3.) POSTER PRESENTATIONS

PP-1

GLUCOSE MONITORING DURING VARIOUS TYPES OF PHYSICAL EXERCISE IN ADOLESCENTS WITH DIABETES

P.Adolfsson*, B.Lindblad

Göteborg Pediatric Growth Research Center, The Sahlgrenska Academy at Göteborg University, The Queen Silvia Children's Hospital, Göteborg, Sweden

Background: Physical exercise improves insulin sensitivity and in some diabetics also glucose control. In what way glucose varies during and after exercise is not fully understood.

Aim: To evaluate 1) if CGMS can detect otherwise undetected episodes of hypo- and hyperglycemias related to physical exercise 2) if the CGMS system is acceptable to adolescents 3) if Hb1Ac was improved after the camps.

Methods: Adolescents (15-18 y) participating in a soccer camp (n=18) and/or cross country skiing and unihoc camp (n=20). CGMS was used during the whole camps (3 and 4 days, resp.)

Paired values for SMBG and CGMS-glucose were obtained 9,3 and 7,3 times per day during the camps. A questionnaire on usefulness of CGMS was answered during the second camp.

Results: The correlation between SMBG and CGMS-glucose values was 0,81 during the first camp and equally good during second camp (0,76).

Hypoglycemic episodes (< 3mmol/L) were detected 266 times, 43 % of these were not detected by SMBG. Hyperglycemic episodes (>15 mmol/L) occurred 120 times, 62 % of these were not detected by SMBG. All adolescents found CGMS useful. After having seen the CGMS charts 11/20 adolescents adjusted their insulin doses taken before and during physical exercise. Six of 20 adolescents adjusted other insulin doses.

However, we could not detect any improvement in HbA1c during the 6-12 months following the camps. HbA1c was 7,51 % (ref. 3,6-5,0) six months before the camps and 7,42 % six months after the camps (p=ns).

Conclusion: CGMS detects almost twice as many hypo- and hyperglycaemic episodes as SMBG, although SMBG was measured much more frequently than during ordinary daily life. CGMS is well accepted by adolescents even during physical exercise.

REDUCING DKA: A PRACTICAL APPROACH

Victoria Alexander* on behalf of DiabNet, Scotland UK
Tayside Institute for Child Health, Dundee, Scotland

Background: Diabetic ketoacidosis (DKA) remains an important cause of morbidity and mortality. In children with established type 1 diabetes, DKA is regarded as a largely preventable complication. DiabNet is a managed clinical network caring for over 400 children and young people with diabetes across 3 areas of Scotland. Our initial audit revealed significant differences in the rate of DKA between the 3 areas. Because of the clinical importance of this, we chose the rate of DKA as an important target in monitoring clinical performance.
Aim: To reduce the incidence of DKA in children with established diabetes
Methods: In order to prevent DKA we felt that there was a need for families to have access to specialist advice for their children when they were unwell. To provide this we ensured that 24 hour telephone support was available by providing an out-of-hours emergency telephone help line which was staffed by 5 nurses who gave advice according to agreed guidelines. The families were sent information leafelts about appropriate use of the help-line. In addition area 3, which had a very high rate of DKA in their clnic population, sent out a separate leaflet (DKA Alert), highlighting the severity of the condition, the presenting symptoms, and advice on when to seek help.
Results: A significant fall in the rate of DKA was observed within 6 months of the 2 interventions. The rate reduced further over the subsequent year.
Baseline 1/5/99-30/4/00: 15.4episodes/100 patients/year
1/5/00-31/10/00: 11.9 episodes/100 patients/year
1/11/00-30/4/01:9.2 episodes/100 patients/year
1/5/01-31/10/01: 5.9 episodes/100 patients/year
Conclusion: DKA can often be prevented by early appropriate use of sick day rules. We have shown that by alerting families to the importance of DKA as a serious complication of diabetes, and by offering 24 hour telephone support for emergencies, that the rate of DKA can be reduced substantially. By working as a network across 3 areas we have been able to share resources and establish the telephone support service. Audit of this service (presented at ISPAD 2001) revealed highly appropriate use by the families and also a high degreee of user satisfaction.Measuring the DKA rate at regular intervals has also given us a tool to monitor our clinical service and allowed us to set targets to work towards.

PP-3

MATRIX METALLOPROTEINASE-2 ACTIVITY (MMP-2) IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES MELLITUS: FOLLOW-UP STUDY.

G. d'Annunzio*, M. A. Avanzini, R. Spadafora, I. Kasirye, °D. Geroldi, °G.Derosa

Dept. of Pediatrics, and °of Internal Medicine and Therapeutics , IRCCS Policlinico San Matteo, Pavia, Italy

Background: Alterations in extracellular matrix synthesis occur in patients with type 1 diabetes mellitus (T1DM) and are involved in the pathogenesis of vascular disease. Matrix metalloproteinases (MMPs) are responsible for extracellular matrix breakdown and their abnormal levels pre-date clinical evidence of diabetic microangiopathy.Aim: To investigate the role of MMP-2 in young patients with T1DM.Methods: We detected serum total active MMP-2 in 13 children and adolescents with T1DM (6m and 7 f, aged 2-14.7 years), evaluated at diagnosis and after a 5-year follow-up. Serum total active MMP-2 was detected by ELISA following activation with p-aminophenylmercuric acetate (APMA). The intra- and inter-assay coefficients of variation (CV) were 4.4% and 18.5%, respectively. In all patients molecular analysis of HLA-DQ region was performed. GADA, IA-A2 and IAA levels were detected at diagnosis and after 5 years. Clinical or subclinical signs of microangiopathic complications (i.e. retinopathy, peripheral neuropathy and nephropathy) were absent in all patients. As controls, 13 age-and sex-matched subjects were considered.Results: No significant difference in serum MMp-2 activity was observed between patients and controls, either at diagnosis (34.7±8.8 ng/ml vs 34.9±6 ng/ml) or after 5 years (34.3±8.6 ng/ml vs 34.9±6 ng/ml. No significant correlation was found between serum MMp-2 activity levels and age, GADA, IA-2, IAA titer, either at diagnosis or after 5 years. Moreover, MMP-2 activity levels were not significantly related to HbA1C values, and no association was observed between serum MMP-2 activity and the number of DQ heterodimers.

Conclusions: In our pediatric patients, no abnormalities in MMP-2 activity are reported, either at diagnosis or during follow-up, and MMP-2 activity is not impaired before the development of microangiopathic complications. Moreover MMp-2 activity is not influenced by the hyperglycemic diabetic milieu, which could induce altered gene expression of MMP-2. On the other hand the pathogenesis of diabetic angiopathy is multifactorial and requires further investigations.

PP-4

TANDEM: A TEAM-BASED INFORMATION TECHNOLOGY (IT) ASSISTED EDUCATION OF YOUNG PATIENTS WITH TYPE 1 DIABETES MELLITUS

G.d'Annunzio*, R. Bellazzi°, C. Castelnovi, C. Pennati, S. Cetta°, M.A. Zanetti§

Dept of Pediatrics, IRCCS Policlinico San Matteo; °Dept. of Computer and Systemic Sciences, and §Dept of Psychology, University of Pavia, Italy

Background: Education is the cornerstone to ameliorate type 1 diabetes mellitus (T1DM) treatment. The aims of educational process, based on individual needs and capability to learn, are to reach children and families in T1DM management, in order to reach a better knowledge and self-esteem.

Aim: To evaluate the IT in the educational process of young patients with T1DM.

Methods: Tandem is a team-based information technology assisted education project for youngsters with T1DM. The team consists of 2 physicians, a psychologist and 3 computer scientists, 7 pts (3m and 4f, aged 14.4+/-3.7 yrs, disease duration 5.3+/-2.7 yrs, HbA1C mean levels 7.9+/-0.9%) with families (Treated Group, TG) and 7 pts matched for age, duration, HbA1c levels (Control Group, CG). The intervention consisted of 6 meetings with the TG, where the main topics about T1DM were explained, between the meetings TG communicated with the physicians and themselves reporting their personal experiences resorting to a Web-based discussion group. An IT-based chat group was available over the Web and accessible by a PC or a Web-TV. The psychologist developed a questionnaire through semi-structured interviews, to evaluate the disease perception and management, social aspects, global self-value (self-efficacy questionnaire, SEQ), finally delivered to TG, CG, parents (P), and physicians (PH1 and PH2).

Results: For each item a 4 points response format was used. As regards SEQ, both TG and CG had a higher score vs PH1 ($p<0.05$) and CG2 vs PH2 ($p<0.05$), reflecting the patients positive perception of T1DM and of the skills to its management. Physician seem to underestimate patient's social integration. Moreover, as regards SEQ, TG showed a higher score vs their P (<0.01and $p<0.05$ respectively), reflecting the parents emotional involvement. HbA1c values before and after the intervention were similar between TG (7.9+/-0.9% vs 8+/-0.7%) and CG (8.24+/-1.2% vs 8.2+/- 1.3%).Conclusions:The tandem improved quality of care, and allowed to explicit some problems related to educational and social aspects of T1DM youngsters, sometimes neglected in routine clinical practice.

LIPOPARTICLES AND GLYCATED LIPOPROTEINS IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES MELLITUS

S Asenjo*, P Bustos, C Radojkovic, M Muñoz, A Martínez, A. Gleisner, N Ulloa.
Fac. Medicina, Fac.Farmacia, Universidad de Concepción, Concepción, Chile.

Atherosclerotic cardiovascular disease is an important cause of morbidity and mortality in diabetic subjects. Therefore, identifying risk factors, such as lipid abnormalities, that explain their cardiovascular risk is essential.

The aim was to assess the prevalence of dyslipidemia and glycated lipoproteins in children and adolescents with type 1 diabetes mellitus (DM1) compared with a control nondiabetic group of similar clinical characteristics.

We studied a total of 32 patients, with a disease evolution range between 1 and 20 years and a mean of glycated hemoglobin (HbA_{1C}) level of 9.8 ± 1.3%. The control group of 30 nondiabetics was matched by sex, age and body mass index (BMI, Kg/m^2). Total cholesterol, LDL cholesterol (LDL-C), HDL cholesterol (HDL-C), trygliceride, lipoprotein (a) [Lp(a)] and apolipoproteins A-I and B were determined. Lipoparticles LpA-I, LpA-I:A-II, LpB and glycated lipoproteins (glyHDL and glyLDL) were quantified by enzymeimmunoassays using monoclonal antibodies.

Both groups were normolipidemics, but the patient group displayed higher trygliceride levels (76.5 vs 54.3 mg%) and a lower apo A-I concentration than controls (122 vs 134 mg%). Both groups showed similar HDL-C concentration, but significant differences were observed in HDL particle concentrations. Diabetic patients showed higher LpA-I and lower LpA-I:A-II concentrations than nondiabetics (54 vs 40 mg%; 69 vs 94 mg%). LpA-I particles were significant and positively correlated with HDL-C in diabetic patients and in the controls but LpA-I:A-II concentration only did in the control group. LpB concentrations were similar for both groups. Diabetics showed a significantly higher mean specific reactivity of glyHDL than nondiabetic subjects (0.50 ± 0.18 vs 0.37 ± 0.11), but this difference was not significant for glyLDL (0.30 ± 0.1 vs 0.28 ± 0.09). No significant differences in Lp(a) values were observed and concentrations above 30 mg% were observed in 33% of subjects within each group. There were no significant correlations between glycated lipoproteins and HbA_{1C}.

In conclusion, DM1 patients showed significant differences, both in qualitative and quantitative composition and glycation degree of HDL lipoparticles which could explain a higher cardiovascular risk. Supported by Grant Nº 200.072.023-1.0.

RETINOPATHY IN YOUNG DIABETICS AT THE RABAT HOSPITAL

A.Balafrej* , B.Benhammou , N.Bennani , A.Jamaï ,Z.Mohcine
Clinic of pediatric diabetology , Clinic of Ophtalmology , Rabat Hospital

Background
Diabetic retinopathy (DR) is a leading cause of blindness in seniors .This major complication could occur earlier when diabetes begins during childhood in patients facing difficult conditions of care
Aim
This study aims to evaluate the frequency and major risk factors of DR with focus on the quality of initial care in diabetic young people .
Methods
515 type 1 diabetic young people are concerned by this retrospective study (263 girls , 252 boys) aged 9 months to 33 years (average 13 years 3/12) monitored in the clinic of diabetology at the Rabat Children's Hospital since 1986 with a mean monitoring duration of 10 years 9/12 (9 months-25 years)and a mean diabetes duration of 15y1/2 (7-28y) Fluoresceine angiography is performed in 124 out of the 261 patients with more than 5 years diabetes duration , at least once (1-7)
Results
68 young diabetics have normal results and 56 showed DR :Non proliferative 53 , pre-proliferative 2 and proliferative 1 case Macular oedema is present among 45 patients DR is diagnosed at an average age of 19 years ½ (11 –26 y) and involves 66% girls vs 44% boys. The prevalence is related to the duration of diabetes: 67% are involved after 10 years and 97% after 15 years. However 3/56 diabetics showed an early onset before 5 years of duration (4-41/2) and 14 before the end of puberty. The average HbAIc rate is 10.35% in the group with retinopathy versus 8.20% in the healthy group. The lack of appropriated initial care is also a risk factor. 70% of the diabetics with retinopathy were not monitored in a specialized unit from the beginning of diabetes versus 10% of healthy cases.Diabetic retinopathy is frequently associated with other complications: cataract: 7 cases, nephropathy: 19 cases, peripheric neuropathy: 19 cases. autonomous neuropathy: 2 cases, growth delay: 22 cases
Conclusion
Because of its possibel young-onset and harmfull prognosis DR, should be prevented through fast and effective care and early screening.

PP-7

ASSOCIATION OF ANGIOTENSIN CONVERTING ENZYME DD GENOTYPE WITH ELEVATED DIASTOLIC BLOOD PRESSURE IN NORMOALBUMINURIC CHILDREN AND ADOLESCENTS WITH TYPE I DIABETES

L. Barkai*, A. Soós, I. Vámosi

Division of Diabetes, Child Health Center,
Borsod County University Hospital, Miskolc
and Postgraduate Institute of Pediatrics, University of Debrecen

Background: It has been suggested that relationship exists between the prevalence of hypertension and the deletion polymorphism of the angiotensin converting enzyme (ACE) gene in patients with type 1 diabetes.

Aim: To assess the distribution of the insertion/deletion (I/D) polymorphism of the ACE gene in type 1 diabetic children and adolescents and to evaluate possible association between ACE genotype and blood pressure (BP).

Methods: 124 normoalbuminuric [albumin excretion rate (AER)<20 μg/min], normotensive (normal clinic BP measurements) type 1 diabetic children and adolescents (male/female: 60/64, age: 14.2±2.5 years, diabetes duration: 5.2±1.8 years) were included in the study. ACE genotypes were assessed by polymerase chain reaction. Twenty-four hour ambulatory blood pressure monitoring were undertaken in all patients.

Results: The ACE genotypes were distributed as follows: 34 (27%) DD, 57 (46%) ID, 33 (27%) II. Age, gender, diabetes duration, HbA1c and body mass index did not differ in the three groups with different genotypes. Patients with DD genotype differed from ID and II patients in having higher mean 24-h diastolic BP (73.8±6.2 vs. 70.2±5.0 and 69.7±6.3 mmHg; p=0.005) and lower diurnal variation in BP (11.8±4.6 vs. 14.2±4.2 and 14.8±4.3 %; p=0.011) as compared with ID and II genotype patients. AER related significantly with 24-h diastolic BP in patients with DD genotype (r=0.35; p=0.032) but not in ID and II patients.

Conclusion: DD genotype is associated with elevated 24-h diastolic BP and less diurnal variation in BP in normoalbuminuric diabetic children and adolescents. Diastolic BP rises concurrently with AER in patients with DD genotype.

INCIDENCE OF DIABETES AND IMMUNOLOGICAL RISK FACTORS IN FAMILIES OF CHILDREN AND ADOLESCENTS WITH DIABETES TYPE 1

J.Bieniasz, R.B.Wasikowa*

Department of Endocrinology for Children and Adolescents, University of Medicine, Wrocław-Poland

Aim: of the study: to evaluate the incidence of diabetes type 1 and type 2 and the incidence of ICA in relatives of children and adolescents with diabetes type 1.

Methods: The study was provided in the years 1993-2000 in two centers in Poland, Cracow and Wrocław. Examined were all relatives of patients with newly diagnosed diabetes type 1. Obtained were data from 332 patients. They concerned 4080 first and second degree relatives.

Results: Diabetes occured in 121 of them (2,96%). 20 were 1st degree relatives and 101 second degree relatives. In 31 relatives (0,76%) diabetes type 1 was diagnosed and in 88 (2,12%) type 2 diabetes. In 2 relatives the type of diabetes was problematic (in diagnosis). Except one mother all patients with type 2 diabetes were 2nd degree relatives . In 512 1st degree relatives examined were ICA. The age of the relatives varied from 0-40 years. Ascertained were positive ICA in 61 relatives (11,9%), in 46 of them (30 males and 31 females) the level was < 20 IDF, in 11 between 21 and 79 IDF and in 4 ? 80 IDF, without differences in the incidence and levels between the both genders. In brothers ICA were observed more often than in sisters (15,38 vs 8,44%). The majority of males with positive ICA (80%) was younger (0-20 years), while majority of females with positive ICA (70,97%) was older (21-40 years) (p=0,007). The biggest group in ICA-positive relatives were siblings - 37 (60,66%). ICA were determined in the reference laboratory in St.Bartholomew Hospital in London as a part of ENDIT programme (European Nicotinamide Diabetes Intervention Trial).

Conclusions: 1. In families of children with type 1 diabetes observed was type 1 and type 2 diabetes, with a significant dominance of type 2 in 2nd degree relatives. 2. ICA were detected most frequently in siblings of children with type 1 diabetes. 3. Positive ICA were present more frequently in brothers than in sisters. 4. ICA were detected in males more frequently in younger age, while in females in the older age.

PP-9

METABOLIC DIFFERENCES IN TYPE 1A AND 1B DIABETES

J.Bodalska-Lipinska*, O.Wegner, W.Mlynarski, K.Wyka, W.Andrzejewski, J.Bodalski

Institute of Pediatrics, Medical University of Lodz, Poland

Aim: The aim of this study was to compare selected metabolic parameters, in children with immune-mediated diabetes and in children with diabetes without presence of ICA, anti-GAD and anti-IA2 antibodies.

Methods: 111 newly diagnosed type 1 diabetic children were divided into two groups: group 1A which included 87 children who were positive for immunological markers of pancreatic islet autoimmunity, and group 1B consisting of 24 children who did not have such markers. Both groups of patients did not differ in terms of *HLA-DRB1* and *HLA-DQB1* alleles. Comparisons were made between these two groups concerning age at onset of diabetes, age- and sex-normalised BMI (Z-score) and serum levels of glycated haemoglobin (HbA1c), fasting C-peptide, LDL and HDL fractions, total cholesterol, and triglycerides. Non-parametric U Mann-Whitney's test was used for statistical analysis.

Results: There was no age difference at onset of diabetes in group 1A in comparison to group 1B (median ± quartile range, 10.7±6.8 vs. 10.6±9.6, respectively). The Z-scores for BMI also did not differ statistically in these two groups (-0.26±1.24 vs. -0.29±1.28, respectively). Thus, the majority of assessed children had lower BMI than average at their sex and age. There was no statistical difference between the C-peptide levels in either group (0.21±0.22 vs. 0.18±0.54, respectively) and in most of the examined children C-peptide level was below the normal range (<0.28 pmol/ml). Higher HbA1c levels were present more often in children from group 1A compared to group 1B (11.±4.3 vs. 8.5±5.3, respectively; p=0,02), but these two groups did not vary in insulin requirement. The levels of triglycerides were significantly higher in group 1B (54.5±28.5 vs. 83.0±57.0, respectively; p=0.01). However, the levels of total cholesterol, LDL and HDL did not differ statistically.

Conclusion: Obtained results may indicate similar stage of beta cells destruction in patients with and without markers of autoimmune process. However, some alterations in outcome of the disease suggest metabolic differences in type 1A and 1B diabetes.

PP-10

COELIAC DISEASE AND DIABETES: A NON CASUAL ASSOCIATION

F. Cardella*, S. Terrana, V. Benigno, C. Malato, F. Meli

Metabolic Disease Dep. , Institute of Pediatrics, University of Palermo , Italy

Background: The prevalence of Coeliac Disease (CD) in general population is estimated around 0.5%, many studies evidence the strong association between CD and Type 1 Diabetes.

Aim: We analysed the prevalence of CD in the diabetic patients attending our Clinic.

Methods: 540 patients (273 M and 267 F; age, 10 months – 20 years) have been screened at least once every year with antigliadin antibodies (AGA IgG and IgA-enzyme immunometric assay), IgA – endomysial antibodies (EMA- indirect immunofluorescence), and anti transglutaminase antibodies (tTG- enzyme immunometric assay with human recombinant antigen). 23 asintomatic patients, whose EMA and/or tTG titer was high for at least 1 year from the onset of diabetes,were subjected to duodenal biopsy that confirmed the diagnosis of CD. In the coeliac population, discovered as said former, we studied weight, height, HbA1c, and episodes of post-prandial hypoglicemia for 12 months prior and after the diagnosios of CD.

Results: 4 patients were already affected by CD at the diabetes onset, so the prevalence of this disease in our population is 5% (27/540), while in the subgroup of patient who were younger than 3 years at onset of diabetes, the prevalence is 8.8% (6/68). This second group seems most likely to develop both disease (χ^2=3.70 p.n.s.). In the 12 months after the diagnosis of CD we noticed an improvement in the pattern of growth in weight ($p<0.0047$), and a decrease in both value of HbA1c (M±DS=7.± 2.1% vs 7 ± 0.9% p.n.s.) and of episodes of sintomatic post-prandial hypoglycemia. Moreover we had a meaningful decrease of EMA and tTG ($p<0.0001$) after the introduction of gluten free diet.

Conclusion: Our results confirm the strong relationship between CD and Type I Diabetes (1:20 vs 1:200 in general population), above all in patients with early onset (1:10 , age< 3 years), and underline the need to screen all Type I diabetic patients for CD. In accordance with literature we found an high diagnostic predictivity of EMA and tTG showing their fundamental role as screening and follow-up tests for silent CD. We confirm the main role of intestinal biopsy for CD diagnosis.

The metabolic index improve after free gluten diet.

PP-11

PREVALENCE OF MICROVASCULAR COMPLICATIONS IN TYPE I DIABETES CHILDREN AFTER 15 YEARS OF FOLLOW-UP

F. Cardella* , V. Meli, V. Benigno, F. Meli

Metabolic Disease Dep.,Institute of Pediatrics, University of Palermo, Italy

Background: The DCCT and EDIC demonstrated that intensive therapy of type 1 diabetes,with the aim of achieving near-normal glucose control and HbA1c concentrations, reduces the risk of microvascular complications.

Aims: The aim of our study is to evalued the prevalence of microvascular complications in a cohort of 105 diabetic children aged at the onset of disease 4,93+/-3,69 ,followed for 15 years or more.

Methods: We studied 105 diabetic children (49 M and 56 F) aged at last visit 21.52+/-3.55 years over 15 years' duration (21.48 +/- 3.67)

All patients were assigned to intensive therapy by three or more daily insulin injections, and their family are guided by self-monitoring blood glucose and adjusting daily insulin dosage, dietary intake and exercise. Patients were examined every three months or more if necessary, HbA1c was evalued every three months (HPLC).

All patients have screened regularly for retinopathy (fundus oculi annually and if necessary fluorangiography),nephropaty (microalbuminuria overnight twice or three times of year,immunoturbidimetric method: AER) and neuropathy (median and tibial nerve conduction velocity and sensitive latency after 10 year or more of disease).

Results : HbA1c during the follow-up is 7.33% +/- 1.27, AER overnight is 8.84 +/- 10 mcg/min, insulin requirement is 0.83 +/- 0.23 U/Kg/die , Rapid/Interm insulin ratio is 3.6 +/- 1.6. At the end of the study we found: Retinopathy 3.9% (3 patients with microaneurysm only ; 1 patient with proliferant diabetic retinopathy traited with laser-therapy) ; Transient microalbuninuria 4.76% (5 patient with overnigth AER >= 20 mcg/min improved with hypoproteic diet < 0.8 gr/kg/die and better metabolic control); Subclinical Neuropathy 10.4% (11 patients with persistent subclinical deterioration of tibial sensitive latency).

Conclusions: Our results confirm importance of intensive therapy in children with type 1 diabetes for delaying onset of the diabetic retinopathy, nephropathy and neuropathy. Our patients have low prevalence of microvascular complications after 15 years or more of disease v.s. DCCT and EDIC. Metabolic control is very good during the follow-up. Education and compliance at self management represent the very good method to delay long term complications and to prevent severe hypoglicemic events.

PREVALENCE OF CELIAC DISEASE AND FAMILY RISK FACTOR IN ITALIAN CHILDREN AND ADOLESCENTS AFFECTED BY T1DM

F Cerutti on behalf of the Diabetes Study Group of SIEDP

Background: since the development of specific and sensitive markers of screening for celiac disease (CD), a higher than previously reported prevalence of the disorder in children and adolescent with T1DM has been observed ranging from 2-7%. The association of T1DM and CD is partially explained by similar genetic involvement.

Aims: to evaluate the prevalence of CD in a large cohort of Italian diabetic children and adolescents followed by 24 Centres for Childhood Diabetes during the year 2000. To trust the hypothesis that the prevalence of CD is higher in diabetic children with a diabetic sibling than in sporadic cases.

Method: 24 of 47 Centres for Childhood Diabetes members of the Diabetes Study Group of SIEDP agreed to collect the total number of all the patients affected by T1DM and to report personal and clinical data of all the diabetic patients diagnosed as celiac in their populations. Criteria for CD diagnosis were positive jejunal biopsy and/or positive EMA or TGA screening on at least 3 separate determinations.

Results: among the 3535 dabetic patients (mean age 9.8±5.2, duration of diabetes 7.5± 4.3 ys, m/f ratio 1:0.4) followed by the partecipating Centres, CD was diagnosed in 253 children and adolescents giving a prevalence rate of 7.1%. Consistent with previous data the group of patients with both diseases had a higher female to male ratio and were of a younger age at onset than the group of patients with T1DM only. When the total population was divided in 3 subgroups: (group A: 782 diabetic only children, group B: 2531 diabetic children with no diabetic siblings, group C: 222 diabetic children with at least one diabetic sibling) no significant difference in the prevalence of CD was observed among the 3 subgroups (6%, 7.4%, 8%).

Conclusions: our data demonstrated that the prevalence of CD in Italian children and adolescents with T1DM is in the highest range reported in literature.

Being member of a multiple T1DM family doesn‘t seem to confere an increased risk for CD onset.

HIGH PREVALENCE OF COELIAC DISEASE IN SIBLINGS OF TYPE 1 DIABETIC CHILDREN

V. Cherubini*, E. Fabiani, P. Scalari, A. Iannilli, F. Carle, A. Pinelli, P. Piccinini, S. Francolini, R. Gesuita, C. Catassi, GV Coppa.
University Department of Paediatrics, Ancona, Italy

Background: Increased prevalence of celiac disease (CD) in patients with type 1 diabetes (T1D) has been widely reported. First-degree relatives of T1D patients have an increased risk of autoimmune disorders, even included untreated CD.
Aim: To analyse the prevalence of CD among siblings of T1D children and to look for the association with HLA DQB1*02 allele.
Methods: By the regional population-base registry of the Marche region, Italy, we recruited 188 families with at least one diabetic child. IgA-endomysium antibodies (EMAs) were measured in 180 diabetic children and in their 116 healthy siblings. Two diabetic children have been diagnosed with CD before diabetes. IgA-transglutaminase autoantibodies (TGAs) were tested in EMAs negative subjects. All subjects with positive serological results underwent jejunal biopsy. HLA DQB1 genotyping was done in diabetic children, healthy siblings and in 1865 subjects from the general population of the same region.
Results: Jejunal biopsy was consistent with CD in 9 out of 11 EMAs positive diabetic children, and in one EMA negative and TTG positive diabetic boy. Among non-diabetic siblings, CD was diagnosed in a girl with IgA deficiency and high level of antigliadin IgG antibodies, in 4 EMA positive subjects, and in 1 EMA negative and TGA positive boy. The prevalence of CD was significantly higher in both diabetic children (6.6%, 95%C.I.:3.5-11.2) and in their non-diabetic siblings (5.2%, 95%C.I.:1.9-10.9) than in normal schoolchildren of the same region. A higher prevalence of HLADQB1*02 allele was found in diabetic children (62.8%, 95%C.I.: 53.2-71.7) and in non-diabetic siblings (53.0%, C.I.: 41.7-64.1), compared with healthy subjects (31.2%, 95% C.I.:29.1-33.3).
Conclusion: The prevalence of CD in siblings of diabetic children was high and similar to that found in diabetic patients. We assume that the high prevalence of HLA DQB1*02 in non-diabetic siblings may reflect the genetic predisposition to CD of these children. These results suggest that in our region a routine serological screening for CD is recommended to all healthy siblings of children with T1D.

USEFULNESS OF A TEST FOR 3 β-HYDROXYBUTYRATE (3HB) IN THE MANAGEMENT OF DKA

G. Chiari *, M. Vanelli , C. Capuano, B. Ghidini, P. Zanasi

Department of Paediatrics, Diabetes Unit, University of Parma, Italy

Background: Hand-held devices for quantitative tests of 3HB levels in capillary blood have recently been introduced in the clinical practice offering new options for monitoring DKA in children.

Aim: To evaluate whether the direct measurement of 3HB enhances effectively the management of DKA in newly diagnosed diabetic children.

Methods: Twenty children with DKA (venous pH < 7.25 or blood bicarbonate <16 mmol/l and urine ketone bodies > 2+) were studied and treated according to a standard low-dose insulin infusion protocol. Ten of them (6 M and 4 F, 7.13±4.63 years old; venous pH mean value 7.23±0.063; blood bicarbonate mean level 10.2±2.4 mmol/l) were randomly monitored using a commercial test for urine ketone bodies (UKB) (Group 1) and other ten (5M and 5 F, 7.53±4.09 years old; venous pH 7.21±0.014; blood bicarbonate 9.2±1.34 mmol/l) by MediSense Optium Ketone Sensor for 3HB, a system able to provide an assay within 30 seconds using 5 μl of capillary blood (Group 2).

Results: Contrary to UKB, 3HB levels appeared to be correlated with: i) HbA1c values on admission (R^2=0.89, p<0.001); ii) latent period before diagnosis of diabetes (R^2=0.91, p<0.001); iii) changes in venous pH values (R^2=0.90, p<0.001), blood bicarbonate (R^2=0.84, p<0.001) and capillary blood levels (R^2=0.90, p<0.001) during the course of treatment for DKA. Required time to achieve the definitive resolution of DKA in Group 2 patients (3HB values < 1.00 mmol/l) was related to the values of 3HB on admission (R^2=0.74, p<0.002). Determination of 3HB showed that acidosis in Group 2 patients cleared 4 to 9.5 hours earlier than in those of Group 1 monitored with UKB determination. The patients of Group 2 left insulin infusion and intensive care stay 6.5±1.5 hours earlier than those of Group 1. The effective information on 3HB normalization led also to save in Group 2 patients more than 250 laboratory investigations.

Conclusion: quantitative determination of 3HB levels in capillary blood seems to offer additional useful information for monitoring of acidosis in newly diagnosed diabetic children and for reducing time and costs of the management of DKA in an intensive care unit.

THE NEUROD1 POLYMORPHISM Ala45Thr IS ASSOCIATED WITH TYPE 1 DIABETES MELLITUS IN THE CZECH POPULATION

O. Cinek*[1], P. Drevinek[1], B. Bendlova[2], M. Snajderova[1], J. Vavrinec[1]
1:2nd Department of Paediatrics, 2nd Medical School, Charles University and 2: Institute of Endocrinology; Prague, the Czech Republic

Background and Aims: The Ala45Thr polymorphism in NEUROD1 exon 2 is associated with Type 1 diabetes mellitus (DM) in several populations, while only scarce data are available on associations of another NEUROD1 polymorphism, Pro197His. We therefore performed a study on association of the two NEUROD1 polymorphisms with Type 1 DM in the Czech population.
Methods: We compared 285 children with Type 1 DM manifested under the age of 15 years to 289 non-diabetic control children. The Ala45Thr and Pro197His polymorphisms were assigned by novel real-time allele-specific PCR assays in the TaqMan format. Data were analysed using multivariate logistic regression.
Results: An association of the Ala45Thr polymorphism with Type 1 DM was observed after adjusting for the insulin gene -23HphI genotype and for presence of the Type 1 DM-associated HLA-DQB1*0302-DQA1*03 and DQB1*0201-DQA1*05 molecules: the 45Thr positivity conferred a significant risk of Type 1 DM (OR=2.02, CI 95% 1.26-3.26, P=0.004). This 45Thr-conferred risk was apparent only in models adjusted for presence of the HLA-DQ susceptibility molecules. No association was observed for the Pro197His mutation which was carried by 5.3% patients and 5.9% controls.
Conclusions: Our results confirm that the NEUROD1 Ala45Thr polymorphism is associated to Type 1 DM. The Ala45Thr is unlikely to act as the primary factor within the gene, as the DM susceptibility is conferred by 45Ala in the Danes, but by 45Thr in the Japanese and the Czechs. The association is substantially modified by yet unknown interaction with the HLA-DQ risk factors. Our study also demonstrates the potential of the real-time allele-specific PCR, capable of specific allelic discrimination over a wide range of DNA concentration and quality.

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RELATIONSHIP BETWEEN COELIAC DISEASE, TYPE 1 DIABETES AND OTHER AUTOIMMUNE DISEASES

M. Cotellessa, L. Minicucci, M. Testa, I. Bertini, E. Bazzigalupi*, R. Pastore*, E. Bosi*, R. Lorini.

*Dept of Pediatrics, Gaslini Institute, Genoa;*S. Raffaele Hospital, Milan, Italy*

Background: Type 1 Diabetes (T1D), as coeliac disease (CD), may be induced by feeding a diet containing wheat gliadin and related proteins. Both these conditions require genetic predisposition and have a prodromal period.

Aim: 1) to test the hypothesis of a relationship between gluten intake and autoimmune diseases, 2) to evaluate the effect of gluten-free diet on T1D.

Methods: we evaluated immunologic markers of T1D (GADA, IAA, IA-2A) and of CD (TGLC-Ab) in first degree relatives (FDR) of T1D and CD, and in other autoimmune diseases. Subjects with almost one immunologic marker were studied for genetic typing and metabolic marker (first phase insulin response-FPIR). Gluten free diet were adopted in subjects with one immunologic marker (corfirmed in two determinations), with genotype at risk for T1D, with or without metabolic marker, and without TGLC-Ab.

Results: up to now we tested 130/232 T1D FDR, 46/154 CD FDR, 80/88 patients with juvenile chronic arthritis (JCA). Among the T1D FDR, 7 subjects (1 sister and 1 brother, 4 parents, and a daughter) showed immunologic marker: the parents with confirmed positivity, the daughter (with all 3 serum markers), are undergoing diagnostic iter: Moreover the sister and the brother, (with 3 autoantibodies, 4 and 1 heterodimerous respectively, and pathologic FPIR), are undergoing gluten-free diet for a twelve-months period. Two patients with JCA presented GADA positivity. All the subjects were TGLC-Ab negative.

Conclusions: we are going to evaluate variations in immunologic markers and FPIR after 12 months of gluten-free diet (1 sister is now at her 11 month of gluten-free diet).

RESIDUAL β-CELL FUNCTION TWO YEARS AFTER DIAGNOSIS OF TYPE 1 DIABETES: EFFECTS OF INTENSIVE INSULIN THERAPY AND NICOTINAMIDE

A Crinò*†, R Schiaffini†, P Ciampalini†, S Spera†, N Visalli††, P Patera†, S Manfrini††, P Pozzilli†† and the IMDIAB Group

†Bambino Gesù Children's Hospital; ††Campus Biomedico University – Rome, ITALY

Background. Data on C-peptide in patients with recent onset Type 1 diabetes (T1DM) on intensive insulin therapy (IIT) associated with nicotinamide (NA) are available only up to one year after diagnosis. The majority of patients without NA therapy shows at this time a reduction of β-cell function.

Aims**.** To evaluate residual β-cell function in T1DM children and adolescents continuing both NA and IIT up to two years after diagnosis.

Methods**.** We collected data from 24 patients (M:F = 15:9; mean age: 13.7 ± 3.9 years) with T1DM in whom NA at a dose of 25 mg/Kg b.w. was added from diagnosis (< 4 weeks) to IIT and continued up to two years after diagnosis. C-peptide (ng/ml), HbA_{1c} (%) and insulin requirement (IU/Kg b.w.) were evaluated at 3 months intervals.

Results. Mean C-peptide at two years was 0.66 ng/ml ± 0.80 SD; compared to the time of diagnosis (0.56 ng/ml ± 0.50 SD) a mean increase of 16% was observed (p = ns). At 1 year mean C-peptide was 0.85 ± 0.62 ng/ml with a mean increase of 32% (p = ns). Mean HbA_{1c} was 10.3% ± 2 SD, 5.5% ± 0.8 SD and 6.2% ± 1 SD ($p<0.0001$ for both evaluations), respectively at onset of diabetes, at 1 and at 2 years. Mean insulin dose was at two years of 0.63 IU ± 0.30 SD, with a significant ($p<0.0001$) decrease compared to basal value (1.01 IU ± 0.23 SD)

Conclusions. The combination therapy of NA and IIT in T1DM patients seems to preserve β-cell function up to two years after diagnosis. The increase of C-peptide observed in this study was never observed in our experience on over 500 T1DM patients regularly followed from diagnosis in the IMDIAB series. We therefore recommend the association of NA with IIT in all newly diagnosed T1DM patients for periods longer than one year in order to obtain a consistent protection of β-cell function.

Prepubertal children are at high risk of intramuscular insulin administration based upon subcutaneous fat thickness

W. S. Cutfield[1], J. M. Peart[1], J., M. D. Thompson[1], J. Holt[1], C. A. Jefferies[1], S. A. Lawton[2], P. L. Hofman*[1]

[1]Paediatrics, University of Auckland, Auckland, NEW ZEALAND, [2]Diabetes Devices, Novo Nordisk, Copenhagen, DENMARK.

Background and Aims: Intramuscular insulin injections occur frequently in diabetic children and are more frequent in thinner patients. To further elucidate which children are at high risk we investigated the range of subcutaneous (SC) fat thickness in diabetic children.

Materials and Methods: 73 healthy diabetic children (age 6.3-14.3 years, BMI standard deviation score (SDS) 1.0±1.4) were enrolled. All subjects had ultrasound assessment of abdominal, anterior thigh and buttock (SC) fat.

Results: There was a significant correlation between BMI and SC fat thickness (r^2=0.59 abdomen, r^2=0.44 thigh and r^2=0.44 buttock; p<0.0001). Prepubertal girls (n=16) tended to have thicker SC abdominal fat than boys (n=22, 9.9±1.0 vs 7.5±0.9mm;p<0.09), and this difference was more pronounced in pubertal girls (n=24) compared to pubertal boys (n=9) (12.8±1.5 vs 5.8±0.7mm; p=0.001). There was no difference in thigh SC fat thickness between pre pubertal girls and boys (9.1±0.8 vs 8.3±0.5mm) but pubertal girls had greater SC thigh fat than boys (11.0±0.5 vs 7.1±0.7mm;p< 0.0001). Prepubertal girls also had thicker SC buttock fat (20.7±1.6 vs 16.1±1.1 mm;p=0.02) and this was amplified at puberty (23.7±1.7vs 13.7±2.0 mm;p= 0.002). Using a vertical 8mm needle and an unpinched injection technique, IM injections would be predicted to occur in the abdomen in 69% of boys and 35% of girls, while in the thigh IM injections would be predicted to occur in 54% of boys and 22% of girls. Pinching the abdomen increased fat depth by 55.8±4.2 % and the thigh by 15.0 ±2.0%. The increase in fat depth was correlated with the initial fat thickness at both abdomen (r^2=0.95) and thigh (r^2=0.88). Pinching thighs with SC fat < 10mm and pinching abdomens with SC fat < 5mm resulted in no increase in fat depth.

Conclusion: Based upon SC fat thickness prepubertal children, especially boys are at high risk of intramuscular insulin administration. In very thin children pinching does not increase fat depth, especially on the thigh which should be avoided as an injection site.

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

H. Dorchy *, C. Van Vlaenderen, M.-P. Roggemans

Diabetology Clinic, University Children's Hospital, Brussels, Belgium

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.

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GENEPOLYMORPHISMS AND HYPOGLYCAEMIA IN CHILDREN WITH TYPE 1 DIABETES

A. Dost*, J. Füllenbach, N. Sarimese, RW. Holl, L.Gortner, J. Kreuder

Department of Pediatrics, University of Giessen, Germany

Polymorphisms of the genes of the renin-angiotensin-aldosterone-system (RAAS) have been recognized as risk factors for arterial hypertension and cardiovascular disease in diabetic patients. Lately, an increased rate of severe hypoglycaemia has also been associated with elevated levels of the angiotensin converting enzyme (AGE) and the deletion allele of the ACE-gene in adult diabetic patients

In this study, we compared the rate of severe hypoglycaemia with the frequency of certain polymorphic alleles in the RAAS, the intracellular signaltransducer G-protein (GNB3) or adrenoreceptors in a group of paediatric patients with diabetes type 1.

170 diabetic children and adolescents (84 boys/96 girls,age 3-23y, median HbA1c 7,5%, median diabetes duration 155 month) reported the number and severity of hypoglycaemia at their regular visits in our diabetes clinic. The rate of severe hypoglyceamia (ISPAD grade 2 and 3) in the years 1999-2001 was compared to the genomic polymorphisms: ACE: insertion/deletion (I/D), aldosteron-synthase: C344T, G-protein-ß3-subunit (GNB3): C825T, angiotensin II receptor 1 (ATR): A1166C, angiotensinogen (AGT): M235T, endothelial NO-synthase: G894T and intron4-deletion/insertion (D/I), ß2-adrenoreceptor: A46G and C79G.

26% of the patients reported severe hypoglycaemia, the overall rate of severe hypoglycaemia was 0,56/patient/per 3 years, the rate of coma or seizures was 0,23/patient/ per 3 years. There was no significant association between the rate of severe hypoglycaemia and the determined gene polymorphisms in our patients. However, patients with the C/C-genotype of ATR tended to have a lower incidence of severe hypoglycaemia (p=0,052).

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IMPAIRED GLUCOSE TOLERANCE AND TYPE 2 DIABETES IN OBESE HUNGARIAN CHILDREN

E. Erhardt*, D. Molnár, G. Soltész

Department of Paediatrics, Faculty of Medicine, University of Pécs, Pécs, Hungary

Background: The relationship between obesity and Type 2 diabetes mellitus (DM) is well established. Current global trends indicate that the rate of obesity in children and adolescents is increasing dramatically. Consequently, there has been an increase in the incidence of DM and impaired glucose tolerance (IGT) in this population.

Aim: To examine the prevalence of IGT and DM in obese Hungarian children according to the guidelines of the American Diabetes Association and WHO criteria. The effect of a six-month diet and life-style changes were also assessed in the children with IGT and DM.

Methods: 208 (119 boys and 89 girls) obese volunteers were studied (age: 12.7±2.8 years; body weight: 79.6±21.9 kg; BMI: 30.9±4.8 kg/m^2). Oral glucose tolerance test (OGTT) was carried out after an overnight fast with the measurements of plasma glucose (PG) and Se insulin (I).

Results: IGT was found in 32 children (15.4%), while the prevalence of DM was 1.9 % (n=4). HbA1c was normal in every case.

A maximum 1500 kcal/day energy- and 250 g/day carbohydrate intake and a regular exercise were recommended. After six months the OGTT was repeated in 14 children with IGT and in all diabetic children. In children with IGT, the reduction in body weight and BMI during this period did not reach statistical significance, but there was a significant ($p<0.001$) decrease in the level of PG at 120 min during OGTT (8.6±0.7 vs 7.0±1.2; mean±SD). Fasting and 120 min. I levels were also significantly decreased (29.1±9.2 vs 18.8±8.0 μIU/ml; and 168.7±92.9 vs 117.4±85.9 μIU/ml, respectively) ($p<0.001$). Similar changes were found in diabetic children.

Conclusion: Life-style and dietary changes of sixth months duration can improve glucose intolerance and hyperinsulinaemia in obese children with IGT and DM.