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**FTY720 prevents autoimmune diabetes
but not stimulation and expansion of autoreactive T cells**

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Background: The autoimmune diabetes of the DRBB rat shares important similarities with autoimmune diabetes in humans. We have tested the ability of FTY720 to prevent autoimmune diabetes in DRBB rat. FTY720 is a novel immunomodulator that has been efficacious in a variety of transplant and autoimmune models without inducing a generalized immunosuppressed state.

Methods: Autoimmune (AUTO) diabetes was induced by treatment with RT6.1 T cell depleting antibody and poly-IC starting at 4 wk of age. FTY720 1 mg/kg/day was administered seven days a week intraperitoneally starting at 0, 5, 7, and 14 days of depletion. If diabetes did not develop, the dose of FTY720 was tapered over 9 weeks and then stopped. The rats that did not develop diabetes were maintained for 60 days following the last dose of FTY720 (6 months of age) before undergoing a second course of depletion.

Results: FTY720 starting at day 0, 5, 7, and 14 of depletion prevented diabetes in 100%, 100%, 50%, and 20% of the DRBB rat compared to 0% of the control rats. Surviving rats in the 5, 7, and 14 day groups developed diabetes after discontinuation of the FTY720. Histological examination indicated insulitis in control rats between 7-11 days of depletion and end-stage insulitis by 18 days of depletion compared to negligible insulitis in rats without diabetes. Redepletion at 6 months of age in the surviving 0 day rats resulted in ultimate development of diabetes in 25% of these rats compared to none of the age matched controls.

Histology and immunohistochemistry of the pancreas from rats that did not develop diabetes were not different from untreated rats. The insulitis was present in control rats by 7-11days following the start of depletion.

Conclusion: We conclude that treatment with FTY720 can prevent autoimmune diabetes if administered either before stimulation and expansion of the autoreactive T cells or in the early stages of insulitis.

P-22

**Antibodies increase Coxsackie virus B4-induced production
of interferon-α by peripheral blood mononuclear cells
from patients with type 1 diabetes**

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Background: We have previously reported that Coxsackie virus (CV) B4 genome and interferon (IFN)-α can be detected in peripheral blood of patients with type 1 diabetes (T1D). We have reported that CVB4 infection of peripheral blood mononuclear cells (PBMCs) and CVB4-induced synthesis of IFN-α by these cells *in vitro* can be enhanced through interactions between CVB4 and specific non-neutralizing antibodies isolated from plasma of healthy subjects and a receptor for CVB called CAR (Coxsackie virus and adenovirus receptor).

Methods: In the present study we investigated whether a preferential IFN-α response of PBMCs to CVB4 exists in patients with T1D compared with healthy subjects and whether antibodies play a role.

Results: In patients with T1D, the levels of CVB4-induced production of IFN-α by PBMC were higher, individual CVB4-induced production of IFN-α was more frequent and increased levels of IFN-α were obtained in CVB4-infected whole blood cultures. The IFN-α inducing activity of plasma and IgGs from patients with T1D mixed with CVB4 and then added to PBMCs was high in comparison with healthy subjects. The CVB4-induced production of IFN-α by PBMC was investigated. Supernatants generated by heating PBMC from patients with T1D responsive to CVB4 exhibited IFN-α enhancing activity in combination with CVB4. This activity was inhibited by specific antibodies for FcγRI, FcγRII and CAR.

Conclusion: These data show that CVB4, through interactions with circulating and/or cell-bound IgGs, can strongly induce the production of IFN-α by PBMCs from patients with T1D.

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Longitudinal observation of enterovirus and adenovirus quantity in stools from babies at the highest genetic risk of type 1 diabetes

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Background: Enteroviruses belong to the most suspected triggers of auto-immune insulitis. In the Norwegian 'MIDIA' study, newborns from the general population are screened for the highest HLA-associated genetic risk of type 1 diabetes (T1D). Those with the high-risk genotype are followed up by questionnaires, serum samples for beta-cell autoantibodies, and stool samples for enterovirus and adenovirus. The aim is to find a time coincidence between beta-cell autoantibody seroconversion and infection with enterovirus. Adenovirus is tested as a representative of commonly occurring viruses which have not previously been implicated in T1D pathogenesis.

Methods: Results of samples at one-month intervals from 72 high-risk children aged 3-20 months. Stool samples were collected by parents and mailed to the laboratory. RNA and DNA were co-purified using QiaAmp RNA Viral kit. Enterovirus quantity was assayed using one-tube real-time RT-PCR, with armored RNA as a quantitative standard. Adenovirus subgroup A to C (except serotype 31) was quantified by real-time PCR assay.

Results: The parents collected and mailed 557 (93%) out of 597 monthly samples. Enterovirus was present in 59/557 (10.6%) samples. Longitudinal analysis was performed in 32 subjects older than 12 months, mean follow-up time being 11.3 ± 3.0 months (mean$\pm$SD). Eight children (26%) were positive for enterovirus on 2-6 occasions, 9 (28%) had one positivity for enterovirus and only 15 (47%) were permanently enterovirus-negative. Both persistent infections with dynamic changes in enterovirus quantity and serial infections were observed in individuals with multiple positive samples. Adenovirus was positive in 5.3% samples, with both persistent and serial infections.

Conclusions: The study shows high occurrence of enterovirus infection in the first 2 years of life. Since enteroviruses persist in the gut for up to several months, stool tests give reliable information on enterovirus infection, duration and type of the virus. Quantification of enterovirus from stool offers additional information on the exposure. The good cooperation of the parents shows that collecting stool samples is perceived as non-invasive and easy.

P-24

Neonatal diabetes mellitus and cytomegalovirus infection

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Background: Cytomegalovirus infection is a known risk factor for neonatal diabetes mellitus. The effects of congenital CMV infection may vary from a congenital syndrome to an asymptomatic course. Perinatal transmission is common, and the most important sources of virus are genital tract secretions at delivery and breast milk.

Patient report: The boy was born from the 3rd pregnancy of twins via Caesarean section. The first pregnancy ceased by miscarriage at 8 weeks of gestation, the first child died aged 5 months following the reconstructive operation of combined heart disease. This pregnancy was uneventful; at the 38th week of gestation it was terminated by section due to diagnosed intrauterine growth retardation. The newborn was born small for gestational age, his weight was 1880 g, and height 46 cm. The boy had mild asphyxia; he had an additional finger at the thumb of the right hand, and left cryptorchidism. The boy was breast-fed. On the 18th day of life he developed glucosuria of >55 mmol/l, and hyperglycaemia of 17.7 mmol/l without ketonuria. Neonatal diabetes mellitus was diagnosed and insulin therapy was initiated. The insulin requirement was 1.2 U/24 h, i.e. 0.34 U/kg/24 h. At 5 months of age the additional finger was removed from the right hand; the patient developed secondary focal pneumonia, progressive pulmocardial insufficiency, hypoxia, cerebral oedema, and died. Pathology investigation: the boy was ill with chronic cytomegalovirus infection, which mainly manifested in salivary glands and lungs. Pathologically altered cells, reminiscent of "eyes of owls", and abundant infiltration of lymphocytes were detected. The twin sister of the patient, born with normal weight (3100 g), without abnormalities, was not breast-fed. Her growth and development were normal. She did not develop diabetes mellitus. Investigated for cytomegalovirus infection, her IgM serology was negative, IgG was positive at 1:9300.

Conclusion: All neonates with diabetes, especially small for gestational age, should be screened for CMV infection.

P-25

**Prevalence of thyroid autoantibodies in children
and adolescents with type 1 diabetes in Kuwait**

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Background: Autoimmune thyroid diseases (ATD) are the most common form of autoimmune disorders occurring in patients with type 1 diabetes (T1DM). Thyroid autoantibodies (TH-AAb) are specific markers for ATD. They appear in the blood early before any clinical or biochemical signs of thyroid dysfunction. Their frequency in T1DM varies from 17-40%

Methods: A cross-sectional study was conducted in a total of 289 diabetic children and adolescents attending the outpatient diabetic clinic since 1992, of whom 198 were enrolled in the study and longitudinally followed for two years. The diagnosis of ATD was based on: detection of TH-AAb (microsomal thyroid antibodies, MsA, thyroglobulin antibodies, TgA) and thyroid function tests (TFT: serum TSH, free thyroxin). TH-AAb and TFT were measured at the first clinical visit and then annually. In the presence of TH-AAb, TFT were repeated at 6-month intervals.

Results: Of the 198 diabetic patients 98 (49.5%) were boys and 100 (50.5%) girls. TH-AAb were found in 52 (26.3%) patients, 29 (55.8%) girls and 23 (44.2%) boys. In either sex TH-AAb were mainly found after the development of puberty: 71.4% postpubertal vs. 28.6% prepubertal (p<0.001). MsA were detected in 37 (71.2%) diabetic children and TgA in 24 (46.2%), (p<0.005). The prevalence was not statistically different in patients with diabetes duration of >5 years and patients with <5 years duration: 59.6% vs 40.4%. Twelve patients (23%) with positive TH-AAb had ATD with overt or subclinical hypothyroidism. Only two patients (3.8%) showed hyperthyroidism. Eight patients (15.3%) developed another autoimmune disease, e.g. celiac disease with positive AAbs (antigliadine and endomysial AAbs).

Conclusion: Children with T1DM are at high risk of developing ATD. We recommend annual screening for TH-AAb and for those positive periodic TFT. Antibodies should be checked at diagnosis and at 1-2 year intervals to identify a high risk group. Patients with type 1 diabetes and ATD should be evaluated for AAbs against other organs such as celiac disease.

P-26

Autoimmune thyroiditis in type 1 young diabetics:
A prospective study of 419 patients
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Background: The association between autoimmune thyroiditis and type 1 diabetes could have a negative impact on growth and metabolic control. Its frequency is variously reported. Our aim was to determine the prevalence of antithyroid peroxidase antibodies (ATPO) and dysthyroidism in young diabetics.

Methods: 419 patients with type 1 diabetes (209 F, 210 M) aged 13.5±5.9 yr with mean diabetes duration of 5.5±4.8 yr (0-20 yr) were involved in the study. Metabolic control was assessed by mean HbA1c. ATPO (nl<20 IU/l), triiodothyronine (T3, nl 1.6-3.8 pg/ml), thyroxine (T4, nl 9-18 pg/ml) and TSH (nl 0.2-4 µU/l) were measured by radioimmunoassay; HbA1c by ion exchange resin chromatography (nl 4-6%).

Results: 53 patients with diabetes (12.6%) aged 14.6±6.4 yr with diabetes duration 6.1±5.2 yr (0-19.2 yr) had positive ATPO (mean 408 UI/l; 21.3-9424). Among them, 10 patients had hypothyroidism (mean TSH 15.2 µU/l; 5.7-50) of whom seven had normal T3 and T4, and three had T4 <9 pg/ml and/or T3 <1.6 pg/ml and four presented with goiter; the latter had a significantly higher mean ATPO (1670 IU/l; 21.3-9424). Two patients with positive ATPO had TSH <0.2 µU/l with, in one case, T4 >18 pg/ml and T3 >3.8 pg/ml and evidence of clinical hyper-thyroidism. There was no significant difference between the group with positive ATPO and the negative patients in terms of age, diabetes duration, BMI (19.14±3.47 vs 18.59±3.23) or mean annual HbA1c (8.6±2.1 vs 9.3±2.5). Patients with hypothyroidism had the same parameters with a slightly non-significant height difference (mean SD 1.15 vs 0.94 for the normal group).

Conclusions: This study confirms the frequency of autoimmune thyroiditis in young people with diabetes and its often latent presentation. No impact on metabolic control was found.

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**Thyroid autoimmunity in children with coexisting
type 1 diabetes mellitus and celiac disease: A multicenter study**

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Background: Children with type 1 diabetes mellitus (DM) are known to be more prone to develop thyroid autoimmunity (TAI); moreover, TAI occurs more frequently in patients with celiac disease (CD). These associations are explained partially by a common genetic background. Further, one ongoing autoimmune process may stimulate additional ones. We therefore assessed whether TAI occurs more frequently in children with coexisting DM and CD compared to children with DM only. Furthermore, we investigated the clinical course of TAI in diabetic children with and without CD.

Methods: We performed a retrospective case-control study comparing 84 children with DM and CD to 167 diabetic children without CD (controls), matched by age (14.9±6.2 years, mean±SD) and the age at DM onset. Markers of TAI (autoantibodies againts thyroid peroxidase and thyroglobulin), thyroid function (TSH, free T4) and HbA1c were recorded retrospectively. Diagnosis of TAI was based on thyroid autoantibodies found repeatedly positive on two or more consecutive occasions and/or thyroid dysfunction.

Results: TAI was diagnosed in 11/83 (13%) cases and 32/167 controls (19%, n.s.). Age at TAI diagnosis did not differ between the groups (11.4±4.1 vs. 12.6±6.7 years, n.s.). Thyroid dysfunction was disclosed in 8 out of 11 cases with TAI (73%), and in 17/32 (53%) controls (n.s.). We did not observe any impact of TAI on HbA1c in either cases or controls during the 4.9±2.8 years of TAI follow-up.

Conclusions: The prevalence of TAI did not differ between children with both DM and CD, and children with DM alone. Although we observed an insignificantly higher frequency of thyroid dysfunction in children with DM and CD, we conclude that occurrence of TAI in diabetic children is not related to coexisting CD.

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**Silent (screening detected) celiac disease in children
with type 1 diabetes mellitus: A multicenter case control study**

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Background: Celiac disease (CD) is more prevalent in children with diabetes mellitus type 1 (DM) than in the non-diabetic population. Most of the patients with DM and associated CD do not suffer typical gastrointestinal symptoms. There is no agreement on the clinical relevance of silent CD in DM and only few data exist on follow-up.

Methods: 98 diabetic patients (54 males and 44 females) from 11 centers were diagnosed as having potential or silent CD by screening for EMA or ATGA and subsequent biopsy. Two control groups in the same center were chosen (stratified by age and age at DM onset) who were negative for EMA/ATGA during the same period (n=195, 94 males, 98 females). Height, weight, HbA1c, insulin dosage and acute complications were documented at least every 6 months for one year of follow up on a standardized form.

Results: Mean age at onset of diabetes was 6.5 ± 4.1 yr and diagnosis of CD was made at 10.0 ± 5.4 yr. Biopsy showed in 74 cases total or subtotal atrophy, in 13 cases IEL and in seven cases normal mucosa. In two cases no clear result was found and in two further cases no biopsy was performed. The mean observation period after the diagnosis of CD was 3.3 ± 1.9 yr. Mean HbA1c was similar in cases and controls ($8.6\pm1.4\%$ vs $8.5\pm1.3\%$). There was no difference in the frequency of severe hypoglycemia and ketoacidosis. The insulin dosage was comparable in both groups (0.7 ± 0.2 U/kg vs 0.7 ± 0.2 U/kg). BMI-SDS at CD diagnosis (0.57 ± 1.24 vs 0.52 ± 1.07) and height-SDS (0.14 ± 1.13 vs 0.30 ± 0.95) did not differ between cases and controls. After CD diagnosis BMI SDS declined ($p <0.05$) in boys, while girls with silent CD showed a significant decrease in height ($p<0.02$) and BMI SDS ($p<0.05$).

Conclusion: In a cohort of 98 diabetic patients with silent CD there was no obvious influence of CD on metabolic control but a negative influence on growth and weight gain even during the short observation period of our study.

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Relationship between coeliac disease and type 1 diabetes

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Background: Type 1 diabetes (T1D), as coeliac disease (CD), may be induced by feeding a diet containing wheat gliadin and related proteins. Both conditions require genetic predisposition and have a prodromal period. The aim of the study was to test the hypothesis of a relationship between gluten intake and type 1 diabetes and to evaluate the effect of gluten-free diet on T1D.

Methods: We evaluated immunologic markers for T1D (GADA, IAA, IA-2A) and for CD (EMA, TGCA) in first-degree relatives (FDR) of T1D and CD patients. Subjects with at least one immunologic marker for T1D underwent HLA typing and metabolic studies (first phase insulin response [FPIR] to intravenous glucose tolerance test [IVGTT]). A gluten-free diet was adopted in subjects with one immunologic marker for T1D (confirmed in two determinations), with genotype at risk for T1D, with or without metabolic markers, and without CD immunologic markers.

Results: We tested 196/232 T1D-FDR and 105/148 CD-FDR. Among the T1D-FDR, seven subjects showed immunologic markers: two of 33 siblings (6%), four of 160 parents (2.5%), and one of three offspring (33.3%). The parents with confirmed positivity and one of the offspring (a daughter) with all three serum markers are undergoing diagnostic tests. Two siblings (a sister and a brother), both with three autoantibodies, pathologic FPIR and with four and one susceptible heterodimers respectively, have been fed a gluten-free diet for a 12-month period, without any effect on metabolic and immunologic markers. Among the CD-FDR, three subjects were positive for T1D immunologic markers: two parents (2.4%) and one sister (4.3%); they all are undergoing diagnostic tests.

Conclusion: Relatives of T1D and CD patients seem to have a similar prevalence of T1D immunologic markers. Gluten-free diet did not influence immunologic and metabolic markers in tested T1D-FDR.

P-30

Celiac disease in type 1 diabetes:
Growth and bone mineralization
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Background: Children with type 1 diabetes (TID) are at an increased risk for celiac disease (CD), which is treated with a gluten-free diet (GFD). Both TID and CD are associated with growth failure, pubertal delay, delayed bone maturation and decreased bone mineralization. Testing for IgA anti-tissue transglutaminase antibodies (TG) is a highly sensitive method to screen for CD. However, the benefit of early diagnosis of screening-identified CD in children with TID is unknown. This must be weighed against the adverse effect of a second chronic disease and medical advice to follow a diabetic plus a GFD, which requires additional lifestyle changes. The purpose of this study is to evaluate the benefit of early diagnosis and treatment of screening-identified CD in children with TID.

Methods: A prospective, 1-year, three-group observational cohort study has been designed comparing TID+TG+GFD- (untreated study group) to TID+TG+GFD+ (treated control group) and to TID+TG- (negative control group). Main outcome variables include measures of growth (height, weight, bone age, IGF-I, IGFBP3, T4), nutrition (ferritin, VitB12, pre-albumin), bone mineralization (lumbar spine DEXA scan, PTH, VitD, bone-specific ALP), intestinal permeability and diabetes control.

Results: Participation by families has been enthusiastic. To date 120 TID+TG+ children have been identified, including 96 of 924 (10.4%) T1D+ children undergoing routine screening for TG. Small bowel biopsy has been performed in 47 of 120 (39%) of which 30 (64%) have had villous atrophy consistent with active CD. Ten of the 11 children who have begun the 1-year observational period have normal bone age and mineralization, one has delayed bone age (-4 yr) and decreased mineralization.

Conclusion: To families of screening-identified TID+TG+ children, participation in a study to assess the need for a GFD is viewed positively. This study may provide evidence on which to base recommendations on (1) routine TG testing for CD in children with TID and (2) the benefit of early treatment with a GFD.

P-31

Comparison of biphasic insulin aspart and human insulin including biphasic human insulin in children with type 1 diabetes

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Background: Adolescents with diabetes need a treatment which offers optimal blood glucose control and minimal interference with a normal lifestyle.

Methods: In this randomised, open-labelled, parallel group, four-month efficacy and safety trial, two groups of adolescents with type 1 diabetes were compared. One group, BIAsp, had injections three times daily immediately before meals with BIAsp30 (a mixture of 30% soluble and 70% protamin-bound insulin aspart); the other, HI+BHI, had injections 30 minutes before meals with soluble human insulin (HI) twice daily and biphasic human insulin 30 (BHI30) once daily, usually at breakfast, supplemented with NPH insulin if necessary

Results: 80 boys and 87 girls aged 10-17 years were included in the trial, 86 in the BIAsp and 81 in HI+BHI group. Mean baseline HbA_{1c} was around 9.5% and body mass index (BMI) 21.1 kg/m^2 in both groups. During the treatment, the primary endpoint, average prandial increase in blood glucose, was reduced in both groups by approximately 1 mmol/L and HbA_{1c} decreased by about 0.2% in both groups. BMI increased in both groups but interestingly the increase was lowest in the BIAsp group (p=0.004) in spite of a slightly higher insulin consumption in this group. Frequency of hypo-glycaemic episodes (BG < 2.8 mM or symptoms alone) and adverse events were not significantly different in the two treatment groups.

Conclusion: Efficacy and safety evaluations were similar for the two treatments. BMI increased significantly less in the BIAsp group compared to the HI+BHI group.

P-32

Comparable pharmacokinetics of insulin detemir in children, adolescents and adults with type 1 diabetes

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Background: The pharmacokinetics (PK) of the soluble basal insulin analogue insulin detemir has only been studied in adults. The aim of this trial was to compare the PK in children (6-12 yrs), adolescents (13-17 yrs), and adults (18-65 yrs) for insulin detemir and NPH insulin, respectively.

Methods: 34 (16M/18F) patients with type 1 diabetes on at least twice daily insulin therapy were randomised in this single centre, open-label, cross over trial: 13 children, (mean age: 10.4 yrs, BMI: 17.9 kg/m^2, duration of diabetes: 2.9 yrs), 10 adolescents, (15.1 yrs, 21.1 kg/m^2, 8.1 yrs) and 11 adults (22.8 yrs, 23.4 kg/m^2, 9.8 yrs). Patients received single s.c. injections of 0.5 U/kg detemir or 0.5 U/kg NPH shortly before breakfast on two dosing days separated by a wash-out period of 7 to 14 days. Serum levels of insulin detemir and human insulin were assessed over 24 hours.

Results: No significant differences were found in the overall comparison between age groups for AUC_{0-24h} or C_{max} for either insulin detemir or NPH.

Endpoints	Patients	Insulin detemir			NPH insulin		
		Ratio	95% CI	p-value	Ratio	95% CI	p-value
AUC_{0-24h}[a]	Childr./adol./adults			0.61[b]			0.08[b]
	Children/adults	1.10	[0.81; 1.50]		2.92	[1.14; 7.44]	
	Adolesc./adults	0.95	[0.70; 1.30]		1.93	[0.77; 4.83]	
C_{max}	Childr./adol./adults			0.41[b]			0.12[b]
	Children/adults	1.24	[0.86; 1.79]		3.24	[1.06; 9.95]	
	Adolesc/adults	1.02	[0.71; 1.47]		2.07	[0.69; 6.20]	

[a] AUC_{0-24h}: Area under the curve, [b] Overall comparison across age groups

Pair-wise comparisons between children and adults and between adolescents and adults supported these findings for insulin detemir, while a tendency towards a difference between children and adults was found for NPH. Coefficient of variation (CV) between patients within each age group for AUC_{0-24h} ranged fom 20-42% for insulin detemir and 70-118% for NPH. CV for C_{max} was also lower with insulin detemir (24-55%) compared to NPH (81-100%). Insulin detemir was well tolerated in all age groups.

Conclusion: These data indicate that individual dose-titration of the basal insulin analogue detemir can be based on uniform guidelines for all age groups with the benefit of less between-subject variation compared to NPH.

P-33

Experience with insulin glargine in children and adolescents with type 1 diabetes: A 6-18 month follow-up study

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Background: Insulin glargine (Lantus[®]) is a new basal insulin analogue with a protracted and flat profile of action. Extensive clinical trials have demonstrated its efficacy and safety in both adults and children.The aim of this study was to observe the effect of insulin glargine on metabolic control in paediatric patients with type 1 diabetes in a clinical setting.

Methods: Twenty patients (8-18 years, mean 13.6 ± 3.5 yrs; duration of disease 5.6 ± 3.9 yrs) received prandial insulin (regular or lispro or aspart) plus insulin glargine once or twice daily at breakfast and/or suppertime or bedtime. Metabolic control was evaluated as the mean values of HbA1c, comparing the mean of the year before the study begun and after insulin glargine initiation (6-18 months, mean 12.1 ± 2.5 months). A control group (25 patients) of type 1 diabetic patients on NPH and regular insulin, matched for age and disease duration, was also evaluated.

Results: After 6-18 months, the group treated with insulin glargine showed significantly improved HbA_{1c} levels ($7.1\pm1.2\%$ vs. $8.0\pm1.1\%$, $p<0.02$), while no difference was observed in the NPH insulin group ($8.4\pm0\%$ vs. $8.2\pm1.1\%$, NS). No difference was observed between insulin glargine and NPH at baseline, but after follow-up the insulin glargine group showed better control than the NPH insulin group ($p<0.01$). There was a tendency towards less symptomatic hypoglycaemia in the insulin glargine group compared with the NPH insulin group. No severe hypoglycaemia was observed in either insulin glargine or NPH insulin groups. None of the patients using insulin glargine wanted to return to their former long-acting insulin preparation.

Conclusions: After 6-18 months follow-up, insulin glargine may be associated with better control in paediatric patients with type 1 diabetes, when compared with patients on NPH insulin.

P-34

Diabetic control and quality of life in children with type 1 diabetes mellitus (type 1 DM) on insulin glargine (Lantus®)

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Background: The long-acting insulin analog glargine (Lantus®) became a therapy option for children with type 1 DM after FDA approval in 2001. A combination of Lantus with multiple doses of rapid-acting insulin (Humalog® or Novolog®) offers an alternative for achievement of improved glycemic control and increased flexibility of life style. We evaluated the impact of Lantus therapy (single daily injection of Lantus; rapid-acting insulin before or after meals) on glycemic control and quality of life in children previously treated with conventional insulin therapy (NPH before breakfast and bedtime snack, rapid-acting insulin before breakfast, dinner, and bedtime snack).

Methods: The effect of Lantus therapy on diabetic control was determined by comparing HbA1c levels at baseline, 3, 6, 9, and 12 months in 61 children aged 2-19 years. The duration of Lantus therapy ranged from 3-12 months. The effect of Lantus therapy on quality of life was determined through self and/or parent report. The patient (or family member for younger child) was asked a series of questions concerning aspects of daily living and how the Lantus therapy has impacted their life, either positively or negatively.

Results: HbA1c (mean±SD) at baseline was 9.0±1.6. Levels did not change significantly from baseline at 3 months (8.9±1.5, n=56), 6 months (8.6±1.8, n=38), 9 months (8.5±1.3, n=20), and 12 months (9.0±1.6, n=12). All patients reported improvement in quality of life, and were uniformly satisfied with Lantus therapy. Children and/or parents expressed satisfaction due to greater flexibility with timing of meals and amount of food they could eat. All patients felt that the need for more frequent insulin injections was the major disadvantage of Lantus therapy, but indicated that the benefit of a more flexible life style outweighed the disadvantage of multiple injections. Two patients were switched back to conventional therapy due to inability to perform the necessary calculations and insulin administration at lunch time.

Conclusion: Lantus therapy improved quality of life in our patients with type 1 DM, but there was no significant improvement in glycemic control.

P-35

Effect of the addition of metformin to insulin therapy in adolescents and young adults with type 1 diabetes mellitus

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Background: Insulin resistance may play a role in deterioration of glycemic control in some adolescents and young adults with type 1 diabetes. Metformin is thought to exert its hypoglycemic effect by increasing peripheral sensitivity to insulin and decreasing hepatic glucose output. Metformin also promotes weight loss in obese patients.

Aim: To evaluate the effect of metformin in addition to conventional insulin therapy for adolescents and young adults with type 1 diabetes.

Methods: Eight consecutive patients with type 1 diabetes, two males and six females, aged 20.1 ± 4.0 (15-26) years, were studied. They were relatively obese with BMI of 24.2 ± 1.8 (21.3-26.7) and had high HbA1c of 9.5 ± 1.2 (8.4-12.4)% despite high dose requirement of insulin of 74.0 ± 31.2 (48-148) U/d. Metformin at the dose of 500-750 mg daily was administered to the patients in addition to insulin therapy for one year.

Results: HbA1c, BMI and insulin dose were compared at baseline, 3 mo, 6 mo and 12 mo following the administration of metformin. HbA1c was lowered, BMI was reduced and insulin requirement decreased significantly after the metformin therapy ($*p < 0.05$, $**p < 0.01$ vs. baseline). There were no side effects including anemia and lactic acidosis during the study period.

	Baseline	**3 mo**	**6 mo**	**12 mo**
HbA1c (%)	9.5 ± 1.2	$8.6 \pm 1.4**$	$8.4 \pm 1.3**$	$8.1 \pm 1.0*$
BMI	24.2 ± 1.8	$23.9 \pm 1.7*$	23.8 ± 1.8	23.3 ± 2.1
Insulin (U/d)	74.0 ± 31.2	$69.8 \pm 29.7*$	$68.7 \pm 29.8**$	$75.1 \pm 34.1*$

Conclusions: Metformin is safe and may represent a useful adjunct to management of type 1 diabetes in adolescents and young adults who have poor glycemic control with reduction of insulin dose and body weight.

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Basal-bolus insulin treatment in 122 children and adolescents with DM1: Improvement in control - glargine vs. CSII

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Background: Intensified treatment has been shown to improve HbA1c in DM1. We compared the results of basal-bolus insulin in 122 children and adolescents with DM1 treated with either glargine + lispro/aspart or insulin pump (CSII). All patients used insulin to CHO ratios and correction doses.

Method: We reviewed the results of all 191 patients started on treatment with glargine (84) and CSII (107) between 6/2001and 6/2002. Study sample consisted 122 patients, 62 glargine and 60 CSII, who met criteria of having ≥ 3 follow-up visits/yr. Glargine treated patients were 12.2±1.6 yrs, DM duration 4.2±1.8 yrs, and CSII treated yrs 11.6±1.4 yrs, DM duration 5.3±3.3 yrs.

Results: Both groups showed statistically significant improvement in HbA1c. Patients treated with CSII had lower HbA1c at baseline and CSII treated patients had statistically more significant improvement over the treatment period. The difference in HbA1c in the two groups became smaller by the end of the treatment period. HbA1c results (normal 3-6%):

Time	Lantus	Pump
Base	9.2 ± 1.7	8.1 ± 1.3
3 mo	8.6 ± 1.6, p=0.003	7.7 ± 1.1, p=0.001
6 mo	8.8 ± 1.7, p=0.0003	7.6 ± 1.2, p=0.0003
1 year	8.4 ± 1.3, p=0.0001	7.5 ± 1.2, p<0.0001

P values are for comparisons from baseline, using paired T-test.

Unpaired comparison between Lantus and pump: base: 0.000006; 3 mo: 0.006; 6 mo: 0.0002; 1 year: 0.007.

Conclusions: Treatment with basal-bolus insulin significantly improves DM control in patients treated with either glargine + lispro/aspart or CSII. The decrease in mean HbA1c was greater in the glargine group but the CSII patients individually had a statistically greater improvement in HbA1c. Severe hypoglycemia occurred < 0.02 events/patient/yr in both groups and was not significantly different between groups.

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Evening exercise in adolescents with T1D on MDI or CSII

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Background: Patients with T1D on CSII have fewer hypoglycemic events in everyday life as compared to their peers on multiple daily injections (MDI). Fewer data are available on hypoglycemic events in adolescents with T1D on CSII after exercise.

Methods: Nineteen adolescents on MDI (age 17.2 ± 3.4 years, HbA1c $8.6 \pm 1.4\%$) and 20 matched adolescents on CSII (age 17.7 ± 4.5 years, HbA1c $8.1 \pm 1.2\%$) were put on fixed diet on day 1 of the investigation. CGMS was installed. On day 2 at 5 p.m. all participants started a $10 + 30$ minute treadmill exercise programmed at 70% of their calculated maximal physical load. Patients on MDI were instructed to reduce the pre-dinner bolus and bedtime insulin dose by 10%. Patients on CSII were disconnected from the pump during the exercise and instructed to reduce the pre-dinner bolus by 10%. CGMS glucose data were analyzed on day 3.

Results: Insulin dose was lower at baseline in the CSII group ($p=0.03$). The duration or number of hypoglycemic events was not increased during the night after the exercise as compared to the night before it in the CSII group. The number of patients with hypoglycemic episodes (BG <3.0 mmol/L) during the night after exercise was higher ($p=0.02$) in the MDI group. The duration of hypoglycemic episodes was inversely correlated to HbA1c ($p=0.03$) in the CSII group.

Conclusion: Patients on CSII are less likely to have a hypoglycemic episode after an evening exercise as compared to the night before exercise or to the patients on MDI. Lower HbA1c was correlated with increased duration of hypoglycemic events in patients on CSII.

P-38

Variability in insulin dosing by children and adolescents with type 1 diabetes mellitus on insulin pumps

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Background: Data from the Diabetes Complications and Control Trial (DCCT) confirm the benefit of intensive insulin therapy in adolescents with type 1 diabetes. Therefore, many practitioners prescribe insulin pumps for children and adolescents with type 1 diabetes. Such devices allow patients greater flexibility to modify insulin doses and also the practitioners to document how much insulin is actually being given. We hypothesized that children and adolescents with type 1 diabetes on insulin pumps would be giving fewer insulin boluses than were prescribed.

Methods: To address this question, we accessed the memory from insulin pumps in 33 of our patients seen in the Diabetes Clinic over a 2-month period (mean age 12.3 years, range 4 to 18.2 years). Data from the 3-4 weeks prior to the visit were analyzed. All patients had been instructed to give 3 to 6 boluses of insulin per day.

Results: The average number of basal rates used per day was 2.9 ± 0.3 (range 1 to 7). The mean lowest number of boluses given on at least one day by these patients was 2.8 ± 0.3, while the mean highest number of boluses given on at least one day was 7.9 ± 0.6. In one-third of the patients there was at least one day when fewer than 3 boluses were given; 17/33 had at least one day when more than 6 boluses were given. Over the week prior to the appointment, the patients' insulin doses ranged from an average low of 0.6 ± 0.3 U/kg/day up to an average high of 1.1 ± 0.05 U/kg/day with $45.4 \pm 2.4\%$ of the insulin as basal doses and $54.6 \pm 2.4\%$ as bolus doses. The insulin pumps were suspended an average of 26.3 ± 5.1 minutes per day (range 0 to 113.79 min per day). Average HbA_{1c} was $7.8 \pm 0.2\%$ (normal 4.0-6.3%).

Conclusions: We conclude that diabetic control in children and adolescents on insulin pumps may be excellent, but patients are frequently giving both fewer and more insulin boluses than prescribed.

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Twelve-month assessment of therapy with continuous subcutaneous insulin infusion in children with type 1 diabetes

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Background: The aim of the study was to assess therapy with continuous subcutaneous insulin infusion using insulin pumps in children with type 1 diabetes.

Methods: In a group of 38 children (22 girls and 16 boys) with type 1 diabetes, aged 6-19 years (mean age 12.7 ± 4.2), with a mean duration of the disease of 3.97 ± 1.93 years the following parameters were assessed in a 12-month observation: 24-hour insulin requirement (U/kg), body mass index (BMI) and glycosylated haemoglobin (HbA1c, using HPLC method). After 6 and 12 months of treatment the parameters were compared with baseline values before therapy. The insulin used in pumps was lispro (32 children) and aspart (6 children). The group of 38 children was divided into two age subgroups: I (n=10): 6-9 years, mean age 6.65 ± 0.9 yrs and II (n=28): 11-19 years, mean age 14.9 ± 2,3 yrs.

Results: There were no significant changes for either HbA1c values or BMI during the follow-up, either in the total group of patients or in the subgroups according to age. However, a significant difference was observed for the 24-hour insulin requirements in group I which decreased from an average of 0.91±0.12 U/kg at baseline to 0.74 ± 0.12 U/kg after 12 months.

Conclusion: Continuous subcutaneous insulin infusion is an effective model of insulin therapy.

P-40

One-year treatment with subcutaneous insulin infusion pump:
Evaluation in a department of paediatrics

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Background: Insulin pump therapy in type 1 diabetes can improve glycemic control, especially in cases of severe hypoglycemia, unstable diabetes despite correct treatment (due to young age, life style or unexplained), recurrent diabetic ketoacidosis and hypoglycemia unawareness. Since 2001, this type of treatment is covered by the French social security system permitting its enlarged use in children.

Methods: 25 children aged between 1 and 16 years who were previously treated by 3 to 4 insulin injections per day were offered continuous sub-cutaneous insulin infusion treatment by pump. Cases as indicated by legislation included 7 cases of unstable diabetes in very young children, 9 cases of severe hypoglycemia, 3 with high HbA1c in spite of adapted treatment, 5 brittle diabetes, 1 personal demand. Continuous blood glucose levels were recorded during 3 days prior to pump treatment which was initiated during a one week hospitalization in the referent centre for pump education and repeated a few weeks later. The children were regularly followed-up through medical visits and the staff of the center. The families were encouraged to send glycemic results by fax every week. An annual check-up was carried out during a one-day hospitalization permitting review of pump techniques and analysis of the course of the disease from the beginning of pump treatment: HbA1c levels, number of severe hypo- and hyperglycemic episodes, number of hospitalizations. The degree of treatment satisfaction was evaluated as consequent changes in lifestyle.

Results: Results were analyzed by age and the initial indication of treatment. The reasons of early treatment suspension in some children were also studied.

Conclusions: All children who fit indications do not benefit from pump treatment. For better pump management, it seems necessary to make the following changes: preliminary psychological evaluation, sufficient education of school staff, and regular review of pump techniques.