Diabetes Acute and Chronic Complications II

P/THU/01

Impaired 24-hour blood pressure variation and endothelial function in adolescents with type 1 diabetes

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Objectives: The aim of the study was to assess endothelial function and subclinical inflammation in type 1 diabetes children with blunted 24-hour BP variation.

Design and methods: The study group comprised 18 children (mean age 13.1 ± 3.2 years, diabetes duration 5.0 ± 2.4 years, HbA_{1C} 7.4 ± 1.4%) with abnormal circadian BP rhythm (''non-dippers''). The controls were 21 gender-, age-, body weight-, and diabetes duration- matched type 1 diabetes children with normal 24-hour BP profile (DM1 controls) and 13 gender-, age-, body weight-matched healthy children (healthy controls). All subjects had ambulatory blood pressure monitoring performed (Spacelabs 90207 ABPM device) as well as plasma adhesion molecules sVCAM and sICAM, sE-selectin, TNF-?, IL-6 and adiponectin measured in a fasting state.

Results: 'Non-dipping' type 1 diabetes children presented with a tendency to greater microalbuminuria than 'dipping' diabetes patients (15.0 ± 19.6 vs. 9.6 ± 7.7 ug/ml, $p > 0.05$), however no other differences in the analyzed endothelial function or inflammatory markers nor in blood glucose control or plasma lipids levels were found between these groups. Moreover, the whole group of children with type 1 diabetes were found to have greater plasma sVCAM and IL-6 concentrations than healthy controls (1249 ± 463 vs. 857 ± 312 ng/ml, $p < 0.01$, and 7.4 ± 6.6 vs. 3.9 ± 1.4 pg/ml, $p < 0.05$, respectively).

Conclusions: Abnormal 24-hour BP variation in adolescents with type 1 diabetes is not associated with increased vascular damage assessed through endothelial dysfunction measurement or presence of elevated plasma inflammatory markers. However, signs of increased endothelium activity and subclinical inflammation are well present even in satisfactorily controlled type 1 diabetes children.

P/THU/02

Assessment of the skeletal status in pre-pubertal children with type 1 diabetes mellitus: a case-match study

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Despite the major progress in the diagnostic of bone metabolism, there is still no agreement wheather disturbances in skeletal status appear already in children with type 1 diabetes mellitus (T1DM). In most of studies decreased bone mineral content was demonstrated.

Objective: The aim of the study was to assess the skeletal status of pre-pubertal children with T1DM by means of Quantitative Ultrasound (QUS).

Methods: 57 pre-pubertal (Tanner stage = 1) children (37 ♂, 20 ♀) aged 3-12 (mean ± SD 7.88 ± 2.47) were included in this study (group 1). The mean duration of diabetes was 3.14 ± 1.61 years. The control group (group 2) comprises of 171healthy children (111 ♂, 60 ♀) in the age of 3–12 years (7.9 ± 2.39). Control subjects were included in the study in the case-match way. Their clinical data were collected at the examination provided for screening purposes.

Determination of anthropometric data was perfomed. QUS was used to measure amplitude dependent speed of sound (AdSOS, m/s) at hand phalanges. Metabolic control of T1DM was assessed by means of HbA1c. Mean HbA1c values from whole T1DM duration(W), last year (Y) and the day of examination (D) were taken into consideration. History of severe hypoglyceamia and ketoacidosis was collected.

Results: Group 1 and 2 did not differ with respect to relative body mass index (rBMI) and AdSOS- values. In group 1 there were no significant differences in means of AdSOS between boys and girls. Also patients with positive history of acute complications did not present any change in bone status. In the group 1 boys showed significant higher values of rBMI in comparison with girls (0.04[-0.24–0.31] vs. -0.47 [-0.76–-0.17], $p < 0.05$). A significant relation was revealed between AdSOS and HbA1c D (-0.1, [-0.38–0.36] vs. 1.47 [-2.85–-0.10], $p < 0.05$). Significantly lower AdSOS values were noted in subjects with HbA1c D and $Y > 7.5$ (-0.18 [-0.34–-0.01] vs.-1.47 [-2.85–-0.10] and -0.21 [-0.37–-0.05] vs. -1.77 [-9.61–6.06]).

Conclusions: The skeletal status in pre-pubertal patients with T1DM does not differ from the one observed in healthy children. The insufficient metabolic control of T1DM seems to affect the bone quality.

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P/THU/03

Mean platelet values in obese children with insulin resistance

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Objectives: Mean platelet volume (MPV) is an indicator of platelet activation. It has been shown that patients with metabolic syndrome have higher MPV compared to control subjects. The obesity and insulin resistance are risk factors for atherosclerosis. The present study, we aimed to compare MPV values between obese children with insulin resistance and healthy controls.

Methods: We measured MPV in 31 obese children and adolescent with insulin resistance (mean: 12.1 ± 2.2 years) and 60 age matched healthy controls. In obese children, fasting glucose, insulin levels, serum lipids were measured and HOMA-IR score was calculated. Insulin resistance was determined according to insulin responses during OGTT.

Results: Mean MPV value was not different between obese children with insulin resistance and control (9.0 ± 1.2 and 9.0 ± 1.1 respectively). MPV also was not found to be correlated with HOMA score, fasting insulin level, Fasting glucose/insulin ratio and waist to hip ratio and serum lipid levels and obesity duration.

Conclusion: Contrary to adult studies we could not find any difference in MPV values between obese children with insulin resistance and healthy controls.

P/THU/04

An unusual presentation of type 1 diabetes mellitus – case report

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Cataract is a rare complication of Type 1 Diabetes Mellitus (T1DM) at presentation. Only a few case reports of cataract being discovered at presentation are found in the literature.

We report a13 year old girl who presented to the ophthalmology emergency with sudden onset of blurred vision due to cataract. She was found to have significant hyperglycaemia despite reporting minimal diabetic symptoms. No other cause was found to explain the cataract. In spite of her vision improving in the subsequent weeks following glycaemic control (reduction of HbA1C from 17.6% to 7.7%) some degree of cataract remained.

This case shows that cataract could be the first manifestation of T1DM and present as sudden deterioration of vision.T1DM is on the increase and it is likely that more cases of cataract may be found at presentation. While emphasizing the importance of measuring blood sugar in all asymptomatic children with cataract we would also recommend opthalmological review in all newly diagnosed T1DM patients.

P/THU/05

Autoimmune hypothyroidism in children with type 1 diabetes mellitus (DM1) and compensated hypothyroidism in adolescents with DM1

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Aims: We wanted to assess the extent of hypothyroidism, both overt and compensated in our patients to help us organize our services to give our patients the best possible care, using the best available evidence.

Methods: Retrospective case notes reviews of children with DM1 and thyroid screening results in adolescents.

Results: Three (3) children with DM1 out of one hundred and fifty (150) who we are currently treating had overt auto-immune hypothyroidism. They were all females. The youngest was diagnosed at four (4) years, when she presented with symptoms and signs of hypothyroidism after 4 weeks history of viral URTI. Her mother suffered from hypothyroidism and lupus disease. She then was diagnosed with DM1when she presented with polyuria and polydipsia at seven (7) years.

The second child was diagnosed with compensated hypothyroidism at nine years (9). Her thyroid-screening test, mainly TSH was abnormal at the time of DM1diagnosis. There was a positive family history of DM in her family, but no hypothyroidism.

The third child was diagnosed simultaneously of overt auto-immune hypothyroidism and DM1 at twelve years of age, when she was investigated for obesity (BMI 35) and chronic constipation.

Thyroid screening tests: we identified six patients with borderline abnormal TFT, mainly TSH (5.9–10.1 umol/l) ref. (0.5–5.5) out of ninety six (96) adolescents with DM1, who had TFT tested at 16–17 years, as part of annual screening. Four (4) were females and two (2) were males. They all had poorly controlled DM; HbA1C (8.7%–14%).

Conclusion: Our screening did not include TAAB, so we are unable to know how many of our patients might be positive. Our overt hypothyroidism in children with DM1was 2%, and compensated hypothyroidism in adolescents with DM1 was nearly 6%, both of which broadly agree with reported prevalence.

P/THU/06

Assessment of high senstivity C-reactive protein and its association with microalbuminuria in type I diabetic children

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Background: Clinical studies have suggested a relationship between pro-inflammatory cytokines and diabetic nephropathy (DN).

Objective: The study aimed at comparing high sensitivity C-reactive protein level in children with T1DM. Also to find out the association between high sensitivity C- reactive protein and microalbuminuria.

Methods: Thirty five healthy controls and 35 diabetic child their mean age (14.7 ± 3.4) and mean duration IDDM (5.1 ± 0.7), were included. All were normotensive. High sensitivity C reactive protein (HsCRP), albumin/creatinine ratio (ACR) in early morning urine sample, lipid profile, HbA1c, and serum creatinine were measured.

Results: HsCRP was significantly higher in diabetic children (0.077 ± 0.018) than control group (0.019 ± 0.02) ($p < 0.5$). HsCRP was higher in diabetic with microalbuminuria. (0.09 ± 0.03) than those with no microalbuminuria (0.74 ± 0.1) but the difference was not significant.(p 0.1) ACR was correlated positively with age at onset of IDDM (r 0.26), total cholesterol (r0.49) and triglycerides (r0.36). According to ROC curve analysis, HsCRP cut-off value that best identified children with microalbuminuria approximated 0.09 mg/l (sensitivity 66.7%, specificity 79.3%).

Conclusion: HsCRP is higher in type I diabetic children compared with normal ones. Further study on large number with different duration of IDDM to find out if HsCRP is an early marker of diabetic nephropathy.

P/THU/07

Scleroderma-like syndrome (SLS) with scleredema in a child with insulin dependent diabetes mellitus (IDDM)

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Background: Microvascular complications of IDDM are well recognized in paediatrics. The occurrence of skin and joint disease especially scleredema (thickening and non-pitting induration of the skin), and scleroderma-like syndrome (limited joint mobility and digital sclerosis) are rarely reported in the literature.

Aim: To present a case of scleroderma-like syndrome with scleredema in an adolescent with IDDM.

Results: A 13 year old boy with IDDM, diagnosed at the age of 7 years, presented in diabetic ketoacidosis. Compliance had been poor since diagnosis and he had been lost to follow-up over the last 4 years. At initial presentation, his C-peptide was < 0.5 ug/l and his Hba1c was 17.7%, the latest being 12.5%. He had several complications related to poor diabetic control namely growth failure, microalbuminuria with nephrotic- range proteinuria,

sensory neuropathy and bilateral cataracts. He also had sclerodactyly with digital sclerosis and limited joint mobility of his wrists and small joints of the hands. There was scleredema of the upper limbs, back and lower limbs. Skin biopsy revealed atrophy of the epidermis together with focal hyalinization of the dermal collagen consistent with scleredema secondary to diabetes. Markers for scleroderma and antinuclear antibodies were negative. The patient was managed with respect to his diabetic control and received rehabilitative therapy for his hands. He improved over the following 2 months.

Conclusion: We have presented a patient with multiple complications related to poor diabetic control, including rare rheumatological and cutaneous sequelae. Limited joint mobility also serves as a marker for and may even precede the microvascular complications of IDDM. This emphasizes the importance of a full skeletal survey at each diabetic consultation.

P/THU/08

Prevalence of cardio-metabolic risk factors in a cohort of children and young people (CYP) with type 1 diabetes mellitus (T1DM)

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Macrovascular disease is the major cause of death in patients with T1DM reducing life expectancy by 20–25 years. The risk factors are not dissimilar to those that constitute the metabolic syndrome suggesting an equally active management programme as seen in type 2 DM may be required. We assessed the prevalence of these factors in CYP with T1D and related results to estimates of diabetes control and insulin regimen (age 13.1 (3.4) years) (44M) of 200 CYP underwent Annual Review in 2007 with measurement of fasting lipids, blood pressure, urinary albumin excretion and estimation of body mass index (BMI). World Health Organisation definitions of the Metabolic Syndrome (MS) were used adaptations of blood pressure, BMI and lipid cut-points for the paediatric population. CYP were grouped according to whether there were between 0 and 4 components of MS present. All data were converted to standard deviation scores (SDS) using appropriate standards for analysis.

Mean height and weight of the CYP were 0.17 (1.23) and 0.60 (0.90) SDS respectively. Average insulin dose was 0.97 (0.38) U/kg/day with 15.5% using twice daily, 45.4% MDI and 39.1% CSII regimens. 64.3% had no features of MS while 27.6% had one, 6.1% two and 2% three components. Females were three times more likely to have features of MS than males (OR 2.9 95%CI 1.2-7.1) (X^2 5.9, p = 0.015). The presence of one or more features of the MS increased the likelihood of microalbuminuria (OR 9.2 95%CI 1.1-9.2) (X^2 5.3, p = 0.02). Neither insulin dose nor current HbA1c were associated with the prevalence of MS factors but insulin pump therapy was more likely to associate with a lower risk for factors (OR 0.32 95%CI 0.1-0.8) (X^2 6.1, p = 0.013).

These data suggest that the prevalence of two or more factors of the MS in this population is 8.1%. The higher female prevalence relates in part to a higher BMI. The mode of delivery of insulin rather than dose appeared to have an impact on the likelihood of risk factor development. The observations suggest that targeted management of these risk factors is warranted early in CYP with T1DM.

P/THU/09

Diabetes mellitus, exocrine pancreatic deficiency, hypertrichosis, hyperpigmentation, and chronic inflammation: confirmation of a syndrome

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Type 1 diabetes mellitus is characterised by dysregulation of the immune system causing inflammation and selective destruction of pancreatic beta-cells. Mild to moderate pancreatic exocrine insufficiency is found in patients with type 1 diabetes. Diabetes mellitus may also be part of a syndrome occasionally involving hair and skin abnormalities. We report our observation on two siblings with insulin-dependent diabetes, severe exocrine pancreatic deficiency, pigmented hypertrichotic skin patches with induration and chronic inflammation. The first sibling presented at 9 months of age with hypertrichosis and hyperpigmentation, particularly on her back and legs and then developed diabetes mellitus at the age of 4 years. The second sibling presented with exactly the same clinical features but at a later age of 12 years. Both siblings have severe pancreatic exocrine deficiency with chronic persistent inflammation. They also have severe growth retardation and elder sibling in addition has pubertal delay. Some of the clinical features in these siblings resemble those described by Prendiville et al (1) although our patients have additional features. The chronic inflammatory response in both siblings is highly suggestive of some form of immune dysregulation. The presence of consanguinity in the parents and similarity of clinical features in the siblings are suggestive of a novel autoimmune disorder, possibly secondary to autosomal recessive inheritance.

Reference:

1. Prendiville J, Rogers M, Kan A, de Castro F, Wong M, Junker A, Becknell C, Schultz K. Pigmented hypertrichotic dermatosis and insulin dependent diabetes: manifestations of a unique genetic disorder? Pediatr Dermatol 2007 Mar–Apr; 24(2): 101–7.

P/THU/10

Adiponectin level in children with type 1 diabetes mellitus and its relation to carotid-artery intima and media thickness

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Background: Adiponectin is an anti-inflammatory and antiatherogenic hormone. It inhibits neointimal thickening and vascular smooth muscle cell proliferation.

Aim: The aim of this study to evaluate adiponectin level and its relation to carotid intima media thickness (cIMT) in children with T1DM.

Subjects and methods: Forty-six diabetic children mean age (13.59 ± 3.64 years). The mean duration of diabetes (40.35 ± 2.19 years).the mean HbA1C (8.35 ± 2.92). Thirty six healthy control subjects took part in this cross-sectional study. All children had normal blood pressure for age and sex and no microalbuminuria. Adiponectin, albumin/creatinine ratio (ACR) in early morning urine sample, lipid profile, and HbA1c, were measured.

Results: Adiponectin level was significantly lower in children with T1 DM than control (9.49 ± 1.74) and (10.31 ± 1.45) respectively P 0.02. Children with T1DM had significantly higher cIMT than control (0.57 ± 0.08) and (0.43 ± 0.07) respectively P 0.00. Adiponectin level correlated negatively with cIMT P0.01. Diabetic children with good metabolic control (A1C < 7) had no significant difference in Adiponectin level compared to control (10.22 ± 0.81) and (10.31 ± 1.45) P0.82, although they had higher cIMT (0.49 ± 0.064) and (0.43 ± 0.049) P0.00 .The most fitting factor that can predict cIMT was BMI t3.61 P0.00. Adiponectin was significantly higher and cIMT was significantly lower in those with good (10.22 ± 0.81) (0.49 ± 0.064) than those with poor metabolic control (9.27 ± 1.74) (0.62 ± 0.081).
Conclusion: Diabetic children had lower level of Adiponectin than control. There was no significant difference in adiponectin level in diabetic children with good metabolic control than healthy children.

Diabetes Care, Education, Psychosocial Issues III

P/THU/11

Adolescent care in South Africa: a human rights issue

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Adolescents are frequently the last group considered when it comes to the supply and management of health care. This is partly due to their lack of power and partly due to the conception that they are a particularly healthy group. While the latter statement may be true for many, adolescents comprise a large proportion of the population in South Africa, estimated to be 21%, which is almost 10 million people.
Where does the adolescent fit in?
In most public hospitals, adolescents (children from the age of 13) are admitted to the adult service. This contrary to the Constitution, which declares that children are persons under the age of 18. In the same way that there has to be special provision in the courts and in the prisons for children, there has to be special provision for children between the ages of 13 and 18 in the health-care system. This is currently not the case.
Development: Paediatricians are constantly concerned with growth and development in their patients; this applies equally to all patients, from the neonate to the late adolescent. By contrast, physicians do not consider development in their patients at all. Furthermore they frequently have little understanding of the mental world of the adolescent. Consequently erratic behaviour and wilful misbehaviour is often ascribed to adolescents when this is not the case. Being looked after by health-care providers who have a prima facie distrust of their patients is unhealthy, unfair, and frankly unethical.
Conclusion: It is clear that paediatricians are best qualified to look after adolescents. Furthermore, adolescents do not fit in well in adult wards. There is also the situation that paediatric services are frequently well-organised in contrast to the adult health care services. Consequently there should be adolescent clinics for all common chronic diseases, there should be separate adolescent wards where the patients are cared for by interested nurses and specialist paediatricians, and the adolescent services should be completely and totally separated from the adult services. It should be clear that these requirements are not optional extras or ''nice-to-haves'', but are absolutely essential in terms of the imperatives of Human Rights.

P/THU/12

Diabetes youth leadership training as a core to a diabetes camp program and achievement of self-empowered diabetes control

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Aim: Diabetes camp programs form an integral part of diabetes care. They are ideal for giving parents a break and create an ideal opportunity for training in a non-threatening environment. Children learn to have fun with diabetes and share ups and downs with new friends and form lasting relationships. Our aim was to train diabetes youth leaders (DYLs) to facilitate the safe and smooth operation of the camps. Through an intensive education program DYLs would be equipped with knowledge and leadership skills.
Methods: Twenty three teenagers with reasonable diabetes control and leadership traits were selected from major centres in South Africa to attend a weekend training camp in May 2005. The training was extensive and covered pathophysiology of diabetes, insulin usage including insulin pump therapy, hypoglycaemia prevention and hyperglycaemia and sick-day management. How diet and exercise influence blood sugars, injection techniques and logistics of camping and leadership skills training.
Results: Since inception 50 teenagers have undergone training. Ten of the teens from the Johannesburg region have been used at regular camps throughout 2005–2008. The Average HbA1c prior to the training was 8.9% and nearly 3 years after 7.2%. Half are on CSII, the other half on MDI.

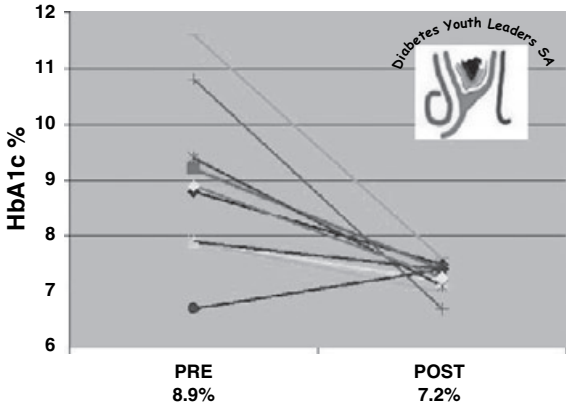

Figure 1. Pre and Post HbA1c

Discussion: The training program was a major success. The DYLs have become role models to other campers, have created support groups in their own communities and founded the first national diabetes youth foundation (FYWD) in South Africa. They have become ambassadors for diabetes and have in fact hosted question and answer sessions at a national diabetes conference attended by over 150 doctors and allied professionals. The HbA_{1c} improvement was immediate and sustained, during a developmental period when most HbA_{1c}'s are on the rise.

P/THU/13

Confidence in diabetes self-management and locus of control at the time of transition to adult care

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Objectives: In a prospective study the conventional regimen of direct transfer at the age of 18-19 y to the adult clinic was compared to a new regimen including 2 years of preparation for the transfer on an individual and group level.

Methods: All patients at our clinic born 1988 (n = 45) and 1989 (n = 50) were at the age of 16 y asked to participate in the study of which 27% and 46% respectively accepted. Of these patients 66% respectively 48% used insulin pumps. The patients were offered combined meetings with diabetologists and diabetes nurses from both the pediatric and adult clinic at four occasions before transfer and were introduced to the routines of adult outpatient clinic 1 year in advance. They were also offered four group sessions. The first meeting included cooking while choices of food was discussed and prepared in company with dieticians from both clinics. At other occasions sexuality, physical activity, drugs and coping strategies were discussed.

Results: HbA1c was stable on 8.4% for those patients born 1988 from 16–18 years when transfer was performed. Corresponding value was a rise from 8.4 to 8.8% for patients born 1989. There was a sign greater number of patients who had increased their confident in their abilities to manage their diabetes ($p = 0.007$). There was also an increase in the number of patients who have a greater internal locus of control ($p = 0.007$). The number of patients needing contact with health services did not increase or decrease over the transfer period.

Conclusions: The regimen of transfer is of importance for the patients and cooperation strategies between pediatric and adult clinics should be recognized in guidelines.

P/THU/14

Diabetes in transition: how and where are our patients now? Glycaemic control and uptake of diabetes services in young people aged 15 to 25

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Introduction: Transition is a process that attends to the medical, psychosocial and educational needs of young people as they transfer to adult-orientated care. At our institution, a young adult diabetes service (YADS) was developed 15 years ago to cater for young people aged 15 to 25 years. Within one multidisciplinary clinic, paediatric and adult diabetes specialists work together to facilitate transition from paediatric to adult care.

Objectives: i) To assess glycaemic control, frequency of follow up, and continuity of care in a cohort of young people aged 15 to 25, and uptake of the YADS clinic service.

ii) To identify individuals lost to follow up by a diabetes specialist service.

Methods: We undertook a questionnaire based survey by mail or telephone of young people in the area served by our health service to assess how many were accessing specialist diabetes services (including YADS) and possible barriers to attendance. Ethics approval was obtained for the survey to be carried out. Lost to follow up was defined as attendance at a specialist service less frequently than 12 months.

Results: Four hundred eligible young people in the Southern Health catchment area were sent questionnaires. To date, 310 (62.5%) have been contactable; of these 243 (49%) have agreed to complete the survey, 67 (13.5%) declined to participate. Mean HbA1c among survey responders (by self report) is 8.32%; this compares to 8.7% for the clinic as a whole. Mean time since last HbA1c (by self report) was 3.0 months (range 1–24 months) with 64% being seen within 3 months. Young people attending YADS were more likely to have been seen within 3 months than patients not attending YADS ($p < 0.05$ $?^2$ test). Among responders, 63.3% attend YADS, 30.2% another specialist diabetes service and 6.4% have no specialist input. At least 5% of responders were seen less frequently than 12 monthly, indicating loss to follow up.

Conclusions: Regular follow up and reasonable glycaemic control is demonstrated among responders in this challenging age group. Continuity of care is provided for many through YADS. So far only 62% of the survey group has been contactable and includes those with better attendance and glycaemic control. A significant minority remain lost to follow up and have not been reached through our survey approach. Further strategies need to be developed to access this challenging group.

P/THU/15

Validation of a questionnaire of knowledge for type 1 diabetes children and adolescents and their parents

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Objective: To evaluate the impact of an educative programme on the knowledge of children (> 10 year), adolescents and parents in a national survey.

Methods: A national Educative Committee has elaborated a ready-to-use educative programme for the newly diagnosed patients, in order to make education accessible to all care-givers, patients and parents. A first step in the evaluation of this programme, a standardized questionnaire of knowledge has been validated. Based on the content of the programme, 310 questions (true/false) were elaborated and entered in a systematic process to select 50 questions for a final validated questionnaire. This process has implicated the contribution of 2500 patients or parents, in diabetic camps and 33 pediatric centers, of the Educative Committee following specific statistical analyses (hierarchical cluster analysis using Ward minimum variance method, test-retest), and a 5 year-long effort. With the initial questions (n = 310), 3/4 of the participants gave more than 70% of good answers; the selective process eliminated mostly "easy" questions, decreasing the number of "good" answerers by about 10% and increasing differences with age; a change viewed as favourable in an educative perspective. The distribution of the various themes (insulin, monitoring, dose adjustment, emergencies, diet ...) was unchanged along the selective process.

Results: The final questionnaire has been tested in 3023 children (> 10 years) and adolescents (49% girls, 51% boys; 14.0 ± 2.5 years) and their parents (6063 questionnaires), in 115 pediatric centers. The questionnaire was completed by the child plus the mother in 58% of cases, the father in 12% and both parents in 15%. 80% of the responders knew the educative programme and more than 60% consulted regularly. 60% of the mothers gave more than 80% of good answers, 50% of fathers and 40% of children (all ages together). Detailed analyses is evaluating: specific changes in knowledge with age; relationship in knowledge between children and parents; correlations with duration of diabetes, HbA1c, treatment regimen, and socio-demographic characteristics; knowledege among centers and their characteristics.

Conclusion: A questionnaire of knowledge has been validated and used in a national survey of children and adolescents with type 1 diabetes and their parents.

P/THU/16

Development of the Mulago Hospital pediatric diabetes program

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Objective: Pediatric diabetes has a high mortality rate in sub-Saharan Africa. Mulago Hospital is the national pediatric referral center in Uganda, associated with the Makerere University Medical School. A visit by a US pediatric endocrinologist in summer 2007 revealed significant problems, including a critical and life-threatening lack of insulin and other diabetes supplies, inconsistent ability to get a blood glucose measurement in the hospital or clinic (and no home glucose monitoring), poor understanding of diabetes pathophysiology and treatment by nurses and residents, no pediatric diabetes protocols, and no education materials for either health care providers or patients. A collaboration was formed to develop the infrastructure and expertise necessary for a self-sustaining pediatric diabetes program in Uganda.

Methods: A multidisciplinary pediatric diabetes team was formed, led by Mulago pediatrician Dr Grace Buwule. The team includes a senior pediatrician, a junior pediatrician, a pharmacist, two pediatric nurses, and a nutritionist. University of Minnesota personnel have visited Mulago on multiple occasions and have sponsored a visit by the Ugandan team to Minnesota for education and training.

Results: Formal protocols have been developed for hospital diabetes screening and for inpatient and outpatient treatment using the insulin types commonly available in Uganda. Patient education and self-management materials were created and are being translated into local languages. Dr Buwule has organized on-going educational lectures for pediatric residents and nurses. The pharmacist and the UM team are exploring options for improving insulin insecurity for pediatric patients. A record keeping system has been established to monitor both patient and program outcomes.

Conclusions: The Mulago Pediatric Diabetes team has taken the first steps towards promoting early detection of diabetes in children, delivery of consistent quality of care, providing patient self-management education and ongoing education to nurses and pediatric residents (the next generation of pediatricians), and improving the availability of affordable medication and supplies. The long-term goal is that after 3 years the program will be sufficiently developed and self-sustaining to allow establishment of outreach programs to other hospitals and clinics in Uganda.

P/THU/17

Do adolescents with type 1 diabetes have a different health perception than their peers?

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Objective: Evaluate health perception of adolescents with T1DM.

Methodology: In a multi-center cross sectional study, clinical data and questionnaires including 3 questions from the HBSC[1] (health perception, standard symptom checklist (subjective health complaints) and life satisfaction (Cantril ladder)) were completed by adolescents with t1dm, from 21 centres from 19 countries.

Results: Questionnaires were completed by 2062 adolescents (age: 14.4 ± 2.3 years; 50.6% male; diabetes duration: 6.1 ± 3.5 years; HbA1c 8.2% ± 1.4). Analysis of variance, indicates significant gender differences for all measures, with girls reporting more complaints, being less satisfied and have poorer self rated health ($p < .001$). Older participants reported less satisfaction ($r = .12$; $p < 001$) and poorer health ($r = 16$; $p < 001$). There were also significant differences between diabetes centers for measures of life satisfaction ($F = 3.00$; df = 20; $p < .001$), adolescents rating of their health ($F = 3.21$; df = 2; $p < .001$) and the number of subjective complaints ($F = 4.79$; df = 2; $p < .001$). Life satisfaction and self-rated health were correlated with BMI ($r = .15$; $r = .11$; $p < .001$), frequency of DKA ($r = .12$; $r = .09$; $p < .001$) and HbA1c ($r = .22$; $r = .12$; $p < .001$). Comparing the adolescents health perceptions with a large international survey[1], using the same measures, significantly (χ^2 - 12.38; df = 2; $p < .01$) more adolescents with diabetes rate their health as fair or poor (%).

Conclusion: Health perception of adolescents with t1dm seems to differ from their peer group (HBSC). As time and background country may have an impact on the perceived health, a comparison with the peer group in HSG countries in the year 2005 is necessary.

[1]www.hbsc.org

P/THU/18

Active intervention programme for diabetes management - audit

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Background: The Active Intervention Programme (AIP) is a nurse-led diabetes programme established with the aim to support and motivate individuals whose HbA1c equals to or exceeds 9%. Our department has approximately 450 attendees with type 1 diabetes, ranging in age from 18 months to 18 years. Patients are reviewed three monthly, glycemic control (HbA1c) measured using Bayers DCA 2000. AIP involves regular contact with a clinical nurse specialist and dietitian, a clinical psychologist and medical social worker are available as deemed necessary. Attendees are reviewed outside of routine clinic appointments in an informal setting during which the attendees' lifestyle and Diabetes management is discussed with the aim of empowering the individual to manage their Diabetes safely and promote optimal control.

Objective: This was a retrospective audit with the aim of assessing the value of a more intensive less formal approach to review.

Method: Forty five (females n = 31) of the 90 individuals who attended AIP in the past 2 years were chosen at random. The age range was 8–17 years. Age, gender, reported insulin dose (IU/Kg/day), HbA1c, participation in AIP, severe hypoglycaemic episodes and Diabetic Ketoacidosis (DKA) were reviewed. Changes were assessed statistically using a paired *t*-test.

Results: Improvements in HbA1c were found, with an average decrease of 0.9% at 2 years (10.3%–9.4%). A statistically significant reduction in HbA1c was noted between 0 and 6 months ($p = 0.003$) and 0 and 12 months ($p = 0.008$). However there was no significant difference between baseline values and those measure at 18 and 24 months ($p = 0.3$).There was no statistical difference in reported insulin dose from initial contact to completion of the Programme.

Conclusion: The audit's findings highlighted that an informal multidisciplinary approach to Diabetes management can effect a

sustained improvement in HbA1c even up to 2 years. This was statistically significant for the first year of follow up but became less so after this. The improvement in HbA1c was not associated with an increase in insulin dosage implying probable non-compliance issues in the first instance.

P/THU/19

Impact of diabetes education on type 1 diabetes control in children and adolescents during the years 2003–2004–2005, Córdoba

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Aims: To know about the impact that the Annual Cycles of Diabetes Education (ACDE) have on type1 diabetes treatment in children and adolescents through its effect on HbA1C values and hospitalizations.
Methods: The HbA1C and hospitalizations due to type1 diabetes complications in 40 children and adolescents; 17 of whom were boys that attended the ACDE for 3 years, attending the Hospital de Niños de la Santisima Trinidad with an average age of 12 ± 3 ranging from 4 to 18 were analyzed. The disease average time was 4.12 ± 2 years. The number of annual hospitalizations and HbAC values of the previous year and the subsequent 1, 2 and 3 years were considered. The HbAC1 was analyzed by the automatic immunochemical method.
Results: The HbA1C level before entering the ACDE was 11.54% ± 3; 1 year later: 11.46% ± 3.2; 2 years after: 11.23% ± 2.8; 3 years later: 10.9% ± 2.6. The first year: $p = NS$, the second year $p = NS$, the third one $p < 0.008$. Hospitalization number due to complications the year before ACDE was 17, suffered by 6 patients and the average of the subsequent 3 years was 13.98 ± 1.2. Though the relationship was non significant the first year, on the second one it was $p < 0.001$ and the third $p < 0.002$.
Conclusions: i) The decreased number of hospitalizations due to complications was highly significant from the second year of ACDE. ii) HbA1C levels were significantly reduced from the third year.

P/THU/20

Examining the influence of local dishes and changing lifestyles of the masses in relation to diabetes mellitus prevalence

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Background: Researching on impact of local dishes and lifestyles of the masses on diabetes in relation to common local factors either directly or indirectly.
Method: Diabetics living within reach are visited regularly for about 6 month prior the research. This gives the opportunity to observe their eating habits, food dishes each loves or eats most, compliance to education lessons at clinic ground; then assessing their blood sugars for 3–6 months.
Results: Because of certain factors, some of which were noted as: cultural, ignorance, illiteracy, poverty and depression; the eating habits alongside blood sugars were closely inter-related. Culturally, some title holders like chiefs that are diagnosed with diabetes mellitus-whether educated or not, even after counseling, are bound to cultural demands requiring sacrifices maybe on daily basis compulsorily followed by feasting uncontrollably; some could not keep educational lessons into practice due to ignorance, illiteracy, or poverty. Others are seen not able to control their appetites and meal quantities each session, others frequently feed on fatty or dense starchy local dishes-perhaps known as the tribés favorite or so which can be related to depression as they are fully aware of the consequences and often refusing the their situations.
Conclusion: A good number of people in the clinic estimated up to 50% are known to have average glucose control BUT victims of the results stated above constitute the ''roller coaster'' and complications group. They are known to have common features or complaints of urinary tract infection, abscesses, vision problems. There is really much work to be done BUT the diabetes professionals are not there.

P/THU/21

Effects of surgical periodontal therapy on metabolic controls of diabetes

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Objectives: Diabetes mellitus is the most prevalent metabolic diseases and periodontal disease is the sixth complication of diabetes. These two diseases can aggravate each other. The object of this study was to evaluate the effect of surgical periodontal therapy on metabolic controls of NIDDM patients with juvenile periodontitis.
Methods: This semi-experimental study was performed on 18 young patients with NIDDM and also moderate to advanced juvenile periodontitis (age: 19.3 ± 2.1 years). First of all, periodontal indices including probing depth, clinical attachment level, gingival bleeding index, plaque index and laboratory tests such as FBS and HBA1c were evaluated. Then, oral hygiene instruction, scaling and surgical flap-debridements were performed. All the indices and tests were re-evaluated 3 months after final surgery. Non-parametric tests with an alpha error level less than 5 % determined the statistical significance.
Results: All periodontal indices were decreased significantly. Laboratory tests were significantly decreased only in the patients with poorer diabetic control (HBA1c > 7%).
Conclusions: We strongly recommend that periodontal surgery can be a good way to delete potential oral source of infection in peoples with diabetes.

Diabetes Genetics, Immunology

P/THU/22

Serum 25 OH vitamin D status is similar in healthy controls and subjects with or at risk for type 1 diabetes

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Objectives: Type 1 Diabetes (T1D) has the classical hallmarks of an autoimmune disease, with both environmental and genetic factors playing a role in the disorder's etiopathogenesis. Vit D (Vit D) polymorphisms have been associated with risk for T1D. Other studies have indicated that subjects developing T1D have lower serum levels of Vit D. In animal models of T1D, removal of Vit D accelerates onset of T1D and pharmacological treatment with Vit D analogues prevents or delays the disease. Therefore, we questioned whether serum levels of 25 OH Vit D from subjects associated with a risk for T1D in a solar rich environment (Florida, USA).
Methods: Banked serum from healthy subjects (n = 151), T1D (n = 157; 45 onset < 5 months; 112 onset > 5 months) and first degree relatives (n = 109) were analyzed. A commercial ELISA

was utilized to measure 25 OH Vit D levels (duplicate). The intra- and inter-assay coefficients of variation were 10.7% and 13.2% respectively. Statistical analysis was conducted using the Kruskal Wallis non-parametric test with Dunn's post-test.

Results: Serum levels of 25 OH Vit D (nmol/l; mean ± SD) were 70.3 ± 64.0 in controls; 54.9 ± 30.0 in new onset T1D; 68.9 ± 70.1 in long standing T1D; and 58.3 ± 35.0 in first degree relatives. These levels were not different from each other ($p > 0.05$). We also looked into effects of sunlight by comparing serum levels of 25 OH Vit D using published average UV indices for each month of the year and found no statistical association. Further, age and gender did not associate with Vit D levels. Interestingly, a finding that was consistent in all groups was that approximately two-thirds of individuals from each group contained less than 75 nmol/l; a level recently suggested as a cut-off for Vit D insufficiency.

Conclusions: We found no evidence that serum 25 OH Vit D correlates with T1D. However even in a geographical location with abundant sunshine and Vit D fortification of cow's milk, there may be an under appreciated relative deficiency. These data question studies suggesting that low levels of Vit D are directly associated with disease risk, but additional longitudinal studies will likely be required to further ascribe any association with T1D.

P/THU/23

Th1 and Th2 cytokine regulation in juvenile patients with both diabetes mellitus type 1 and asthma

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Background and objective: We recently demonstrated that patients with both Th1 mediated (T1DM, type 1 diabetes mellitus) and Th2 mediated (asthma) autoimmune diseases express a unique Th1 and Th2 cytokine pattern, which is different from patients with one disease only and controls. This may result from regulatory cytokine defect. Our aim was to further clarify the role of the regulatory cytokine IL-10 in these patients.

Methods: Patients were matched by gender, age and disease duration, to 4 paired groups: T1DM and asthma, asthma only, T1DM only and healthy controls. Each group included 11 patients, 3 females and 8 males, mean age 19 years. Peripheral blood mononuclear cells (PBMC) were isolated from whole blood. Levels of IL-10 in the serum and from PHA and LPS stimulated PBMC were determined using Enzyme-linked immunosorbent assay (ELISA). In-groups statistical analysis was performed using Spearman correlation. Between-groups analysis was performed using the Wilcoxon Signed Rank Test. Results were significant if $p < 0.05$.

Results: Patients with both asthma and diabetes had similar serum level of IL-10 as healthy controls (7.36 pg/ml, 5.03 pg/ml, respectively). Patients with asthma only had significantly higher serum level of IL-10 compared to controls (82.06 pg/ml vs. 5.03 pg/ml, $p = 0.024$). In contrast, patients with asthma only demonstrated significantly lower IL-10 levels after PBMC stimulation with PHA as compared to those with both asthma and diabetes (2393.75 pg/ml vs. 4911.52 pg/ml, $p = 0.006$). Healthy subjects displayed similar stimulated IL-10 levels to patients with both diabetes and asthma (4456.03 pg/ml and 4911.52 pg/ml, respectively). IL-10 secretion following LPS stimulation was lower compared to PHA in all groups, without differences.

Conclusion: The different pattern of un-stimulated and stimulated IL-10 levels in these patients may suggest a possible defect in their immune regulation. Further determination of the IL-18 and IL-12 regulatory cytokines is currently underway and will be discussed.

P/THU/24

Neonatal diabetes mellitus: the first investigations of more frequent mutations in Russia

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Neonatal diabetes mellitus (NDM) is rare (1 per 400 000 newborn), but genetically heterogeneous disease with manifestation in first 6 month of life. There are two main groups: transient NDM and permanent NDM. The more frequent mutations revealed in Kir 6.2 and SUR 1 genes. Interestingly, that the presence of these mutations allows to change insulin therapy to sulfanil urea medications in most cases.

Objectives: To investigate the spectrum of mutation in Kir 6.2 and SUR1 genes.

Materials and methods: At the present time genetic materials is received from 9 families with child (2M/7F) from different Russian regions. The children's age is from 1 month to 9 years, the age of diagnosis is from 1 day to 3 month, age of gestation is from 33 to 40 weeks. SGA was occurred in 2 patients. The birth weight was from 1300 to 3140 grams. The onset glycemia was from 15.0 mmol/l to 50.0 mmol/l. Transient NDM occurred in two patients at the time of examination. DEND syndromes were revealed in 1 patient. The full sequence of Kir 6.2 genes was performed in 9 patients.

Results: One patient has frequent mutation Arg201His, another patient has novel mutation Ile284Phe in heterozygous position. Three patients was revealed substitute Ile284Phe also in heterozygous position. A Pathogenetic significance of this mutation is unclear and it should be required further investigation. Interestingly, four patient has substitute Glu23Lys in homo- and heterozygous positions. There are some publications describing that this polymorphism is a one of genetic factors predisposing to DM type 2.

Conclusion: This data demonstrates the existing genetic heterogeneity of NDM. It requires further obligate performing the wide spectrum of molecular investigation for this disorder.

P/THU/25

Diabetes specific auto-antibodies and β-cell function 3–5 years after the diagnosis in diabetic children

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Objective: The fate of diabetes specific antibodies and residual β-cell function (RBF) over time after diagnosis of type 1 diabetes

(DM) in children are not well characterized. In the future, immune intervention aiming to reduce autoimmunity and preserve RBF might be an option. The aim of the study was to examine auto-antibodies (A) against GAD65 and IA-2 at diagnosis and after 3–5 years of DM and to study the association between GAD65A and IA-2A and RBF 3–5 years after diagnosis.

Methods: Three hundred and forty-eight children (176 males) with a mean (SD) age of 12.9 (3.3) years, and type 1 DM for 3–5 years were included. GAD65A and IA-2A were assessed at diagnosis (n = 263) and after 3–5 years. RBF was assessed by testing meal stimulated C-peptide (MCP).

Results: Of the 348 children 71% were GAD65A positive (levels > 10 U/ml), 66% were IA-2A positive (levels > 5 U/ml), 21% had only GAD65A, 16% only IA-2A and 13% were antibody negative 3–5 years after diagnosis. At onset the antibody distribution was: GAD65A - 91%, IA-2A - 78%, GAD65A only - 19%, IA-2A only – 6.5% and 3% were antibody negative. Mean GAD65A and IA-2A levels were significantly higher at diagnosis than after 3–5 years of DM, $p < 0.0001$ Of the 263 children with antibody examination at diagnosis and after 3–5 years of DM, 140 had no RBF (MCP < 0.01 nmol/l), 75 had a low RBF ($0.01 \leq$ MCP < 0.1 nmol/l), and 48 had a high RBF (MCP ≥ 0.1 nmol/l) after 3–5 years of DM.

		GAD65A (U/ml)	GAD65A (U/ml)	GAD65A		IA-2A (U/ml)	IA-2A (U/ml)	IA-2A	
	n	At onset (mean)	After 3–5 years	Difference	*t*-test	At onset	After 3–5 years	Difference	*t*-test
Non-RBF	140	177.2	94.6	-82,6	P < 0.00001	141.2	61.4	-79.8	p < 0,00001
Low-RBF	75	174.4	105.1	-69.3	p < 0.00001	122.4	65.8	-56.6	p < 0.00001
High-RBF	48	157.0	127.7	-29.3	p < 0.02	119.4	72.5	-46.9	p < 0.00005
			ANOVA	p < 0.02			ANOVA	p < 0.02	

The table shows the association between mean antibody level at diagnosis and after 3–5 years of DM stratified for high, low and no RBF after 3–5 years of DM.

Conclusions: A large percentage of children diagnosed with type 1 DM have a residual β-cell function after 3–5 years of DM. GAD65A and IA-2A decreased significantly after diagnosis. The highest mean antibody level at diagnosis was found in children with no RBF after 3–5 years DM, and the highest mean antibody level after 3–5 years of DM was found in children with a high RBF after 3–5 years. If immune-modulation with preservation of β-cells becomes an option, this might be an offer also after 3–5 years of DM to children with high GAD65A and IA-2A and RBF.

P/THU/26

The -174 G to C polymorphism of interleukin-6 gene and its association with body mass index in women with type 1 diabetes mellitus

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Introduction: Interleukin-6 is an inflammatory cytokine carrying the -174 G to C polymorphism in the promoter region. The presence of a G allele has been linked to an earlier onset of type 1 diabetes mellitus (DM1), and to hyper androgenism and higher body mass index (BMI) in healthy women.

Aim: To evaluate the association of the -174 G/C polymorphism of the interleukin-6 gene (*IL-6*) with body mass index (BMI) and hyper androgenism in DM1 women in a case-control study.

Methods: Patients with DM1 (n = 99, age 17.8 ± 1.1 year) and healthy non-hyper androgenic women and girls (n = 109, age 18.8 ± 1.2 year) were studied. BMI Z score was calculated. Serum testosterone, androstenedione, DHEA-S levels were measured in serum obtained during follicular phase. The -174 G/C IL-6 polymorphism was evaluated by the polymerase chain reaction (PCR) followed by restriction enzyme analysis.

Results: Both groups had a similar genotype distribution and allele frequency (Table). An association of the GG genotype with BMI Z score was observed in adult DM1 women only. DM1 women with a GG genotype had a higher BMI-Z score compared to those with CG genotype (1.0 ± 0.1 and 0.65 ± 0.1, respectively, p = 0.04). Androgen levels were similar in women of both groups with different genotypes.

-174 G/C IL-6 polymorphism	DM1 (n = 109)	Controls (n = 99)
Genotype (N/frequency)		
GG	67/0.615	65/0.656
GC	39/0.360	25/0.252
CC	3/0.025	9/0.091
Allele frequency (%)		
G	79.4	78.2
C	20.6	21.3

Conclusions: -174 G/C polymorphism of *IL-6* may influence body weight gain in DM1 women. Our data suggest that pro-inflammatory genotypes may be related to the susceptibility to a higher body weight observed in some DM1 women (Fondecyt 1050452).

P/THU/27

Is -174GG interleukin-6 gene polymorphism associated with protective function against microvascular complications in children and adolescents with diabetes mellitus type 1?

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Introduction: Many studies have reported that in addition to metabolic and genetic factors also immunological factors contribute to diabetes mellitus profile. IL-6 is a multifunctional cytokine, affecting proliferation and differentiation of a wide variety of cells, including B lymphocytes. Previously published investigations have shown that the level of secreted IL-6 depends on the G/C polymorphism at the position- 174.

Aims: The aim of our study was to analyze the distribution of the IL-6 -174G/C polymorphism as well as the relationship between the G/C polymorphism and incidence of micro angiopathy in children and adolescents with DM type 1.

Materials and methods: Two hundred and thirty-six children and adolescents with DMT1 and 164 healthy controls were enrolled in the study. Basic laboratory data and ophthalmologic examination were obtained for all the patients. Serum and urine levels of IL-6 were measured by ELISA method. Genomic DNA was isolated with the DNA Blood Mini Kit according to the manufacturer

protocol. IL-6 gene polymorphism at position -174 was analyzed by PCR-RFLP method. PCR was performed using primers: 5'CAGAAGAACTCAGATGACTGG 3'and 5'GCTGGGCTCC-TGGAGGGG 3'and its products were digested with SfaNI enzyme.

Results: There were no significant differences in the clinical characteristics as well as metabolic parameters between the genotypes (GG, GC and CC). Diabetic patients and healthy controls had distinct distribution of the IL-6 -174G/C genotypes. The frequency of the -174GG genotype was lower in patients with diabetes mellitus. Patients with retinopathy having the -174CC and GC genotypes were characterized by higher plasma and urine levels of IL-6 compared with those with C allele, as compared with those who also had C allele but presented no sign of diabetic complications. Analysis of the patients presenting no sign of late diabetic complications revealed that those with the GG genotype were characterized by higher levels of plasma and urine IL-6 compared with those who had C allele.

Conclusions: We have found that the IL6 -174GG homozygotes were under-represented in the DMT1 children and that these patients were free from retinopathy and nephropathy. Our study suggests that the IL6-174GG genotype may be associated with a protective effect against diabetic micro angiopathy.

P/THU/28
HLA-haplotypes in some Russian Federation populations

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Aim: To detect, related with type 1 diabetes development, susceptible and protective haplotypes of HLA locus in Bashkiria, Vologda, Buryatia, Moscow and Yakutia regions populations.

Material and methods: HLA-genotyping was performed in 364 patients with type 1 diabetes and in 638 control subjects in the mentioned above populations. Class II HLA genotyping was based on PCR-SSO DNA typing techniques.

Results: The major susceptible haplotype DRB1*4-DQA1*301-DQB1*302 in European populations has been registered in all groups studied, however in acts as the major susceptible one [odds ratios' (OR) > 8] only in Bashkiria population; in other ethnic groups OR values varied from 4 to 6. The second highly susceptible haplotype DRB1*17(03)-DQA1*501-DQB1*201 in European populations has been registered in all our populations except Buryate one, moreover in Yakute population its OR was > 8 whereas in all other populations OR values were about 4. Protective haplotype DRB1*15-DQA1*102-DQB1*602/8 was registered four out of five (except yakute) populations; OR values varied from 0.04 to 0.25 in all groups studied; however it acts as the most ''strong'' protective one (OR > 0.04) only in Vologda population. The second protective haplotype DRB1*13-DQA1*103-DQB1*602/8 in European populations is registered in three populations, except Buryate and Bashkiria ones, moreover, in Moscow population its OR value was 0.006, while in other populations it was weaker (OR = 0.28; 0.29). Besides traditional for Europeans haplotypes the unique haplotypes have been detected in the populations studied. In Moscow population susceptible haplotypes DRB1*4-DQA1*301-DQB1*304 and in Vologda population - DRB1*16-DQA1*102-DQB1*602(8) have not been associated with diabetes in any ethnic groups studied in Russian Federation territory. The most highly protective allele DQB1*602(8) is represented in the latter haplotype, that set it apart from all the susceptible haplotypes. The susceptible haplotype DRB1*08-DQA1*301-DQB1*302 has been discovered in Buryate population. There have been also discovered protective haplotypes, unique for separate ethnic groups: DRB1*13-DQA1*501-DQB1*301 - for Moscow population (OR = 0.1), DRB1*9-DQA1*301-DQB1*303 - for Yakute population (= 0.15), DRB1*7-DQA1*201-DQB1*303 - for Vologda population (= 0.16).

Conclusion: Molecular-genetic studies showed significant ethnic differences in haplotypes of HLA locus and their distribution according frequency and relative risk values.

P/THU/29
Simultaneous onset of type 1 diabetes in monozygotic twins

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The relative risk for type 1 diabetes monozygotic twins is significantly related to proband diagnosis before 5 years of age and reaches 65% for concordant twins. The interval between the first and second diagnosis usually ranges from several months to three years. We report the case of a pair of monozygotic twins who developed simultaneous onset of type 1 diabetes. Two identical female twins, 6 years old, were hospitalized because polypsia, polyuria and hyperglycemia for 3–4 months. The twins had been healthy until the admission. Familial history was negative for T2DM o T1DM. On admission blood sugar were: 399 mg/dl and 269 mg/dl respectively; pH: 7.46 and 7.44 with normal ABE and HCO_3-; urinary sugar was detected with few of ketones; HbA1c were 12.1% and 12.0%; C-peptide was 0.20 ng/ml and 0.30 ng/ml, respectively. Insulin treatment was started. In both twins endocrine and immunological assessement: ICA (islet cells auto-antidodies) negative in both; anti-GAD (glutamic acid decarboxylase) antibodies negative in the first twin and positive in second twin (= 5.80 U/ml); normal thyroid function; negative thyroid antibodies; screening for celiac disease was negative. No evidence (clinical or serological) of recent viral or bacterial infection was found. In the first year of follow-up the twins had a good metabolic control with similar insulin requirement, (0.8 U/Kg/die vs. 0.7 U/Kg/die), and HbA1c levels (HbA1c 6.0–6.5% vs. 6.8–6.9%). The HLA status was: 0101; 0102; DQB1 *0604; 0501; DR 1.13. Interestingly DQB1* non-Asp-57 alleles (0604) and of DQA1* 0102, considered neutral and protective respectively, was found. Although concordance rates type 1 diabetes for monozygotic twins are high (13–65%), nevertheless a simultaneous onset, and a similar course of disease, and of metabolic control are unusual, as well as the HLA allelic variants of our cases. Furthermore, clinical history, absence of viral infection before the onset, may suggest a role for genetic factors other than HLA genes in our twins. Thorough genetic evaluation is requested in these cases.

P/THU/30
Relationship of adiponectin levels and autoimmunity in children with new onset type 1 diabetes (T1D)

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Objectives: Adiponectin is involved in the pathophysiology of obesity and, as a marker of insulin sensitivity; its measurement in T1D may advance the study of the accelerator hypothesis. Our aims were to (i) determine adiponectin levels in children with T1D before insulin therapy (D0), 3–5 days after initiation of insulin

therapy (D5) and after 2–4 months of therapy (M3), (ii) determine the impact of race, gender, BMI on adiponectin levels at each time, and (iii) examine the relationship between adiponectin levels and islet cell auto antibody (AA) spreading.

Methods: We studied 175 new onset T1D patients (mean age 11.3 ± 3.8 years) from the Children's Hospital of Pittsburgh Diabetes Registry. Blacks with available serum samples (n = 84) were matched by sex, age and year of diagnosis with White children (n = 91).

Results: Blacks were more often overweight (BMI ≥ 85th percenile) than Whites (47.3 vs. 14.3%, $p < 0.001$) and had fewer positive AA (43.2 vs. 70% with ≥ 3 + AA, $p < 0.001$). Serum adiponectin levels measured by RIA increased significantly by M3 (mean D0 13.7 ± 0.7 vs. D5 19.9 ± 1.2 vs. M3 21.9 ± 1.6 μg/ml, $p = 0.02$). A significant early increment was confirmed in 33 paired samples from D0 to D5 (14 .8 ± 1.3 vs. 18.7 ± 1.5 μg/ml, $p = 0.001$). Females had a trend towards higher levels at D0 (15.1 ± 1.1 vs. 12.5 ± 0.9 μg/ml, $p = 0.07$) and D5 (22.4 ± 1.9 vs. 17.9 ± 1.4 μg/ml, $p = 0.06$) & there was no correlation with age. Although Whites had higher adiponectin levels than Blacks at D0 (15.6 ± 1 vs. 11.3 ± 0.9, $p = 0.002$), this difference did not persist after adjusting for BMI. As expected, adiponectin levels were lower in over than normal weight subjects (D0 9.5 ± 0.8 vs. 16.01 ± 0.9, $p < 0.001$; D5 13.2 ± 3.2 vs. 21.5 ± 1.5 μg/ml, $p = 0.015$) and, even in the AA positive patients (Type 1a), there was a negative correlation between adiponectin and BMI (D0 $r = -0.45$, $p < 0.001$, D5 $r = -0.60$, $p < 0.001$). At M3, the number of positive AA correlated with adiponectin levels ($r = 0.37$, $p = 0.007$).

Conclusion: Adiponectin levels in T1D children are related to BMI and increase early with insulin treatment. Low adiponectin, reflecting insulin resistance at M3, appears to be associated with fewer numbers of positive auto-antibodies. This suggests acceleration of clinical presentation of T1aD in insulin resistant children, rather than acceleration of the autoimmune process.

P/THU/31

Th2 response in newly diagnosed children with type 1 diabetes and their healthy siblings

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Objectives: Type 1 diabetes (T1DM) is an immune mediated disease, developed on the basis of complex gene-environment interactions. The current view concerning the role of T cells is a disturbed balance between helper T cells (Th) the Th1/Th2 or a reduced suppression from Treg (Th3) cells. Type 1 diabetes is thought to be mediated by Th1 cytokines and several studies have found higher levels of Th1 cytokines in diabetics; whereas atopid diseases and allergy is a Th2 mediated disease. This is supported by some studies were atopic disease is low in diabetics; whereas others have found a high percentage of atopic disease in diabetic populations. The objective of the present study was to estimate Th2 activity in newly diagnosed children and their healthy siblings.

Methods: Data for the study is derived from a large population-based register of diabetic children with an attached bio bank. It is a random sample in newly diagnosed children with blood sampling less than 3 month after onset collected 1997–2005 and their siblings. Blood samples are stored at minus 80 degrees until analysis. Cytokines are measured using 25-multiplex high-capacity method for simultaneous determination of 23 cytokines. The immunoglobulins were measured by rate-nephelometry on Immage.

Results: There were 481 cases and 479 siblings included. Six siblings developed diabetes from 0.5–3.4 years after blood sampling. The IgE level was above the 95% cut off limit in 96 (20%) of the cases and in 81 (17%) of the siblings this difference were insignificant ($p = 0.22$). The percentage of children with high levels of IgE varied from 12% in 2002 to 32% in 2001 with no clear trend of increasing levels over the year. The Th2 cytokines IL-4 and IL-10 increased significantly with an increase of more than 10% per year in both siblings and cases 1997–2005. The IL-4 levels were lower in healthy siblings at a given IL-10 level compared to cases.

Conclusions: The role of the Th1/Th2 balance is important for pharmaceutical intervention trials with immune therapy. There are no former studies of IgE levels in newly diagnosed children and their healthy siblings. The percentage of children both cases and controls with high levels of IgE is remarkable high in this group indicating that not only Th1 activity is high but also Th2. This supports the theory that it is more likely that the increasing trend in diabetes is caused by a lower level of regulatory mechanism than a simple Th1/Th2 imbalance.

P/THU/32

HLA-DRB1, DQB1 and DQA1 alleles are associated with increased risk of type 1 diabetes in Tyvinian children

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Objectives: The HLA-DRB1, DQB1 and DQA1 alleles are preferentially associated with predisposition to type 1 diabetes (T1DM). Analysis of the HLA genetic profile may be important for the screening of subjects at risk of IDDM. There are ethnic variations in the genetic susceptibility to T1DM. Our aim was to determine the HLA-DRB1, DQB1 and DQA1 alleles are associated with increased risk of type 1 diabetes in Tyvinian children.

Methods: We examined 15 patients with T1D and 164 healthy controls. All were Tyvinians, indigenous inhabitants of Siberia (Mongoloids). Diabetes was diagnosed according to the clinical and laboratory criteria. The HLA-typing for 14 DRB1 alleles, 8 DQA1 alleles and 13 DQB1 alleles was performed by polymerase chain reaction with sequence-specific primers (DNA-Technology, Russia). Statistical analysis was performed using the Excoffer, Schneider and Kuffer package. Relative risk (RR) has been calculated using Woolf´s method. All p values quoted were corrected by the Bonferroni test.

Results: We found the HLA-markers of predisposition to T1DM in Tyvinian children: HLA DRB1*03 (frequency 26.7% in the group with T1DM vs. 6.3% in controls, $RR = 6.1$, $p < 0.05$), DQA1*0501 (50.0% vs. 24.4%; $RR = 5.1$, $p < 0.05$), and DQB1*0201 (33.3% vs. 13.4%; $RR = 4.4$; $p < 0.05$). Analysis of the HLA haplotypes showed, that the haplotype DRB1*03 - DQA1*0501 - DQB1*0201 was associated with an increased risk of IDDM ($RR = 6.3$, $p < 0.05$). The highest relative risk was revealed for the classical genotype DRB1*03 - DQA1*0501 - DQB1*0201/DRB1*04 - DQA1*0301 - DQB1*0302 ($RR = 409$, $p < 0.001$).

Conclusions: This study indicate that HLA DRB1*03; DQA1*0501; DQB1*0201 alleles, and also DRB1*03 - DQA1*0501 - DQB1*0201 and DRB1*03 - DQA1*0501 - DQB1*0201/DRB1*04 - DQA1*0301 - DQB1*0302 haplotypes are associated with T1DM in Tyvinian children.

P/THU/33

Study of the genetic pre-disposition in children with diabetogenic risk

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From a genetic point of view diabetes is a complex polygenic disease, for the developing of which, a variable number of susceptibility and protective genes, with incomplete penetrance, are contributing.

Aim: The present study attempted to find out class II - HLA alleles in a group of children with diabetogenic risk.

Material and method: The studied lot included 2 subgroups: the first subgroup included 25 obese children in whom we determined anthropometric indexes (weight, height, waist) and biologically explored: the glucidic metabolism by fasting glycemia, serum C peptide (ng/ml), glycated hemoglobin (HbA1c), but also oral glucose tolerance test (OGTT) coupled with the evaluation of serum insulin levels. The second subgroup included 41 children (aged 3 months – 18 years) grouped as follows: group A = 32 children (siblings of type 1 DM kids), group B = 5 children followed-up for impaired fasting glucose, group C = one 3 months old infant of a diabetic mother. In this subgroup we determined the anthropometric indexes (weight, height, waist) and, biologically, we evaluated the glucidic metabolism through fasting glycemia and glycated hemoglobin (HbA1c) and the metabolism of lipids through serum lipids, cholesterol, triglycerides and HDLc. Class II HLA alleles were typed in 20 patients from this subgroup.

Results: In the studied lot, typing of class II HLA alleles revealed that of the 20 subjects evaluated, 25% were DRB1*04, while 15% were DRB1*03. In all typed cases serum C peptide and also the glycated hemoglobin ranged between normal limits.

Conclusions: Genetic pre-disposition represents the backgroud for the development of the autoimmune beta-cell destructive process, but the occurence of type 1 DM requires also the involvement of some trigger factors which are often hardly to distiguish.

Monogenic Diabetes Forms and Their Treatment

P/THU/34

Persistence pays when a diagnosis of monogenic diabetes is suspected

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Objectives: The majority of young people with diabetes have type 1, but differential diagnosis is important as this has implications for treatment. Monogenic diabetes may be suspected when there is a dominant family history of early onset diabetes (< 25 years) over two or more generations. We report a case with a partial gene deletion in Hepatocyte Nuclear Factor-1A (*HNF1A*).

Methods: The proband was diagnosed with diabetes at 13 years. She is Caucasian, slim (BMI 25th centile) and presented with glycosuria/ketonuria, RBG11 mmol/l and HbA1c 6.8%. Glutamic acid decarboxylase and islet cell antibodies were negative. An oral glucose tolerance test indicated FBG 6.0 mmol/l, 2 h 13.9 mmol/l. The proband has a needle phobia and was distressed at the prospect of insulin injections. Her family history indicated dominant inheritance of diabetes through 5 generations. This combined with a reduction in blood glucose levels on no treatment, raised suspicions regarding a possible diagnosis of monogenic diabetes. She was monitored carefully and treated symptomatically whilst investigations were carried out on family members. She was well controlled on 20 mg Gliclazide, HbA1c 6.7%. Her mother was diagnosed at 18 years and insulin treated in pregnancy but later controlled on Glimepiride/Metformin. She was sensitive to sulphonylureas (SUs), a characteristic of patients with *HNF1A* diabetes.

Results: Genetic testing was performed on the proband's mother initially. She tested negative for *HNF1A*, *HNF4A*, MIDD and Familial Partial Lipodystrophy. Blood was then taken from all available family members, with/without diabetes for linkage studies. Two years later new laboratory techniques were introduced and dosage analysis by MLPA identified a heterozygous partial *HNF1A* gene deletion mutation of exon 1 in the proband and her mother (Ellard *et al* 2007).

Conclusions: In this case, the clinical phenotype appeared consistent with *HNF1A* diabetes but the genetic tests available at the time were not confirmatory. It was worth pursuing genetic testing as the family were reassured to have a definitive diagnosis and the proband was successfully treated with low dose SUs and was spared from insulin injections. It also allowed appropriate genetic information/counselling to be given to family members.

Reference: Ellard, S *et al* (2007) Partial and whole gene deletion mutations of the *GCK* and *HNF1A* genes in maturity-onset diabetes of the young. Diabetologia, 50: 2313-2317.

P/THU/35

IPEX syndrome: immune dysregulation polyendocrinopathy enteropathy X-linked syndrome

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Objective: To characterize a significant series of patients with IPEX (Immune dysregulation Poly endocrinopathy Enteropathy X-linked), a rare syndrome of dysimmunity, X-linked transmitted, affecting boys, caused by mutations of the *FOXP3* gene coding for a transcription factor, for the development of a regulating pattern in T lymphocytes maintaining immune homeostasis. IPEX causes several organs alterations, the two major ones being a severe autoimmune exsudative enteropathy and an insulin-dependent diabetes mellitus with poorly defined clinical, biological, immunological et anatomo-pathological characteristics.

Methods and results: Among 12 patients diagnosed with IPEX, between 1986 and 2006, 6 presented diabetes, of early onset (1 day to 3.5 months), revealing the disease in 4 of 6 cases by severe ketoacidosis (blood glucose 13–68 mmol/l). Diabetes was generally insulin-dependent, with no specific characteristics (insulin resistance in one case), but glycemic control was often particularly difficult in the context of major adjuvant therapies (parenteral nutrition, corticosteroids). Diabetes was associated with exsudative enteropathy in all 6 cases, eczema (n = 4), anaemia (n = 4) thrombopenia (n = 3), cardiac (n = 2) and other manifestations (n = 4). Five of the patients died, one at 7 months, 4 between 21 and 32 months. Diabetes specific auto antibodies were rare in our patients (n = 2), while they have often

been found in previously published cases, but at least another organ specific autoantibody has been identified in all our patients. Anatomopathological study of the pancreas, in 2 of the patients, has shown the total and specific disappearance of the beta cells and their precursors, without any insulitis.

Conclusions: IPEX diabetes is thus a specific form of autoimmune diabetes, with an early and very rapid destruction of the beta cells. Diabetes is generally not influenced by immuno suppressive treatments, even when enteropathy responds favorably, but diabetes has reversed in one of our cases after bone marrow transplantation.

P/THU/36

Stopping insulin and improving adherence to treatment with confirmed molecular genetic diagnosis

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Objectives: Young people with diabetes frequently have poor control and insulin resistance requiring large doses of insulin during puberty, often complicated by reduced treatment adherence during this time. Achieving HbA1c levels within targets ≤ 7.5% with insulin doses of < 1 unit/kg/day is unusual, as requirements increase by 30–50% during puberty (Tfayli and Arslanian 2007). Monogenic diabetes may be suspected in such cases, especially when there is a strong family history. We report a case of Hepatocyte Nuclear Factor-1A (*HNF1A*) diabetes.

Methods: The proband was diagnosed with diabetes at 13 years, presenting with diabetic ketoacidosis, RBG 33.5 mmol/l and HbA1c 10.3%. He is Caucasian and has a family history of diabetes affecting his mother (who was diagnosed when pregnant), maternal grandmother and, on his father's side, an uncle, aunt, grandmother and cousin with type 2. The proband achieved HbA1c levels of 6.3–7.7% maintained on low doses of insulin (0.43 units/kg/day) for three years, despite being in puberty and growing rapidly. He often failed to attend clinic appointments, admitted to missing insulin doses and did not monitor blood glucose. The good HbA1c levels on low doses of insulin three years post diagnosis, combined with his family history, raised suspicions of monogenic diabetes. Islet cell antibodies were negative, reinforcing the possibility of an alternative diagnosis to type 1 and genetic testing was performed.

Results: The proband and his mother were found to have a frameshift mutation in exon 4 of *HNF1A*. Patients with *HNF1A* diabetes are sensitive to sulphonylureas but are at risk of diabetic complications e.g. retinopathy, nephropathy and cardiovascular disease; achieving good glycaemic control remains important. The proband stopped insulin treatment and started 40 mg Gliclazide with reduction in HbA1c from 7.7% to 6.2%. He was happier, more adherent to treatment and attended clinic more frequently.

Conclusions: Young people with atypical diabetes, a strong family history and good control during puberty on low doses of insulin may be suspected of having monogenic diabetes. A diagnosis of *HNF1A* diabetes following molecular genetic testing allowed insulin to cease, leading to increased quality of life and improved adherence to medication.

Reference:

Tfayli, H, Arslanian, S (2007) The challenge of adolescence: hormonal changes and sensitivity to insulin. Diabetes Voice 52: 28–30.

P/THU/37

Neonatal diabetes mellitus due to mutation of gene KCNJ11 encoding subunit KIR6.2 of sulfonylurea receptor

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Objectives: Mutations of gene KCNJ11 can be expressed as both transient and permanent neonatal diabetes mellitus. In one third of patients, due to lesion of ATP-sensitive channels in muscle, a delayed brain development is observed, which is called the DEND-syndrome (Developmental delay, Epilepsy, and Neonatal Diabetes).

Object of study and methods: This work presents description of a child with neonatal diabetes mellitus developed due to mutation in the gene KCNJ11.

Results: In the boy Yu., at the age of 7 months, by chance, hyperglycemia (12.1 mmol/l) was revealed. It is known from the case history that at once after birth a deformation of the left shin was observed; roentgenography of tibial bone showed a pathological impacted fracture at the border of the proximal meta epiphysis. At the age of 3 month, tonic convulsions in hands and feet appeared in the child; they were repeated daily 4–5 times a day. During the convulsions, apnea was also observed. Objectively, on the medial surface of the left thigh there is a mixed hemangioma of the right color, 1.5 × 3 cm, and on the right gluteus - a capillary hemangioma, 1 cm in diameter. Muscle tone of extremities and back is decreased. The level of glycemia varied from 8.6 to 12.1 mmol/l, while after feeding - up to 20.5 mmol/l. The level of glucosylated hemoglobin $HbA1_c$ amounted to 14.1%. Sequestration of the gene KCNJ11 revealed the presence of missence-mutation 51 leading to replacement of alanine by glutamic acid. Taking into account the presence of neonatal diabetes, episyndrome, and delay of development, the DEND-syndrome that is one of clinical manifestations of mutation in the gene KCNJ11 was diagnosed.

Conclusions: This case of neonatal diabetes mellitus due to mutation in the gene KCNJ11 is of interest, as during making out the diagnosis there were absent such diabetes symptoms as thirst and polyuria. Besides, there were present the neurological disturbances known as the DEND-syndrome.

P/THU/38

Very low doses of glibenclamide as successful replacement for insulin therapy in a patient with neonatal diabetes due to a mutation of KCNJ11 gene encoding Kir6.2

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Introduction: Permanent neonatal diabetes mellitus (PNDM) is a rare form of insulin dependent diabetes diagnosed within the first six months of life. Recently, activating mutation in the KCNJ11 gene encoding Kir6.2 subunit of the adenosine triphosphate - sensitive potassium (K_{ATP})channel have been described as the most frequent cause of PNDM. Under physiological circumstances K_{ATP} channel closure plays a central role in glucose-stimulated insulin secretion from pancreatic beta cells. Sulphonylurea drugs stimulate insulin secretion by binding to and closing K_{ATP} channels

and thus, bypassing beta cell metabolism and stimulating insulin release. Most patients need very high doses of sulphonylureas.
Aim: We describe patient with PNDM in whom insulin therapy was successfully switched to low doses of oral glibenclamide.
Results: Our patient is now a 5.5-year-old boy diagnosed with PNDM at the age of 3 months. When diagnosed he had severe hyperglycaemia (64.8 mmol/l) and ketoacidosis (pH 6.97, serum bicarbonate 4.2 mmol/l). Autoimmune antibodies [glutamic acid decarboxilase (GAD), islet cell (ICA) and thyrosine phosphatise (IA-2) antibodies] were negative. Insulin therapy was started, and moderate glycaemic control was achieved (HbA1c 7.1–8.6%). C-peptide concentrations were low in two samples (0.13 nmol/l and 0.09 nmol/l; referent range 0.2–1.3 nmol/l). At the age of 20 months the insulin requirement were reduced (required insulin dose was 0.3 IU/kg/day). At the age of 4.5 years, KCNJ11 gene was sequenced and found that the boy carries a *de novo* activating R201H mutation. Insulin therapy was switched to oral glibenclamide. Very low doses of glibenclamide (initially 0.175 mg/kg/day, lowered to 0.12 mg/kg/day in the next 6 months) were sufficient to attain excellent glycaemic control (HbA1c 6.0%, 3 and 6 months after switching to glibenclamide). Oscillations in blood glucose levels were in a narrow range and an adequate rise in basal C-peptide concentration was detected (0.4 nmol/l).
Conclusion: The first PNDM patient in Croatia was found to have a genetic defect impairing the Kir6.2 subunit of the K_{ATP} channel. Very low doses of oral glibenclamide provided better metabolic control and undoubtedly better quality of life compared with previous insulin therapy.

P/THU/39

Efficacy of glibenclamide treatment in a child with permanent neonatal diabetes mellitus due to a KCNJ11 (Kir6.2) mutation

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Beta-cell insulin secretion is regulated by the closure of ATP-sensitive potassium channels (K_{ATP}) which is composed by SUR1 (ABCC8) and Kir6.2 (KCNJ11) subunits. Activating mutations in KCNJ11 gene reduce sensitivity to ATP inhibition and are responsible for 30 to 58% of permanent neonatal diabetes (PNDM) cases. Recent studies demonstrated that oral sulfonylureas could improve insulin secretion by closing K_{ATP} channels in an ATP-independent route, representing a therapeutical option in PNDM metabolic control, improving also the neurological symptoms in some cases.
Objective: To evaluate the efficacy of glibenclamide treatment in a child with PNDM by comparing it with insulin therapy.
Methods: A 4 years old female child with severe development delay, epilepsy and neonatal diabetes (DEND syndrome) in insulin therapy since 5 months of life, carrying a C166Y mutation in KCNJ11 gene, was switched from insulin (0.2 UI/kg/day) to glibenclamide (1.5 mg/kg/day) treatment, in a 4 weeks observational period, followed by insulin reintroduction. Glucose, insulin, C-peptide responses in OGTT were compared before and after glibenclamide switching; the 8-points capillary glucose profile and the hypoglycemia frequency recorded in Camit-Pro software of the Accuchek meters as well as the mean HbA1c levels were compared before and during glibenclamide switching and also after insulin reintroduction.
Results: Glucose response in OGTT was higher during glibenclamide therapy ($p < 0.01$) and it was noticed a trend to more frequent hypoglycemic episodes with insulin. Neither differences in neurological symptoms, nor side effects were observed.
Conclusion: The insufficient efficacy of glibenclamide in this case may be related specifically to this mutation.

P/THU/40

Neonatal diabetes due to KCNJ11 mutation, transfer from insulin pump therapy to sulfonylurea

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Introduction: Neonatal diabetes is known to be caused by gene mutations. The clinical approach and therapy depend on the type of gene mutation. Kir 6.2 mutations can cause permanent or transient neonatal diabetes. Therapy with sulfonylurea has shown good results in achieving good metabolic control in these babies.
Objective: To present a boy with neonatal diabetes and modalities of therapy.
Case report: A 50 days old baby boy presented with restlessness, weight loss, irritability, and severe ketoacidosis. At admission he was extremely dehydrated, oliguric and emaciated. Initial glycaemia was extremely high, almost immeasurable (76 mmol/l), ketons were strongly positive. Severe acidosis was confirmed, with pH of 7.01 and BE -26.5 mmol/l. Sodium was 164 mEq/l and potassium 3.6 mEq/l. HbA1c was 12.3 %. C-peptide level was 0.2 ng/ml. Standard protocol for treatment of diabetic ketoacidosis was applied. Continuous insulin infusion with rapid acting insulin was initiated. Two episodes of short but generalized seizures occurred during the initial four hours after diagnosis. Slow decrease of glycaemia followed accompanied with electrolyte correction and improvement of the condition of the baby. Although an intensive insulin therapy with four daily doses of insulin was initiated during the post-ketotic phase, glycaemia was very unstable with frequent peaks of hyperglycemia. The boy failed to gain weight during the first three weeks after diagnosis. Therefore, he was started on insulin pump. The condition of the baby improved immediately, he started gaining weight and the HbA1c measured 6 weeks after initiation of pump therapy decreased to 8.7%. Molecular analysis confirmed a common gene mutation in neonatal diabetes, V59M, in the KCNJ11 gene. Insulin was gradually replaced with glibenclamide tapered to 0.8 mg/kg divided in two doses daily. After three months on glibenclamide the HbA1c was 5.7% without hypoglycemia or hyperglycemia, and C-peptide values normalized to 1.7 ng/ml. At six months of age the baby is healthy, and no signs of developmental delay are present.
Conclusion: Molecular diagnosis should be performed in patients with neonatal diabetes. In patients with KCNJ11 mutation glibenclamide should be a therapy of choice. Close follow up of the development of this patient is warranted.

P/THU/41

Treatment of a child with neonatal diabetes mellitus due to mutation of gene KCNJ11 with glibenclamide

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Objectives: At present, for treatment of neonatal diabetes mellitus, it is preferable to use preparations of sulfonylurea. On the

background of such treatment, in the majority of patients previously treated with insulin, it becomes possible to cancel insulin therapy and to achieve improvement in compensation of carbohydrate metabolism. Some researchers recommend use of glibenclamide, 0.3–0.4 mg/kg per day. However, in some cases, higher doses of the preparation have to be prescribed.

Methods: We observe a child in whom at the age of 7 months the neonatal diabetes mellitus due to mutation in the gene KCNJ11 was diagnosed. At making out the diagnosis the glycemia level varied from 8.6 mmol/l to 12.1 mmol/l, while after feeding - up to 20.5 mmol/l; the level of glycosylated hemoglobin $HbA1_c$ amounted to 14.1%.

Results: In April, 2007, we started a course of treatment by insulin glargin, 1 U, and the child showed a reduction of the glycemia level to 2 mmol/l. In connection with this, his mother refused to make him insulin injections. Without the treatment the glycemia level rose up to 25–30 mmol/l every day. Last August we began to treat him by glibenclamide («Maninil 1.75», Berlin-Chemie AG/Menarini Group», Germany), 0.44 mg twice a day (0.88 mg/day). Since there was no effect, we had to increase the daily glibenclamide dose to 3.5 mg twice a day (7 mg/day, 0.77 mg/kg) and the glycemia level rose up to 10–14 mmol/l. However, two or four times a week the glycemia level rose up to 20–28 mmol/l. The mother of this child failed to explain what caused the peaks of hyperglycemia. Once within three or four days the daily glibenclamide dose was lowered to 1.75 mg/day; then she increased the dose to 3.5 mg/day (0.3 mg/kg), which caused the glycemia reduction to 10–15 mmol/l. The $HbA1_c$ level 3 months after the beginning of treatment with glibenclamide decreased to 13.9%, after 6 months - to 12.7%, after 9 months - to 9.1%.

Conclusion: This case shows efficiency of treatment of neonatal diabetes mellitus due to mutation of gene KCNJ11 with glibenclamide at a dose of 0.3–0.77 mg/kg/day.

Pumps and Sensors II

P/THU/42

Evaluation of post-prandial glycemic profiles in children with type 1 diabetes mellitus using continuous glucose monitoring

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Methods: In 33children (20 boys), aged 8.55 ± 3.22 years, with a good metabolic control (HbA_{1c} = 6.61 ± 0.64%), T1DM duration of 3.57 ± 2.27 years, and daily insulin requirement of0.68 ± 0.22 U/kg, the Medtronic Guardian RT™ device was applied. 166 3-hour post-prandial glycemic profiles were analyzed. Analysis consisted of: time and value of maximum glycemia and 2-hours post-prandial glycemia. Meals were divided depending on beginning time to morning (6^{00}–12^{00}), afternoon (12^{00}–17^{00}) and evening (17^{00}–21^{00}) and depending on initial glycemia (< 70, 70–90, 90–135 and > 135 mg/dl).

Results: No differences in maximum glycemia time between morning, afternoon and evening meals were found (1:20, 1:04, 1:22 hour:min respectively). Maximum glycemias were significantly higher than 2-hour postprandial glycemias (1.19, 1.36, 1.43 times respectively). Time to maximum glycemia was the shortest for meals with initial glycemia > 135 mg/dl, longer for 90–135, 70–90 and < 70 mg/dl meals (1:04,1:15, 1:20, 1:55 hour:min respectively). Maximum glycemias were significantly higher than 2-hour post-prandial glycemias (1.32, 1.32, 1.24, 1.18 times respectively).

Conclusions: In addition to 2-hour after meal glycemia, an earlier blood glucose measurement should be considered to detect post-prandial hyperglycemias.

P/THU/43

Reducing glycaemic variability and HbA1c with the FreeStyle Navigator® continuous glucose monitoring system in young adults with type 1 diabetes (T1D)

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Objectives: To investigate the use and impact of the FreeStyle Navigator Continuous Glucose Monitoring System (FSN-CGM) under home use conditions in self-management of diabetes.

Methods: The study was for 60 days of continuous sensor wear in patients with T1D at home. The patients performed sensor insertions and calibrations. Real-time data and alarms were not available for the first 20 days (masked phase). Real-time data, trend arrows and threshold alarms for hypo- and hyperglycaemia were un-masked for the next 40 days. For the masked phase, patients were instructed to make all treatment decisions based on capillary BG tests only performed with the built-in FreeStyle BG meter. In the un-masked phase, subjects were instructed to make treatment decisions based on FSN-CGM except during hypoglycaemia or rapidly changing glucose values when confirmatory capillary BG test was performed prior to self-management decisions. The primary endpoint was to demonstrate a reduction in time spent outside euglycaemia (70–180 mg/dl) between the first 20 days (phase A) and last 20 days (phase B) of the study. Both phases were compared for a number of specified measures of glycaemic variability by paired t-test. HbA1c was recorded by DCA 2000 at the start and end of the study.

Results: Twenty-seven adult patients with T1D (51.8% male) were included and completed the study (mean age 33.0 ± 10.3 years; diabetes duration 18.2 ± 10.9 years). 21/27 patients were on CSII, the remaining on MDI. Comparing phase A and phase B, patients had a significant reduction of the time spent outside euglycaemia from 10.2 to 8.8 hours/day ($p < 0.05$). There were significant reductions in glucose SD from 61 to 55 mg/dl ($p < 0.01$), hyperglycaemic time (> 180 mg/dl) from 9.5 to 8.2 hours/day ($p < 0.05$), and the High Blood Glucose Index (HBGI) risk score from 9.0 to 7.6 ($p = 0.025$). Hypoglycaemic time (< 70 mg/dl) decreased from 0.74 to 0.59 hours/day without statistical significance ($p > 0.05$). Mean HbA1c fell from 7.3 ± 1.0% at baseline to 6.7 ± 0.7% at the end of the study ($p < 0.001$). During the study, two adverse events occurred for an adhesive reaction and bleeding/pain on sensor insertion; no serious adverse events were reported.

Conclusions: Data of this study indicate that the use of the FreeStyle Navigator Continuous Glucose Monitoring System has a positive effect on self-management of diabetes concerning glycaemic control and glycaemic variability.

P/THU/44

Impact of pump therapy on long-term glycemia in children and adolescents with type 1 diabetes mellitus

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Objectives: To determine the long-term effect of insulin pump therapy on glycemia in children and adolescents with type 1 diabetes mellitus (T1D).

Methods: We examined the intra-individual changes in mean annual HbA1c (A1c) in the first pediatric patients (n = 210) with T1D who had used pump therapy for at least 2 years in the Diabetes Program at Childreńs Hospital Boston. At pump start, mean age was 11.7 ± 4.4 (SD) years (y), T1D duration 4.2 ± 3.4 years, A1c 7.9 ± 0.96%, and 47% female.

Results: Mean annual A1c two years and one year before starting pump therapy were 7.8 ± 1.0% and 7.8 ± 0.8%, respectively; and mean annual A1c one and two years post-pump start were 7.5 ± 0.8% and 7.7 ± 0.8%, respectively. Mean annual A1c 2 years post-pump start was 0.13% lower than one year before starting pump therapy.

Table shows percentage of patients whose mean annual A1c met American Diabetes Association (ADA) age-specific glycemia targets over two years pre- and post-pump start (< 6 years 7.5–8.5%, 6–12 years ≤ 8%, ≥ 13 years ≤ 7.5%).

ADA age category, n	2 years pre-pump	1 year pre-pump	1 year post-pump	2 years post-pump
< 6 y, n = 23	65	22	17	30
6–12 y, n = 87	55	48	64	67
≥13 y, n = 100	37	30	39	33

We analyzed mean annual A1c 1 year pre- and 1 year post-pump start: 43% never achieved ADA age-specific A1c targets, 27% remained within target, and 20% who initially exceeded their targets at -1 year were able to achieve targets in the first year of pump therapy. Within one year of starting pump therapy, patients ≥ 6 year were more likely than those < 6 year to achieve their age-specific target ranges. A mixed model analysis revealed two significant factors that predicted a child ≥ 6 year will achieve age-specific target A1c value one year post-pump start: shorter duration of T1D at pump start (p = 0.0005) and bolus:basal ratio > 1.0 (p = 0.0027). Age at pump start, gender, number of clinic visits, and choice of infusion set did not predict who would achieve target A1c.

Conclusions: Pump therapy enabled 43/210 (20%) children and adolescents whose A1c exceeded target levels on multiple injection therapy to achieve and maintain age-specific A1c targets. Optimizing bolus:basal dose ratios is an important factor contributing to the achievement of target A1c.

P/THU/45

3.5-year assessment of therapy with continuous subcutaneous insulin infusion in children with type 1 diabetes

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The aim of the study was to assess treatment with continuous subcutaneous insulin infusion (CSII) in children with type 1 diabetes mellitus (T1DM), starting therapy before the age of 11 and followed for 3.5-years.

Material and methods: Following groups were observed: group: CSII- 40 children (24 girls), mean age 6.47 ± 2.13 years, using insulin pumps and group: MDI- 36 patients (21 girls), mean age 7.13 ± 1.83 years, treated with a conventional intensive method or multiple injections. The group MDI was comparable to the group CSII in terms of age at the onset of follow-up, basal values of glycosylated haemoglobin (HbA1c), daily insulin requirement (DIR) and centiles of the body height, weight and BMI. The duration of the disease in the group CSII and MDI was 2.6 and 1.5 years respectively, p < 0.05.The groups had been compared since inclusion to the study, and subsequently every 6 months in relation to: DIR (U/kg/24 hours), metabolic control (HbA1c), physical development (centiles for height, weight and BMI) and complications (number of severe hypoglycaemia and number of diabetic ketoacidosis - DKA per 100 patients/year).

Results: HbA1c was significantly lower in the CSII group in comparison to the MDI group only in the 6th and in the 42nd month of the follow-up (6.95 vs. 7.29%, and 6.91 vs. 7.43% respectively; p < 0.05). In the CSII group, the basal HbA1c value of 7.1% decreased significantly to values of 6.95%, 6.84%, 6.83% and 6.88% in the 6th, 18th, 30th and 36th months respectively (p < 0.05). Such statistical significance was not found in the group MDI. In the group CSII, DIR was significantly lower in the 6th and 18th month of the follow-up (0.64 and 0.73 U/kg/24 h respectively; p < 0.05). Increase of DIR in the MDI group was significantly greater as compared to the group CSII in all time intervals. The number of acute complications in the group CSII was comparable to the group MDI and it was assessed 1.43 vs. 1.6/100 patients/year for DKA, and 7.14 vs. 7.94/100 patients/year for severe hypoglycaemia. Height and weight centiles did not differ in both groups. BMI centiles decreased significantly in most time intervals in the group CSII.

Conclusions: CSII allows for achievement and maintenance of the normal metabolic control as well as stable daily insulin requirement but lower DIR as compared with the MDI method. CSII is a safe model of treatment, assuring normal and harmonious development of a child.

P/THU/46

Utility and efficacy of diasend as a tool to ameliorate metabolic control in children and adolescents with type 1 diabetes using CSII therapy

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Background and aim: To date it is difficult sometime to follow-up insulin therapy in patients with type 1 diabetes, especially when they switch from MDI to CSII. To correctly analyze the impact of the therapy on metabolic control, the patient need to go to the

hospital to download pumps and/or meters data into computer using dedicated software. The aim of our study is to evaluate the utility and efficacy of Diasend, an easy home uploading tool, on metabolic control in children and adolescents with type 1 diabetes using CSII therapy.

Materials and methods: We enrolled 13 children and adolescents, aged 4–18 years (mean: 14.5 ± 5.9 years), with type 1 diabetes from 7.9 ± 4.8 years, using pump therapy (IR1200 or IR2020, Animas). We gave to each patient a Diasend station to easy upload data from glucose meters and insulin pump. The patients have been instructed to download data at least once a week (more if necessary) for 3/6 months. The physician reviewed the data online and then sent suggestion to each patient. Metabolic control, the primary endpoint, will be evaluated as HbA1c at baseline, and after 1, 3, 6 months after using Diasend, and 3 and 6 months after finishing Diasend use. Secondary endpoints will be changing in insulin requirement (IR), BMI, number of hypoglycaemic episodes and glycaemic fluctuations.

Results: We present the preliminary encouraging data after the first month of using Diasend. A significant decrease in HbA1c was observed (7.56 ± 0.0.95 vs. 7.29 ± 0.57%, p = 0.025); we also observed a slight decrease in IR (0.80 ± 0.14 vs. 0.77 ± 0.08, U/kg/die, p NS), while BMI did not change (20.65 ± 3.97 vs. 20.60 ± 4.18 kg/m2, p NS). A reduction in glycaemic variability and in the number of hypoglycaemic episodes was also observed.

Conclusions: Even if our data are very preliminary, they are encouraging about the possibility to gain a better control using Diasend in children and adolescents with T1DM. We need to complete our study in order to confirm these first results.

P/THU/47

The optimal type of bolus following a pizza meal in children and adolescents with type 1 diabetes

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Background and aim: We attempted to identify an optimal insulin pump meal bolus by comparing post-prandial blood sugar levels following 6 methods of insulin pump meal blousing for a consistent pizza meal.

Materials and methods: We evaluated 26 children and adolescents, aged 4–22 years (mean 14.81 ± 4.28 years) with type 1 diabetes mellitus (T1DM) from 1 to 19 years (8.23 ± 4.41 years), BMI 22.16 ± 4.28 kg/m^2,in therapy with subcutaneous insulin infusion (insulin requirement 0.84 ± 0.32 U/kg/day). Each patient participated in a study to compare post-prandial glucose values following 6 meal bolus regimens for a consistent pizza meal. Each patient utilized the following aspart regimens on three consecutive days, and glucose values were recorded with SMBG: a) 6-hour dual-wave bolus (30% of insulin given immediately and 30% given over a 6-hour period) given 15 min prior a pizza ''margherita'' meal; b) 6-hour dual-wave bolus (30% of insulin given immediately and 30% given over a 6-hour period) given just before a pizza ''margherita'' meal; c) a single-wave bolus (100% of insulin given immediately) given 15 min before a pizza ''margherita'' meal; d) a single-wave bolus (100% of insulin given immediately) given just before a pizza ''margherita'' meal; e) 6-hour dual-wave bolus (30% of insulin given immediately and 30% given over a 6-hour period) given 15 min prior a pizza with vegetables meal; and f) a single-wave bolus (100% of insulin given immediately) given 15 min before a pizza with vegetables meal.

Total CHO was kept constant for each meal; insulin dose was calculated according to glycaemic value and CHO, using ISF and INS:CHO ratio personalized for each patient.

Results: The results are shown in the table (significance are vs. the time 0 for each type of bolus).

Type of bolus	T0	T30	T60	T90	T120	T180	T240	T300	T360
Double-wave 6-h bolus 15 min before	151 ± 74 NS	157 ± 75 NS	180 ± 89 NS	176 ± 93 NS	187 ± 81 0.056	172 ± 81 NS	144 ± 92 NS	122 ± 57 0.019	97 ± 41 0.001
Double-wave 6-h bolus just before	98 ± 46 NS 0.004 VS bolus 1	139 ± 52 0.011	144 ± 54 0.0004	135 ± 57 0.0007	151 ± 58 0.001	149 ± 66 0.001	136 ± 58 0.003	148 ± 67 0.0005	129 ± 73 0.01
Single-wave bolus 15 min before	132 ± 58 NS	136 ± 54 NS	134 ± 62 NS	148 ± 72 NS	156 ± 70 0.03	145 ± 67 NS	141 ± 50 NS	137 ± 58 NS	144 ± 68 NS
Single-wave bolus just before	129 ± 65 NS	130 ± 58 NS	118 ± 68 NS	131 ± 79 NS	152 ± 77 NS	153 ± 74 NS	174 ± 63 0.048	176 ± 76 0.035	176 ± 68 0.035
Double-wave 6-h bolus 15 min before (vegetables)	149 ± 56 NS	159 ± 62 NS	176 ± 55 0.005	175 ± 77 0.06	198 ± 75 0.0005	191 ± 78 0.001	168 ± 68 0.015	142 ± 64 NS	119 ± 67 0.01
Single-wave bolus 15 min before (vegetables	115 ± 56 NS	109 ± 58 NS	106 ± 45 NS	109 ± 49 NS	120 ± 53 NS	141 ± 58 NS	153 ± 65 NS	168 ± 69 0.01	160 ± 79 0.002

Conclusion: Use of a dual-wave bolus extended over a 6-hour period following a pizza meal if given 15 min before provided significantly less post-prandial hyperglycaemia during the 6-hour period. Single-wave bolus could be used only if given 15 min before meal and if the pizza is served with some vegetables, even if we observed a rise in glycaemic values in the last 2 hours of the study.

Pumps and Sensors II, New Insulins

P/THU/48

Efficacy and safety of insulin glulisine versus insulin lispro as part of a basal-bolus insulin regimen in children and adolescents with type 1 diabetes

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Objectives: This study assessed the efficacy and safety of insulin glulisine (GLU) versus insulin lispro (LIS) in children and adolescents with type 1 diabetes mellitus (T1DM) treated with insulin glargine (glargine) once daily or NPH twice daily as basal insulin.

Methods: This 26-week, multicentre, open, centrally randomised, parallel-group, non-inferiority trial was conducted in 572 children and adolescents (aged 4–17 years) with T1DM (HbA_{1c} 6–11%) who were using glargine once daily (evening) or NPH twice daily as basal insulin. Subjects received GLU (n = 277) or LIS (n = 295) 0–15 min pre-meal.

Results: Baseline characteristics were (GLU versus LIS; mean ± SD): age 12.5 ± 3.1 vs. 12.6 ± 2.9 years; body mass index 20.8 ± 3.4 vs. 20.5 ± 3.3 kg/m^2; HbA_{1c} 8.2 ± 1.1 vs. 8.2 ± 1.0% (33% achieved American Diabetes Association [ADA] age-specific HbA_{1c} target); diabetes duration 5.3 ± 3.6 vs. 5.2 ± 3.2 years; treatment at randomisation (baseline): NPH 30.3 vs. 27.1%, glargine 69.7 vs. 72.9%. Most patients had 3–4 bolus insulin injections (GLU [58.0%] and LIS [60.5%]), which remained stable throughout the study. GLU versus LIS baseline-to-endpoint HbA_{1c} changes were similar (adjusted mean change:

0.10 vs. 0.16%; between-treatment difference, GLU-LIS: -0.06, 95% CI: [-0.24; 0.12], pre-specified non-inferiority margin: 0.4%). Overall, for all age groups together, the percentage of patients achieving ADA age-specific HbA_{1c} targets at endpoint was significantly higher ($p = 0.0386$) with GLU (38.4%) versus LIS (32.0%). The difference was most pronounced in adolescents (13–17 years), with 31.1 vs. 21.1% of subjects achieving their ADA age-specific HbA_{1c} target < 7.5% at endpoint ($p = 0.0251$). From Month 4 to endpoint, symptomatic hypoglycaemia rates (all and severe) were similar (GLU versus LIS: 3.10 vs. 2.91 and 0.06 vs. 0.07 events/patient-month, respectively). Frequency and type of adverse events (AEs), serious AEs or hypoglycaemia reported as serious AEs were similar between the two groups.

Conclusions: GLU was as effective and safe as LIS, allowing higher numbers of patients to reach ADA age-specific HbA_{1c} targets, particularly amongst adolescents aged 13–17 years. (This study was supported by sanofi-aventis.)

P/THU/49

Intensification of type 1 diabetes mellitus (DM 1) treatment: efficacy of detemir as basal insulin

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Short-acting insulin analogues as pre-prandial bolus showed more predictable effect and less hypoglycemic events, however the extent of benefit of the new long-acting analogues as basal insulin is still not fully established.

Objective: To evaluate the efficacy of the Detemir 2 shots/day + short-acting analogue regimen in a DM 1 pediatric population.

Methods: Forty-nine patients in NPH human insulin 3 shots/day + short-acting analogue were randomized in prospective and controlled study for 24 weeks. NPH human insulin (syringe) was switched to Detemir insulin (flexpen) in a 1:1 dose rate, splitting 2/3 before breakfast and 1/3 at bedtime. The mean capillary glucose levels and the frequency of hypoglycemia in the previous 90 days of NPH regimen were recorded in Camit-Pro software of Accuchek meters and were compared to those of the last 90 days of Detemir regimen. The mean HbA1c levels in NPH regimen were compared to those of the initial, 60, 120 and 180 days after the beginning of Detemir. Insulin doses (U/kg/day) and BMI (kg/m^2) in both regimens were also compared.

Results: The mean HbA1c level at the end of Detemir regimen was lower than that in the beginning (9.3 vs. 10.7%; $p < 0.05$) and Detemir dose at the end was higher than NPH dose in a 1.26:1 rate ($p < 0.001$). Patients' satisfaction with the pen injector was greater than with syringes.

Conclusion: Detemir 2 shots/day regimen as basal insulin was more efficient than NPH 3 shots/day only in a dose rate of 1.26:1, respectively.

P/THU/50

Increase of insulin requirements after changing from U40 to U100 insulin in children and adolescents with type 1 diabetes without effect on the metabolic status

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Aim: In Germany several companies have stopped the production of U40 insulin. In a prospective study we analysed possible problems concerning patients' handling with new insulin and vials when changing from U40 to U100 preparations. Furthermore, we examined if insulin change had a metabolic effect in children and adolescents with type 1 diabetes.

Methods: Fifty-one patients (29 boys, 22 girls) comprising 8.7% of our outpatient clinic cohort treated with 4 daily injections switched from U40 to U100 insulin. Every patient had been offered training by a diabetes educator before change. Clinical parameters like HbA1c (DCA 2000, Bayer Diagnostics), insulin requirements (U/kg), number of moderate (blood glucose < 50 mg/dl) and severe hypoglycaemic events (coma, cerebral convulsion) were studied before and 12 weeks after the transfer to U100 insulin. Difficulties with insulin handling have been evaluated using questionnaires with a five staged like rt-scale (1 = no problems/not useful; 5 = great problems/very useful).

Results: Baseline characteristics of study patients were: age 11.9(4.0–19.1) years, diabetes duration 3.2 (0.3–17.9) years, HbA1c 7.0 (5.6–8.9) %, daily insulin requirements 0.76 (0.19–1.27) U/kg (median, range). After 12 weeks, insulin requirements increased significantly to 0.84 (0.41–1.46) U/kg($p = 0.007$). There was no significant change in HbA1c ($p = 0.261$), number of moderate ($p = 0.579$) and of severe hypoglycaemic events/3 months ($p = 0.083$).Before change, 9.8% of the patients had moderate to greater difficulties with the preparation of insulin injections. After switch to U100 insulin, significantly more patients (19.6%) faced such problems ($p = 0.006$). In particular, problems with reading of insulin units on the syringes increased from 11.8% to 21.6% ($p = 0.002$). However, number of attempts to prepare the insulin injection or number of bubbles in the syringe did not increase ($p = 0.086$). 64.3% of patients assessed the training as very helpful.

Conclusion: Despite a significant increase of subjective problems with insulin handling, there was no effect on metabolic status of children and adolescents with type 1 diabetes. There was no increase in the number of hypoglycaemic events using the higher concentrated insulin. However, the significant increase of daily insulin requirements using U100 insulin remains unclear, although previous studies have shown that action profiles of U40 insulin are faster.

Type 2 Diabetes in Children

P/THU/51

How common is type 2 diabetes in a large tertiary hospital-based diabetes service?

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Objectives: The prevalence of type 2 diabetes mellitus (T2DM) in youth is increasing, primarily due to increases in childhood obesity. At the time of diagnosis, diabetes classification can be difficult and some individuals may be misclassified on presenting features. Recent evidence shows that T2DM in youth is associated with increased morbidity and decreased compliance, and management strategies differ from those with type 1 diabetes. Correct diabetes sub-classification is therefore essential. The aim of this study was to determine the prevalence of T2DM within our diabetes service (Royal Children's Hospital (RCH), Melbourne, Australia).

Methods: Study approval was granted by the RCH Human Research Ethics Committee. A retrospective clinical audit of the diabetes service was undertaken and medical records of autoantibody negative patients were examined. Information was extracted relating to baseline auxology, presentation, biochemistry and treatment. Data collection was performed using a standardized proforma, and diabetes classification was performed by 2

independent pediatric diabetologists, using the American Diabetes Association guidelines.
Results: 935 of 1475 children/adolescents with diabetes had at least one recorded autoantibody result, with 170/935 (18.2%) testing negative. Further data collection was performed for 168 of these 170 patients. Twenty-nine were subsequently excluded (as 9 did not have clinically confirmed diabetes and 20 had been transferred out of the service). Of the remaining patients, 113/139 (81.3%) had Type 1 diabetes, 17/139 (12.2%) had T2DM, 2/139 (1.4%) had syndromic diabetes, 3/139 (2.2%) had Permanent Neonatal Diabetes Mellitus, 3/139 (2.2%) had diabetes secondary to cystic fibrosis or pancreatitis, and 1/139 (0.7%) had confirmed Maturity-Onset Diabetes of the Young (MODY). Of the 17 patients with T2DM, three may warrant MODY testing.
Conclusions: Despite current concerns, the occurrence of T2DM within our large diabetes service appears to be relatively infrequent (17/935; 1.8%). While this figure may be an underestimate, it is likely that significant numbers of patients with T2DM are not being enrolled into diabetes services. Our study also highlights the difficulties encountered in attempting to correctly classify children/adolescents with diabetes. We now need to urgently address these issues by developing consistent clinical practice guidelines that will allow correct identification, before this problem becomes pandemic.

P/THU/52

Frequencies in the other components of the metabolic syndrome based on the new IDF criteria among children with type 2 diabetes at the time of diagnosis

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Type 2 diabetes is well known to have high frequencies of the other components of the metabolic syndrome (MS).
Objective: We examined the frequencies in the other components of MS based on the new IDF criteria among children with type 2 diabetes at the time of diagnosis.
Methods: The study involved 112 Japanese children residing Tokyo Metropolitan Area, 45 males and 67 females, aged 12.9 ± 1.6 (10–16) years, diagnosed as having type 2 diabetes. They were diagnosed through the urine glucose screening program at schools during the period from 1990–2006. Body weight, blood pressure and fasting levels of serum triglycerides (TG) and HDL-cholesterol (HDL-C) were evaluated at the time of diagnosis of diabetes. The components of MS were defined based on the new IDF criteria for children aged 10- < 16 years (2007); TG: more than 150 mg/dl, HDL-C: less than 40 mg/dl, systolic blood pressure: more than 130 mmHg or diastolic blood pressure: more than 85 mmHg. Obesity was defined as more than 20.0% percent overweight based on the age- and height-matched ideal weight, because the waist circumferences were rarely measured among the subjects.
Results: Eighty-three per cent of the patients had obesity. The prevalence of high TG was 33.0% and that in low HDL-C was 21.4% among the patients. Elevated blood pressure was identified in 11.6%. There were no statistical differences of these frequencies in gender. 15.2% of the patients, including 89.5% of non-obese patients, had no other components except for diabetes. 49.1% had only the one component; the majority was the presence of obesity. 17.0% had the two components; the majority was the presence of obesity and high TG. 18.8% had three or more of the components in addition to diabetes.
Conclusions: We found a high prevalence of the MS components; the majority was the presence of obesity and high TG, in addition to hyperglycemia among Japanese children with newly diagnosed type 2 diabetes. Early detection of the MS components is of importance for preventing cardiovascular disease in a latter age.

P/THU/53

Metformin monotherapy in children and adolescents with type 2 diabetes mellitus in Japan – an analysis of responders and non-responders

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Objectives: The clinical trial by the Study Group supported by the Health and Labor Research Grants was conducted whether 750 mg/day and its double dose of metformin can be applied to Japanese pediatric patients with T2DM. We analyzed the patients who were effective (responders) or were not effective (non-responders) in this trial.
Methods: This study was an open, not-randomized single arm trial. The primary efficacy outcome measure was a significant improvement of HbA1c by metformin in patients (20 > ages ≥ 10 y/o), enrolled either if any anti-diabetic medication had not been given at least for 28 days before study (naïve patients) or only metformin without any other anti-diabetic medication had been taken at dose of 750 mg/day at least for 28 days before study (already-on patients). The secondary efficacy outcome measures including fasting plasma glucose (FPG), etc. In both groups metformin was given at 750 mg/day for the first 12 weeks. For the second 12 weeks, metformin dosed up at 1,500 mg/day, if HbA1c exceeded ≥ 6.5% at 12 week, whereas metformin dose remained at 750 mg/day, if HbA1c was < 6.4% at 12 week. Finally 47 patients were enrolled and 4 patients were off trial with various reasons. 30 patients were effective (responders) and 13 patients were not effective (non-responders), among whom 5 patients were discontinued at 12 weeks whose HbA1c level exceeded 10% which was criterion of off trial. We included these 5 patients as non-responders for this analysis. We analyzed the difference of various factors between two groups at entry of the clinician trial.
Results: The average age at entry, gender, SDS-BMI, waist size, serum lipids, leptin, adiponectin, HOMA-R were not different between two groups. The responder group had more naïve patients ($\chi^2 = 4.08$, $p < 0.04$), less deteriorated metabolic control (HbA1c ($p = 0.06$), FPG ($p = 0.07$), glycated albumin ($p = 0.03$). Fasting serum insulin of responders and non-responders were 28.7 ± 20.5, 15.6 ± 10.7 μU/ml ($p = 0.036$), CPR were 4.51 ± 1.77, 3.04 ± 1.26 ng/ml ($p = 0.015$), HOMA-β were 101.8 ± 2.6, 41.1 ± 3.1% ($p = 0.01$) respectively and were significantly elevated in responder group patients.
Conclusions: Patients with responder group were more naïve and less deteriorated metabolic control and possessed more insulin secretary capacity. Insulin resistance such as HOMA-R, SDS-BMI was not factors for effectiveness of Metoformin monotherapy.

P/THU/54

Baseline characteristics of child- and adolescent-onset type 2 diabetes: from a longitudinal nationwide survey on diabetic complications in Japan

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Diabetes is not a disease for the elderly but affects middle-age group, as well as children and adolescents. Papers regarding type 2 diabetes among children and adolescents have been reported from both developed and developing countries. We also reported that the proportion of type 2 diabetes in children under 19 years old occupied nearly 50% of all children with diabetes. Moreover, Urakami et al. reported that the increase in the frequency is strongly related to an increasing prevalence of obesity, based on the analyses on the urine glucose mass screening for school children in the Tokyo Metropolitan Area. On the other hand, wide scanning of the long-term diabetic complications of such patients has been done only in one diabetes special hospital, demonstrating that approximately 12% developed severe diabetic vascular complications in their 30s. Therefore, a longitudinal nationwide survey to prospectively observe the progression of diabetes complications and its risk factors has launched in 2006. The data-base of approximately 1,000 people with type 2 diabetes will be created. At the end of January 2008, 729 patients were enrolled under the criteria of the onset age of less than 19 years old and current age under 29 years old; 535 by internists (I group) and 169 by Pediatricians (P group). The proportion of the patients who were detected by urine glucose screening in I group and P groups were (male/ female) 49/67% and 73/75%, respectively. The maximum previous BMI were 33, 29, 29 and 29, respectively. The waist circumferences were 96, 85, 91, and 84 cm, respectively. HOMA-IR index was related to BMI. Such obese patients with type 2 diabetes had also hypertension and dyslipidemia. Photocoagulation therapy had been done in 35 patients and clinical nephropathy was in 17 patients. One patient had already one toe amputation. In conclusion, both male and female were obese with a tendency of having hypertension and dyslipidemia, suggesting that there may be metabolic syndrome exist at the upper stream before the development of diabetes.

P/THU/55

Case reports of two sisters with type A insulin resistance

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Objective: Type A insulin resistance is extremely rare disease and it is characterized hyperinsulinemia, hyperandrogenemia, polycystic ovary and normal serum lipid levels. This entity is usually seen in adolescent and associated with type 2 diabetes.

Method: Case 1: A 13 $^{7/12}$ -year-old girl was referred to clinic for the evaluation of hirsutism. Her parents have abdominal obesity. Birth weight was 2400 g. She had sensorineural deafness due to meningitis. Physical examination revealed severe signs of insulin resistance including grade 4 acanthosis nigricans (AN) over the axillary and inguinal regions. Hirsutism scored was 19 on Ferryman and Galway scoring. The body mass index (BMI = 19.5 kg/m^2) was normal. Bone age was 15 years. Pubertal development was Tanner V. HbA1c was 7.6%. HOMA-IR was 50.4. Testosterone 2.08 ng/ml and androstenedion was 3.7 ng/ml. Pelvic USG examination showed right ovarian volume was 8.5 ml, left ovarian volume was 4.9 ml and there were peripheral located polycystic ovaries on both ovaries.
Case 2: Sister of the case 1. She complained gain weight, darkness of skin of neck, axillary and inguinal region. She was overweight. She had grade 4 AN over the upper eyelid, axillary, antecubitally, inguinal region and inguinal region. Her pubertal development was Tanner II. HbA1c was 7%. HOMA-IR was 3.7. Testosterone 0.39 ng/ml and androstenedion was 2.05 ng/ml Pelvic USG examination revealed right ovarian volume was 3.7 ml, left ovarian volume was 5.4 ml.There were no abnormalities in gonadotrophins, estradiol, and prolactine and thyroid function tests in both sisters. Her and her sister's fasting serum lipids were within normal range. Results of the oral glucose tolerance test (OGTT) of both girls revealed severe insulin resistance and type 2 diabetes (glucose at 120 min of OGTT was 301 mg/dl and 302 mg/dl, respectively). The results of ACTH stimulation and dexamethasone suppression test of both sisters were normal. The girls treated with metformine (2000 mg/day.

Conclusion: Since rare cause of the type II diabetes, Type A insulin resistance is keep on the mind when met the girls with hyperinsulinemia and hyperandrogenemia.

P/THU/56

Diabetic risk factors in offspring of patients with diabetes type 2

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There are many commonly known risk factors of type 2 diabetes. One of them is the occurence of the disease in 1st degree relatives. The aim of the present study was: i). To evaluate the threat of type 2 diabetes in adult children of patients with type 2 diabetes; ii). To analyse the frequency of type 2 diabetes and other disorders in offspring of parents with type 2 diabetes; iii).To analyse following parameters; iv). To detect metabolic disorders before clinical manifestation and the development of macro - and micro-anopathy; v). In case of disorders to introduce early prevention and treatment; vi). To evaluate the influence of sex and age on the metabolic disorders. Included in the study were 197 declared as healthy probands, children from parents with type 2 diabetes, aged 18–71 years, 71 men and 126 women. In 74 of the probands the father has type 2 diabetes, mean age 42 years, in 121 the mother, mean age 43 years. In one case both the father and the mother has diabetes type 2. All the offspring were divided in age groups. Group 1: 18–44 years, group 2 over 44 years and in subgroups depending on sex. All the examined offsprings has had following examinations: BMJ, fasting glycemia 2 times, OGTT, cholesterol, TG, HDL, LDL insulinemia, peptide C, HbA1C, indirect insulinresistance index.

Results: Hyperglycemia was ascertained in 37%, including unknown diabetes type 2 in 25% in the group with a diabetic father. In the group with a diabetic mother unknown diabetes type 2 was shown in 23%.In the whole group 58% of the offspring were

overweight or obese, glycemia disorders existed in 44%, especially in the age group over 44 years. More than half of the examined offsprings has an increased level of cholesterol and HbA1c, especially in sons of diabetic fathers, aged over 44 years. The increased level of insulin peptide C, HbA1c, BMI and blood pressure correlated with the age over 44 years and with the male sex.

Conclusions:

1. Offspring of parents with type 2 diabetes are a group of high risk for the development of diabetes type2.
2. Necessary is a complex examination and furthermore a close monitoring of the risk factors for diabetes, in offspring of parents with type 2 diabetes.