

2.) ORAL PRESENTATIONS

OP-1

RHABDOMYOLYSIS, ANEMIA AND THROMBOPENIA IN DIABETIC KETOACIDOSIS

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Background: Rhabdomyolysis during diabetic ketoacidosis has occasionally been reported. As far as we know the combination with anemia and thrombopenia has not been described earlier.

Aim: To report on this complication of diabetic ketoacidosis.

Methods: The clinical presentation and laboratory results of a 15-month old patient are described.

Results: A 15-month-old boy presented with lethargy and vomiting since 3 days. On admission he was comatose and severely dehydrated. Admission laboratory values indicated severe hyperglycemia (1600 mg/dl), a serum Na⁺ concentration of 155 meq/l, acidosis and ketonuria. The boy received sodium bicarbonate and normal saline (10 ml/kg) intravenously and 2 U/kg of regular insulin subcutaneously before the insulin infusion was started. Six hours later glycemia had dropped to 580 mg/dl and the serum sodium concentration increased to 179 meq/l. Glucose infusion was progressively introduced and the serum Na⁺ concentration normalised over 12 hours. 36 hours after admission seizures developed. Papiledema was not present and a CT of the brain was normal. Over the next 24 hours the boy's circulation and consciousness improved but it was noted that he was very quiet and immobile. Serum creatine kinase was determined and was greatly increased (maximum 37700 U/l on day 7) as were GOT, GPT and LDH. Concomitant with the increase in CK, a drastic fall in hemoglobine and thrombocytes was noted: hemoglobine fell from 10,5 g/dl on admission to 6.3 mg/dl on day 7. The thrombocytes decreased until 16000/ μ l. Renal function remained normal. The boy received a blood -and platelet transfusion and during the following days laboratory values recovered.

Conclusion: Rhabdomyolysis seems to be related to rehydration and/or correction of the hyperosmolar state. This patient had a rapid correction of both hyperglycemia and hypernatremia, resulting in osmolar shifts. This resulted in cerebral oedema (convulsions) and rhabdomyolysis. We suggest that these osmolar shifts also caused the anemia and thrombopenia in our patient. This case demonstrates once more that a slow correction of hyperglycemia and hypernatremia is a condition sine qua non in the treatment of diabetic ketoacidosis.

patients in whom an acceptable glycemc control is difficult to achieve despite insulin therapy.

SOURCES OF ERRORS IN SELF-MONITORING OF BLOOD GLUCOSE IN 100 YOUNG DIABETICS

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Background: Self-monitoring of blood glucose (SMBG) has become increasingly important in the treatment plan of people with diabetes. Identifying sources of error in SBGM can have a significant clinical impact.

Aim: The objective of the present study was to evaluate the testing skills in diabetic children and adolescents.

Methods: The study included 100 patients (46 females and 54 males) with an age of 8-18 years and a mean duration of diabetes of 4.5 years. They were autonomous for SMBG: an experienced diabetes nurse had taught earlier how to proceed. The daily frequency of SMBG was 4 in 79 patients, 3 in 11, and 2 in 10. The observations of their performance of blood glucose monitoring skills were done twice, during 2 consecutive visits at the diabetes clinic at a mean interval of 2 months. Each patient was observed by a specialized nurse who scored the child's testing behavior with an observation grid, according to 45 items. After the first observation, children and adolescents were given feedback on the identified errors. The second observation allowed scoring the improvements. Statistical analysis included stepwise regression.

Results: During the first observation, nearly 90 % of the patients made 3 or more mistakes, 69 % more than 5, and 10 % more than 10. During the second observation, these frequencies fell to 17, 2, and 0 %. The main errors were the following (first vs second observation, in % of patients): 1) not washing hands: 54 vs 3; 2) incorrect setting for hour and date: 47 vs 2, and 17 vs 2; 3) no knowledge of the meaning of "HI" (blood glucose >500 or 600 mg/dl): 55 vs 3; 4) no knowledge of the meaning of "LO" (<10 or 20 mg/dl): 49 vs 1; 5) insufficient blood drop: 19 vs 10. In the stepwise procedure, the best predictive variable of errors, during the 2 observations, was younger age, while duration of diabetes and of autonomy for SMBG, frequency of SMBG and glycated haemoglobin were removed from the model.

Conclusion: It is important to periodically assess diabetic children and adolescents' SMGB technique in order to correct the mistakes. Younger children need closer supervision. The use of an observation grid allows an accurate analysis of the numerous possible errors.

HEMOSTATIC RISKFACTORS, METABOLIC CONTROL, AND MICROALBUMINURIA IN DIABETES MELLITUS TYPE I

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Background: Diabetic angiopathy is a major complication of diabetes mellitus type I. Microvascular complications are associated with endothelial cell alterations and hypercoagulability.

Aim: To investigate a possible correlation between microalbuminuria and markers of endothelial cell alteration and hypercoagulability in patients with type I diabetes.

Methods: Microalbuminuria, von Willebrand factor-Ag (vWf-Ag), P-Selectin-Ag, factors VIIc and VIIIc, tissue-plasminogen activator-Ag (tPA-Ag), plasminogen activator inhibitor-1-Ag (PAI-1-Ag), and metabolic control (HbA1c) were investigated in 81 patients.

Results: Median age of patients was 15.7 years (6.2-53.6), median duration of diabetes was 8.2 years (1.4-33.2), microalbuminuria was 5.8 $\mu\text{g}/\text{min}$ (0.24-66), median HbA1c calculated from last 10 visits was 8.0 % (6.4-12.5). There was no correlation between microalbuminuria and markers of endothelial cell alteration or hemostatic factors. In contrast, we found significant correlations between HbA1c and vWf-Ag ($r=0.31$, $p<0.005$), P-Selectin-Ag ($r=0.25$, $p<0.05$), factor VIIc ($r=0.27$, $p<0.01$), factor VIIIc ($r=0.37$, $p<0.001$), and tPA-Ag ($r=0.33$, $p<0.005$). These correlations stayed significant after adjustment for age and duration of diabetes. Patients with HbA1c values $< 8\%$ showed significant lower plasma levels of P-Selectin ($p<0.01$), Factor VIIc ($p<0.05$), Factor VIIIc ($p<0.005$), and PAI-1-Ag ($p<0.05$) compared to patients with HbA1c values $> 8\%$.

Conclusion: Type I diabetes patients with poor metabolic control show higher plasma levels of hemostatic risk factors. Markers of endothelial cell activation do not correlate with microalbuminuria.

ETHNICITY AND SOCIAL STATUS AS MAJOR CONTRIBUTING FACTORS TO METABOLIC CONTROL

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Ethnicity has been proven to be a major determinant of poorer metabolic control. Social status might contribute to outcome as well. In Germany the vast majority of patients is covered by a general health insurance. Privately insured patients usually have a higher social status. So we wanted to study, how ethnic background and social status -reflected by different insurances - influence the management and outcome of children and adolescents with diabetes mellitus.

Methods and Materials: From 1.1.1990 - 31.12.2001 n=535 patients were treated at the Olgahospital Stuttgart, one of the referral centers for pediatric diabetology in Southwest-Germany. Data were collected with the well known DPV-System, copied and sent to Ulm for statistical analysis (SAS-program).

Results: Data from n=424 German patients and n=109 of foreign origin were available for analysis. Germans were older and followed up longer (15 vs. 12,7 years, p=0,0001; 6,74 y. vs. 5,12y., p=0,0007). Hba1_c was significantly lower (8,21% vs. 8,85%, p=0,0018). The number of injections was higher (3,37 vs. 3,22, p=0,0153). While Germans stayed longer in hospital (8,29 d vs. 7,85 d), the percentage of admittance was lower (18,9% vs. 24,8%). There was no difference between dose, BMI or frequency of severe hypoglycemia.

Concerning social status reflected by different types of insurance, there were differences in BMI and dose for n=96 privately insured vs. n=439 covered by health insurance (19,65 kg/m² vs. 20,21, p <0,02; 0,75 U/kg BW vs. 0,82, p= 0,0312). Privately insured patients were younger (13,66 y. vs. 14,72) and followed up shorter (6,02 y. vs. 6,47). Hba1_c was lower, as well as the number of injections (8,24% vs. 8,35% p<0,02; 3,27 vs. 3,35, n.s.).

Discussion: German patients show significantly better metabolic longterm-results compared to patients of foreign origin. The kind of insurance influenced it to a lesser degree. Exact statistical comparison of the 4 subgroups was limited, because the subgroup of private insured non-Germans was too low (14 out of 109 = 12,8% vs. 82 out of 424 = 19,4%) in the health insured group.

Conclusion: For further clarification a nation-wide study has to be performed. The DPV-system is the ideal basis, for data of more than 50% of the pediatric patients with diabetes in Germany are already included in this database.

**THE IMPACT OF BMI AND THE METABOLIC SYNDROME
FOR MICROVASCULAR DISEASE IN ADOLESCENTS WITH
TYPE I DIABETES MELLITUS**

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Background: The early signs of microvascular disease leading to diabetic retinopathy and kidney failure often have their onset in adolescence. In the total age cohort of the DCCT, high BMI was an additional prognostic factor for retinopathy over glycaemic control¹. We therefore hypothesise that features of metabolic syndrome influence the early development of microvascular disease in adolescents with type 1 diabetes mellitus.

Aim: To identify whether BMI and other features of metabolic syndrome (blood pressure, lipid abnormalities) are risk factors for the development of diabetic complications.

Methods: We analysed 1306 adolescents (600 boys and 706 girls) with type 1 diabetes at the median age of 16 years and median duration of 7 years. BMI SDS (median BMI SDS girls 0.47, boys 0.28), blood pressure percentiles, cholesterol, HbA1c, insulin dose/weight, age and duration were recorded at the time of complication assessment. Logistic regression was performed with these predictors with complications as the outcome. Retinopathy was defined as microaneurysm or haemorrhage in one eye. Abnormal urinary albumin excretion rate (AER) was defined as a mean of three measurements greater than 7.5µg/min (AER > 7.5).

Results: In girls, significant risk factors for retinopathy were BMI SDS (OR 1.38), age (OR 1.16) and diabetes duration (OR 1.18), but only age (OR 1.18) and duration (OR 1.21) were significant in boys.

Significant risk factors for AER > 7.5 were diastolic blood pressure percentile (OR 1.03), duration (OR 1.09), HbA1c (OR 1.22) and BMI SDS <0.11 (first quartile) (OR 1.96) in girls, diastolic blood pressure percentile (OR 1.01), duration (OR 1.14) and BMI >85th percentile (OR 1.80) in boys.

Conclusion: Higher BMI SDS increased the risk for retinopathy in girls and AER > 7.5 in boys. Higher diastolic blood pressure increased the risk of AER > 7.5 in both boys and girls.

¹Zhang L et al. Diabetes Care 2001; 24:1275-9

LONGTERM TRACKING OF METABOLIC CONTROL: HBA1C DURING REMISSION PREDICTS HBA1C IN ADULTHOOD IN PATIENTS WITH CHILDHOOD ONSET TYPE-1-DIABETES.

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Background: It is still controversial whether early metabolic control in patients with childhood-onset diabetes is relevant for the subsequent course of the disease. So far, few long-term data on HbA1c in pediatric patients are available.

Patients and Methods: The DPV computer system provides standardized prospective documentation of diabetes-related parameters. From 9 pediatric centers, continuous follow-up of metabolic control from a prepubertal onset of diabetes through remission (duration < 2 years), the prepubertal-postremission phase (duration ≥ 2 years, age ≤ 11 years), puberty (age 11-18) to young adulthood (age 18-25) was available for 78 patients (34 boys, 44 girls; mean age at onset: 6.1±2.2 years, mean age at last documented visit: 19.5±1.7 years). Based on the local normal range, HbA1c-values were mathematically standardized to the DCCT method (normal: 4.05–6.05%). For each patient, the median of all measurements during the 5 phases of diabetes was calculated.

Results: At onset, HbA1c averaged 8.7%, decreasing to 6.7% during remission. Subsequently, HbA1c increased to 7.6% during the prepubertal phase, with a further increase to 8.7% both for puberty and adulthood. When median HbA1c values during the different phases were correlated, a significant relation was present between HbA1c during remission and HbA1c in adulthood ($r = +0.38$, $p < 0.0005$). An identical correlation was present between metabolic control during remission and the pubertal period ($r = +0.36$, $p < 0.0015$). All relationships were present for boys and girls. Remarkably, no correlation existed between HbA1c at onset of diabetes and HbA1c during puberty or adulthood.

Conclusions: These data demonstrate longterm tracking of metabolic control despite the increase in HbA1c associated with puberty. HbA1c during remission - but not HbA1c at diagnosis of diabetes - predicts the subsequent course of the disease in patients with young onset, indicating the importance of an early therapeutic focus on good metabolic control.

INCREASED RISK OF OTHER AUTOIMMUNE DISORDERS IN CHILDREN WITH TYPE 1 DIABETES MELLITUS

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Background: Autoimmune disease (AD) is characterized by humoral or cell-mediated immune response to organ specific or systemic self antigens. Given the clustering of ADs in the same patient, the different phenotypes represent a spectrum of immune dysregulation. The **aim** of the study was to assess the prevalence of other ADs in our cohort with type 1 diabetes mellitus (DM). **Methods:** Four hundred diabetic children (age: 1.1-19.25 years) were investigated. Different ADs were recognized by clinical symptoms and/or by specific serological testing. Screening for celiac disease (CD) was performed in 194 diabetic children by testing for anti-endomysium antibody (AEA). In subjects proven positive for AEA, diagnosis of CD was confirmed by jejunal biopsy. Screening for thyroid disease (TD) was carried out in 90 diabetic children with determination of anti-thyroglobulin and anti-thyroid peroxidase antibodies, together with measurement of serum thyroid and thyroid stimulating hormone levels. **Results:** Out of 42 AEA positive subjects, diagnosis of CD was confirmed in 31 children (16 %) with jejunal biopsy. Thyroid related auto-antibodies were present in 12 diabetic children (13.3 %). Four children (4.4 %) appeared to be euthyroid; hyperthyroidism was found in 2 children (2 %) and hypothyroidism was diagnosed in 6 patients (6.7 %). In the whole diabetic cohort, 29 children (7.3 %) had vitiligo, and juvenile rheumatoid arthritis was diagnosed in 1 child by clinical symptoms. Combined occurrence of type 1 DM with other ADs was observed in 62 children (15.5 %). Fifty five diabetic patients (13.8 %) had 1; 6 patients (1.5 %) had 2 additional ADs. One diabetic patient was suffering from type 3 polyglandular syndrome. Age at onset of diabetes appeared to be significantly ($p<0.05$) lower in patients with multiple ADs than in children with DM alone. **Conclusions:** The prevalence of CD and thyroid related ADs is higher than expected in children with type 1 DM. Since both diseases can initially be silent, it is advisable to test diabetic children for anti-endomysium and anti-thyroid antibodies. The prevalence of other ADs appeared to be closely related to younger age at diagnosis of DM.

SECULAR CLUSTERS CHARACTERIZE THE APPEARANCE OF DIABETES-ASSOCIATED AUTOANTIBODIES IN EARLY CHILDHOOD

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Background: Several environmental factors like fetal or childhood viral infections, nutritional factors such as cow's milk proteins, vaccinations, psychosocial stress and enhanced weight and height gain have been associated with the development of type 1 diabetes. Among these factors only infections show clear seasonal variation.

Aim: To study whether diabetes-associated autoantibodies appear as secular clusters; as they are the best known sign of the activation of β -cell directed autoimmunity.

Methods: From more than 50,000 consecutive newborn infants, a cohort of children (n=6,215) carrying increased HLA-conferred genetic susceptibility to type 1 diabetes was selected at birth and tightly followed-up. Recruitment began in November 1994. This analysis comprises data collected by June 2001. ICA was measured at 3-, 6- and 12-month intervals and IAA, GADA and IA-2A were analyzed in all samples if ICA were found. As the exact day of autoantibody seroconversion is unknown between the two consecutive samples, the probability for autoantibody seroconversion was calculated for every follow-up day of each child.

Results: ICA was found in 231 children. The probable time for the appearance of the first autoantibody in these children peaked periodically showing usually one major peak per year, during late summer to early winter.

Conclusion: Our data showing such peaks suggest that specific infectious triggers are involved in β -cell damaging autoimmune process, either alone, or in combination with (a) stable factor(s), e.g. components in nutrition.

ESSENTIAL FATTY ACIDS AND THEIR LONG-CHAIN METABOLITES IN PLASMA LIPIDS OF DIABETIC CHILDREN

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Background: In obese children, disturbances of essential fatty acid metabolism were found to be associated with abnormal glucose homeostasis, i.e. with impaired glucose tolerance (Decsi et al., *Lipids* 35: 1179-1184, 2000).

Aim: To investigate whether essential fatty acid status is also disturbed in another common abnormality of glucose homeostasis, i.e. in diabetes mellitus.

Methods: Fatty acid composition of plasma lipid classes was determined by high-resolution capillary gas-liquid chromatography in children with insulin dependent diabetes mellitus (n = 40, age: 12.0±3.9 years, weight: 44.5±16.7 kg, HbA_{1c}: 9.24±2.29 %, duration of diabetes: 6.41±3.63 years) and in healthy controls (n = 40, age: 12.4±3.5 years, weight: 44.7±14.7 kg).

Results: Values of the essential fatty acids, linoleic acid (C18:2n-6) and α -linolenic acid (C18:3n-3) were significantly higher, whereas values of the principal long-chain polyunsaturated fatty acids, arachidonic acid (C20:4n-6) and docosahexaenoic acid (C22:6n-3) were significantly lower in diabetic children than in controls (**table**). The product/substrate ratio for the Δ -6-desaturase enzyme (C18:3n-6/C18:2n-6) was significantly lower in diabetic children than in controls (phospholipids: 0.002 [0.001] versus 0.003 [0.003], sterol esters: 0.010 [0.006] versus 0.012 [0.012], median [IQR], p < 0.05).

Table: Fatty acid composition of plasma lipids in diabetic children (DM) and in controls (CO). Data are median (IQR), ^a = p < 0.05, ^b = p < 0.01, ^c = p < 0.001

Fatty acid	<i>Phospholipids</i>		<i>Sterol esters</i>	
	DM	CO	DM	CO
C18:2n-6	23.00 (2.35) ^c	18.13 (2.54) ^c	58.49 (4.43) ^c	53.47 (3.48) ^c
C20:4n-6	10.73 (2.34) ^a	11.53 (2.50) ^a	6.63 (1.67) ^b	8.30 (2.72) ^b
C18:3n-3	0.12 (0.06) ^c	0.07 (0.07) ^c	0.33 (0.13)	0.27 (0.15)
C22:6n-3	2.23 (0.63) ^c	2.77 (0.98) ^c	0.37 (0.17) ^c	0.50 (0.21) ^c

Conclusions: 1. In the present study, availability of arachidonic and docosahexaenoic acids was significantly reduced in diabetic children as compared to controls. 2. The fatty acid status observed in diabetic children in this study suggests that an enhanced dietary supply of long-chain polyunsaturated fatty acids (but not that of essential fatty acids) may be beneficial.

**DEAD IN BED SYNDROME IN YOUNG DIABETIC PATIENTS
IN JAPAN**

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Background: In 1991, a number of unexpected and unexplained deaths in young type 1 diabetic patients were reported in Great Britain. Twenty-two cases were identified belonging to the so-called 'dead in bed syndrome' (1) patient found dead in a disturbed bed; (2) patient observed to be in good health condition the day before; (3) no clinical evidence of late complications.

Aim: To clarify the frequency of dead in bed syndrome in Japan, we did national wide investigation about sudden death in young Japanese type 1 diabetic patients.

Methods: Firstly we sent the primary questionnaire of asking the sudden death cases to the children's hospitals and university hospitals (the total were 108 centers) in Japan. Secondary we sent next letters to the hospitals having the sudden death cases for getting further detail data.

Results: 95% centers (90.5%) returned the questionnaires. 16 sudden death cases were gathered. In 12 cases, we could get the detailed information. Four cases died because of chronic diabetic complications. Other eight cases were found to be unexplained death cases and 3 out of eight cases satisfied the criteria of the 'dead in bed syndrome'.

Conclusions: There were a number of sudden unexplained deaths including 'dead in bed syndrome' in young Japanese type 1 diabetic patients.

RESIDUAL INSULIN SECRETION DURING THE FIRST YEAR AFTER DIAGNOSIS.

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Background and aim: To identify factors associated with residual insulin secretion and duration of the remission period in newly diagnosed children and adolescents with type 1 diabetes. To relate these factors to the individual insulin treatment regimens at onset.

Methods: Multicenter longitudinal investigation with 19 participating paediatric centres from 15 countries in Europe and Japan. Clinical information and blood samples were collected from 275 children and adolescents less than 16 years with newly diagnosed type-1 diabetes. Year of birth, sex, duration of symptoms, height, weight, and insulin regimen were recorded. Blood glucose, pH/HCO₃ were measured locally, while HbA_{1c} and C-peptide were analysed centrally. HbA_{1c} normal range: 4.4-6.3% ; mean 5.4%. A stimulated C-peptide Boost-test was carried out in each subject at 1, 6 and 12 months after diagnosis.

Results: The average stimulated C-peptide decreased significantly from 463 ± 20 picomol/l (mean ± SEM) at 1 month to 382 ± 22 picomol/l at 6 months (p<0.0001) and to 273 ± 19 at 12 months (p<0.0001). The joint effect of variables: Gender, age, pH, standard bicarbonate and IV treatment, on the C-peptide response at 12 months was investigated. Multiple regression analysis showed that young age was significantly (p< 0.001) associated with reduced C-peptide at 1, 6 and 12 months while low standard bicarbonate at onset showed a significant (p< 0.01) independent association with reduced C-peptide at 12 months. IV insulin during the first week after diagnosis had no significant effect on any of the C-peptide responses. A remission phase (HbA_{1c} <6%) occurred in 17% at 3 months follow-up, in 13% at 6 months, in 5% at 9 months and 3% at 12 months. HbA_{1c} was significantly higher (p<0.01) in the young age group (0-5 years) after 3 months suggesting shorter remission.

Conclusion: Young age and severe acidosis at disease onset are associated with lower residual beta-cell function during the first year of insulin treatment. Initial management by IV insulin does not appear to affect the endogenous insulin secretion at 12 months compared to SC.

GIRLS AT FIVE ARE INTRINSICALLY MORE INSULIN RESISTANT THAN BOYS (THE **EarlyBird STUDY)**

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Background: A consistent feature of type II diabetes in young populations is the predominance of girls over boys. Girls are reportedly more insulin resistant than boys, but it is unclear how much of the difference can be explained merely by adiposity and pubertal stage. **Aims:** to establish whether there is an intrinsic difference in insulin resistance between girls and boys. **Methods:** EarlyBird is a non-intervention prospective cohort study designed to establish which children acquire insulin resistance, and why. It is monitoring 307 healthy children from school entry to the age of sixteen. Outcome measures include insulin resistance (IR) by HOMA and its metabolic correlates, blood pressure, anthropometric measures, physical activity and resting energy expenditure. **Results:** IR was 34.6% higher in girls than boys (0.868 v 0.645, $p < 0.001$). Triglycerides were significantly higher in the girls (0.70 v 0.58 mmol/l, $p < 0.001$), and HDL cholesterol (1.42 v 1.51 mmol/l, $p = 0.02$) and SHBG (103.0 v 111.5 nmol/l, $p = 0.05$) lower. Girls carried more subcutaneous fat (4.75 v 3.86 cm, $p < 0.001$) than boys despite similar body weights. Height, weight, waist circumference and visceral fat correlated significantly with IR in both sexes ($r \geq 0.20$, $p \leq 0.05$ for all correlations). Boys took more physical activity than girls (36.4 v 34.0 units, $p < 0.01$). No significant correlation was observed in either sex between physical activity and IR. Resting energy expenditure did not correlate in either sex with IR, independently of current weight. Even after accounting for anthropometric variables, resting energy expenditure and physical activity, girls remained 33.2% more insulin resistant than boys ($p < 0.001$). **Conclusion:** Pre-pubertal girls are intrinsically more insulin resistant than boys, and the metabolic disturbances associated with insulin resistance are more advanced in girls even at this early age. The difference is substantial and may account for the predominance of females among childhood-onset type II diabetes reported worldwide. There may have been evolutionary advantage from the difference, and understanding the factor(s) responsible may yield important clues to mechanisms of insulin resistance. Sex-linked genes may account for the difference.

**FREQUENCY AND CLINICAL PRESENTATION OF
KETOACIDOSIS AT ONSET OF TYPE 1 DIABETES
MELLITUS IN CHILDREN**

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Background: Since 1987 patients with newly-diagnosed diabetes mellitus type 1 under the age of 15 are being registered in Baden-Wuerttemberg (BW), Germany.

Aim: To describe frequency and clinical presentation of diabetic ketoacidosis (DKA) at onset of type 1 diabetes mellitus in children.

Methods: All 31 pediatric departments in BW and one diabetes center participated in this study. The degree of ascertainment is 97.2%. Hospital records of 2,121 children below 15 yrs of age were examined retrospectively. According to Rosenbloom and Kitabchi, DKA is defined as glucose > 250 mg/dL, pH < 7.30 or bicarbonate < 15 mmol/L and ketonuria. Statistical analysis was done after logarithmic transformation.

Results: 1. 26.3% (n = 558) of all patients presented with DKA. The mean age was 7.9 years. The frequency of DKA is higher in girls than in boys (28.9% vs. 23.8%; p = 0.0079). The 0-4-yr-olds suffered most frequently (p < 0.0001) from ketoacidosis (36.0%) compared to the 5-9-yr-olds (23.7%) and the 10-14-yr-olds (23.4%).

2. The mean blood glucose was 515 mg/dL (geometric mean) with a 95% central range from 276 to 1,101 mg/dL.

3. 23.3% of all patients with DKA presented with altered level of consciousness. 10.9% of these had clinical signs of coma. No deaths occurred.

4. The total number of ketoacidosis is higher in winter than in summer. However, the proportion of ketoacidosis does not increase concurrently with the number of diabetes manifestations (27.1% in summer vs. 25.7% in winter).

Conclusion: The proportion of DKA in children with newly-diagnosed diabetes mellitus is significant. Especially children < 5 yrs and girls face an increased risk of developing complications arising from DKA.

**EFFECTS OF GLYCEMIA AND INSULINEMIA ON
FIBRINOLITIC ACTIVITY AND PLASMINOGEN
ACTIVATOR INHIBITOR TYPE 1 IN THE RAT**

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Background: Decreased plasma fibrinolytic activity and elevated plasma levels of plasminogen activator inhibitor type 1 (PAI-1) may contribute to accelerate atherothrombosis in diabetes.

Aim: To observe whether hyperglycemia and hyperinsulinemia, common findings in type 2 diabetes, acutely affect plasma fibrinolysis in vivo.

Methods: We evaluated plasma fibrinolysis (lysis of fibrin plates, free PAI-I activity and t-PA activity) in the rat after a hyperglycemic euinsulinemic clamp (n=8), an euglycemic hyperinsulinemic clamp (n=7) or a saline infusion (n=15).

Results: Plasma fibrinolytic activity was sharply reduced after both the hyperglycemic and hyperinsulinemic clamps as compared to the respective controls (mean lysis areas on the fibrin plate, 139 ± 21 vs. 323 ± 30 mm², $p < 0.001$; 78 ± 27 vs. 312 ± 27 mm², $p < 0.001$, respectively). Plasma PAI-1 activity was greater after both hyperglycemic and hyperinsulinemic clamps as compared to saline infusion (6.6 ± 2.6 vs. 1.6 ± 0.6 IU/ml, $p < 0.001$; 26 ± 4 vs. 1.3 ± 0.7 IU/ml, $p < 0.0001$, respectively). Plasma t-PA activity was significantly reduced both after the hyperglycemic (0.36 ± 0.15 vs. 2.17 ± 0.18 IU/ml in controls, $p < 0.001$) and the hyperinsulinemic (0.3 ± 0.1 vs. 2.3 ± 0.3 IU/ml in control, $p < 0.001$) clamps.

Conclusion: These data show that in vivo both acute hyperglycemia and acute hyperinsulinemia can decrease plasma fibrinolytic potential and that this is due to increased plasma PAI-1 and decreased free t-PA activities

**GLUCOSE AND INSULIN INDEPENDENTLY REDUCE
THE FIBRINOLYTIC POTENTIAL OF HUMAN
VASCULAR SMOOTH CELLS IN CULTURE**

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Background: Hyperglycaemia and hyperinsulinaemia have both been related to accelerated atherosclerosis in type 2 diabetes mellitus. Plasma fibrinolytic potential is reduced in patients with diabetes. It is also known that glucose and insulin can modulate plasminogen activator inhibitor (PAI-1) and tissue-plasminogen activator (t-PA) secretion and can therefore regulate local fibrinolysis.

Aim: To assess the role of insulin and glucose in regulating PAI-1 and t-PA production in cultured vSMC.

Methods: Arterial vSMC explanted from human umbilical cords were cultured and exposed to increasing concentrations of glucose (5, 12, 20, 27, 35 mmol/l) or insulin (0.1, 0.5, 1, 10 nmol/l) in a serum free medium. After 24 hours, PAI-1 and t-PA antigens and activity were evaluated in the culture medium; in cells exposed to 20 mmol/l glucose and to 0.5 nmol/l insulin PAI-1 gene expression was also evaluated.

Results: An increase in PAI-1 antigen was observed at each glucose concentration (by 138, 169, 251 and 357 % as compared to 5 mmol/l glucose) which was paralleled by an increase in PAI-1 activity. t-PA concentration was also increased by glucose but its activity was sharply reduced. An increase in PAI-1 antigen was detected at each insulin level (by 121, 128, 156 and 300 % as compared to no insulin). PAI-1 activity was slightly increased at the lowest insulin concentrations but markedly increased by 10 nmol/l insulin. t-PA antigen was also increased by insulin; however, its activity was markedly reduced at each concentration. As compared to control cells, PAI-1 mRNA was increased by 2.5 and 2.0 fold by 20 mmol/l glucose and 0.5 nmol/l insulin, respectively.

Conclusion: In human vSMC both glucose and insulin can affect the fibrinolytic balance so as to reduce fibrinolytic potential. This might contribute to decreased local fibrinolysis and thereby accelerate the atherothrombotic process patients with diabetes.

DEGENERATIVE VASCULAR CHANGES IN DIABETIC CHILDREN MEASURED BY NIRS

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Background: Diabetes is an important risk factor for the development of degenerative vascular changes, whereby microvascular changes might start even in infancy.

Aim: The aim of the study was to measure forearm blood flow (FBF) at rest and after exercise using near infrared spectroscopy (NIRS) in order to detect possible microvascular changes in children and adolescents with diabetes.

Patients and Methods: FBF measured by NIRS during venous occlusion was analysed. Measurements were performed at rest and after one minute rhythmic handgrip exercise.

Diabetic patients (n=15) were matched for age to healthy children and adolescents (n=15) for comparison. In 40 diabetic patients (age:14.2±2.6years; diabetes duration:5.2±3.5years) FBF at rest and changes of FBF after exercise were calculated and correlated with age, body mass index, duration of diabetes, HbA1 and blood glucose levels.

Preliminary results: FBF at rest was significantly lower in diabetic group ($1.8 \pm 1.1 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$) compared to healthy group ($2.9 \pm 1.3 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$).

In diabetic patients FBF after exercise increased significantly ($+0.6 \pm 0.6 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$). Changes of FBF did not correlate with age or body mass index, but correlated with duration of diabetes, HbA1 and blood glucose levels, whereby the increase of FBF was reduced with increasing duration, HbA1 and blood glucose levels.

Conclusion: By means of NIRS we were able to detect a reduced forearm blood flow in children and adolescents with diabetes with impaired hyperemic response related to duration of diabetes, HbA1, and blood glucose levels. These data suggest that NIRS might provide a tool in future to detect non invasively diabetic vascular changes, which seems to be present even in children and adolescents.

SCREENING FOR AUTOANTIBODIES IN CHILDREN AND ADULTS WITH TYPE I DIABETES

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Background: The increased prevalence of associated autoimmune disorders such as Hashimoto Thyroiditis, Graves' disease and coeliac disease in patients with type I diabetes is well known. There are only a few reports about screening for other organ-specific autoantibodies in patients with diabetes I.

Aim: The aim of this study was to determine the frequency of associated autoantibodies in children and adults with type I diabetes to detect autoimmune disorders early, which are often asymptomatic, and to devise a screening programme for patients with type I diabetes.

Methods: We examined 102 sera from patients with type I diabetes. 63 adults (23 female and 40 male, age 18-51) and 39 children (17 girls and 22 boys, age 6-16 years). The duration of diabetes ranged from 2-33 years in adults and from 3-14 years in children. Autoantibodies to adrenal gland, ovary, testes, kidney, liver, thyroid, coeliac disease specific AB (EMA and ARA), gastric parietal cells AB (GPA), circulating immune complexes (CIC) and ds-DNA were tested by immunofluorescence. Tg-AB, TPO-AB, TRAB, diabetes-specific antibodies ICA were tested by ELISA. GAD and ICA by RIA.

Results: In 43% of the diabetics one or more autoantibodies were found. There was no positive reaction to ovary, testes and liver. 3,9 % showed only a weak reaction to AB to adrenal gland without clinical symptoms. 9,8% AB to thyroid (7,1 % TG-AB, 6,8 % TPO-AB, 0,9% TRAB) 2,9 % to EMA+ARA, 6,8% only ARA, 17,6% GPA and 1,9 % to ds-DNA were found. 47 % to GAD, 31 % to IA2, 71 % to ICA.

In 8 patients (7,8%) 2 or more autoantibodies were found.

Conclusion: As reported before there was a high frequency in organ-specific-autoantibodies to thyroid (9,8%), and coeliac disease (2,9%), but also gastric parietal cells (17,6 %). All patients were without clinical symptoms. It seems useful to screen for GAP, thyroid-AB and EMA yearly in patients with type 1 diabetes mellitus to detect diabetes associated autoimmune disorders early.

PREVALENCE OF TYPE 1-DIABETES IN GERMANY

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Background: Actual prevalence estimates of Type 1 diabetes in childhood and adolescents are almost lacking for Germany. Aim of the study was to estimate the prevalence of Type 1 diabetes based on data from the German federal state of North Rhine-Westphalia (NRW) covering about one fourth of all children and adolescents in Germany. At the end of 2000, the population under 15 or 20 years of age in NRW amounted to 2.94 and 3.89 million persons, respectively.

Methods: Prevalence estimates were based on the Type 1 diabetes incidence register of NRW. New cases are registered by three data sources, the active hospital-based surveillance system (ESPED), inquiries among practices, and a computer-based documentation for quality control in pediatric diabetology (DPV). Completeness of ascertainment was estimated by the capture-recapture-method using log-linear models. Prevalence estimates (95%-KI) were based on Poisson distribution.

Results: On 31 December 2000, a total of 3,050 and 4,765 diabetic children and adolescents under 15 or 20 years of age were registered in NRW, respectively. Completeness of ascertainment was 93.3% (92.5-94.9%) and 88.1% (87.1-89.1). The respective prevalences (per 100.000 children) were 103.9 (100.2-107.7) and 122.4 (118.9-125.9), implying that 1 out of 1,000 and 1 out of 800 children and adolescents under 15 or 20 years of age has diabetes, respectively. The ascertainment corrected prevalences were 111.4 (107.4-115.4) and 138.9 (135.0-142.9). Prevalences in boys and girls were similar ($p > 0.3$). Projected to the whole of Germany, there are in total 13.400-14.400 and 21.500-24.400 diabetic children and adolescents under 15 or 20 years of age, respectively.

Conclusion: Due to underregistration before 1996 and in the age group 15-19 years, the actual estimates are likely to be lower bounds of the true prevalences. However, even the observed prevalences are twofold higher than estimates from the diabetes register of former East Germany for the late 1980s. This has important implications for the structure of diabetes care.

ASSOCIATED AUTOIMMUNITY IN TYPE 1 DIABETES

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Background: It is well known that type 1 diabetes can be associated with other autoimmune diseases.

Aim: To determine the prevalence of thyroid autoimmunity (anti-TPO and anti-TG) and EMA positivity in diabetic children.

Methods: Point-prevalence of thyroid autoimmunity was estimated in 208, that of EMA positivity was measured in 196 long-standing diabetic patients. Thyroid antibodies have also been measured in 76 newly diagnosed subjects.

Results: Thyroid antibodies were present in 25.5% of diabetic children with about 8 years duration of diabetes and in 17.4% of newly diagnosed subjects. Thyroid autoimmunity in both groups showed female preponderance. There was no difference between patients with and without thyroid autoimmunity in metabolic variables. Thyroid disease was diagnosed in 15 diabetic patients (7.2%) (14/15 females) by detailed endocrine studies. Six patients were hyperthyroid and 9 patients had hypothyroidism. Most of them did not have any clinical symptoms at diagnosis, but all had abnormal TSH levels, while anti-TPO was present in 10 and anti-TG in 9 cases. Three of the patients with thyroid disease had a third manifest autoimmune disorder: dermatomyositis, coeliac disease and Addison's disease.

The prevalence of EMA positivity was 6.6%, 1.5% of the cases had clinical symptoms suggesting coeliac disease (CD), 5.1% of the patients had "silent" CD. At diagnosis of diabetes, EMA positive children were younger as compared to those without endomysium antibodies (5.0 ± 3.6 vs. 8.5 ± 4.7 years, $p=0.008$).

Conclusion: Both thyroid and coeliac autoimmunity are relatively common in diabetic children. Regular screening for specific antibodies is therefore recommended. One out of 4 diabetic children has thyroid antibodies but as only one out of 14 has thyroid dysfunction, antibody screening is to be complemented by TSH measurement. The prevalence of thyroid autoimmunity is increasing by age.

**THE CHARACTERISTICS OF CLINICAL PRESENTATION
OF TYPE 1 DIABETES IN CHILDREN DOES NOT
SIGNIFICANTLY INFLUENCE THE PATTERN OF
RESIDUAL BETA-CELL FUNCTION AND THE LONG
TERM OUTCOME**

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Background : It is a common belief that an early diagnosis of type 1 diabetes is a considerable event in term of positive long-term consequences.

Aim: To compare the effects of the clinical presentation of type 1 diabetes in children on residual β -cell secretion and long-term metabolic control.

Methods :This retrospective study was conducted in 66 diabetic children with age at diagnosis ranging from 0.7 to 14.8 years. The patients showed opposite characteristics at diagnosis: either ketoacidosis (Group 1, n. 29) or absence of ketoacidosis associated with severe (Group 2, n. 12) or mild hyperglycemia (Group 3, n. 25). A regular follow-up was available for at least 10 years (10-32 yrs) in all the cases and for 20 yrs in 23 cases. C-peptide levels were measured since diagnosis for the first years of disease until they became permanently undetectable. At 10, 15, 20 yrs of disease, glycated hemoglobin, insulin requirement, urinary albumin excretion and retinal status were evaluated.

Results : C-peptide levels at diagnosis were undetectable in about 20% of the cases both with and without ketoacidosis. Mean C-peptide levels at diagnosis, duration of measurable C-peptide levels and its maximum value found during follow-up were not significantly different in the 3 groups and were not correlated with glycated hemoglobin calculated throughout the whole period. No differences were found between the groups of patients concerning glycated hemoglobin values and insulin dose at 10,15, 20 yrs of disease. The prevalence of retinopathy and nephropathy was not statistically different in the 3 groups.

Conclusion: The severity of clinical presentation at diagnosis does not significantly influence residual beta-cell function, long-term metabolic control and the risk of late complications.

**METFORMIN IMPROVES GLYCAEMIC CONTROL IN
ADOLESCENTS WITH TYPE 1 DIABETES**

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Background: Metabolic control often deteriorates and weight is gained during puberty in children with Type 1 diabetes. Alternative therapeutic strategies are needed when optimized insulin regimen fails to regulate the metabolic control.

Aim: The aim of the present study was to investigate whether addition of metformin for three months improves metabolic control and insulin sensitivity in poorly controlled adolescents with Type 1 diabetes.

Methods: Twenty-six adolescents with Type 1 diabetes (18 females, 8 males) were included in a double-blind placebo controlled trial. The mean age was 16.9 ± 1.6 years, mean HbA_{1c} was 9.5 ± 1.1 % and the daily dosage of insulin was 1.2 ± 0.3 U/kg. The primary endpoint, glycated haemoglobin (HbA_{1c}), was measured every 4 weeks with a HPLC method (upper reference limit 5.3 %). An euglycaemic hyperinsulinaemic clamp was performed at baseline and at the end of the trial after 3 months to measure peripheral insulin sensitivity. Hepatic insulin sensitivity was estimated with IGF-I and IGFBP-1 measurements.

Results: We found a significant reduction in HbA_{1c} from baseline to the end of the study in the group treated with metformin (9.6 vs 8.7%; $p < 0.05$). The HbA_{1c} was unchanged in the placebo group (9.5 vs 9.2 %; ns). We found no change in body-mass index, insulin dose, IGF-I concentrations, blood lipid levels or peripheral insulin sensitivity in neither of the groups. IGFBP-1 concentrations were reduced in the metformin group, although not statistically significant (123 µg/l vs 57 µg/l). Side effects were mild, no case of diabetic ketoacidosis or severe hypoglycaemia occurred during the study period.

Conclusion: In this double-blind placebo controlled study we found that metformin improves metabolic control in adolescents with Type 1 diabetes. Our data suggest that the effect might be mediated by increased hepatic insulin sensitivity. Further larger studies are needed to confirm these results.

**PREVALENCE OF OVERWEIGHT AND OBESITY IN
MALE ADOLESCENTS IN AUSTRIA.
A POPULATIONBASED STUDY**

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Background: Available prevalence data on obesity in childhood and adolescents show considerable geographic variation. The highest rates are observed in Eastern and Southern European countries, while Northern European countries tend to have lower rates .Even within countries there may be marked regional variability. For Austria only selfreported data on weight and height or data on a limited cohort of school children exists.

Aim: The aim of the present population based study was to analyse the prevalence of overweight and obesity in young Austrian males, to describe a possible time trend during the observation period 1985-2000 and to define regional differences within the country

Methods:

Information from the nationwide Military Service Conscription Register from 1985 to 2000 was employed for the study. The present data set comprises data of 180 550 young men ageing eighteen years

Measurements of height and weight were performed. Overweight was defined as BMI > 25,00 kg/m² and obesity as BMI > 30,00 kg/m².

Beside height and weight data information on place of residence of the young men was used for the study. Chi-squares and student t-tests were calculated to test group differences with respect to their statistical significance

Results: The prevalence of overweight increased from 10.9 to 15.5 % and of obesity from 1.8 to 4.9 % during the observation period. A significant regional trend was found with higher values in the Eastern part of Austria.(p < 0.001)

Mean BMI was 22.15 + 0.34 kg/m² (x ± SD) in 1985 and showed a significant increase (P < 0 .001) during the study period to 22.68 0.25 kg/m² (x ± SD)

Conclusion: T We observed a strong upward trend for BMI in young males in Austria between the year 1985 and 2000. The steepest increase was found in the prevalence of obesity and in the Western part of Austria . A significant regional difference could be documented during the whole study period.

**DELINEATION OF RISK FACTORS FOR EARLY
CORONARY ARTERY DISEASE DIAGNOSED BY
ULTRAFAST ELECTRON BEAM TOMOGRAPHY
IN YOUNG ADULTS WITH TYPE I DIABETES MELLITUS**

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Background: Little data exists regarding the early natural history of Coronary Artery Disease (CAD) in young adults with type 1 diabetes and risk factors associated with this diagnosis. Electron Beam Tomography (EBT) allows non-invasive measurement of small calcifications within coronary arteries. This marker for atherosclerosis, may identify those at risk before clinical symptoms of CAD become manifest.

Aims: This study was designed to assess the prevalence of CAD in a cohort of young adults with established type 1 diabetes utilizing EBT as a marker for CAD. In those with positive EBT, risk factors would be delineated.

Methods: 101 subjects aged 17-28 years with type 1 diabetes of over 5 years duration, and no history of underlying heart disease underwent cardiac EBT with calcium scoring. In addition, a medical history and physical examination were obtained to document the presence of cardiac risk factors as well as evidence of microvasculopathy and diabetic arthropathy. Laboratory evaluation was performed to measure fasting lipids, homocysteine levels, and Lp(a) in addition to urinary microalbumin and hemoglobin A1C. Contingency table analysis was used to assess bivariate relationships. Logistic regression was then employed to construct a parsimonious model of independent risk factors. All statistical hypotheses were tested at $\alpha=0.05$.

Results: 11/101 (10.9%) of subjects had positive cardiac EBTs. Smokers were nearly 5 times more likely than nonsmokers to have a positive EBT ($p=0.03$). In addition, each 10 mg/dl increment of Lp(a) was associated with a 10% increased risk for positive EBT ($p=.05$), after controlling for potentially confounding factors.

Conclusion: This study suggests that the prevalence of early CAD as evidenced by positive EBT in young adults with type 1 diabetes is significant. Our findings also indicate that smoking and Lp(a) levels independently predict the presence of CAD.

HIGHER MATERNAL AGE AT DELIVERY, AND LOWER BIRTH ORDERS INCREASE RISK OF CHILDHOOD TYPE 1 DIABETES MELLITUS IN THE OFFSPRING

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Background: Type 1 diabetes mellitus (DM) is a consequence of absolute insulinopenia resulting from autoimmune destruction of pancreatic β -cells. Although genetic susceptibility to Type 1 DM is well defined, the non-genetic component of the disease aetiology still remains unclear

Aims: In several populations, maternal age at delivery and birth order have been demonstrated to variously affect the risk of Type 1 diabetes mellitus in the offspring. The aim of the present study was to investigate this relation in the Czech population.

Methods: Questionnaire data on 640 children with childhood-onset Type 1 DM and data on 50 random controls to each case, obtained from the National Birth Registry and matched for the calendar year of birth, were analysed using multivariate logistic regression.

Results: The risk of Type 1 DM increases with higher maternal age at birth of the child (OR=1.07, CI 95% 1.04-1.09 per year), and decreases with rising birth order (OR=0.69, CI 95% 0.61-0.78 per increment in birth order) in a model including also paternal age, parental education, sex, birth weight, and birth length. While the effect of birth order seems to be proportional, the effect of maternal age is most pronounced in the youngest mothers (<20 years of age, OR=0.57, CI 95% 0.40-0.80 relative to the age band 20-24), and in mothers giving birth at an advanced age (35 years or more, OR=1.76, CI 95% 1.11-2.81 relative to age 20-24).

Conclusions: Our study provides further evidence that the risk of Type 1 diabetes in the offspring increases with higher maternal age at delivery and lower birth order.

This study was supported by the Ministry of Education of the Czech Republic (grants No 111300003, FRVS-1158/01) and the Czech Diabetes Society.

STANDARD BICARBONATE RATHER THAN pH IS ASSOCIATED WITH CONTINUING ENDOGENOUS INSULIN SECRETION AT 12 MONTHS AFTER ONSET.

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Background: There is no general consensus on the definition of DKA in children and adolescents. Some use pH for the evaluation, others use standard bicarbonate.

Aim: To investigate the relationship between the two parameters and to study whether pH or standard bicarbonate is the best predictor for the endogenous insulin secretion after 12 months.

Methods: Multicenter longitudinal investigation with 19 participating paediatric centres from 15 countries in Europe and Japan. Clinical information and blood samples were collected from approximately 275 children and adolescents less than 16 years with newly diagnosed type-1 diabetes. On admission corresponding values for pH and standard bicarbonate were available in 248 children. pH/HCO₃ were measured locally, while C-peptide samples were shipped to the Steno Diabetes Center, Denmark and analysed centrally. A stimulated C-peptide Boost test was carried out in each subject at 1, 6 and 12 months after diagnosis.

Results: The patients were classified as mild DKA when pH was below 7.3, moderate DKA pH below 7.2 and severe DKA pH below 7.1. The corresponding limits for HCO₃ were calculated. pH 7.3 corresponded to HCO₃ 17 mmol/l (91.1 agreement) pH 7.2 corresponded to HCO₃ 9.5 mmol/l (96.0% agreement) while pH 7.1 corresponded to HCO₃ 5.4 mmol/l (98.4 % agreement). The joint effect of sex, age, blood glucose, HbA_{1c}, IV treatment, pH and HCO₃ on stimulated C-peptide at 12 months was investigated. Multiple regression analysis showed that only young age (p<0.001) and low HCO₃ rather than pH (p<0.01), at onset was significantly associated with reduced beta-cell function at 12 months.

Conclusion: In children and adolescents with DKA, the standard bicarbonate may be a better marker of the severity of DKA than pH at onset of the disease.

**BONE QUALITY ASSESSMENT BY QUANTITATIVE
ULTRASOUND OF PROXIMAL PHALANXES IN
PATIENTS WITH TYPE 1 DIABETES MELLITUS**

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Background: Owing to derangements in the secretion of peculiar regulators of bone formation (insulin, insulin like growth factor-1), Type 1 diabetes mellitus (T1DM) may have negative effects on bone. Quantitative ultrasound (QUS) is a new non invasive method which has been recently proposed in the study of bone architecture, elasticity and bone mineral density.

Aim: To assess bone quality by QUS in a large group of children and adolescents with T1DM in relation to duration and quality of metabolic control.

Methods: Eighty-four children and adolescents (44 males) with T1DM (age 11.9 ± 4.2 years, range 3-23 years; duration 4.2 ± 3.2 years, range onset-15 years) were studied. Amplitude-dependent speed of sound (AD-SoS, m/s) was measured through the distal end of the first phalanx diaphysis of the last four fingers of the hand by an ultrasound device (DBM Sonic 1200, IGEA, Carpi, Italy). AD-SoS values were then expressed as z-scores, calculated on the Italian standards for age and sex provided by the manufacturer. Linear correlations between AD-SoS z-scores and duration or long term metabolic control (mean of the HbA1c values measured in the previous year, HbA1c-year) were sought.

Results: Mean value of the AD-SoS z-score was -0.33 ± 1.3 (95% IC -0.61 ; -0.06). Eight patients (9.5%) had values < -2 SD. No significant difference in the AD-SoS z-score was found between males (-0.23 ± 1.15) and females (-0.44 ± 1.39). A negative correlation was found between AD-SoS z-score and duration ($r -0.26$; $p = 0.02$) or HbA1c-year ($r -0.34$, $p = 0.002$).

Conclusion: QUS assessment may be a useful tool in the screening of bone disturbance during childhood and adolescence. Our study shows that the architectural organization of bone may be influenced by poor metabolic control in young patients with long standing type 1 diabetes. Optimization of metabolic control in growing diabetic children may prevent osteoporosis in later life.

**VONWILLEBRAND FACTOR IN CHILDREN WITH
DIABETES: RELATIONSHIP BETWEEN ENDOTHELIAL
DYSFUNCTION AND MICROALBUMINURIA**

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Background: It has been shown that type 1 diabetic patients with persistent albuminuria have elevated plasma vonWillebrand factor (vWF) concentrations.

Aim: To evaluate plasma fibrinogen, vWf and vWf propeptide concentrations in a large group of patients with onset of diabetes during childhood and to determine whether an increase of vWf and its propeptide levels precedes and may predict the development of persistent microalbuminuria.

Methods: One hundred and two type 1 diabetic patients were studied. They were divided into two groups according to the presence or absence of persistent microalbuminuria at the end of follow-up. Control group consisted of 80 age and sex-matched healthy volunteers. Patients were followed-up for at least 8 years. Fibrinogen, vWf and vWf propeptide levels were evaluated every year in all patients during the entire follow-up

Results: At the beginning of the study there was no significant difference in fibrinogen, vWf and vWf propeptide levels between patients and healthy controls. During the follow-up, an increase of plasma vWf and vWf propeptide was observed in the group of patients who later developed microalbuminuria compared with those who remained normoalbuminuric. This increase started three years and become statistically significant ($p < 0.01$) two years before the onset of microalbuminuria, persisting until the end of the study. During the whole follow-up the plasma values of fibrinogen persisted in the normal range.

Conclusion: An increase in plasma concentration of vWf and vWf propeptide precedes the onset of persistent microalbuminuria in youngsters with type 1 diabetes and, therefore, can be useful to identify patients with onset of diabetes during childhood at risk to develop incipient nephropathy later in life.

A NOVEL MOTIVATIONAL GROUP INTERVENTION IMPROVES HbA_{1c} IN ADOLESCENTS WITH TYPE 1 DIABETES

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Background: Adolescence is frequently a time of poorer diabetic control. A recent systematic review found that most psycho-educational interventions produce only a mean 0.33 SD change in HbA_{1c}. Motivational enhancement is a new psychological approach that may improve control in adolescent diabetes.

Methods: 69 young people with aged 11-17 years with poorly controlled diabetes (HbA_{1c} >8.5%) were invited to pilot a novel small group treatment involving elements of motivational enhancement, cognitive-behavioural therapy and narrative therapy. 21 young people (cases) entered groups and attended for 6 weekly/fortnightly sessions. 20 of the remaining subjects were recruited as controls. HbA_{1c} for the 12 months preceding and 3-6 months after intervention were compared. Self-efficacy (SE) was measured before and after intervention.

	Cases n=21		Controls n=20	
Sex Male	6 (28%)		12 (60%)	
Female	15 (72%)		8 (40%)	
Age	13.0 SE.52		13.25 SE.46	
BMI SDS score	0.87 SE.19		1.05 SE.19	
Mean HbA _{1c} pre-intervention	10.2 SD 1.5		10.0 SD 1.5	
Mean HbA _{1c} 3-6 months post-group	9.0 SD 1.3		10.0 SD 1.7	
Self-Efficacy in Diabetes (SED)	Pre	Post	Pre	Post
	145.2	158.0	158.6	161.6

The intervention produced a significant drop of 1.2% in HbA_{1c} in cases (p<.003) compared to no change in controls. Post-intervention HbA_{1c} was significantly lower in the cases (p <.04). SE increased in cases (p<.01).

Conclusions: This pilot intervention produced a highly significant drop in HbA_{1c} (effect size of 0.8 SD), which is clinically meaningful and greater than that found in a recent systematic review. The intervention increased case SE to levels similar to controls. This suggests that SE itself is not sufficient for good control, but that motivation enhancement may empower adolescents to use innate resources to improve HbA_{1c}. Further research is needed on motivational enhancement therapy to improve glycaemic control in adolescents with diabetes.

**PREDICTING INSULIN RESISTANCE IN
CONTEMPORARY CHILDREN: GENES, GESTATION
OR CURRENT WEIGHT: (THE **EarlyBird** STUDY)**

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Background: Insulin resistance, and with it type 2 diabetes, are increasing in contemporary children. Attempts to explain the increase have explored links with genes, gestation and post-natal weight. The fetal insulin and thrifty phenotype hypotheses both predict low birth weight, the fetal insulin hypothesis predicts an inverse relationship between paternal insulin resistance and birth weight of his offspring and the accelerator hypothesis predicts the earlier (accelerated) development of insulin resistance in children who acquire excess weight. **Aims:** To examine the three hypotheses using contemporary data from a recent (1995) UK birth cohort. **Methods:** EarlyBird is a prospective cohort study of 307 trios comprising randomly selected healthy five-year-olds and their parents. Among many measures designed to monitor the emergence of insulin resistance and its metabolic impact are birth weight, current weight/BMI, insulin resistance (HOMA) and its metabolic correlates. Baseline data (mean age of cohort 4.8 years) are presented here. **Results:** 1. Only 1.4% of term infants were of low birth weight (<2,500g). 2. There was no significant relationship between birth weight and insulin resistance at five years ($r=-0.11$). 3. Correlations between paternal insulin resistance corrected for BMI and birth weight of his offspring were weak, inverse in girls ($r=-0.20$, $p=0.05$) but direct in boys ($r=0.18$, $p=0.05$). 4. Insulin resistance was correlated with current weight (girls $r=0.33$, $p<0.001$; boys $r=0.18$, $p<0.05$) and to weight centiles (SDS) crossed (excess weight gained) between birth and five years (girls $r=0.30$, $p<0.001$; boys $r=0.21$, $p=0.01$). 5. In a covariate analysis, the SDS crossed did not improve on current weight in the prediction of insulin resistance. **Conclusions:** Predictions of low birth weight were not met in this study, which cannot explain insulin resistance in contemporary children by the fetal insulin or thrifty phenotype hypotheses. Indeed, birth weight and insulin resistance no longer correlate today. Current weight, of which excess weight was merely a co-correlate, best predicted insulin resistance at five years, consistent with the accelerator hypothesis.

EXTREME OBESE CHILDREN AND ADOLESCENTS OF MULTIETHNIC ORIGIN REPRESENT A HIGH-RISK GROUP FOR TYPE 2 DIABETES

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Background: Obesity is an emerging problem in developed countries. While in the US-population ethnic risk groups for secondary complications have been identified there is a lack of data concerning multiethnic populations.

Aims: The purpose of the study was to evaluate the risk for type 2 diabetes among a clinical selected multiethnic group of extreme obese patients.

Methods: 593 obese children were seen in the paediatric endocrine outpatient department in 2001. The BMI of all patients was above the 97th percentile, and none of the patients belonged to so far identified ethnic risk-groups. To identify high-risk individuals for type 2 diabetes, 63 patients meeting at least 2 of the modified ADA criteria were further investigated with an oral glucose tolerance test. Criteria were: a) type 2 diabetes in a close relative, b) clinical signs of metabolic syndrome. Further investigations included serum lipid metabolism, thyroid function and fasting cortisol levels. Insulin sensitivity was measured by calculation of fasting HOMA and Insulin sensitivity index (ISI 0,120).

Results: The mean BMI-SDS of the sample was +7,5 SD. It consisted of 65% caucasian (n=41), 19% turkish (n=12), 5% african (n=3) and 11% other (n=7) children. 38% (n=24) of the patients had impaired glucose tolerance (IGT) and 3% (n=2) had type 2 diabetes. Moreover, insulin resistance (HOMA < 0,3) was found in 73% (n=46). Children with IGT had significantly higher insulin levels in the fasting state (p = 0,002), at 60 min (p=0,012) and 120 min. (p=0,001) during the OGTT and lower ISI (p=0,002) than children with normal glucose tolerance. IGT was found in 39% (n=16) of the caucasian and 42% (n=5) of the turkish children. Thus, pathologic HOMA was found in 87,5% of IGT children and in 52,3% of the non-IGT group. HbA1c was elevated in 14 % (n=9) of the total sample without correlation to IGT or HOMA values.

Conclusions: IGT is frequent in extreme obese children screened according to the ADA criteria. In relation to the portion of turkish population in the sample area turkish as well as caucasian children with extreme obesity represent a high risk groups for type 2 diabetes. Preventive intervention is needed in this high-risk population to diminish the risk for early manifestation of type 2 diabetes.

**TESTING THE ACCELERATOR HYPOTHESIS: TYPE 1
DIABETES PRESENTS EARLIER IN THE FATTER CHILD
(THE *EarlyBird* STUDY)**

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Background: The Accelerator Hypothesis asserts that the rising incidence of type 1 diabetes (T1D), like that of type 2 diabetes (T2D), is related to increasing insulin resistance (IR), rather than to viruses, toxins or 'sanitisation' of the environment. The hypothesis predicts that T1D, like T2D, will appear earlier (ie will be accelerated) in the fatter child. We have shown previously that fatter children are more insulin resistant. Here we have examined the relationship between fatness and age at diagnosis of T1D. **Aims:** To test the hypothesis that the onset of type 1 diabetes is accelerated in fatter children. **Methods:** Analysis of 94 diabetic children with T1D (49 boys and 45 girls), presenting consecutively over a 20 year period, whose birth weight adjusted for gestation (W SDS-B), body mass at diagnosis (BMI SDS-D) and age at diagnosis (1-16 years) were known, and whose excess weight gain since birth (Δ W SDS) was calculated. **Results:** Age at diagnosis was related (inversely) to BMI SDS-D ($r = -0.39$, $p < 0.001$) to W SDS-D ($r = -0.29$, $p < 0.01$) and to Δ W SDS ($r = -0.33$, $p < 0.001$). There was no relationship between W SDS-B and W SDS-D ($r = 0.07$, $p = 0.47$), but there was a strong inverse correlation between W SDS-D and Δ W SDS ($r = -0.73$, $p < 0.001$). Although diabetes was no more frequent in the boys, they presented at a significantly younger mean age than the girls (boys: 6.74y, girls: 8.32y, $p = 0.049$). However, the boys were substantially fatter than the girls at diagnosis (BMI SDS-D boys: + 0.56, girls: - 0.08, $p = 0.006$) and the difference in age at presentation was lost when corrected for BMI SDS-D (boys 7.12y, girls: 7.90y, $p = 0.31$). **Conclusions:** It has been known for some years that children who develop T1D are heavier as infants than their non-diabetic peers. This report goes further, and shows for the first time that the onset of T1D is accelerated by fatness. The data support the Accelerator Hypothesis and point to excess weight avoidance as a means of preventing T1D as well as T2D. Lifestyle intervention trials have been successful in preventing T2D, and might be considered following ENDIT for the prevention of T1D.

**RE-WARMING INDEX OF THE LOWER LEG ASSESSED
BY INFRARED THERMOGRAPHY IN ADOLESCENTS
WITH TYPE 1 DIABETES**

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Background: Neuropathy is one of the most common late complications of diabetes mellitus. Autonomic neuropathy leads to a reduction of skin blood flow. Infrared thermography is an easily applicable method to record the pattern of surface temperature in individuals, reflecting the conditions of skin microcirculation.

Aim: To find out whether infrared thermography before and after challenge of the lower leg in cold water may be a useful tool to detect autonomic neuropathy in adolescent asymptomatic patients with type 1 diabetes and to assess the optimal setting of skin temperature measurements.

Methods: Twenty-five adolescents with a duration of type 1 diabetes of at least 10 years and moderate metabolic control were compared with age- and sex-matched controls. Seven defined sites of the lower leg were assessed by use of infrared thermography before and for ten minutes after exposure of the leg to 14°C cold water.

Results: Re-warming indexes of the skin temperature ten minutes after exposure to cold water were significantly lower at the tip of the fifth toe ($p=0.002$) and at the inner ankle ($p=0.042$) in patients when compared with healthy controls. Re-warming indexes of the five other sites were not significantly different in patients and controls.

Conclusion: Infrared thermography of the lower leg before and 10 minutes after cold water exposure is a useful tool to detect abnormalities of skin microcirculation especially at the tip of the fifth toe and the inner ankle, pointing towards autonomic neuropathy in adolescents even with a relatively short duration of type 1 diabetes. The method is easily applicable and may therefore be used even in young children.