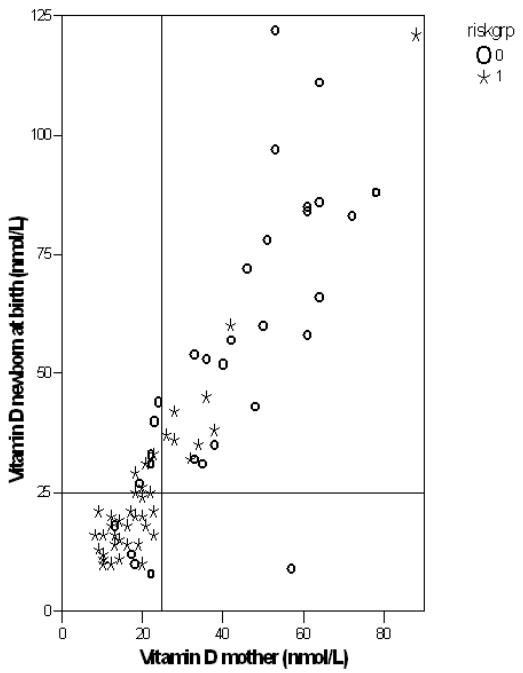
Background: Women with dark pigmentation or concealing clothing are at increased risk of vitamin D deficiency due to limited sun exposure.
Objective: We conducted a study primarily aimed at determining the prevalence of vitamin D deficiency of newborn infants of mothers at risk of vitamin D deficiency because of dark skin or the wearing of concealing clothes (such as a veil), compared to a group supposed not to be at risk. A second aim was to correlate vitamin D concentration of these newborns to biochemical parameters of bone turnover at birth.
Patients and Methods: A prospective was audit conducted on the obstetric and pediatric departments, between April 2004 and February 2006. Eighty-seven healthy pregnant mothers, with either with dark skin and/or concealing clothing (risk group) or with light skin (control group), and their newborns were included. Third trimester and cord blood vitamin D levels and biochemical parameters of bone metabolism were measured.
Results: A significant difference in the prevalence of vitamin D deficiency (25-hydroxyvitamin D3 <25 nmol/L) between newborns born to mothers at risk and newborns born to mothers in the control group (63% vs 16%; p<0.0001) was found. Cord blood 25-hydroxyvitamin D3 was not significantly correlated with ionized calcium, phoshorus, alkaline fosfatase or parathyroid hormone. Mean alkaline phosphatase concentrations were higher in the risk group compared with controls(p-value 0.05), which can be a sign of increased bone turnover.
Conclusions: Newborn infants of mothers with dark skin or of mothers wearing concealing clothes are at great risk of vitamin D deficiency at birth. Clinical implications are unknown. Further research is necessary to determine the long-term consequences of maternal and neonatal vitamin D deficiency in order to issue guidelines on vitamin D supplementation during pregnancy.



PO2-233 Calcium, PTH and Vitamin D

Oxidative stress in children with nutritional vitamin D deficiency

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Objective: To investigate in vivo the oxidative stress level in the children with nutritional vitamin D deficiency.
Methods: Twenty patients with nutritional rickets were occured study group and treated with 300.000 U D3 and calcium lactate. Before and after treatment serum concentration of calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), intact parathormone (PTH), 25-hydroxy vitamin D (25 (OH) D), and oxidative stress markers such as nitric oxide (NO), malondialdehyde (MDA), and glutathione (GSH) were measured. Concentrations of pre and post treatment oxidative stress markers of the study group were compared with that of control group.
Results: After treatment serum Ca, P, and 25 (OH) D levels significantly increased, while the mean serum ALP and PTH levels significantly decreased.

Characteristic	Pre-treatment	Post-treatment	p
Ca (mg/dl)	6.2±1.7	9.7±0.4	0.001
P (mg/dl)	3.8±1.4	5.6±0.7	0.01
ALP (IU/L)	1099±449	810±320	0.05
PTH (pg/ml)	386±213	51±24	0.001
25 (OH) D (ng/ml)	6±3.6	70±33.8	0.001

The mean pre-treatment NO level of the study group was significantly lower than that of both post-treatment study group and the control group (p<0.01), while the mean pre-treatment MDA and GSH levels were not significantly different than those of both post-treatment study group and the control group (p>0.05).

	Study group		Control group	
Parameters	Pre-treatment	Post-treatment		p
NO (μmol/L)	1.5±1.8	5.21±3.47	5.92±3.4	0.01
MDA (μmol/L)	6.6±2.2	7.0±2.4	7.3±2.8	0.89
GHS (μmol/L)	7.7±2.6	7.5±2.4	7.3±3.9	0.96

The 25 (OH) D concentration of the study group positively correlated with Ca and P concentrations (r=0.697; p<0.001 and r=0.584; p<0.001, respectively), while it negatively correlated with ALP and PTH concentrations (r= -0.342; p<0.05 and r= -0.62; p<0.001, respectively). The NO concentration of the study group positively correlated with Ca, P, and 25 (OH) D concentrations (r=0.458; p<0.01, r=0.34; p<0.05 and r=0.429; p<0.01, respectively), whereas it negatively correlated with PTH concentration (r= -0.46; p<0.01).
Conclusions: Nutritional vitamin D deficiency does not cause oxidative stress in the organism and decreases the serum NO level, probably as a consequence of hypocalcaemia.

PO2-234 Calcium, PTH and Vitamin D

Subcutaneous calcifications in 37 patients with Albright hereditary osteodystrophy

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Subcutaneous calcifications, together with small stature, obesity, mental retardation and brachydactyly, are one of the defining signs of the heterogeneous Albright Hereditary Osteodystrophy (AHO) phenotype described in Pseudohypoparathiroism (PHP). However, the prevalence, timing in appearance, correlation with Ca/P/PTH metabolism and evolution of this sign has not been so far established.

These issues were investigated in a subset of 37 AHO patients, genetically characterized for the presence of a causal mutation in the GNAS gene.
Subcutaneous calcifications were present in 16/37 (43%) of the considered AHO patients. They involved mainly the trunk and the lower limbs, but also the upper limbs, without any face involvement. They are often represented by 2-3 elements spread in a single body region, ranging from 3 mm to 5 cm. The mean age of onset was 4.5 years (ranging from 2 months-12 years). In 12/16 (75%) the Ca/P metabolism was normal at the time of calcification appearence, in 3/16 (18%) hypoCa/hperP was present, in 1/16 (6%) hyperP only. In 13/16 (81.2%) they do not progress, were present with other AHO signs, as well as hormonal derangement (PTH/TSH resistances), thus represented one of the sign supporting the PHP diagnosis. In 3/37 subjects they were the single sign present at the onset, suggesting a condition of Progressive osseous heteroplasia (POH). The follow-up of 6-10 years allowed to disclose the other signs of AHO/PHP, thus defining the 3 conditions as allelic variants.
In conclusion, subcutaneous calcifications in AHO patients represent a precocious sign, not always concomitant to plasma Ca/P/ PTH impairment; they usually do not show a progression. In few patients they can be a single sign that has to be carefully monitored, as it can be the first sign of the AHO/ PHP condition.

PO2-235 Calcium, PTH and Vitamin D

Selective deficiency of Gs-alpha and the possible role of alternative gene products of the GNAS locus in Albright hereditary osteodystrophy and pseudohypoparathyroidism type Ia

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Objective: Albright hereditary osteodystrophy (AHO) and Pseudohypoparathyroidism type Ia (PHPIa) are caused by inherited deficiency of the alpha-subunit of stimulatory G proteins. Gs-alpha is encoded by the GNAS gene. While exon 1 of GNAS is exclusively involved in expression of Gsalpha, further gene products such as NESP55, Exon 1a and XLalpha-s are transcribed from alternative promoter regions of this highly complex gene locus, using in part the same coding region as Gs-alpha. Thus, mutations in exon 1 are predicted to concern selectively Gs-alpha, whereas mutations in exon 2-13 could alter several gene products. However, it is not known, whether the deficiency of alternative gene products contributes to the AHO and PHPIa phenotype or if it is even alone causative for some specific AHO symptoms. In the latter case, mutations affecting exon 1 concerning selectively Gs-alpha would lead to a different phenotype than mutations in exon 2-13.
Patient and methods: We investigated the GNAS gene and the Gs-alpha protein activity of a girl representing with short stature, subcutaneous calcifications, brachymetacarpia, mental retardation and biochemical evidence for peptide hormone resistance. Moreover, we reviewed mutations of exon 1 that have been described previously.
Results: We detected a novel heterozygous 1bp insertion in exon 1 and a diminished protein activity to 62% (reference range 85-115%). Furthermore, we found that almost all mutations described in exon 1 lead to an AHO phenotype that does not show obvious differences from those provoked by mutations in exon 2-13.
Conclusion: Our results and the analysis of all described mutations in exon 1 indicates that deficiency of Gs-alpha is sufficient for the expression of an AHO phenotype. However, a modifying influence of alternative gene products of GNAS on the AHO phenotype needs to be further investigated.

PO2-236 Calcium, PTH and Vitamin D

Acrodysostosis - a clinical sign of pseudohypoparathyroidism type II?

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Pseudohypoparathyroidism (PHP) describes several disease entities with diminished or absent sensitivity to parathormone. We distinguish PHP IA, associated with clinical signs of Albright hereditary osteodystrophy (AHO) and due to diminished activity of Gsalpha protein, from PHP IC where patients also have signs of AHO, but Gsalpha protein activity is normal. In PHP IB, patients have a normal phenotype and normal Gsalpha protein activity, as PTH-resistance is localized to the kidney because of an imprinting defect. PHP IA to C are due to mutations in the GNAS locus. In contrast, PHP II is most likely due to a defect in cyclic AMP metabolism in the kidney in response to PTH. This disorder is less known and a clinical phenotype not well described.
We present two patients with short stature, developmental delay, and short, stubby fingers with laboratory values suggestive of PHP II. Patient 1 (P1) was 4;5 years old at presentation with a length of 96.7 cm (0.6 centile), weight 12.8 kg (3 centile). PTH 110 pg/ml (15-55), Ca 2.2 mmol/L, Gsalpha activity normal in erythrocyte membranes, urinary cAMP/creatinine 3900 nmol/mmol (180-555). Patient 2 (P2) was 5 years old and had a height of 99 cm (-3,48 SDS) and a weight of 16 kg (3 centile). His PTH was elevated to 144 pg/ml, Gsalpha activity normal, urinary cAMP/creatinine 3900 nmol/mmol. Other endocrine abnormalities were not found and vitamin D deficiency excluded.
In both children, the GNAS gene was investigated and only the wild-type sequence was detected. On X-ray of the left hand, severe shortening of the digits was noted, leading to a diagnosis of acrodysostosis.
We conclude that presentation of PHP II may mimic some clinical features of AHO with bone involvement and short stature, however, bone symptoms are more severe and the disorder can be distinguished by highly elevated urinary cAMP and normal Gsalpha activity from PHP IA. The underlying defect needs to be elucidated.

PO2-237 Calcium, PTH and Vitamin D

Hypoparathyroidism-deafness-renal dysplasia (HDR) syndrome: an underdiagnosed cause of hypoparathyroidism

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Background: The combination of hypoparathyroidism, deafness, and renal dysplasia was first recognized as a syndrome (HDR syndrome) in 1992. It is an autosomal dominant disorder caused by loss of function mutations in the dual zinc finger transcription factor GATA3. However the clinical spectrum of the disease may be variable as shown by our report of 3 affected subjects from one family.
Population: The boy was admitted to our clinic at the age of 6.7 years because of hypocalcemic tonico-clonic seizure due to hypoparathyroidism (PTH 8 pg/ml; normal range 10-55). His personal history showed neonatal seizure with transient hypocalcemia (1.49 mmol/L) and normal PTH level (PTH 45 pg/mL), moderate hearing loss diagnosed at 4.2 years, and urinary tract infection at 6.7 years due to vesicoureteral reflux (VUR). His 14-months sister also had transient neonatal hypocalcemia, VUR diagnosed at 8 months, and a systematic screening for hypoparathyroidism showed that Ca was 1,50 mmol/L and PTH 2 pg/mL. She had no hearing loss. The mother had congenital deafness and a history of repeated pyelonephritis. Systematic blood test at the age of 39 years also found hypoparathyroidism.
Results: Molecular study in the 3 subjects showed a deletion of 4 bases in the fourth exon of the GATA3 gene, resulting in the premature termination of translation at codon 355 with loss of the second zinc finger domain.
Conclusion: This observation underlined the clinical variability of the HDR

syndrome due to a GATA3 loss-of-function mutation in 3 subjects from one family. Whether isolated hypoparathyroidism may be due to GATA3 mutations remains to be studied.

PO2-238 Calcium, PTH and Vitamin D

Neonatal severe hyperparathyroidism (NSHPT) — report of a new point mutation of CASR gene

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Neonatal severe hyperparathyroidism (NSHPT) is a rare disease, resulting from the homozygotic mutation in the calcium-sensing receptor (CASR) gene.

We present a case where a de novo mutation was identified. On the 16th day of life, a female newborn presenting with progressive hypotonia, feeding refusal, dehydration, hypercalcemia was transferred to us. She was the first daughter of an unrelated couple. On admission she was lethargic and she developed respiratory acidosis; total calcium, ionized calcium, and urinary calcium/creatinine relation were 26.9 mg/dL, 3.1 mmol/L, 3.5 respectively; PTH levels were markedly increased [PTH: 1254 pg/mL (RV: 12-65)]; radiological evaluation revealed marked osteopenia and long bones "greenstick fractures".

Both cervical ultrasonography and MRI showed increased parathyroid glands but 99mTc-Sestamibi scintigraphy showed normal parathyroid glands. Subtotal parathyroidectomy (3 out of 4 parathyroid glands) was performed. Histopathologic examination revealed hyperplasia/adenoma of clear cells.

As PTH levels and calcemia remained high, total parathyroidectomy with implantation of ¼ of one gland was performed. Calcemia and PTH returned to normal levels. She is now 12 months old, clinically well, with normal PTH and calcium levels, without any medication. DNA sequencing and restriction enzyme analysis of CASR gene (exons 2-4, 7) revealed a new homozygous point mutation at nucleotide 679, resulting in the replacement of CGA (arginine residue) for a TGA (Stop) at codon 227 (R227X); this may predict the premature termination of translation in exon 4, which encodes part of the extracellular domain of the CASR. Both parents have high normal calcium levels and increased urinary calcium/creatinine relation; they also have the same mutation in heterozygoty. NSHPT complexity requires a multidisciplinary approach to minimize morbidity. Total parathyroidectomy is usually needed to control hypercalcaemia. The identification of the mutation allows for genetic counselling purposes.

PO2-239 Calcium, PTH and Vitamin D

The investigation of hypercalcaemia in childhood

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Background: Hypercalcaemia occurs in up to 0.5% of children and establishing an underlying diagnosis is important. Anecdotally, we found that some hypercalcaemic patients had not been investigated to acceptable standards.

Aim: To determine whether hypercalcaemia during childhood was investigated appropriately at a tertiary referral centre.

Method: Over a 12 month time period using a results database, children <16 yrs with a serum calcium (Ca) level > 2.85 mmol/l were identified. A retrospective case-note analysis was undertaken in those individuals with a serum Ca > 3 mmol/l.

Results: 213 children had Ca > 2.85 mmol/l, the majority were < 12 months old. Only 10% had been fully investigated. Of those not fully investigated, the calcium normalised in 45%, remained abnormal in 27% and was not repeated in 28%. 23 cases had Ca >3.00mmol/l; of these 7 did not have a repeat Ca measurement, in 9 a diagnosis was achieved and in 8 the initial result was spurious. Only 4 individuals were symptomatic (n=3 constipation; n=1 lethargy). 5/23 had a renal USS (n=1 abnormal).

Conclusions: Our results demonstrate considerable numbers of children had hypercalcaemia but in many cases the investigation was incomplete, thus the underlying diagnosis may have been missed. A serum Ca > 3.0 mmol/l was associated with significant pathology. However, the majority of individuals were asymptomatic despite elevated serum Ca, which may have led clinicians to be falsely reassured in not proceeding with further investigations. We therefore recommend formal reminders on result slips to repeat Ca levels and suggestions for further investigations, to improve this outcome.

PO2-240 Calcium, PTH and Vitamin D

Phosphate binder and calcitonin as adjuvant therapy in treating hyperphosphatemic tumoral calcinosis

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Hyperphosphatemic familial tumoral calcinosis is a rare autosomal recessive metabolic disorder characterized by the progressive deposition of basic calcium phosphate crystals in periarticular spaces and soft tissues. This 10-year old girl presented with swelling and pain in the right hip region. Two years prior to presentation she was fell on stairs at school and injured her hip. She has been otherwise healthy. On examination a 10x10cm hard, non-tender swelling with well-defined margin was felt in upper lateral part of her left thigh. She walked with a mild limp but has a full range of movement in her hips. Another small painless mobile hard mass about 2 cm was felt around the left elbow joint without any effect on movement. No other masses could be felt. Systemic examination of her nervous, skeletal and cardiovascular system was normal. Radiograph of the right hip revealed irregular calcified mass around the right hip mainly along the lateral aspect extending up to the upper part of the metaphysic..MRI study revealed ill-defined space-occupying lesion arising mainly from the gluteus maximus with heterogeneous signal intensity, extending laterally to the subcutaneous fat. Tc-99 MDP bone scintigraphy demonstrated abnormal uptake in the right gluteal soft tissue region . Investigations showed high phosphorus 2.7mmol/l (1.45-1.78), normal calcium, Alkaline phosphatase (ALP), and PTH , Low 25(OH) cholecalciferol. Renal function was normal. ESR = 47mm/1h.

Incisional biopsy was consistent with the diagnosis of tumoral calcinosis. The calcified mass was excised. Because of elevated serum phosphate she was started on phosphate binder (sevalamer 800mg 5 times daily) in addition to dietary phosphate restriction . She was started on Calcitonin nasal spray.

Her serum phosphate stabilized between. 1.78 and 2.1mmol/L with normal serum calcium and ALP concentrations. One year after excision the patient had no evidence of recurrence. Unexpectedly, her 25OH-vit D was low but we were cautious to treat her with vitamin D to avoid increased intestinal calcium absorption &, hence increase any deposition of calcium. The present case had hyperphosphatemia, normocalcemia and normal renal function with solitary calcification with no history of previous soft tissue calcification (primary hyperphosphatemic tumoral calcinosis). However she had low vitamin D concentration. Treatment for this rare condition is obviously surgical, and phosphate decreases after incision. She responded well to treatment with a phosphorus binder (sevalamer) and calcitonin as adjuvant therapy to surgical removal.

PO2-241 Calcium, PTH and Vitamin D

Recombinant parathormone (Forsteo) replacement therapy in a girl with permanent resistant hypoparathyroidism secondary to total thyroidectomy

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The use of human recombinant parathyroid hormone in children with hypoparathyroidism is limited. Here, we report the use of human recombinant parathyroid hormone (Forsteo) replacement therapy in a girl with permanent hypoparathyroidism secondary to total thyroidectomy. A-14-year old girl was hospitalized because of hyperthyroidism. The diagnosis was Grave's disease. PTU (15 mg/kg/day) and methimazole (1.5 mg/kg/day) treatments at maximum doses were not able to control hyperthyroidism; instead they resulted in side effects. There was no chance of radioactive iodine treatment because of the huge size of the thyroid gland. It was considered contraindicated because of too much radioactive iodine required. Therefore, total thyroidectomy was performed. She was placed on L-thyroxine replacement therapy with a dose of 100 µg/m2/day after surgery. Unfortunately, permanent hypoparathyroidism developed after surgery and serum PTH levels were undetectable. Although high doses of oral calcium, calcitriol and a diet with reduced phosphate intake were started, she was hospitalized several times with severe symptoms of hypocalcaemia and hyperphosphatemia and given intravenous calcium injections for several times. Her normal calcium metabolism was not maintained by oral calcium lactate with a dose of up to 4x 60g/day and calcitriol 2x3 µg/day. Therefore, at the age of 17, subcutaneous recombinant parathyroid hormone was started at a dose of 20 µg twice daily (40 µg/day). In about 15 days, calcium and phosphate returned to normal ranges and there was no requirement for calcitirol and oral calcium replacement. Treatment with twice daily sc PTH (Forteo) was found to be able to maintain normal serum calcium levels and to be effective in treating hypoparathyroidism. It seems that absolute lack of parathyroid hormone leads to vitamin D resistance. Further research is needed to elucidate the role of PTH for vitamin D action.

PO3-242 Cancer and Hormones

Evaluation of puberty and gonadal function in pediatric patient survivors of cancer

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The highest survival in the childhood cancer worries about the late effects of the cancer and its treatment. The main goal of this work is to extend the knowledge of the sequels around puberty and gonadic function in the survivors of childhood cancer.
The study group included patients with background of childhood cancer, in remission, with ages 7 to 18 years: 126 patients, 72 boys and 54 girls. The control group have the same range of ages: 58 boys and 56 girls. A complete clinical evaluation was carried out in all cases. A determination of the basal serum concentration of FSH, LH, testosterone, estradiol and inhibin B were carried out. Group of study: With regard to the puberal development, 6% of males presented puberal delay and 15% of girls advanced puberty (13%) or precocious (2%). Comparing the group of the study versus the control group, the males in pubertal stage II, FSH, LH and testosterone were significantly higher (2,71 UI/L vs 1,55 UI/L, 2,00 UI/L vs 0,90 UI/L and 6,2 nmol/L vs 1,6 nmol/L), and in the stage III the significant differences were maintained for LH (3,20 UI/L vs 1,68 UI/L) and testosterone (12,9 nmol/L vs 4,7 nmol/L).
In girls at stage I, the inhibin B was significantly lower in the group of the study (<10 pg/ml vs 21 pg/ml). Among males, 19 (26,4%) presented tubular insufficiency, whereas in girls, 11 (20,4%) had partial ovarian insufficiency.
The prepubertal age at the start of the treatment does not prevent the ulterior gonadic damage. All the children treated of a cancer must be supervised carefully during their puberty, by both clinical and analytical procedures.

PO3-243 Cancer and Hormones

Body Mass Index (BMI) evaluation in survivors from childhood cancer

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In the last 20 yrs the prevalence of overweight and obesity in children and adolescents has increased in developed countries. These data are of particular concern in survivors from childhood malignancies considering the exacerbating effects of dyslipidemia, hypertension, hyperinsulinism on their long term sequelae.
The aim of the study was to evaluate the BMI distribution in a broad series of paediatric cancer survivors followed up in a single centre and to show a possible correlation between type of disease, sex, age and follow up.
We reviewed the clinical charts of 358 pts (210 M) and calculated the latest BMI SD according to the Italian population cross sectional data, at a mean age 15.9±5.2 yrs (range 4.9-32.6 yrs) after a mean follow up of 8.4±4 yrs (range 3-24.5 yrs). Patients are subdivided for type of malignancy and in 6 groups according to age of BMI assessment. They are considered underweight for BMI SD <-1, normal weight for BMI SD between -1 and 1, overweight for BMI >1 and ≤ 2, obese for values >2. Data are shown in the table. Overweight and obese pts are about 20%, while cerebral tumors in both sexes and Hodgkin's disease, only in males, have the highest % of BMI>1SD. Age at BMI assessment and duration of follow up do not show any correleation with BMI;we find the highest prevalence of BMI >1SD in males >17≤24 yrs (38.5 %) and females >6≤12 (30%). Our study shows underweight pts in 16% of cases both in males and females with highest prevalence in pts >14≤17 yrs.
Long term survivors of paediatric cancer are at risk of overweight and obesity and our study seems to confirm the same prevalence as in the general population. Pts treated for Hodgkin's disease and cerebral tumors are more likely to become overweight. Underweight prevalence seems higher in adolescents. Careful assessment of caloric intake and metabolic parameters is necessary during the follow-up of childhood malignacies to prevent obesity related sequelae or nutritional deficiencies.

	Males					Females				
	N	underweight %	normal %	overweight %	obese %	N	underweight %	normal %	overweight %	obese %
Patients	210	16	60	20.5	3.5	148	16	694	16	4
Acute lymphoblastic leukemia	54	18.6	61	18.5	2.0	50	18	64	12	6
Hodgkin's disease	30	17	47	33	3.0	13	8.0	69	15	8.0
Non Hodgkin's lymphoma	41	19.5	58.5	15	7.0	10	0	100	0	0
Bone malignancy	7.0	29	43	28	0	5	0	80	20	0
Other leukemia	9.0	22	56	22	0	2	0	0	100	0
Renal tumor	14	14	86	0	0	24	21	62	17	0
Neuroblastoma	15	0	67	26	7	11	18	64	18	0
Cerebral tumor	11	9.0	54.5	36	0	10	10	50	40	0
Soft tissue sarcoma	11	27	55	18	0	7	29	57	14	0
Others	18	5.5	72	17	5.5	16	25	56	6	13
Age (yrs)										
≤6	6	17	83	0	0	2	0	100	0	0
>6≤12	38	13	60.5	24	2.5	40	12.5	80	22.5	7.5
>12≤14	31	13	64	23	0	14	14	72	7	7
>14≤17	44	27	52.5	18	2.5	33	21	61	15	3
>17≤24	78	23	38.5	31	7.5	52	17.5	65.5	15	2
>24	13	16	60	20.5	3.5	7	16.5	64	15.5	4
mean±SD follow-up (yrs)	8.4 ±4	9 ±4	8.5 ±4	8 ±4	9 ±6		9 ±4	8 ±4	8 ±4	7 ±4

PO3-244 Cancer and Hormones

Growth hormone, IGF-I, IGFBP-3 and growth after stem cell transplantation in children and adolescents

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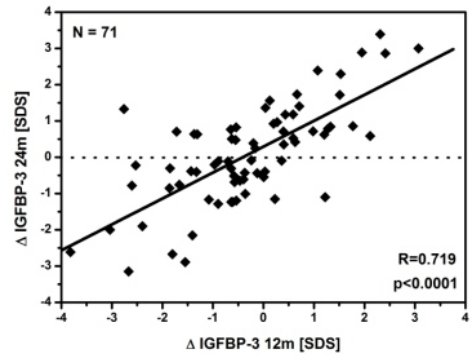
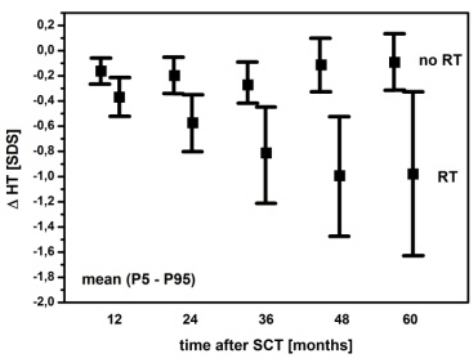
To study growth hormone (GH) status, IGF-I and IGFBP-3 levels and growth before and after stem cell transplantation (SCT). 416 patients (40% female) aged 8.4 years (median, range 0.1 - 22.6) were followed-up according to a standardised late-effects protocol for 5 years. Height (HT), weight (WT), pubertal status and IGF-I and IGFBP-3 levels were assessed. A growth hormone stimulation test was performed before SCT. The median maximum GH peak (maxGH) in the arginine test before SCT was 8.8 ng/ml (0.4 - 44.7), N = 172, with 19 % ≤ 4 ng/ml, 27% > 4 and < 8 ng/ml and 54% ≥ 8 ng/ml. maxGH was not correlated to IGF-I (SDS) and IGFBP-3 (SDS), HT-SDS, difference between HT-SDS and target HT-SDS (ΔTHT), changes in HT-SDS (ΔHT-SDS) during follow-up and prior radiotherapy treatment. The 3 groups did not differ. maxGH was negatively correlated to BMI (SDS). IGF-I (SDS) and IGFBP-3 (SDS) were pos. correlated over the entire follow-up period.
Increases in IGF-I (ΔIGF-I) within the first year pos. correlated with ΔIGF-I during further follow-up. ΔIGF-I and ΔIGFBP-3 were pos. correlated during 3 years after SCT. IGF-I and IGFBP-3 were pos. correlated with HT-SDS over the entire follow-up. Prior radiotherapy was not correlated to HT-SDS, ΔTHT and IGF-I and IGFBP-3 levels. ΔHTSDS after 2, 3, 4 and 5 years was correlated with radiotherapy given as part of the SCT regimen. Taking HT-SDS before SCT into account, HT-SDS after 1 to 5 years was correlated to the presence or absence of radiotherapy for SCT. ΔHT-SDS was pos. correlated to ΔWT-SDS over the entire follow-up. ΔHT-SDS after ½ and 1 year were pos. correlated with ΔHT-SDS during further follow-up. Early increases after SCT in HT-SDS, IGF-I and IGFBP-3 may enable us to predict changes during follow-up.
After SCT, IGF-I and IGFBP-3 seem to be in part differentially regulated. The growth inhibiting effect of SCT related radiotherapy may be detected from 2 years after SCT. Results from GH stimulation tests must be carefully interpreted.





PO3-245 Cancer and Hormones

Endocrine, cognitive and functional outcomes in survivors of childhood posterior fossa brain tumours

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Purpose: To evaluate endocrine, cognitive and functional outcomes in long-term cranially irradiated, survivors of childhood posterior fossa tumours (PFTs).
Methods: 16 survivors of childhood PFT of mean age (SD) 22.3 (4.1) years, diagnosed at 6.0 (2.8) years, and attending an endocrine late effects follow-up clinic were studied. All had received surgery, 30-35Gy neuraxial irradiation and 20Gy tumour boost as part of initial treatment. The Wechsler Intelligence Scale-Revised (WAIS-R) was administered. Education years, occupational status, endocrine and health status were recorded.
Results: GH deficiency was isolated in all but one patient (who also had TSH and GnRH deficiency). 2 females with primary hypothyroidism, (one with gonadal failure) and one female with gonadal failure alone, had all received adjuvant chemotherapy with spinal irradiation. Two patients had motor deficits and 3 required anticonvulsants. None had visual impairment, and just one had mild auditory impairment.
Patients had a mean (SD) WAIS-R FIQ of 80.1 (10.9),suggesting mild intellectual impairment which did not correlate with age at diagnosis. They had 14.4 (2.1) education years, all but two in mainstream schools. 5 had education statements and a further 6 received some concessions or support. 7 were in paid employment and only 1 was unemployed; 7 were academic students and 1 required support in the community.
Summary: Radiation-based therapeutic strategies for PFTs cause GH deficiency, with other primary glandular deficits, sensory and motor late effects increasing with the addition of chemotherapy. PFTs at any childhood age hamper performance on general intelligence tests such as WAIS-R, in adulthood. Despite reduced intellectual skills, patients can achieve a reasonable education level and gainful paid employment in adulthood.
Conclusion: Since the intellectual and functional outlook for PFT survivors is positive and therapeutic strategies are now increasing in intensity, they should routinely have access to neuro-endocrine surveillance and rehabilitation in the long term.

PO3-246 Cancer and Hormones

Hypothalamic-pituitary function in 22 subjects with pediatric-onset Langerhans cell histiocytosis

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Langerhans cell histiocytosis (LCH) is a rare disorder in which granulomatous deposits occur at multiple sites within the body, but which often involves the hypothalamic-pituitary axis. Although diabetes insipidus (DI) is a well recognized complication, the frequency of anterior pituitary involvement has not been well defined. The frequency and progression of LCH-related anterior pituitary dysfunction and the response to treatment were evaluated in 22 subjects (14 M – 8F) with histologically proven LCH. Mean age at diagnosis was 5.6±4.4yrs, mean follow-up 6.9±2.7yrs. Five subjects (4M -1F) with DI (Group A), were compared to 17 subjects (10M – 7F) without DI (Group B). Height and BMI (expressed as SD scores), and basal or dynamic pituitary function assessment were yearly performed. All the patients underwent hypothalamic-pituitary magnetic resonance imaging (MRI) scanning. Group A: 4/5 subjects showed during the follow-up growth hormone deficiency (GHD); one also hypothyroidism and precocious puberty.
MRI was pathologic only in 2pts (1 pituitary stalk thickening, 1 small pituitary gland). Height decreased from -0.1±1.2 SDS at diagnosis (T0) to –1.4±1.0

SDS at the last examination (T1). BMI-SDS did not change at T0 (1.3±0.7) and T1 (0.9±0.8). Group B: none of the 17 subjects showed signs of pituitary dysfunction or pituitary abnormalities at MRI scanning. Mean height did not change at T0 (0.2±0.9 SDS) and T1 (0.4±1.0 SDS). BMI-SDS did not change during the follow-up. Height did not differ between Groups A and B at T0, but was lower ($p<0.05$) in Group A at T1. BMI did not differ between the two groups. In LCH subjects, DI may be associated with anterior pituitary dysfunction (GHD, hypothyroidism, or precocious puberty), also without pituitary abnormalities at MRI scanning. Therefore, these patients should undergo prolonged clinical and endocrine assessment, to establish anteriory pituitary deficiency and provide appropriate hormonal replacement.

PO3-247 Cancer and Hormones

Diabetes insipidus and a runny ear: a short-cut to diagnosing Langerhans cell histiocytosis

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Langerhans cell histiocytosis (LCH) of the pituitary hypothalamic region can be difficult to diagnose without a potentially harmful biopsy, yet accurate diagnosis is vitally important to guide further therapy. We present a patient with diabetes insipidus where the diagnosed by biopsy from the external ear canal.
Our patient presented at the age of 3 9/12 years with polyuria and polydipsia. Diabetes insipidus was diagnosed without evidence of other pituitary hormones being affected. An MRI scan showed a thickened pituitary stalk and lack of the hyperintense signal of the posterior pituitary.
Since our patient had had some refractory episodes of otorrhea in the past we proceeded with an otolanryngologic examination. Biopsy of granulating tissue from the external ear canal revealed infiltrates of CD1A-positive Langerhans cells.
It is not infrequent that LCH affects the ear and the pituitary hypothalamic region simultaneously. Since the external ear is much more readily accessible for biopsy than the pituitary hypothalamic region any patient with diabetes insipidus should be carefully asked for a history of "ear infections".

PO3-248 Cancer and Hormones

Development of poorly differentiated metastatic neuroendocrine tumour in immunodeficient state

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Hyper IgM (HIGM) syndrome is characterized by recurrent bacterial and opportunistic infections. There are a few case reports of HIGM syndrome associated with gastrointestinal tumours, but not of pancreatic origin.
We report a case of a boy, who presented with severe neutropenia at age of 1 year. Diagnosis of HIGM type1 was established at age of 4 years. Severe watery diarrhoea and hypokalemia developed at age of 5 years, supposed to be the manifestations of the immunodeficient state. Mild hepatomegaly was detected at age of 7 years. Abdominal ultrasonography demonstrated multiple solid hepatic masses. Histopathologic evaluation of the liver biopsy resulted in the diagnosis of metastatis of a neuroendocrine tumour. Child was referred to our oncological department. Metastatic vasoactive intestinal peptide (VIP)-producing tumour was supposed. Abdominal ultrasonography, computed tomography and Iodine-131-metaiodobenzylguanidine (I-131-MIBG) scintigraphy failed to localize the primary tumour. Laboratory measurement of VIP concentration was not available. Plasma chromogranin
A concentration was 662.9 ng/ml (reference range, 10-98 ng/ml). Octreotide therapy was introduced (75 µg/dose, three times daily). Significant symptomatic improvement was observed short after the start of octreotide therapy, consistent with the diagnosis of VIPoma. Systemic chemotherapy was also administered (etoposide, cisplatin). Three weeks after the start of octreotide therapy, the patient died of sudden cardiovascular collapse.
At autopsy the primary tumour (8 mm in diameter) was localized in the pancreatic body with multiple hepatic and intestinal metastases. Pathogenetic factors leading to tumourigenesis in immunodeficient state are not known. Presented case gives an unique association of HIGM syndrome and pancreatic neuroendocrine tumour.

PO3-249 Cancer and Hormones

Pseudopseudohypoparathyroidism (PPHP) and juvenile granulosa cell tumor (JGCT) of the ovary: association or coincidence?

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Pseudopseudohypoparathyroidism (PPHP) is a clinically and genetically heterogeneous disorder. Patients with PPHP present with Albright Hereditary Osteodystrophy and Gs deficiency without hormone resistance, as well as with multiple hormone resistance alone. A 12.5 yr old girl presented recurrent episodes of metrorrhagia and galactorrhea the last 4 months before admission.
Breast development had occurred only 6 months before her 1st period. Pubertal stage was Tanner B4, PH4, height -0.59 SD and weight +1.15 SD with a target height of +0.25 SD. Bone age was 12 yr. She had mild mental retardation on the basis of a recognized cognitive disorder and a history of absence seizures since early infancy. Physical examination revealed a lunar face, short 4th and 5th metacarpals and metatarsals, mild generalized hirsutism and acne, and an abdominal mass. Ultrasound showed an abdominal mass measuring 12x10x8 cm in the place of the right ovary. LH and FSH were undetectable with high estradiol 166 pg/ml and testosterone 3.55 ng/ml, relative hyperprolactinaemia 26.8 ng/ml, high fasting glucose 110 mg/dl, high normal TSH 3.08 mIU/ml with low normal FT4 0.94 ng/dl and negative thyroid autoantibodies. The right ovary, indistinguishable from the mass, was removed along with the right salpinx by laparoscopy. Juvenile Granulosa Cell tumor (FIGO stage 1A) was diagnosed. Metrorrhagia stopped and the patient lost rapidly weight whilst the hyperandrogenism receded. All laboratory tests normalized soon after surgery, apart from TSH, which led to L-thyroxine replacement.
Normal menarche occurred 9 months after tumor resection. Granulosa cell tumors are rare ovarian neoplasms accounting for about 3-5% of all ovarian malignancies. The juvenile type is considered more aggressive but prognosis is good when diagnosed early and the patient can be treated with surgery alone. It is unclear whether there is a relationship between the two disorders. Elucidation of the molecular defect may shed light on whether a common pathogenetic mechanism exists.

PO1-250 Diabetes and Insulin 1

New ABCC8 mutations in neonatal diabetes, clinical features and therapeutic consequences

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Activating mutations in the ABCC8 gene that encodes the SUR1 regulatory subunit of the pancreatic islet ATP-sensitive potassium (KATP) channel (sulfonylureas receptor) cause both permanent and transient neonatal diabetes mellitus (NDM). Recently, we have described the novel mechanism where

basal Mg-nucleotide-dependent stimulatory action of SUR1 on the KIR6.2 pore is increased leading to NDM.
We identified eight heterozygous missense ABCC8 mutations in eight of 16 patients with neonatal diabetes newly studied, six of which have not yet been reported: E208K, A269D, V324M, R825W, R1379H, V1523M. The two other mutations, L582V and R1182Q, had been previously described by our group in three independent families with transient NDM cases (TNDM). The six novel mutations were not found in 300 diabetic subjects or in 140 unrelated normoglycemic individuals of European white origin. The six new heterozygous ABCC8 mutations were found in four TNDM, with a median duration of initial insulin therapy of 17 months (range 0.5-38), one PNDM and one too young to be defined yet.
Most of these mutations map to key functional domains of SUR1. Altogether, in our cohort of NDM, 17 out of 50 patients so far screened for ABCC8 (all are negative for chromosome 6, Kir6.2 and glucokinase anomalies) are carriers of a SUR1 mutation: 3 of 22 (14%) in PNDM, 13 of 25 (52%) in TNDM and one of three patients not yet defined as permanent or transient.
Although ketoacidosis is frequent at presentation, SUR1 mutations associate mainly with transient hyperglycemia with possible recurrence later in life.
One SUR1-TNDM patient with diabetes recurrence later on, was successfully transferred from insulin injections to sulfonylureas. In some of the cases that are familial, diabetes is not always present in the adult carriers of SUR1 mutations supporting variability in their clinical expressivity that remains to be fully explained.

PO1-251 Diabetes and Insulin 1

Neonatal diabetes mellitus due to pancreatic agenesis: a new case report

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Neonatal diabetes mellitus (NDM) is a rare entity (1:500 000) defined as hyperglycemia occurring in the first month of life, lasting more than 2 weeks and requiring insulin for management. NDM is classified as transient (TNDM) or permanent (PNDM). We report a 10-months-old girl with PNDM due to pancreatic agenesis, born at 34 gestational weeks: weight 1568g (<-2.0 SDS), length 41cm (<-2.0 SDS). At the 5th day of life she presented hyperglycemia (712mg/dL) with polyuria, glycosuria and metabolic acidosis. Autoimmune antibodies [tyrosine phosphatase (IA2), glutamic acid decarboxilase (GAD) and insulin autoantibodies (IAA)] were negative, levels of circulating C-peptide and insulin were low [0.1 (1.1 — 4.4) ng/mL and <0.2 (2.6 — 24.9) µU/mL, respectively]. At the 23rd day of life diagnosis of a left sided diaphragmatic hernia with surgical repair without complications.
Despite tight glycemic control, the gain of weight was unsatisfactory, exocrine pancreas insufficiency was diagnosed and pancreatic enzymes were replaced. Magnetic resonance imaging showed absence of pancreas and disclosed any other congenital abnormalities. Three reported cases of pancreatic agenesis showed genetic mutations: two in the insulin promoter factor 1 (IPF-1) and one in the PTF1A gene, latter associated with cerebellar agenesis. In our patient no mutations in the IPF-1 gene were found and PTF1A gene was not analysed. At the current age of 10 months the infant presents a growth catch-up [7610g, 67cm (both >-2.0 SDS)] and a normal neurological development.
The glycemic control achieved by insulin (initially continuous low-dose intravenous infusion, later subcutaneous injections) is satisfactory. Actual HbA1c 7.4%, without episodes of severe hypoglycemia. We want to point out that pancreatic agenesis is a rare cause of NDM but an important differential diagnosis. Precocious diagnosis and adequate treatment of both endocrine and exocrine pancreatic insufficiency may permit survival and a normal development.

PO1-252 Diabetes and Insulin 1

Glibenclamide therapy in patients with insulin-treated neonatal diabetes due to a mutation of the KCNJ11 gene encoding Kir6.2

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Permanent neonatal diabetes (PND) is a rare form of diabetes characterized by insulin-requiring hyperglycemia diagnosed within the first three months of life. In most cases, the causes are not known. Recently, mutations in the KCNJ11 gene encoding the Kir6.2 subunit of the ATP-sensitive K+ channel have been described in patients with PND. KATP channels play a central role in glucose-stimulated insulin secretion from pancreatic beta cells. We report the first two Korean cases with PND due to a lysine-to-arginine substitution at position 170 (K179R) in case 1, and a valine-to-methionine substitution at position 59 (V59M) in mutations of KCNJ11 encoding Kir6.2 in case 2.
After several years of insulin therapy, these patients were switched to oral glibenclamide therapy at a daily dose of 0.8-0.9 mg/kg. Their basal c-peptide levels increased after one week of glibenclamide therapy, and one month later, the insulin and c-peptide levels were in the normal range without any episodes of hyperglycemia or hypoglycemia. These patients remain well and off insulin at 12 and 22 months follow-up. These cases demonstrated that oral sulfonylurea may be the treatment of choice in PND patients with KCNJ11 mutations even at a young age.

PO1-253 Diabetes and Insulin 1

Non-autoimmune neonatal diabetes mellitus with cataract, deafness, cerebellar atrophy, growth and developmental delay

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A 6 month-old girl was diagnosed with ketotic diabetes. She was a full-term born baby with IUGR and a transient hypoxia during delivery. The parents were healthy and non consanguineous. She experienced a normal development until this age. At the age of 11 months, she underwent surgery for bilateral cataract and was diagnosed with bilateral profound sensory deafness. No optic nerve atrophy was found at ophthalmologic control. During the following months, she presented a major developmental delay with poor tonus, motor delay, autistic behaviour and microcephaly. The cerebral MRI performed at the age of 19 months showed cerebellar and vermis atrophy. Since the age of 17 months, continuous enteral feeding was started because of major eating difficulties, inducing a severe growth delay, despite the correct tratment of diabetes by means of a subcutaneous insulin pump and the absence of malabsorption. The biological investigations found: negative anti-beta cell immunofluorescent and anti-soluble antigen antibodies; negative blood, urine and cerebrospinal fluid investigations for mitochondrial disorders. Genetical findings were: normal standard XX karyotype, normal Kir6 — 2 gene, no abnormal polymorphism of the length of mitochondrial DNA fragments, nor any mutation in the regions implicated in MELAS, NARP and MERRF mitochondrial syndromes. In contrast, genetic investigations for Wolfram syndrome showed a yet unknown heterozygous E 809 K non-sense mutation in the WFS1-gene.

PO1-254 Diabetes and Insulin 1

Four novel mutations, including the first gross deletion in TCF1, identified in HNF4 alpha, GCK and TCF1 in patients with MODY in Israel

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Maturity onset diabetes of the young (MODY) is characterized by a primary defect in insulin secretion with nonketotic hyperglycemia, monogenic autosomal dominant mode of inheritance, age at onset less than 25 years, and lack of autoantibodies. The aims of the study were to characterize the genetic basis of MODY in different ethnic groups in the Israeli population.
Fifty-nine unrelated Israeli subjects with MODY were assessed for mutations in the three common MODY genes: hepatocyte nuclear factor (HNF)-4 alpha, glucokinase (GCK), and transcription factor 1 (TCF1).
Overall, eleven mutations in twelve unrelated families were found (20.3% of cases), for a relative frequency of 1.7% for MODY1, 8.5% for MODY2, and 10.1% for MODY3. Four mutations were novel including the first gross deletion ever described in this gene.
The low overall mutation frequency found here may suggest the involvement of other, yet unidentified, genes in the etiology of MODY in Israel.

PO1-255 Diabetes and Insulin 1

Association of MODY8 with abnormalities in fatty acid metabolism

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We have recently characterized a novel syndrome of diabetes and pancreatic exocrine insufficiency (MODY8) due to carboxyl-esterase lipase (CEL) mutations. We have further characterized the lipomatosis of pancreas in these patients. Inflammation of the exocrine pancreas is a pathological process in cystic fibrosis, and recent findings suggest primary abnormalities in fatty acid metabolism in plasma and in tissues expressing cystic fibrosis conductance regulator (CFTR) in subjects with homozygous ΔF508 CFTR mutations. In this study we determined whether humans with mutations in the CEL gene have a similar fatty acid abnormality detected in erythrocyte membranes.
We analyzed fatty acids in erythrocyte membranes from 12 diabetic and 11 pre-diabetic subjects in a family with CEL mutations and compared the values to 12 healthy, unrelated individuals. We also evaluated five family members without CEL mutations from the family with CEL mutations.
The ratio of arachidonic to docosahexaenoic acid was reduced in the erythrocyte membranes of non-diabetic CEL mutation carriers ($P<0.001$) as compared with values in healthy control subjects, with values intermediate between these two groups in the diabetic CEL mutation carriers ($P=0.052$). This change was reflected in reduced levels of docosahexaenoic acid.
These data indicate abnormalities in fatty acid metabolism in erythrocyte membranes in non-diabetic CEL mutations carriers similar to those seen in the CFTR-expressing tissues of subjects with cystic fibrosis.

PO1-256 Diabetes and Insulin 1

Glucokinase mutant V455E causing MODY2

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Maturity-Onset Diabetes of the Young is caused by genetic alterations of the signaling pathway which regulates the secretion of insulin. This is caused by mutations of signaling elements like the glucokinase and several transcription factors. The onset is often before 30 years, the inheritance is predominantly autosomal dominant. As there is no strong genotype-phenotype correlation all family members of an affected patient should be investigated.
Our 15 years old index patient showed up with glucosuria and hyperglycemia while suffering from febrile infection.
Oral glucose tolerance testing showed initially in impaired glucose tolerance, after one month the testing was normal. No auto-antibodies typical for IDDM were found. The genetic investigation revealed a homozygous mutation of the glucokinase-gene: Homozygosity for 1364 T > A (Val 455 Glu). Both parents and several members of the family were identified as being heterozygous but showed normal glucose tolerance.
Published functional investigations of mutants of the glucokinase show a wide variety of their enzymatic activity and the clinical pictures of the affected patients were extremely heterogeneous. About 10% of the identified patients show in vitro nearly normal GCK-activity nevertheless leading to diabetes-manifestation. Our patient presents a mutation of the glucokinase leading to one-amino-acid-exchange Val 455 Glu, a putative loss-of-function mutation leading to the clinical picture of MODY2. In the same position of the kinase the mutation Val455Met was described by Glaser et al. 1998 in a patient with familial hyperglycemia due to a constitutively active kinase mutant.
Analyzing the position 455 in the protein model of the kinase by a dynamic interaction method showed a crucial localization of Val 455. This region represents the central point of a complex conformational change of the kinase protein during the switch between the different known states of activity.

PO1-257 Diabetes and Insulin 1

E23K Kir6.2 polymorphism in the Korean early-onset type 2 diabetes

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The G to A mutation in the Kir 6.2, the ATP-sensitive potassium channel subunit, results in the substitution of a highly conserved glutamate (E) residue with lysine (K) and a subsequent negative-to-positive shift in residue charge. In addition, the previous studies have shown to have a relationship with high risk to type 2 diabetes. Our aim was to investigate association of the E23K polymorphism in the KCNJ11 gene with Korean early-onset type 2 diabetes. We studied 33 patients. Among these, type 2 diabetes were 17 and the subjects with maturity-onset diabetes of the young (MODY) were 16. Their age at diagnosis was below 15 years of age. E23K polymorphism was analyzed by direct sequencing of exon1 in the KCNJ11 gene. The EE, EK, and KK genotype percentages of the KCNJ11 E23K polymorphism were 0.364 (12 patients), 0.576 (19 patients) and 0.06 (2 patients) respectively. There was 100% concordance rate between E23K and I337V polymorphisms. E23K polymorphism appears at higher frequency in the Korean children and adolescents with early-onset type 2 diabetes and MODY. But our study was small cohorts, so we need a large scale study in the Korean early-onset type 2 diabetes.

PO1-258 Diabetes and Insulin 1

Obese children and adolescents: prevalence of the metabolic syndrome and risk factors for the development of insulin-resistance and disorders of glucose metabolism

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Background: Obese children and adolescents are at risk for developing a Metabolic Syndrome (MS). Currently little is known about the long term outcome.
Objective and Methods: 126 obese children and adolescents (BMI≥ 97th P, 62 boys) at high risk for Diabetes. Mean age 12.96 ± 3.1, mean BMI-SDS 2.85 ± 0.05. 38% had a migration background. To assess glucose metabolism

an oGTT was performed twice. The mean follow-up period was 13.6 months. Therapeutic interventions offered (anti-diabetic drugs, dietician and/or psychologist consultation, exercise programs). Further metabolic parameters: lipid-profile, RR, liver enzymes. Possible impact-factors on insulin-resistance were tested with bivariable logistic analysis.

Results: In 61% a MS was diagnosed, 98% had at least 1 sign of it. Out of 90 patients with normal glucose regulation (NGR, WHO-criteria) at the first oGTT 23.3% developed an impaired glucose regulation (IGR), 4.4% a DM-type 2. Out of n=30 who initially showed IGR 33.3% did not change (41.7% of immigrants vs 27.8% of non-immigrants), 56.7% improved and 10% developed DM-type 2. 8.3% of the immigrants newly developed a DM-type 2 vs 11% of the non-immigrants. Of n=6 who already showed DM-type 2 50% returned to NGR (under treatment), 33.3% to IGR. The proportion of immigrants with DM-type 2 at first oGTT was 6.3% (vs 3.8% of non-immigrants). 77.8% had insulin-resistance at first cut-off. Hypertension (2nd Task Force) was present in 28.2 %, Hyperlipidemia (AHA) in 29.2 %. Onset of puberty is a risk factor for the deterioration of insulin-resistance (ΔR-HOMA $\geq$ 0.2): OR = 8.05, p-value = 0.012, compared postpubertal subjects, as well as weight-gain (ΔBMI-SDS): OR = 2.47, p=0.013.

Conclusions: Obese children and adolescents are at high risk for developing a full MS or signs of it. Insulin-resistance and disorders of glucose metabolism are common. Migrational background seems to increase the risk for diabetes. Onset of puberty remains a major risk for insulin-resistance. Further studies are needed to identify predictors of Insulin-resistance and the outcome of MS.

PO1-259 Diabetes and Insulin 1

Glucose regulation, blood pressure, and body composition in very low birth weight adults

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The association between small size at birth and markers of metabolic syndrome later in life is well established in subjects born at term. Also preterm birth with very low birth weight (less than 1500 g) is associated with higher blood pressure in young adulthood and higher markers of insulin resistance in childhood.

The aim was to assess plasma lipids, body composition, blood pressure, glucose tolerance, and insulin sensitivity in very-low-birth-weight infants in early adulthood. A standard 75-g oral glucose tolerance test with measurements of insulin and glucose at baseline and at 120 minutes was performed in 164 subjects (72 men) with very low birth weight, aged 18 to 27 years, and 168 term-borns (70 men) with similar age, sex, and birth hospital. Blood pressure and plasma lipids were measured. Body composition of 152 very-low-birth-weight subjects and 138 control subjects was measured by dual x-ray absorptiometry (Hologic Discovery A).

Compared with the term control group, very-low-birth-weight subjects had 4.5 mmHg (2.1 to 7.0) higher systolic blood pressure, 6.7 percent higher 2-hour glucose (95 percent confidence interval from 0.8 to 12.9), 16.7 percent higher fasting insulin (4.6 to 30.2), 40.0 percent higher 2 hour insulin (17.5 to 66.8), and 18.9 percent higher homeostasis-model-assessment derived insulin resistance index (5.7 to 33.7). Adjustment for very-low-birth-weight subjects' lower lean body mass did not attenuate these relationships. Trunc/legs fat percent ratio, waist circumference and plasma lipids were similar between the groups.

Young adults born with very low birth weight, in comparison to term-born controls, have higher indices of insulin resistance and glucose intolerance, lower lean body mass and higher blood pressure suggesting that in adult life they may be at higher risk for developing type 2 diabetes, hypertension, and cardiovascular disease.

PO1-260 Diabetes and Insulin 1

Validation of percentiles for insulin sensitivity indexes in healthy caucasian children: WBISI AND HOMA-IR

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Insulin Resistance (IR) is tightly linked to adiposity and is considered a strong predictor for type 2 diabetes mellitus and metabolic syndrome. The epidemic of childhood obesity claims for urgent need to target IR subjects from the very beginning in order to individualise therapeutic management. Although euglycemic clamp is the gold standard to determine IR, more practical methods have been validated. The most widely used are HOMA-IR which takes into account fasting glucose and insulin, while WBISI estimates glucose and insulin excursion after oral load. For both, HOMA-IR and WBISI, normal values have been elaborated for adults while no data exist for the paediatric population.

The purpose of this study was to determine percentile patterns for HOMA-IR and WBISI in prepubertal (Tanner stage 1) Caucasian children.

After physical examination including anthropometric measures and overnight fasting, a standard OGTT was performed on 118 prepubertal normoweight healthy children (62M/56F; age=8.20±2.44 yrs, BMI=15.93±1.14 kg/m2, SDS-BMI=-0.04±0.78). HOMA-IR [(FG•FI)/22.5] and WBISI [10000/$\sqrt{}$ (FI•FG)•(MPG•MSI)] were calculated. Before setting the percentiles, statistical analysis were performed. No differences for age (p=0.771), BMI (p=0.276), SDS-BMI (p=0.457), HOMA-IR (p=0.612), WBISI (p=0.698) and DHEAS (p=0.563) were found between males and females, thus all subjects were analyzed as a single group. Correlation analysis performed was not significant excluding confounding factors [age vs HOMA-IR (p=0.258) and WBISI p=0.321; BMI vs HOMA-IR (p=0.502) and WBISI (p=0.051); SDS-BMI vs HOMA-IR (p=0.810) and WBISI (p=0.162)].

ISI	Subjects n	Range	3rd	10th	25th	50th	75th	90th	97th
HOMA-IR	118	0.57-2.71	0.57	0.64	0.85	1.16	1.53	2.20	2.71
WBISI	118	4.34-16.41	4.34	5.73	6.86	8.97	12.90	15.09	16.41

These reference data are useful to easily detect IR subjects within the prepubertal Caucasian population helping to target those who need intensive therapeutic counselling.

PO1-261 Diabetes and Insulin 1

The features of impaired fasting glucose and associated factors in obese children and adolescents

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Background: The features of impaired fasting glucose hasn't been studied in obesity children and adolescents in China yet.

Objective: To analyze the features of impaired fasting glucose and associated factors in obesity children and adolescents.

Methods: 459 overweight and obesity children and adolescents were recruited. Height, weight, serum fasting blood glucose (FBG), fasting insulin (FINS), leptin and lipid profile were measured, body mass index (BMI), HOMA-IR, HOMA-b, QUICKI were calculated, and the IFG related factors were analyzed.

Results: (1) The FBG, FINS, triglyceride (TG), cholesterol (TC), letptin level and HOMA-IR, HOMA-b in overweight / obesity children were significantly higher than that of normal weight control ($P<0.05$). The insulin sensitivity QUICKI index were insignificantly low than control group ($P<0.05$)。(2) FINS level in normal control group (IFG group:7.66±3.87 μIU/ml, NFG: 7.97±4.02 μIU/ml) were significantly lower than that in obesity group both in NFG group (20.96 ± 14.94 μIU/ml) and IFG group (25.00 ± 21.26 μIU/ml) ($P <0.05$)。(4) The IFG prevalence were 17.21% in obesity and overweight group which

was significantly higher than that in normal control group (2.26%), the FBG levels of IFG children in normal cotnrol children were within 5.6-6.0 mmol/L. IFG were significantly correlated with age, sex, BMI, FINS, leptin, TG, TC and HOMA-IR index with the correlation correlation coefficient between 0.14-0.36.

Conclusion: The prevalence of IFG were significantly higher in overweight and obesity group than normal weight control group. FBG was significantly correlated with other metabolic components. Futher study of the longitudinal change of FBG and IFG may benefit the prevention of children type 2 diabetes and related metabolic syndrome.

PO1-262 Diabetes and Insulin 1

Coxsackie B Virus acts as a triggering environmental factor in the pathogenesis of type 1 diabetes mellitus

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Aetiopathogenesis of Type 1 diabetes mellitus (T1DM) includes genetic, immunologic and environmental factors. Among the latter, conflicting results on the role of Enteroviruses, like Coxsackie B4, have been reported. Our aim was to establish whether Coxsackie B4 is involved in T1DM pathogenesis.

We used pooled IgG immunoglobulins derived from 58 patients (35 M, 23 F) aged 0.8-18.7 years with newly-diagnosed T1DM to screen a random peptide library to identify autoantigen peptides involved in the development of the autoimmune process against β-cells. As controls 50 blood donors were enrolled. We identified an immunodominant peptide showing similarities with human autoantigens such as phogrin (ICAAR) and 6-phosphofructokinase (6PFK), expressed by β-cells; indeed such 12 aa peptide was recognised by 43/58(74%) of patients' sera but by none of the controls'sera. The peptide sequence shows similarity also with viral protein1-VP1, a protein expressed on Coxsackie virus capside. IgG antibodies against the peptide were affinity purified from patients' sera and recognised autoantigens and the viral protein VP1. We suggest that in genetically predisposed individuals, Coxsackie B virus infection may induce an antiviral response able to trigger destruction of β-cells through a molecular mimicry mechanism between VP1 and human autoantigens, leading to the onset of type 1 diabetes mellitus.

PO1-263 Diabetes and Insulin 1

Enterovirus genomes in the blood of children with T1DM at disease onset and one year later

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Background: Enteroviral (EV) infections have been proposed as one triggering environmental factor leading to T1DM. The mechanism(s) through which EV collaborate to beta cell destruction is still unclear. Human EV have long been known as agents of acute diseases, chronic infections being rarely documented.

Objectives and hypotheses: To assess whether T1DM were associated with chronic EV infection, we evaluated the presence of EV RNA genomes both at the time of clinical onset and one year later. Population and/or methods: blood samples of 68 T1D patients (38 boys; age 2-18 years) have been investigated. Detection of EV genomes was performed by RT-PCR using different primer pairs directed to conserved genomic regions. Sensitivity of the amplification methods in use was ?10 genome equivalents per reaction tube. Direct sequencing of purified amplicons allowed identifying EV at the species level.

Results: at onset, EV genomes were detected in 46/68 patients (67%). No viral genomes were detected in 18 healthy control children. Direct amplicon sequencing showed that viruses of the HEV-B and HEV-C species were particularly prevalent. Retesting positive patients one year after clinical onset showed that EV genomes were present in only 1/46 children. Precise conclusions: The results confirm the temporal association of EV infection with the onset of T1DM. We were unable to show persistent EV infection in the blood of most pediatric patients. This, however, does not exclude chronic infection of pancreatic islets.

PO1-264 Diabetes and Insulin 1

Hepatic glycogenosis: a rare cause of hepatomegaly in type 1 diabetes mellitus

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Hepatomegaly, with or without abnormal liver function tests, was a common feature of both pediatric and adult patients with diabetes mellitus.

We are reporting a case of a 16 years old diabetic boy in whom we found hepatomegaly, mildly elevated transaminases and elevated serum lipids never noticed before. Abdominal ultrasound confirmed hepatomegaly; liver biopsy pointed out a picture compatible with glycogenosis. The patient's abnormal liver function tests, elevated serum lipids and hepatomegaly decreased over a period of four weeks with tight metabolic control. This situation was due to overinsulinization because the patient assumed an excessive quantity of food and therefore took an excessive quantity of insulin.

In conclusion, hepatomegaly may be seen in diabetic patients due to hepatic glycogen accumulation as a result of excessive food and insulin consumption. In hepatic glycogenosis the pathological findings improve in four weeks when good metabolic control is provided. Therefore the other reasons must be investigated when hepatomegaly persists for a longer period.

PO1-265 Diabetes and Insulin 1

Evaluating diabetes frequency among relatives of patients with diabetes mellitus

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Background: Resent statistics shows that diabetes is growing in the world, especially in Asian countries. However, the question remains which of the relative groups is more at risk? What type of diabetes is more likely to transmit? The present study was conducted in a large population of diabetic patients in Iran for evaluating Diabetes frequency among relatives of patients with diabetes mellitus.

Material and Methods: The present descriptive – analytic study was conducted on 432 patients randomly selected from among diabetic patients hospitalized in Namazi hospital (Shiraz – Iran) from March 2003 to July 2004. Relatives of diabetic patients divided into three categories. The data were analyzed by "chi square" test (X2-test). P value less than 5% was determined as significant.

Results: The mean age of patients was 48.63 ±14.56 for patients with diabetes type I and 54.96±9.04 for patients with diabetes type II. Diabetes frequency among all three groups of relatives is higher for patients with diabetes type I than those with diabetes type II There was no significant different in diabetes distribution between 1st, 2nd, and 3rd relatives of diabetic patients of both sexes.

Conclusion: Role of mothers in transmitting diabetes is more than that of fathers. Diabetes is more frequent among the 1st relatives of diabetic patients. Diabetic mothers transmit the disease more to their daughters than their sons. In order to improve the society health, we suggest that vast studies without the before mentioned limitations be carried out with regard to differences in race and climate.

PO1-266 Diabetes and Insulin 1

Epidemiological data of type I diabetes mellitus in Turkish children at two different time periods: 1969-1991 and 1991-2006

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Objective: To analyze the epidemiological changes in type I diabetes mellitus in Turkish children in the last four decades.
Methods: We retrospectively analyzed medical records of the patients with Type I Diabetes who admitted to our clinic at two different time periods: 1969-1991 and 1991-2006. We examined the basic epidemiological features of the disease, including gender, age at onset, duration of symptoms, family history and consanguinity.
Results: There were 477 patients in the 1969-1991 group (239 males) and 255 patients in the 1991-2006 group (138 males), 732 patients totally. In the former group, the age at diagnosis ranged from 13 months to 18 years, showing a small peak between 4-6 years of age and a main peak betweeen 12-14 years of age, while in the latter group, it ranged from 6 months to 17 years, with peaks around 2-4, 6-8 and 10-12 years of age. The mean age at diagnosis was significantly lower in the latter group (mean 8.04 years, SD 4.24) compared to that of the former group (mean 9.52 years, SD 3.99), $p<0.001$. This is thought to be due to the earlier peak in the latter group. In addition, in the 1991-2006 group, 12 patients had an affected sibling with diabetes mellitus. In the siblings the mean age at diagnosis (mean 6.92 years, SD 4.43) was lower than that of the index case (mean 8.10 years, SD 4.27), although this was not statistically significant ($p>0.05$). In the 1969-1991 group history of consanguinity was 23.9 %, whereas it was present in 13.7 % of the cases in the 1991-2006 group, reflecting the decrease in the rate of consanginous marriages in our population over the years.
Conclusion: There seems to be a tendency to earlier onset in children with type I diabetes in the last decade in Turkey.

PO1-267 Diabetes and Insulin 1

Diabetes incidence of Italian children living in Germany – an epidemiological approach to the pathogenesis of type 1 diabetes

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Incidence studies of children with type 1 diabetes and different ethnic background are known to provide important insights into the pathogenesis of the disease. Therefore, we have compared the incidence rates (IR) among children in Germany who originally came from high risk (Sardinia) and low risk (continental) parts of Italy with German children and with the reported incidence rates of their home country.
Children from the continental part of Italy were identified by the "Baden-Wuerttemberg (BW) Diabetes Incidence Registry" (DIARY), which has registred 4,017 patients aged 0-14 years who were diagnosed with type 1 diabetes in the period 1987 - 2003. In Germany, children from Sardinia with type 1 diabetes have been registered by means of over 2,000 questionnaires, which were sent to the sixteen Sardinian Clubs in Germany and to all 81 Italian catholic communities.
(1) In Germany (BW), German children suffer from type 1 diabetes more frequently than Italian children (IR 14.8/100,000 per year, 95%-CI 14.4-15.4 vs. IR 10.8/100,000 per year, 95%-CI 8.2-13.6).
(2) Italian children who live in Germany suffer from type 1 diabetes as frequently as Italian children in Italy (IR 10.8/100,000 per year, 95 %-CI 8.2-13.6 vs. 8.4/100,000 per year, 95 %-CI 7.9 – 8.9).
(3) In Germany, Sardinian children suffer from type 1 diabetes more frequently than German children (prevalence 2.3%, 95%-CI 0.5-6.5 vs. 0.11%, 95%-CI 0.11- 0.12). (4) The frequency of type 1 diabetes among Sardinian children living in Germany is comparable to that of Sardinian children living in Sardinia (2.3%, 95%-CI 0.5– 6.5 vs. 0.30%, 95%-CI 0.27 – 0.32).
Our research results show that the children from high and low risk areas of Italy have had incidence rates closer to the rates of their regions of origin than to the rate of German children. This indicates that genetic factors play a predominant role in the pathogenesis of type 1 diabetes.

PO1-268 Diabetes and Insulin 1

The effect of prodromal period on metabolic control of diabetes mellitus type 1

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We aimed to investigate whether the duration of prodromal period and initial laboratory values have effect on metabolic control in first two years following diagnosis in patients with diabetes mellitus type 1 who presented with diabetic ketoacidosis at the onset of the disease.
94 (50 males, 44 females, mean age 7.85±3.83 years) patients with diabetes mellitus type 1 who first presented with DKA at our emergency department were included in this study. All patients attended regular follow-up at our endocrinology department and evaluated clinically and biochemically every three months. The duration of prodromal period, initial insulin, c-peptide, HbA1c and serum glucose levels and avarage HbA1c levels and rehospitalization rates in the following two years were determined from patient records. Statistical correlation between the parameters were analyzed.
It is shown that prodromal period was shorter in young children than in olders ($r=0.236$). We found moderate correlation between the duration of prodromal period and HbA1c levels in the first year ($r=0.472$) while with a mild correlation in the second year ($r=0.371$) and mild correlation between prodromal period and rehospitalization rate in the first year ($r=0.346$, $p=0.001$).
There were no correlation between basal c-peptide levels or HbA1c levels and rehospitalization rate due to DKA. Mild reverse relationship found between the duration of prodromal period and hospitalization time($r=-0.223$, $p=0.046$). Initial serum glucose levels did not have effect on any parameters.
The duration of prodromal period of type 1 diabetes mellitus affected mostly by age and it has effect on metabolic control of disease in the following two years.

PO1-269 Diabetes and Insulin 1

Awareness and early therapy of cerebral edema in diabetic ketoacidosis: two cases

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Cerebral oedema (CE) is the most important complication and major cause of morbidity, mortality of the diabetic ketoacidosis (DKA) in children.
Symptomatic CE occurs in approximately 1% of children. However, sub-clinical CE is thought to occur more frequently. Early recognition of CE and prompt institution of hypertonic therapy may prevent permanent neurological sequelae. We present two patients with DKA and sub-clinical CE treated with mannitol.
Patient 1: Twelve years old girl was presented with severe DKA at first admission. She was also severely dehydrated and normotensive. Laboratory tests revealed 6.97 blood pH, 4.7 mmol/l HCO3, 450 mg/dl BG, 4.1 blood ketone, 319 mosm/l SO, 139.7 mEq/l corrected sodium, 12/15 Glascow Coma Scale (GCS). She was put on insulin and restricted fluid treatment initially. She was treated with mannitol due to persistance of relative hypertension and 12/15 GCS at the12th hour of therapy. She was recovered clinically and biochemically.
Patient 2: S.C. was presented with severe DKA at the age of 17.8 during her diabetic follow-up. She was severely dehydrated at physical examination but normotensive. Laboratory tests revealed 6.88 blood pH, 2.5 HCO3 mmol/l, 475 mg/dl blood glucose (BG), 3.3 blood ketone, 309.7 mosm/l serum osmolality (SO), 139.9 mEq/l corrected sodium, 9/15 GCS. She had a relative hypertension as an early sign of CE, bolus fluid and insulin administration at referring centre and alkaline therapy as a risk. She was treated with restricted fluid and mannitol (0.5 gr/kg/dose) in the first hour of therapy besides insulin. She improved well clinically and biochemically.
CE is primarily clinical diagnosis and warning signs such as headache, vomiting, lethargy, relative bradicardia and hypertension should be searched

at the beginning and during the therapy especially at high risk patients. To avoid the neurological sequelae, physician should not hesitate to administer hypertonic therapy promptly at the very early stages of the treatment.

PO1-270 Diabetes and Insulin 1

Retrospective audit of outcomes two years post-diagnosis in children presenting in diabetic ketoacidosis compared to 'walking wounded' at Queens Medical Centre, Nottingham

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This retrospective audit looked at Hba1c at presentation and two years post presentation in order to establish if any differences were apparent according to whether the child or young person presented with Diabetic Ketoacidosis (DKA) or not. Early identification of patients at risk of poor control could allow targeted intervention Patients diagnosed with diabetes between 2000 and 2004 were identified form the hospital computer system (DIAMOND). Their presentation state was determined from clinical coding or notes review. The patients' HbA1c at presentation and at 2 years post diagnosis were collected. This data was then entered into SBSS. Of the current 256 patients currently seen in Queens Medical Centre, Nottingham 114 were diagnosed with diabetes between 2000 and 2004. Average HbA1c at presentation was 11.01% verses 9.12% at 2 years. Patients who presented in Diabetic ketoacidosis had an initial HbA1c of 10.77% followed by 9.28% at two years.
Patients that presented in Non Diabetic ketoacidosis had an initial HbA1c of 11.12% followed by 9.16% at two years. Splitting HbA1c results by gender and presentation state revealed that there was a difference between girls and boys. Girls had a significantly higher HbA1c at presentation (11.87%) compared with boys (10.24%) At two years, girls who presented in DKA had a statistically significantly better HbA1C compared to those who were well at presentation. The reverse was seen in boys. These results suggest there is a difference between presentation type and sex. Girls who present in non-Diabetic ketoacidosis appear to have a persistently higher HbA1c 2 years following diagnosis whereas in boys the opposite is observed. The reasons for this are unclear but warrant further investigation - socio-economic status may be one confounding factor. Given these results a more targeted education plan focusing on girls may be a possible solution.

PO1-271 Diabetes and Insulin 1

Cytokine response to diabetic ketoacidosis (DKA) in children with type 1 diabetes (T1DM)

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It has been suggested that cytokine release during DKA may be responsible for its acute clinical complications, such as cerebral or pulmonary edema. We determined in newly diagnosed children with T1DM and DKA, plasma levels of cytokines IL-1b, IL-2, IL-6, IL-8, IL-10 and TNF-a with the Luminex XMAP technology, prior to, during and 120 hours after treatment of DKA.
In addition were performed measurements of: WBC, PMN, CRP and also of GH and plasma cortisol. Prior to treatment of DKA, elevated levels of the following were observed: IL-6: 21.3 pg/ml, IL-8: 15.0 pg/ml, IL-10: 58.3 pg/ml, WBC: 14.7x103/ml, PMN: 9.5x103/ml and cortisol: 47.9mg/l.
However, 120 hours after treatment of DKA, a significant decrease of IL-6 (11.9pg/ml, p=0.009), IL-8 (8.9pg/ml, p=0.011), IL-10 (15.4pg/ml, p=0.036), WBC: 7.6x103/ml, p=0.001) and cortisol (26.6mg/l, p=0.044) were observed.
Patients were divided into three groups according to the severity of DKA: a) pH<7.1, b) pH: 7.1-7.2, c) pH: 7.21-7.3. We observed in the three groups that IL-10 and CRP levels increased in parallel with the severity of DKA (IL-10: 122.0 vs 38.8 vs 12.4pg/ml respectively, p=0.035, CRP:17.8 vs 1.7 vs 1.0 mg/L respectively, p=0.003). Moreover pH levels were negatively correlated with IL-6: r=-0.66, p=0.002, IL-8: r=-0.71, p=0.001, IL-10: r=-0.62, p=0.004, WBC: r=-0.75, p=0.001 and cortisol: r=-0.58, p=0.010.
In conclusion, our data support the hypothesis that the metabolic crisis of DKA increases cytokine release and cellular activation. Moreover IL-10, which has been previously reported to have a protective role for the development of DKA complications, was found to have the highest levels and remained increased until pH normalization. Nevertheless, further study is necessary to determine if these cytokine responses result in the capillary perturbation, which is responsible for the development of severe complications of DKA, especially of cerebral edema.

PO1-272 Diabetes and Insulin 1

Abnormal glucose tolerance in transfusion-dependent thalassemic children

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Benefits of transfusion therapy in thalassemia major are well established, however, this treatment lead to chronic iron overload and frequently, to endocrine complications.
The aim of this study is to evaluate the prevalence and risk factors for abnormal glucose tolerance in a cohort of Tunisian transfusion-dependant thalassemic children and to propose a procedure to prevent diabetes mellitus.
Forty patients with transfusion dependant thalassemia aged over ten years took part in this study. Oral glucose tolerance test was performed to determine blood glucose, C peptide and insulin levels. All patients received chelation monotherapy with deferoxamin and switched to combined treatment with deferoxamine and deferiprone if there is an impaired glucose tolerance.
Fisher's exact test was used to identify the potential risk factors, $p < 0,05$ was considered to be statistically significant.
Seven patients had abnormal glucose tolerance (16 %) with impaired glucose tolerance in four cases (9 %) and diabete mellitus in three cases (7 %).
The risk factors for abnormal glucose tolerance found were serum ferritin concentration ($p = 0,008$) and mean pre and post transfusional haemoglobin ($p = 0,019$). Age of patients and iron intake were more elevated in abnormal glucose tolerance group, but did not reach statistical significance (respectively $p = 0,056$ and $0,111$). This may be explained by the little number of patients.
Iron overload is common among transfusion dependant patients who do not receive effective iron chelation therapy. Insulin resistance and a defect in β cell function are of central importance for the development of abnormal glucose tolerance in patients with secondary haemochromatosis due to transfusional iron overload. The combination of deferoxamine and deferiprone is now the most important in managing glucose homeostasis in transfusion dependant thalassemic patients before start of diabete mellitus.

PO1-273 Diabetes and Insulin 1

Does the kind of therapy have an influence on abnormalities of NPY-leptin axis in children with IDDM?

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The abnormalities of functioning of NPY-leptin axis in children with IDDM propably play a great role in diabetes complications,insulin resistance,fat disorders and body composition.The aim of the study was the evalution of NPY,leptin and soluble leptin rp.in prepubertal children with IDDM and estimate the influence of the kind of therapy.
Material and methods: 67 patients and 15 age matched,healthy children were included into the study.All children were prepubertal T<2,suffering from IDDM from more then two years,without any coexisting diseases.All patients were divided into groups according to the kind of therapy:22 were treated with

convencional insulin therapy(CIT),21 with multiple insulin injections(MII) and 24 with continuous subcutaneus insulin infusion(CSII).Blood samples were taken between 7:30 and 8:30 a.m. in hospital in normoglycemia after the night without episodes of hyper or hypoglycamia.All analysis were made by RIA or ELISA commercial kits.
Results: NPY levels were higher in diabetic children in a statistically significant way and were rising with the intensity of treatment(the highest in CSII).Leptin levels were higher in IDDM patients(the highest in MII patients). Soluble leptin rp.levels were higher in IDDM in a statistically significant way(the highest in CSII patients).
Conclusions: 1.The levels of all measured parameters were higher in IDDM patients but onlu NPY and s.leptin rp. in a statistically significant way. 2.The kind of therapy appears to have an influence on the levels of measured parameters.

PO2-274 Diabetes and Insulin 2

Effect of two insulin regimens on levels of glycaemia and glycosylated haemoglobin in prepubertal children with diabetes type 1

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Since the introduction of long and short -acting Insulin analogs , many children were shifted to three or more daily injections to improve metabolic control . To evaluate the effect of these changes on the metabolic control and the levels of glycosylated haemoglobin we studied tow groups of children with diabetes type1 , group 1 with tow injections daily of a mixture of regular and NPH insulin and group 2 with glargine insulin at morning and lispro insulin before each meal . The patients of group 2 were initially using the tow injection regimen. Glycaemia was measured three times daily in each group and glycosylated haemoglobin was quantified each three months in addition to clinical evaluation, especially weight gain. Both groups were observed during twelve month period. Twenty six children were included in the first group and twenty tow in the second group, age in group 1 was 9 ±1.2 years (M ± DS) and in the second group was 9.7 ±0.8 years. No difference in total insulin dose between the groups. Glycaemia in the first group was 125± 25 mg/ dl and in the second group was 110± 19 mg/ dl (not significant). Weight gain in the first group was 2.9 ±0.6 kg and the second group was 3.8 ± 0.5 kg ($p < 0.05$). Glycosylated haemoglobin was 8.5 ± 1.1 % in the first group and 7.6 ± 0.9 % in the second group (not significant). No difference was observed in the frequency of hypoglycaemia between the groups. Conclusions: New insulin regimes using three or more injections daily did not show a significant difference in improving metabolic control in prepuebrtal children, but may cause weight increase. The use of these regimens should be individualized according to every child taking into account the family and activity of the child.

PO2-275 Diabetes and Insulin 2

Impact of insulin glargine on metabolic control and on occurrence of severe hypoglycemia in type 1 diabetic children and adolescents in the last three years

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After the introduction of insulin glargine (Gl) in clinical practice, many studies showed its efficacy in improving metabolic control reducing the frequency of hypoglycemia, also in pediatric patients. The aim of this study was to evaluate the variations in metabolic control in young diabetic patients in the last 3 years and investigate whether the use of Gl, compared to the traditional regimen, was associated with lower HbA1c values and a reduction of severe hypoglycemia.
Out of 149 children and adolescents (76 boys and 73 girls; mean age 13.8 ± 5.7 yrs; mean disease duration 6.9 ± 5.2 yrs) with type 1 diabetes and over 6 years of age, followed-up in our Clinic from 2002 to 2005, 76 patients were switched from human basal insulin to Gl (Group 1), whereas 73 continued the traditional regimen (Group 2). Reasons for switching regimen were frequent episodes of hypoglycaemia, marked dawn phenomenon and bad metabolic control despite good compliance with glucose self monitoring. The 2 groups did not differ for age or disease duration. Mean HbA1c values in 2005 were significantly higher than those at entry in the patients both considered as a whole (8.3 ± 1.2† vs 7.9 ± 1.2 %) and subdivided into group 1 (8.5 ± 1.2 † vs 8.1 ± 1.1 %) and 2 (7.9 ± 1.2 † vs 7.6 ± 1.2 %) (†$p<0.0001$ vs yr 2002; paired t-test). By subdividing the patients according to age (6-10 yrs, 39 cases; 10-20 yrs, 87 cases; > 20 yrs, 23 yrs), the increase in HbA1c values was not present in the older group. In the period of observation the incidence of severe hypoglycaemia was significantly lower in Group 1 ($p=0.0001$). In both groups daily insulin dose and BMI remained unchanged.
In conclusion, our diabetic patients under 20 yrs of age showed a worsening of metabolic control in the last 3 years despite the use of Gl. One possible reason for this result may be the excessive freedom and flexibility offered by new therapeutic regimens. Gl could be helpful in patients at risk of severe hypoglycaemia.

PO2-276 Diabetes and Insulin 2

Daily insulin requirement of children and adolescents with type 1 diabetes - effect of age, gender, BMI and mode of therapy

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Background and Objective: The purpose of this study was to generate insulin-dose-percentiles for children and adolescents with type 1 diabetes (DM1) having the opportunity to assess this important parameter in relation to age and sex.
Methods: Daily insulin doses per weight (ID/kg) were recorded in 22 223 patients with DM1 (2-25 yr of age, duration of DM1 more than 2 yr, 48% female) and insulin-dose-percentiles (ID-Perc) were created statistically. ID-Perc were compared between male and female, and between multiple insulin injection therapy (MIT) and continuous subcutaneous insulin infusion (CSII). A multivariate regression analysis was performed for ID in the third yr of DM1 including ID/kg, body weight (expressed as standard deviation score-body mass index =BMI-SDS), age, gender and insulin delivery regimen (MIT/CSII) as variables.
Results: The 50th ID-Perc (P50) varied between 0.64 IU/kg (age 2 yr), 0.93 IU/kg (age 13 yr) and 0.70 (age 23 yr) increasing from early childhood to adolescence and decreasing towards adulthood. Highest P50 ID in females (0.94 IU/kg) was found at 12 yr and at 14 yr in males (0.92 IU/kg). In patients with ICT the ID was significantly higher compared to patients with CSII (P50: 0.94 IU/kg vs. 0.79 IU/kg at 13 yr). In multivariate regression analysis ID was significantly ($p>0.001$) associated with age, gender, BMI-SDS and insulin delivery regime.
Conclusion: ID-Perc were significantly different during various periods of childhood and were influenced furthermore by gender, body weight and insulin injection regimes. Therefore the presented data (1) provide evidence to interpret individual ID in children and adolescents with DM1 and (2) more specifically to identify children with unusual high (insulin resistance, non compliance) or unusual low (MODY, persistent remission) insulin requirement.

PO2-277 Diabetes and Insulin 2

Insulin aspart versus insulin lispro via continuous subcutaneous insulin infusion (CSII) in young children with type 1 diabetes

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Insulin aspart, a rapid-acting insulin analog, has been shown to be safe and effective in CSII therapy in adults. This substudy analysis of subjects <12 yrs was from a recent 16-week study comparing insulin aspart vs insulin lispro in children and adolescents (4-18 yrs) with type 1 diabetes (T1D) during CSII therapy (298 subjects with T1D ≥1 yr and insulin analog administered via CSII ≥3 months, randomized 2:1 to receive aspart:lispro). Aspart used in CSII was non-inferior to lispro (as measured by change in HbA_{1c} from baseline to end-of-study [EOS]) (95% CI [-0.40, 0.04]). Final HbA_{1c}, fasting plasma glucose (FPG), and daily insulin dose (U/kg) values were not significantly different between treatments (Table). The percentage of subjects who achieved their age-specific ADA HbA_{1c} target (<8.5% for subjects <6 yrs; <8% for subjects 6-11 yrs) was similar between treatment groups.

		Aspart	Lispro	p-value
N		65	33	
HbA1c (mean±SD), %	Baseline	7.91±0.874	7.73±0.707	0.299
	EOS	7.63±0.730	7.73±0.691	0.098
ΔHbA1c (mean±SE), %	Baseline to EOS	-0.19±0.06	-0.01±0.09	0.113
FPG (mean±SE), mg/dl	EOS	165.2±8.45	179.4±11.66	0.329
% subjects at age-specific HbA1c goals	Screening	56.9	667	0.390
	Week 16	72.1	64.5	0.480
Insulin dose, U/kg/day	Week 16	0.80±0.197	0.87±0.168	0.166

Neither major hypoglycemic episodes (requiring third-party assistance) nor minor hypoglycemic episodes (PG<56 mg/dl) were statistically different between the two treatment arms (major: 0.41 for aspart and 0.40 events/subject-year for lispro [p=0.9844]; minor: 84.3 events/subject-year for aspart and 74.1 for lispro [p=0.4058]). One subject in each treatment group experienced diabetic ketoacidosis. There was no difference in the frequency of adverse events between treatment groups.

Insulin aspart is as effective and safe as insulin lispro for CSII use in pediatric subjects 4-11 years of age, with approximately 70% of insulin aspart-treated youth achieving age-specific HbA_{1c} goals.

PO2-278 Diabetes and Insulin 2

Insulin detemir improves glycaemic control and reduces hypoglycaemia without excessive weight gain in children and adolescents with type 1 diabetes: 6-month results from PREDICTIVE™

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PREDICTIVE is a multinational, observational study, assessing the safety and efficacy of insulin detemir in routine clinical practice. We report 26-week results from 119 children aged 0–11 years (49% male; mean age 8.3 years; diabetes duration 3.5 years, mean ± SD BMI 18.4 ± 3.5 kg/m2) and 244 adolescents aged 12–18 years (50% male; mean age 15.1 years; diabetes duration 6.2 years, mean ± SD BMI 22.4 ± 3.8 kg/m2) with type 1 diabetes who transferred to insulin detemir. At follow-up 8 children out of 119 (6.7%) and 16 adolescents out of 244 (6.6%) reported serious adverse drug reactions, including major hypoglycaemic events. At week 26, total hypoglycaemia was significantly reduced in children and adolescents, as well as nocturnal episodes in adolescents (Table). Improvements in glycaemic parameters were reported. As expected for this patient population, weight gain was observed (0.9 kg in children, P<0.01; 0.1 kg in adolescents, P=0.87). Mean total daily insulin dose increased by 0.3 and by 0.1 U/kg in children and adolescents, respectively. Data on number of insulin injections were unavailable for 13% of children and 17% of adolescents. Where data were available, 72% of children and 75% of adolescents used once daily insulin detemir. These data support clinical trial evidence and PREDICTIVE 3-month results, which demonstrated improved glycaemic control and reduced hypoglycaemia, without excessive weight gain, are maintained over 6 months.

Parameter	Baseline	Change at week 26
Children		
Mean HbA1c, % ± SD	8.4±1.8	-0.3±1.6
Mean fasting glucose, mmol/L ± SD	10.5±2.8	-1.4±3.3*
Mean number of hypoglycaemic episodes/patient year:		
Total	58.4	-16.8*
Major	2.9	-0.9
Nocturnal	6.1	-2.7
Adolescents		
Mean HbA1c, % ± SD	9.2±1.9	-0.1±1.6
Mean fasting glucose, mmol/L ± SD	10.1±3.3	-1.2±3.8*
Mean number of hypoglycaemic episodes/patient year:		
Total	44.6	-15.2*
Major	1.4	-0.4
Nocturnal	10.0	-6.4†

*P<0.01; †P<0.05 vs baseline

PO2-279 Diabetes and Insulin 2

Near normalization of metabolic control in type-1 DM using conventional insulin therapy and a 13-point method designed to enhance compliance

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Adequate compliance is expected to improve metabolic control in DM. To determine if adequate compliance improves metabolic control in Type-1 DM using conventional insulin therapy (CIT).
25 Type-1 DM subjects underwent a Stabilization Phase (SP) (21 entered at day(d) -114 and 4 at -28d). Demographics: 17M; 8F; Age 28.6y (9.0); Height 164.8cm (8.53); Weight 62.4kg (8.68); BMI 22.9 (1.97); Duration of DM 9.7 (5.1). During SP all subjects received standard therapy with basal s.c. twice daily (BID) isophane insulin (BID-NPH) and 3 pre-prandial s.c. injections of regular insulin (TID-RI). After SP, subjects entered a 2-cohort 99-d Comparison Phase (CP) with basal BID-NPH and two different modalities of prandial regular insulin administration (0d to +99d). Fructosamine and glycated hemoglobin were measured every two weeks. A 13-point method (13-PM) of clinical measures designed to enhance compliance was prospectively applied.

	N	FRUCTO-SAMINE (mmol/L)		% GLYCATED HEMOGLO-BIN (HbA1c)	
STABILIZATION PHASE (SP) (-114d to 0d)					
Baseline SP 1 (-114d)	21	414.4	(159.5) P≤0.030	8.2	(2.7) P≤0.061
Baseline SP 2 (-28d)	4	358.0	(47.7) P≤0.503	7.6	(0.8) P≤0.391
End of SP (Day 0)	25	331.9	(53.7)	7.0	(0.8)
COMPARISON PHASE (CP) (0d to +99d) (Data reported elsewhere)					
END OF STUDY FOR ALL SUBJECTS					
Day -114 to Day +99	24	335.4	(55.2) P≤0.443	6.5	(0.8) P<0.001
All tests of significance relative to Day 0					

Near normalization of parameters of DM metabolic control was achieved using CIT and a 13-PM designed to enhance compliance. F and HbA1c concentrations documented every 2 weeks improved in all subjects regardless of the type of prandial insulin used. The combination of CIT (lower cost than other alternatives) and enhanced compliance and self-control might help to safely, efficiently and appropriately control Type-1 DM.

PO2-280 Diabetes and Insulin 2

6-month study on the safety and efficacy of an oral insulin (Generex Oral-lyn™) administered at lunchtime in juvenile type-1 DM subjects maintained on basal glargine insulin and pre-breakfast and pre-dinner regular insulin

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Adolescence in DM is associated with hormonal, counter-regulatory and psychological changes that make metabolic control difficult. Injection at lunch time is frequently missed.
To replace lunch-time injected dose for oral insulin Research subjects were 24 adolescents (12M; 12F) and 5 young adults (2M; 3F).
Demographics: Age 15.7y (3.0); Bone Age 14.9(2.7); Height 155.1cm(10.2); Weight 53kg(10.8); BMI 21.9(3.0); DM duration 6.8 (2.6). Initial 21-day stabilization period with Standard therapy (ST): s.c. BID insulin analogue + 3 pre-prandial s.c. regular insulin injections (RI). Comparison Phase: 28 days of ST; thereafter, split doses of Generex Oral-lyn™ replaced the lunch-time injection of RI for 6 months. At study end, 6 independent evaluators blinded to biochemical results assessed compliance using a 9-parameter method. 21 subjects had good compliance (GC); 8 subjects had very poor compliance (PC). GC score: 51.86 (14.97) vs. PC score 14 (10.87) p<0.001.

	N	FRUCTO-SAMINE (mmol/L)		% GLYCATED HEMOGLOBIN (HbA1c)	
ALL SUBJECTS					
Baseline	27	476.9	(130.2)	9.9	(2.4)
End of Regular Phase	29	371.3	(90.6) P<0.001	8.8	(1.8) P<0.001
End of 6-Month Generex Oral-lyn™	27	392.8	(110.3) P≤0.002	8.5	(2.0) P≤0.004
GOOD COMPLIANCE (GC) (72.41%)					
Baseline GC	19	443.4	(102.1)	9.1	(1.9)
End of Regular Phase GC	21	340.9	(54.5) P<0.001	8.1	(1.2) P≤0.002
End of 6-Month Generex Oral-lyn™ Phase GC	21	349.7	(54.4) P<0.001	7.7	(1.1) P≤0.002
POOR COMPLIANCE (PC) (27.58%)					
Baseline PC	8	556.5	(160.9)	11.9	(2.4)
End of Regular Phase PC	8	451.3	(119.5) P≤0.002	10.5	(2.1) P≤0.011
End of 6-Month Generex Oral-lyn™ Phase PC	6	543.7	(127.9) P≤0.863	11.3	(1.9) P≤0.508

29 juvenile Type-1 DM subjects replaced safely and efficiently lunch-time dose of regular insulin for split doses of Generex Oral-lyn™ for 6 months. 21 subjects were identified as having GC and 8 subjects had PC with corresponding DM metabolic control.

PO2-281 Diabetes and Insulin 2

Individual factors affecting glycemic control in pediatric insulin pump users with type 1 diabetes

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Background: Continuous subcutaneous insulin infusion (CSII) provides a safe and effective treatment option in some children and adolescents with type 1 diabetes. There is a need to examine factors that may predict success with this therapeutic modality.
Objective: To find variables with predictive value on glycaemic control in pediatric patients with type 1 diabetes on CSII.
Population and methods: Files of patients on CSII for 1 year or more were analysed. Efficacy of treatment was defined as a significant decrease in HbA1C (≥ 1%) after 1 year on CSII or HbA1c≤7.3%. Patients were divided into good and poor metabolic control (MC) groups.
Results: Thirty patients met the inclusion criteria (12 girls and 18 boys). Mean age of starting pump therapy was 14.4±4.3 years and mean diabetes duration was 6.1±3.5. Six of them were pre-pubertal, 6 in a Tanner stage of 2-4, and 18 were postpubertal. The average HbA1c after 1 year on CSII was 6.8±0.4 in the group of good control, and 8.2±0.8 in the rest of the patients.
Conclusion: BMI, requirements of insulin and daily blood glucose monitoring frequency could be predictive variables of good control in pediatric patients on CSII.

Variables (units)	Good MC group	Poor MC group	p
Patients	21	9	
Sex (%female)	62%	55.6%	0.44
Age at diagnosis (years)	7,4±3,9	10,5±4,3	0.06
Age at pump start (years)	14,2±4,2	14,9±4.9	0.6
Body mass index (BMI) (S.D.)	0,1±0,9	1,2±1,3	0.033
Number of shots in pre-pump regimen	5,5±0,9	5,3±0.9	0.86
Pre-pump insulin requirements (U/Kg/d)	1±0,3	0,8±0,3	0.19
Pre-pump daily blood glucose monitoring (BGM) frequency	7,2±1,7	5,3±1,2	0.007
Pre-pump HbA1C (%)	7,3±1,2	7,6±0,9	0.2
Post-pump insulin requirements (U/Kg/d)	0,9±0,2	0,7±0,2	0.014
Number of basal rates	4,2±1,8	4±1,9	0.8
Post-pump daily BGM frequency	7,8±1,7	6,3±1,7	0.033
Parental status (% married)	85.7	77,8	0.6

PO2-282 Diabetes and Insulin 2

Comparison of metabolic control of pre-prandial s.c. regular insulin versus prandial oral insulin (Generex Oral-lyn™) in adult type-1 DM subjects maintained in basal s.c. BID isophane insulin (NPH)

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The objective was to study safety and efficacy of meal time Generex Oral-lyn™ replacing s.c. injected insulin.
25 Type-1 DM subjects (17M; 8F); Age 28.6y (9.0); Height 164.8cm (8.53); Weight 62.4kg (8.68); BMI 22.9 (1.97); BMI 23.8 (2.0). Duration of DM 9.7 (5.1) years underwent a Stabilization Phase (SP) with standard therapy (ST): Basal s.c. twice daily (BID) isophane insulin (BID-NPH) and 3 pre-prandial s.c. injections of regular insulin (TID-RI) in addition to encouragement to self-control. 99-day Comparison Phase (CP): 11 subjects (5M; 6F) were allocated to a Control Group (CG) and 14 subjects (14M; 2F) to Treated Group (TG). Subjects in the CG continued receiving BID-NPH and TID-RI. Subjects in TG received BID-NPH and TID prandial split doses of Generex Oral-lyn™ (OI). Fructosamine (F) and Glycated Hemoglobin (HbA1c) were determined every 14 days.
After a SP, 25 adult Type-1 DM subjects underwent a 99-day CP). During CP 11 CG subjects received BID-NPH + TID-RI and 14 TG subjects received BID-NPH + TID-OI. Near normalization of parameters of DM metabolic control was achieved in each and all subjects as reflected by continuous improvement in F and HbA1c concentrations documented every 2 weeks.
Direct comparison of HbA1c concentrations demonstrated a superior effect of Generex Oral-lyn™ over s.c. injected regular insulin.

	N	FRUCTO-SAMINE (mmol/L)		% GLYCATED HEMOGLO-BIN (HbA1c)	
COMPARISON PHASE (CP) (99 days)					
Baseline CG (Day 0)	11	355.7	(48.6)	7.3	(0.9)
End of Study CG (+99d)	11	354.6	(57.5) N.S.	6.8	(0.8) P≤0.049
Baseline TG (day 0)	14	313.2	(51.5)	6.8	(0.6)
End of Study TG (+99d)	13	319.2	(49.7) N.S.	6.1	(0.7) P<0.001
HbA1c (CP):7.3 (0.9) to 6.8 (0.8) CG versus 6.8 (0.6) to 6.1 (0.7) TG P≤0.035					
FRUCTOSAMINE (CP): CG versus TG NS					
CG=CONTROL GROUP, TG=TREATED GROUP					

PO2-283 Diabetes and Insulin 2

Insulin aspart versus insulin lispro via continuous subcutaneous insulin infusion (CSII) in children and adolescents with type 1 diabetes

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Insulin aspart, a rapid acting insulin analog, has been shown to be safe and effective in CSII therapy in adults. This study compared insulin aspart vs insulin lispro in children and adolescents with type 1 diabetes (T1D) during CSII therapy. This 16-week clinical trial randomized 298 subjects (2:1 to receive aspart:lispro) ages 4-18 yrs, diagnosed with T1D ≥1 yr and previously treated for ≥3 months with analog insulin administered via CSII. Aspart used in CSII was non-inferior to lispro (as measured by change in HbA_{1c} from baseline to end-of-study [EOS]) (95% CI [-0.27, 0.07]). Final HbA_{1c} and fasting plasma glucose (FPG) values were not significantly different between the treatments (Table).

		Aspart	Lispro	p-value
N		198	100	
HbA1c (mean±SD), %	Baseline	8.04±0.942	8.15±0.841	0.301
	EOS	7.88±0.930	8.07±0.853	0.238
ΔHbA1c (mean±SE), %	Baseline to EOS	-0.15±0.05	-0.05±0.07	0.241
FPG (mean±SD), mg/dl	EOS	166.5±67.28	180.2±82.58	0.113
% subjects at age-specific HbA1c goals	Screening	50.3	40.4	0.138
	Week 16	59.7	43.8	0.014
Insulin dose, U/kg/day	Week 16	0.86±0.237	0.94±0.233	0.018

The percentage of subjects who achieved their age-specific ADA HbA_{1c} targets (<8.5% for subjects <6 yrs; <8% for subjects 6-18 yrs) was significantly greater in the aspart group. Daily insulin dose (U/kg) was significantly lower at Week 16 for subjects treated with aspart, as compared to lispro.

Neither major hypoglycemic episodes (requiring third-party assistance) nor minor hypoglycemic episodes (PG<56 mg/dL) were statistically different between the two treatment arms (major hypo was 0.42 for aspart and 0.3 events/subject-year for lispro [p=0.4824]; minor hypoglycemic events were 77.18 events/subject-year for aspart and 65.95 for lispro [p=0.1287]). Two subjects in each treatment group experienced diabetic ketoacidosis. There was no difference in the frequency of adverse events between treatment groups.
Insulin aspart is as effective and safe as insulin lispro for CSII use in pediatric subjects 4-18 years of age, with approximately 60% of insulin aspart-treated youth achieving age-specific HbA_{1c} goals.

PO2-284 Diabetes and Insulin 2

Continuous glucose monitoring is helpful in the modification and in the assessment of such modified treatment in children and adolescents with type 1 diabetes mellitus

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Self-monitoring of blood glucose (SMBG) is an essential part of intensive insulin therapy. The objective of this prospective study was 1) to modify the treatment of type 1 diabetes (DM1) in a group of children and adolescents based on the results provided by the continuous glucose monitoring (CGM) and 2) to use CGM for the assessment of such modified treatment. 61 patients with DM1 (30 girls) at the mean age of 12.4 yrs (5-17.5 yrs) were studied. 38% participants had good (HbA1c<7%), 33% acceptable (HbA1c 7-8%) and 29% poor (HbA1c>8%) glycemic control. Based on the results of first glucose monitoring (CGM-1) changes in therapy were introduced in all patients by the same physician. After 3-month period of such modified treatment HbA1c was measured again and the second glucose monitoring (CGM-2) was performed in 56 patients. CGM-1 revealed hyperglycemias in all and hypoglycemias in 93% of patients, despite the results of glycemic control. Percentages of patients experiencing hyperglycemias and hypoglycemias did not change in CGM-2, 100% and 91% respectively. No change in neither the number of hypoglycemic episodes (1.4±1.0 vs 1.3±0.9 episodes/patients/day) nor daily insulin dose (0.89±0.25 vs 0.87±0.24 U/kg/day) was seen at the end of the study. Yet, modified therapy resulted in the significant decrease of mean HbA1c value (7.7 vs 7.3%, p<0.01). The beneficial decline was also registered in number of hyperglycemic episodes (2.9±1.0 vs 2.3±0.8 episodes/patients/day, p<0.001) and in their duration (7.3±3.4 vs 5.7±3.1 hours/patient/day, p<0.01). The authors conclude that CGM is helpful in modifying the treatment and in improving HbA1c value without increasing daily insulin dose or risk for developing hyperglycemic or hypoglycemic episodes. However, the results of repeated CGM showed that the improvement in glycemic control did not resolve completely the problem of pathological daily blood glucose fluctuations in children and adolescents with DM1.

PO2-285 Diabetes and Insulin 2

Indications for insulin pump therapy in different age groups - an analysis of 1567 children and adolescents

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Aims: The German working group for pump therapy in pediatric patients has defined seven indications for CSII: dawn phenomenon, reduction of severe hypoglycaemia, improvement of hyperglycaemia, more flexibility, motivation, failure of injection therapy and pregnancy. In this study we analysed age-specific differences for starting CSII in 4 age groups (A:0-4 years, B:5-9 years, C:10-14 years, D:15-19 years). Furthermore we tried to investigate weather the metabolic goals could be reached.
Methods: 1567 children and adolescents (mean age 12.2 years, mean diabetes duration 5.1 years) with documented indications for CSII from the DPV-data base (December 2005) were included.
Results: Dawn phenomenon (27.4%), reduction of hypoglycaemia (20%) and improvement of hyperglycaemia (18.1%) were most frequently indicated for starting CSII. These indications were significantly different between the 4 age groups (p<0.0001). In infants and toddlers (A, n=138) reduction of hypoglycaemia (45.5%) was the most important indication. For treatment in adolescents (C, n=789/D, n=408) dawn phenomenon (32.1%/21.7%) and flexibility (21.6%/25.8%) were the main indications. The rate of severe hypoglycaemia with coma in patients with the indication "reduction of hypoglycaemia" could be reduced (12.1/100 patient years before CSII vs. 3.1 after 1 year, 4.49 at study end). Metabolic control in patients with the treatment goal "improvement of hyperglycaemia" could be lowered significant in the first year of CSII (HbA1c start: 8.77%, after 1 year: 8.47%, p<0.01) and was stable over the study period (8.77 after 36 months).
Conclusions: CSII in children and adolescents is safe and can reduce the rate of severe hypoglycaemia without metabolic deterioration. In patients with poor metabolic control a significant reduction of HbA1c can be achieved in the first year.

PO2-286 Diabetes and Insulin 2

Continuous subcutaneous insulin infusion from the beginning of diabetes in young children: long-term persistent benefits

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Objectives: To evaluate long term metabolic control and satisfaction in very young children treated by continuous subcutaneous insulin infusion (CSII) for type 1 diabetes (T1D) at diagnosis.
Methods: Since 1999, at our hospital, all newly diagnosed T1D children under 6 years old were treated by CSII at time of diagnosis. Prospectively collected data included severe hypoglycaemia and ketoacidosis events, acute hospital admission, BMI, insulin dosage, satisfaction questionnaire and quarterly HbA1c (DCA 2000; Bayer®).
Results: 39 children were included. Only 1 switched to multi-daily injections (MDI) after 6 months for mother psychological intolerance and was excluded. 38 patients continue to chose CSII therapy. Age at onset of T1D: 3.2 ± 1.41 yr (m ± SD). Mean duration of follow-up: 3.8 ±2.1 yr. 42% reach more than 5 years follow-up. Mean HbA1c: 6.9 ± 0.8 % during the first year; 7.4 ± 0.7% during the second year stable during all following years even for patients after 5 years follow-up. Severe hypoglycaemias: 7%patient/year; ketoacidosis: 3%patient/year. Families expressed long term satisfaction.
Discussion: For T1D young child, CSII therapy allows small insulin dosage, flexible and fractionated insulin dosage for unstable and unpredictable young child meals, additional bolus without increased injections to manage hyperglycaemic excursions, adjustable hourly basal rate insulin. CSII has occasionally been used as long term treatment early on time of T1D diagnosis. Though CSII is an alternative means to lower HbA1c levels, reduces the risk of hypoglycaemia. It is safe and effective in the preschool aged children. CSII therapy appears to have persistent benefit even when employed in a regular clinic setting for not selected children. Long term CSII treatment has no appreciable psychological adverse effects or interference with normal activities.
Conclusion: Flexible management by CSII from the onset of diabetes allows young children and their parents to maintain a persistent good metabolic control all over time.

PO2-287 Diabetes and Insulin 2

Effect of treatment with sulodexide in children with type 1 diabetes mellitus

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Aim: to study the influence of low-molecular heparinoid sulodexide on the state of tromboresistance of vessel wall in children with type 1 diabetes mellitus (T1DM).
Patients and methods: 110 children (50 boys, 60 girls) 3–16 y.o. with T1DM were examined. The duration of the disease was: less than 1 year - in 27 patients (HbAc1 7,3±0,3%) – group 1, from 1 to 5 years - in 48 patients (HbAc1 8,9±1,2%) – group 2, more then 5 years - in 35 children (HbAc1 11,4±2,2%) – group 3. Control group: 30 healthy children 3-16 y.o. The indexes of tromboresistance of vessel wall (antiaggregating, anticoagulating, fibrinolytic activity) measured by manjetic method.
Results: Group 1: tromboresistance of vessel wall was normal in 75% patients. Group 2: only 30% patients had normal indexes of antiaggregating, anticoagulating, fibrinolytic activity of vessel wall, the rest 70% had lower indexes. Decrease of tromboresistance of vessel wall was found in 100% patients of group 3. All patients were treated for 1 month with low-molecular heparinoid sulodexide. After course of treatment there was a certain improve of indexes of vessel wall tromboresistance: in groups 1 and 2 increase of antiaggregating, anticoagulating, fibrinolytic activity. There was no improvement of antithrombogenic activity of vessel wall in group 3.
Conclusions: Disorders of tromboresistance of vessel wall in children with T1DM correlated with duration of the disease. Treatment with low-molecular heparinoid sulodexide is effective in correction of vessel wall tromboresistance in early stages of microvascular complications.

PO2-288 Diabetes and Insulin 2

Rapid development of extensive lipoatrophy in a ten years old boy with insulin lispro in insulin pump therapy (CSII)

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Introduction: Lipoatrophy is a cutaneous complication in patients with type 1 diabetes which occurs rarely since the introduction of recombinant human insulin. Single cases have been reported recently with human regular insulin, insulin lispro and glargine with and without CSII.
Case report: We present the case of a now ten years old boy, who was diagnosed with type 1 diabetes at the age of 2.5years. He was treated initially with an intensified therapy of human regular and NPH insulin. Despite fluctuating blood glucose values (hypo- and hyperglycemic levels) he had good metabolic control, HbA1c 6.4-7.2% (reference <6.5). His mother administered 7-8 daily injections. Due to elevated postprandial blood glucose values after breakfast he was switched to lispro in the mornings. When he developed needle phobia he was switched to CSII at the age of 4.5 years. Initially he used human regular insulin (H-Tronin 40) and later lispro when he again showed fluctuating blood glucose values. Steel canulae and site of insertion were changed daily at buttocks. He never showed a cutaneous erythema, but mild lipohypertrophy. His glucose metabolism was well controlled (7.1%) when he developed extensive lipoatrophy to both buttocks of 18 cm in diameter within eight weeks. The catheter site was changed to the thighs. But again, he developed lipoatrophy. For the last six months he used insulin aspart and teflon cannulae inserted abdominally. No further progression of lipoatrophy occurred, but mild lipohypertrophy developed.
Conclusion: This case confirms that topic reactions to insulin therapy are only local cutaneous complications and effectiveness of insulin is preserved. We report for the first time that lipoatrophy was controlled by the use of insulin aspart in conjunction with teflon canula alone.

PO2-289 Diabetes and Insulin 2

Increased adiposity after diagnosis in Italian children with type 1 diabetes mellitus

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The Accelerator Hypothesis argues obesity an environmental factor hastening the clinical onset of diabetes mellitus. Obesity-induced insulin-resistance may upregulate β-cells, which become more susceptible to autoimmunity in genetically predisposed individuals. It has been reported that in pediatric type 1 diabetes younger age at diagnosis was associated with higher BMI-SDSs. We measured BMI-SDS in 174 insulin-treated patients (106 m, 68 f) and followed between 1990-2005. BMI, recorded at 2 to 12 months after diagnosis, was converted to SDS according to Rolland Cacherà standards. Age at diagnosis ranged from 1 to 15.7 years. Patients were divided into 3 groups, according to age at diagnosis: G1: 1-4.99 yrs, G2: 5-9.99 yrs, G3: 10-15.7 yrs. In all patients, BMI-SDS was not different among the 3 groups of patients (p=0.61, F test; ANOVA), and did not change over 1990-2005 (Pearson's correlation coefficient (r): 0.052, p=0.50). There was no significant interaction between age category at diagnosis and category of year of diagnosis (p=0.75); there was no correlation between age and year at diagnosis (r= 0.09; p= 0.23). In 92 patients longitudinally evaluated, BMI-SDSs at diagnosis wasn't higher in G1 than both G2 and G3 (p=0.75; ANOVA). Five years after diagnosis, BMI-SDS was similar across the 3 age-groups (p=0.46; ANOVA). BMI-SDSs increased from diagnosis to 5 years (effect of time: p=0.001; ANOVA).
In contrast to Accelerator Hypothesis, obesity is not a common finding in Italian children at type 1 diabetes diagnosis. As regards BMI as a risk factor in diabetes pathogenesis, it should be established whether patients are more insulin-resistant than controls, and whether greater BMI during childhood could explain insulin-resistance. There might be a threshold at which obesity determines earlier onset of type 1 diabetes, already not reached in our Italian patients. The increased BMI-SDS 5 years after diagnosis could be related to overinulinization due to intensive therapy, and represents a risk factor for the late development of microvascular complications.

PO2-290 Diabetes and Insulin 2

Quality of life and family burden in children with cystic fibrosis related diabetes

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The chronic progressive nature of cystic fibrosis (CF) is associated with increased complications such as CF related diabetes (CFRD) and has potential impact on the health related quality of life (HQOL). QOL and family burden of children with CF and CFRD was assessed. Children with CF aged 10-19years and parents completed KIDSCREEN 10 (generic HRQOL). Parents completed family burden (HAPPI-D) questionnaire. 103 children and their parents participated in the study. 101 children (51 boys and 50girls) and 102 parents (21m/81f) completed questionnaires. (2 children and 1 acutely ill parent were unable to complete). Children were categorized by glucose tolerance testing as normoglycaemic (NCF) 72% and diabetic (CFRD) 28%
Kidscreen: 72%of Children perceived their general health as very good/ excellent (77%NCF; 61%CFRD), 18% as good (18%NCF; 18CFRD) and 10% as fair/poor (6%NCF; 21%CFRD)
Family Burden (HAPPI-D): Parents reported greater family burden in children with diabetes (P<0.03). Concerns relating to child's long-term illness were reported as a major/large burden by 64% of parents (63% of NCF, 65% of CFRD). Restriction of child's social and school activities was large/major burden for 35% CFRD children's parents and 12% NCF (p<0.05). Disruption in family routine was large/major burden for 24% of CFRD group and 12% in NCF. Parents of CFRD children reported poorer child health perception (14% CFRD vs 4.2%NCF) and poorer QOL (14% Parent's of CFRD and 3%NCF perceived their QOL as poor/very poor). Parent perception of general health was greater than child perception (76.2% vs 72.3%).

Diabetes is a common complication of CF. Family burden including medical/ nursing tasks, family routine disruption, social and school activity restriction was higher in CFRD. Parent perception of child's QOL was poorer with diabetes. Concerns relating to children's lon term health were large burden for both groups. Diabetes prevention, detection and treatment are important in care of children with CF. Both parent and child QOL assessment are important in CFRD patient care

PO2-291 Diabetes and Insulin 2

A clinical case: Alström syndrome in two boys

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Alström syndrome was described since 1959. It is inherited in an autosomal recessive manner and characterized by cone-rod dystrophy, obesity, progressive sensorineural hearing impairment, dilated cardiomyopathy, obesity, insulin resistance syndrome, diabetes mellitus type 2. ALMS1 is the only gene currently known to be associated with Alström syndrome. We present two clinical case of this syndrome.
Objective: to investigate the more frequent mutations in ALMS1 gene (2141delCT, 6571delTCAC, 7132insA, C10483T, 10775delC è G10992A). Materials and Methods: a clinical and molecular genetic testing was performed in two patients (see table).
Results: the manifestation of symptoms Alström syndrome.

Patient K, 16 years, male	Patient M, 17 years, male
Inherited nystagmus (6 month) Perinatal encephalopathy, developmental delay (7 month)	Nystagmus, photophobia, retinal hypoplasia (6 month)
progressive visual impairment (11 month)	
Obesity (1 year)	Obesity (2 month)
Cone-rod dystrophy, cross-eye, retinal dystrophy (3 years). Pigmentary clumping (16 years)	chorioretinal atrophy (17years)
Hepatomegaly (6years)	Hepatomegaly (15years)
Progressive sensorineural hearing loss (8 years)	Progressive sensorineural hearing loss
Impaired glucose tolerance (12 years)	
Diabetes Mellitus type 2, HbA1c-10,9% (14 years)	Diabetes Mellitus type 2, HbA1c-9,8% (15 years)
Nephropathy	Nephropathy (13 years)
acantosis nigricans	acantosis nigricans
BP 150-130/110-80 mm hg	BP 150/110 mm hg

A molecular genetic testing: 2141delCT mutation was detected only in healthy mother of patient K. The patient K. and his father had no more frequent mutation. The both healthy parents of patient M. had heterozygous 2141 delCT mutation of ALMS1 gene, and affected child had homozygous mutation.
Conclusion: patients K. and his family is required further detection of more infrequent mutation of ALMS1 gene.

PO2-292 Diabetes and Insulin 2

Psychological problems in diabetic children and adolescents are related to disease duration and metabolic control: a study with children and parent questionnaires

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Few data exist on complete psychological evaluation in children with type 1 DM. Psychological adjustment and quality of life in relationships to HbA1c and duration of illness were investigated in 70 pts with type 1 DM (age 6-18 yrs) and their parents. Pts were subdivided into 3 age groups: group 1 (6-10yrs; n=11), group 2 (11-13yrs; n=23) and group 3 (14-18 yrs; n=36).
They were compared with 70 nondiabetic subjects matched for age, sex and socio economic status. All cases underwent Achenbach's and Rescorla's CBCL, filled in by parents, and YSR, filled in by youths 11-18yrs. Pts and parents completed also the PedsQL by Varni. All parameters were correlated with HbA1c and duration of diabetes. Most correlations were found in group 3, in fact, for parent report, HbA1c levels were correlated positively with anxiety problems (p=.01), depression (p=.03), internalizing score (p=.02), somatic complaints (p=.01) and negatively with general QoL (p=.02). For youths report, in group 3 HbA1c levels were correlated positively with social problems (p=.01) and affective problems (p=.02) and negatively with QoL in physical health (p=.02). For parent report, in the whole group duration of illness is correlated positively with emotional and behavioural problems (Total Score p=.01) and negatively with QoL (p=.02). For parent report, pts of group 3 were significantly worse than controls in several behavioural scales, in total (p=0.01), internalizing (p=.04) and externalizing score (p=.01). We confirm that good metabolic control, duration of diabetes and well being are directly related. Adolescents, above all, are reported by their parents and by themselves as more problematic than non diabetic controls. A worse quality of life and psychological disturbances are more frequent in adolescents and in patients with poorer metabolic control and longer disease duration. Psychological state should be considered in the management of adolescents with diabetes.

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Psychological status of children with type I diabetes mellitus: maternal psychologic state in diabetic children with depressive mood

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The aim of this study was to see an incidence of depression , and to see the characteristics of demographic variables, maternal psychologic state and family environments in adolescent children with type I DM who was in depressive mood. Among children with type I Diabetes Mellitus who participated in a diabetes summer camp which was held between August 6th and 10th, 2006, authors sent questainnaires which included CDI/BDI for children, MMPI and SCL-90 for patients' mothers, and FES which mothers were asked to respond to the 40 patients' house after gaining parents and patients' permission by telephoning. Twenty-three out of 40 patients completed these questainnaires. Study patients consisted of 10 boys and 13 girls. Their mean age was 13.3 years. There were significant differences in maternal MMPI and SCL-90 between depressive and non-depressive group. Among the maternal MMPI, the t-scores of hypochondriasis and hysteria in depressive group were higher than those of non- depressive group. And among the dimension of SCL-90, t-score of depression, anxiety, phobic anxiety and psychoticism in depressive group were higher than those of non-depressive group($p<0.05$). These findings were concordant with prior findings that the mothers of diabeteic childen were more depressed and anxious than the mothers of control children. Though there are several limitation to this study, this study found high incidence rate in children with type I diabetes, and replicate prior findings supporting the effect of type I diabetes on the maternal psychologic state and family functioning. Larger size group is necessary to confirm our findings.

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Thyroid and sexualization process abnormalities in teenager patients with type I diabetes mellitus

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Diabetes mellitus (D.M.) represents a heterogenous group of glycemic disorders, with a diverse endocrine-related pathology. The aim of our study was to find out if ovarian and thyroid disorders have a higher prevalence in DM type I patients compared to normal population.
The study implied a group of 85 patients with DM type I, mean age 16,4±1.1 yrs, and a control group of 130 patients without DM type I, mean age 15.9±2.3 yrs, in which we assessed: the quality of sexualization process, Tanner's stages of sexual development, serum levels of ovarian hormones in luteal phase, thyroid volume and echostructure, serum levels of TSH, F-T4, T3, thyroperoxidase antibodies (ATPO).
Irregular menses in study group were found in 72.6% (61 cases), compared to 20.6% (27 patients) in the control group ($p<0.01$). Breast development in 25 patients (29.7%) from the study group presented last stage development compared to 108 patients (82.4%) in control ($p < 0,01$). Serum levels of ovarian hormones in luteal phase in diabetic patients were abnormal in 61 patients (72.6%) compared to 25 (19.08%) from control group ($p< 0,01$). Ultrasonographic mean thyroid volume was greater in the study group (9.3±0.92ml) compared to control (4.6±1.02ml). TSH levels were 4.6±1.4mU/L for study group and 2.1±1.1 for control. Serum levels of ATPO were elevated in 27 diabetic patients (31.1%) but in only 5 cases (3.8%) from control group ($p< 0.01$).
The results strongly suggest that there is an increased frequency of abnormal ovarian functions in the study group compared to the control group. The results revealed rhythmic alterations of the quality of menstrual cycle, a slight hyperestrogenism, somatic abnormalities of sexualization with micromastia. In diabetic versus non-diabetic patients there is a significantly increased thyroid volume, an increased frequency of thyroid functional abnormalities (especially a subclinic hypothyroidism) and a greater frequency of autoimmune thyroiditis.

PO2-295 Diabetes and Insulin 2

Psychosocial impact of diabetes related activities in young adults with type 1 diabetes mellitus diagnosed in childhood

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Diabetes mellitus (DM) is a chronic disease that often poses difficulties to both patients and health professionals, due to its inherent complexity and the magnitude of the impact it has on one's personality development, coping skills and social life. The current study aims at evaluation of some psychosocial aspects of diabetes in young adults with type 1 DM, and their relation to diabetes control. A total of 23 (11 women) otherwise healthy patients with type 1 DM since childhood, aged 23.7±3.4 years (19—30), were administered the "Psychosocial Aspects of Diabetes Schedule" (Sensky et al., 1996), translated and modified for the needs of this study. Both genders had similar diabetes duration (14.0±5.2 years), control (HbA1c% 8.6±1.9) and treatment (intensified insulin regimen since 4.5±4.5 years). Only 25.0% of the good vs. 57.9% of the bad control group (as defined by the applied instrument) didn't perceive diabetes as a cause of their anxiety; 31.6% of the latter showed low self-esteem and 26.3% were depressed, compared to none of the former.
There was a positive linear relationship between depressive symptoms and anxiety ($r=0.676$, $p<0.001$), low self-esteem ($r=0.617$, $p=0.002$), and poor financial state ($r=0.44$, $p=0.035$). The presence of social support correlated positively with favourable family relations ($p=0.005$) and negatively with depression ($p=0.001$), low self-esteem ($p=0.002$) and anxiety ($p=0.003$). The patients regarding diabetes as mildly or not related to their social and financial difficulties, demonstrated lower HbA1c% - 7.30±1.9 vs. 9.12±1.9, $p=0.05$.
In multiple linear regression overall diabetes control was positively related to participant's willingness to share diabetes allied problems with others ($p=0.009$) and quality of diabetes-related knowledge, while negatively related to diabetes duration ($p=0.003$) and anxiety ($p=0.003$). Our study suggests feasible pathways of improving control and well-being of diabetes patients that possibly ensue childhood and deserve further exploration.

PO2-296 Diabetes and Insulin 2

Does glycated hemoglobin vary according to young diabetics' life styles or attitudes towards diabetes?

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The aim of the study is to identify young diabetics' habits and attitudes that might present correlations with values of their glycated hemoglobin. We analysed 41 subjects, aged 15-19 years, 21 females and 20 males. While attending the out-patients' department for the routine check-ups the subjects are asked to fill in a questionnaire investigating the habits referring to socialization and emancipation processes, levels or awareness of assets and problems regarding diabetes and prevalent reactions when facing the thought of the complications of diabetes. For each subject the value of glycated hemoglobin is recorded.
Analysing the data of the questionnaire combined with the scores of glycated hemoglobin, the sample was divided into 2 groups: one with 30 subjects with glycated hemoglobin 8,4% or lower, the other with 11 subjects with glycated hemoglobin 8,5% or higher. The first group was found more advanced with regard the style of life favouring the emancipation processes (they got higher scores answering the items "My parents allow me to do experiences away from family"); the second group, when confronted with various reactions to the thought of complication ("To try not to indulge in the thought, thinking or doing something else", "To try harder to get a good glycemic control", "To feel depressed seeing the task too difficult", "To ask help or advice to parents, doctors or to other young diabetics"), was found to choose with greater frequency the first option.
The findings drawn from the investigation give us some hints: experiences away from family, important for all adolescents, seem to have positive influence on the treatment of diabetes; for the subjects with the worst glycated hemoglobin who resort more frequently to the defence mechanism of denial a psychological support is advisable to help them to face their problems with a constructive approach.
Keywords: Adolescence, diabetes mellitus type 1

PO2-297 Diabetes and Insulin 2

Smoking and cardiovascular risk factors in juvenile type 1 diabetes

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To evaluate cardiovascular risk factors in juvenile smoking patients with diabetes we examined 94 children and adolescents with type 1 diabetes who were questioned by telephone with respect to their smoking behaviour. 19 of them smoked passively (n=12, at least one member of the family smoked at home) or actively (n=7, more than 1 cigarette per week). In comparison to non-smoking diabetics, the passively smoking diabetics were equally aged (12 years), they had the same weight (48 kg) and length (150 cm), but, surprisingly, the incidence of retinopathy was significantly higher ($p<0.0001$).
In comparison to non-smoking diabetics, the actively smoking diabetics were significantly older (12 vs. 16.3 years), they had higher length (150 vs. 168.7 cm) and weight (48.6 vs. 62.9 kg), but BMI, BMI-SDS and blood pressure values were similar. The HbA1c values were significantly higher (10.2 vs. 7.7%). Cholesterol levels (201 vs. 171 mg/dl, $p<0.004$), LDL-cholesterol (113 vs. 92 mg/dl, $p<0.03$) and apolipoprotein B (95.7 vs. 75.3 mg/dl, $p<0.009$) were increased but L-selectin levels (1413 vs. 1800 ng/ml, $p<0.001$) were decreased. L-selectin negatively correlated with age (Spearman's rank correlation coefficient rho = -0.54, $p<0.00001$), as well as length, weight, BMI, systolic blood pressure and smoking (rho = -0.34, $p<0.004$). In conclusion, passive smoking might contribute to a higher incidence of retinopathy.

Actively smoking diabetics were older than non-smoking diabetics, they had a poorer diabetes control and a more atherogenic lipid profile accumulating their number of cardiovascular risk factors from 1 (diabetes) to at least 4 (in addition smoking, poor diabetes control, hypercholesterolemia). The significantly decreased L-selectin values in smoking diabetic adolescents may be explained by increased consumption of L-selectin by activated endothelial receptors.

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Prevalence of cardiovascular risk factors in Spanish children and adolescents with type 1 diabetes

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Background: Type 1 diabetes mellitus (T1DM) is an independent risk factor for premature cardiovascular disease. The metabolic syndrome (MS) may be involved in the pathogenesis of microvascular complications of T1DM.
Objective: 1.To estimate the prevalence of cardiovascular risk factors (CVRF) in T1DM up to 18 years of age. 2.To assess whether CVRF are related with metabolic glycaemic control. Research design and methods We included 135 patients with a diabetes duration ≥5 yr. Insulin dose (U/Kg/d), urinary albumin excretion rate (AER) and family history of CVRF were analysed. CVRF were defined as follows: HTA (ITF2004), triglycerides (TG) >110mg/dl, HDL cholesterol (C-HDL)<40mg/dl, mean annual HbA1c ≥7.6% (HPLC: nv 5,31 ±0,21) and obesity defined as BMI ≥2SDS(Hernandez). We considered good metabolic control as HbA1c <7.6% (ISPAD), dyslipidemia when TG>110mg/dl and C-HDL<40mg/dl. C-HDL and TG were also expressed in SDS(Lopez). We considered insulin resistance (IR) if insuline dose was >1U/Kg/d in prepubertal and >1.5U/Kg/d in pubertal patients.
Results: The 60% of patients had at least one CVRF, 11.1% had two, and three or four CVRF (MS) were found in 2.2%. Elevated values of HbA1c, HTA and dyslipidemia were found in 51.9%, 9.6% and 8.9% of the cohort. No patient received lipid-lowering nor antihypertensive medication. Only 5.9% of our patients were obese. No patient had abnormal AER. Family history of CVRF was present in 32% of the cohort.

	HbA1c<7.6(n=65)	HbA1c≥7.6(n=70)
Age(yr)	11.8±3.7	12.2±3.5
Sex(%male/female)	55/45	57/43
Prepubertal/pubertal(%)	59.4/40.6	58.6/41.4
BMI(Kg/m2)	0.15±0.9	0.6±1•
HTA(%)	9.2	10
C-HDL(z-score)	0.64±1.5	0.4±1.0
TG(z-score)	-0.37±0.7	0.14±1.0•
Dyslipidemia(%)	3.1	14.3•
Insulin(U/Kg/d)	0.93±0.2	0.92±0.3
IR(%)	32.2	26.2

*p<0.05

Conclusions: Patients with inadequate metabolic control have higher BMI and dyslipidemia. The prevalence of CVD risk factors is high but lower than in other studies. Prevention, early identification and treatment of CVRF are important.

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Lipid profile and antioxidant status in children and adolescents with type 1 diabetes mellitus

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Type 1 diabetes mellitus (T1DM) is associated with the development of micro- and macro-vascular complication generally related to duration of disease, poor glycemic control and lipid abnormalities.
Chronic hyper-glycemia increases production of free radical intermediates which in turn augments oxidative stress. The oxidative stress plays a key role in the development of diabetic complications. In the present study we evaluated the lipid profile, the parameters related to oxidative stress, and the relationships of these parameters with metabolic control of disease in children and adolescents with T1DM.
A total of 58 T1DM patients (11.5±3.49 yr) were studied, matched for age and sex with 36 healthy subjects (9.60±3.21 yr).
In all children serum concentration of total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), triglycerides (TG), lipoprotein(a) (Lp(a)), homocysteine, fibrinogen, MDA, vitamin E (Vit. E), β-carotene, lycopene, retinol, vitamin C reduced (Vit. C-Red) and oxidized (Vit. C-Ox) were measured.
There were no significant different in the levels of TC, LDL-C, and HDL-C between T1DM patients and controls. Serum concentrations of TG in T1DM subjects were significantly lower than in control ones.
No significant difference of total antioxidant status (Vit. E, β-carotene, lycopene, retinol, Vit. C-Red) was demonstrated between T1DM and control groups. Serum levels of Vit. C-Ox were significant higher in patients with T1DM (Table 1). Moreover, prepubertal T1DM subjects showed higher MDA serum concentrations than controls (p<0.01).
In our T1DM patients the satisfactory glycemic control was coupled with normal lipid profile and normal antioxidant levels. These data confirm that an optimal dietary intervention is able to contrast oxidative processes, even if a more attention to diet composition is needed in some T1DM children and adolescent.

	T1DM	Controls	p
Vit. E (mmol/L)	22.97±9.98	19.26±8.58	ns
β-carotene (mmol/L)	0.86±0.81	0.71±1.23	ns
Lycopene (mmol/L)	0.21±0.20	0.10±0.13	0.006
Retinol (mmol/L)	1.03±0.54	1.09±0.42	ns
Vit. C-Red (mmol/L)	51.04±26.94	45.53±24.10	ns
Vit. C-Ox (mmol/L)	7.12±7.16	1.25±3.29	0.0001

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The effects of metabolic control on oxidized low density lipoprotein antibodies in children and adolescents with type 1 diabetes mellitus

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Objectives: To assess oxidized LDL (oxLDL) antibody status in childhood type 1 diabetes mellitus (T1DM) and to investigate the effect of metabolic control on the oxLDL antibodies.
Subjects and Methods: The study included 36 T1DM patients (6.6-18.1 years) and 20 age-, and sex-matched healthy subjects. Serum levels of oxLDL antibodies, lipids, and HbA1c were measured. The patients with diabetes were divided into two groups according to their metabolic control levels. The group I (the patient group with good or fairly good metabolic control; n: 21) and the group II (the patient group with poor metabolic control; n:15) included children with diabetes having an actual HbA1c ≤ 9 and > 9 %, respectively.
Results: The oxLDL antibody level was higher in T1DM patients than in control subjects [278 (37-1289) vs. 110 (37-235) mU/mL] (p < 0.001). The

patients with diabetes in the group I had higher antibody levels against oxLDL [488 (51-1289) mU/mL] than both those in the group II [183 (37-1207) mU/mL], and control group [110 (37-235) mU/mL] ($p < 0.001$). Oxidized LDL antibodies were inversely correlated with actual HbA1c ($r = -0.42$; $p = 0.01$).
Conclusions: Elevated levels of oxLDL antibodies in pediatric patients indicate that the increased lipid peroxidation in type 1 diabetes begins in childhood. Oxidized LDL antibody levels are inversely correlated with actual HbA1c levels in children with diabetes, as shown adult patients. As metabolic control worsens, the free oxLDL antibody levels decrease probably due to immune complex formation, and the atherosclerosis risk increases. The risk can be diminished by improving metabolic control.

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Effect of fasting or non-fasting state on lipoprotein levels in 24 653 children, adolescents and young adults with type 1 diabetes mellitus

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To investigate the effect of fasting or non-fasting blood sampling on lipoprotein levels we collected cholesterol, LDL-, HDL-cholesterol, and triglyceride levels of 24 653 patients below 20 years of age by using the German diabetes documentation and quality management system (DPV).
Patients on lipid-lowering medication were excluded, 52.5% were male. Mean age was 13.4 years; the mean diabetes duration was 5.2 years. 19.2% of the patients were in a fasting state for at least 12 hours; in contrast, 29.3% of them were not in a fasting state. Fasting status was unclear in the remaining 51.5%.
Results:

Mean (mg/dl)	p	Fasting	Non fasting	Questionably
		N=4,745	N=7,218	fasting
				N=12,690
Cholesterol	p<0.001	183±54	178±45	178±42
LDL-Cholesterol	p<0.001	104±38	96±33	100±38
HDL-Cholesterol	n.s.	60±19	62±19	60±18
Triglcerides	p<0.001	102±92	128±96	121±98

Conclusions: 1.The questionably fasting patients were probably not fasting in the majority of patients.2.Cholesterol and LDL-cholesterol were higher in the fasting state compared to the non-fasting state, probably the endogenous synthesis of cholesterol and LDL-cholesterol is more pronounced compared to gut-derived cholesterol resorption and its metabolism within the liver.3.The levels of cholesterol, LDL- and HDL-cholesterol do not differ markedly in fasting or non-fasting state, however, triglycerides do.

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Impaired circadian blood pressure and heart rate variation in association with QT interval prolongation in adolescents with type 1 diabetes

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The aim of our study was to evaluate the diurnal blood pressure (BP) and heart rate variability (HRV) and their possible relationship to the duration of QT interval in adolescents with type 1 diabetes (T1DM). In 48 normotensive, normoalbuminuric diabetic adolescents, with a mean (±SD) age of 17.3 (±4.1) years and a mean (±SD) diabetes duration of 8.5 (±3.3) years, 24hour ambulatory BP was recorded. Moreover 24hour heart rate (HR) monitoring was performed and QT and corrected QT (QTC) intervals were estimated as indices of autonomic function. The patients were divided into two groups according to the absence of decrease (non-dippers) or the decrease (dippers) of nocturnal diastolic BP (DBP). The non-dippers presented, in comparison with the dippers, increased nocturnal mean HR (916.0 vs 764.4 ms, p=0.001, persistent tachycardia). The non-dippers also presented more prolonged QT interval (366.3 vs 347.5 ms, p=0.015), as well as greater end-systolic (28.7 vs 25.9 mm, p=0.004) and end-diastolic left ventricular diameters (47.8 vs 45.5 mm, p=0.037), in comparison with the dippers. During stepwise multiple regression, HR variables (meanHR, SDNN and rMSSD) and LF parameter of HRV were the most important factors affecting DBP ratio and QT interval, respectively. In conclusion, we found that the normotensive diabetic adolescents with impaired nocturnal BP reduction, also presented impaired autonomic function tests, in association with prolonged QT interval and increased left ventricular diameters. These findings suggest that diabetic adolescents who present the non-dipper phenomenon, may need a close follow-up for the possible development of vascular complications, such as cardiac arrhythmias and left-ventricular hypertrophy.

PO3-303 Diabetes and Insulin 3

Serum adiponectin level in children with type 1 diabetes mellitus: relationship to metabolic control and pubertal development

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Adiponectin, a recently discovered cytokine, is produced exclusively by adipocytes. It also has anti-inflammatory and anti-atherogenic properties. Tip 1 diabetes mellitus has been associated with increased risks for cardiovascular disease and aterogenesis.
The aim of the study was the evaluation of serum adiponectin concentrations in pre-pubertal and pubertal children with type 1 diabetes mellitus and relationship at metabolic control. A total of 60 diabetic children with type 1 diabetes mellitus (5.68-18 years of age) and 42 controls (5.97-18 years of age), were studied. The diabetic patients had significantly higher serum adiponectin levels than the healthy controls (35.70±12.40 µg/ml vs 14.27±6.39 µg/ml; P<0.0001). The group of diabetic patients with good metabolic control (HbA1c<8%) had higher serum adiponectin levels than the group of the bad metabolic controls (HbA1c =>8%) but this difference was not statistically significant. There were no significant differences in serum adiponectin levels between prepubertal and pubertal children with type 1 diabetes mellitus. Adiponectin levels of prepubertal diabetic children had significantly higher than prepubertal control subjects (35.54±12.49 µg/ml vs 14.50±7.08 µg/ml; P<0.0001). In the same way, adiponectin levels of pubertal diabetic children had significantly higher than pubertal control subjects (36.09±12.53 µg/ml vs 13.71±4.42 µg/ml; P<0.0001). Many clinical studies have indicated that adiponectin levels are even higher in type 1 diabetic patients suffering from microvascular complications. In this study, we found that serum adiponectin levels with diabetic children without complications had significantly higher than control subjects. The group of diabetic patients with good metabolic controls had higher serum adiponectin levels than the group of the bad metabolic controls but this difference was not statistically significant. Future studies are required to discover whether pathogenically related to development of diabetic complications or represent a beneficial counter-regulatory response.