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DIABETES RESEARCH AND CLINICAL PRACTICE

Diabetes Research and Clinical Practice 44 (Suppl.) (1999) S1–S39

# Abstracts for ISPAD '99, 24–27 April 1999

## O1

**Twenty year incidence of Type 1 diabetes in Hungarian children (1978–1997)**

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The Hungarian Childhood Diabetes Register has collected the data of all newly diagnosed children aged 0–14 years since 01 January 1978. After a ten-year retrospective period, prospective registration has started in 1989 as part of the EURODIAB ACE network. Data of the primary source (hospital records) were validated by using the records of summer camps for diabetic children. The completeness of ascertainment (estimated by the capture-recapture method) was over 96%. Poisson regression models were used to study differences in incidence between age groups and boys and girls. Likelihood ratio Chi-square tests were used to assess the significance of the terms in this model.

During the last twenty years there was evidence of a highly significant linear trend ($X^2 = 165,9$ df = 1 $P < 0,001$) showing an increase of 4,8% per annum (95%CI 4,0% to 5,5%) in incidence. The incidence rose from 3,8 per 100 000 in 1978 to 10,7 per 100 000 in 1997. The increase in incidence was similar for both sexes and for all age groups but was most pronounced in the oldest age group. There was no evidence of a difference in linear trend between age groups ($X^2 = 3,44$ df = 2 $P = 0,18$). Two peaks with considerably higher incidence rates compared to earlier years occurred during this period, one in 1985 and the other in 1993. These were mainly due to the sharp increase in the incidence of age group 5 to 9 ys.

More cases were diagnosed during autumn and winter than during spring and summer. This considerable seasonal variation was similar for boys and girls. The age -specific incidence rate was the highest in the age group 10 to 14 ys and the lowest in children less than 5 ys for both sexes. The incidence was slightly lower among boys than among girls. This difference in incidence between sexes was, however confined to the two older age groups.

In 121 of the 1239 families (9,7%), one of parents (5,8 percent of the fathers and 3,7 percent of the mothers) was also reported to have Type 1 diabetes and in 3 (0,2%) families both parents had Type 1 diabetes. 22 (2,3%) of the diabetic children had a sibling with Type 1 diabetes.

Our results clearly show that the incidence is rapidly increasing in Hungary. It can be predicted that with the present rate of increase, the incidence will be over 20 per 100000 by the end of next twenty years.

## O2

**At what age do patients leave pediatric treatment centers? A German multicenter study on 2008 patients leaving pediatric care**

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*Background*: The transferral of patients from pediatric to adult diabetes care is often unstructured and very little is known about the age at which patients switch from pediatric diabetes care to adult diabetologists.

*Methods*: The German Pediatric Working Group on Quality Control in Diabetes has establised a prospective, computer-based documentation program. Relevant data can be anonymized and extracted for central analysis. For the first round of this effort (August of 1998), 41 pediatric centers contributed their data, encomprising a total of 6671 patients. The number of patients documented at each center varied between 18 and 959, only 4 centers had documented more than 300 patients. If a patient had not shown up at a center for at least one year, it was assumed that this patient had left the continuous care at this center. Using this definition, 2008 patients were no longer at the respective pediatric treatment center.

*Results*: The median age at which patients had left the center was 16.9 years [Q1-Q3: 13.1–19.9 years] with a corresponding duration of diabetes of 7.7 years [3.1–11.3 years]. Girls left slightly earlier (median age 16.6 years) compared to boys (17.2 years, $p < 0.02$). There was a wide difference among the centers with respect to the average age at which patients left, ranging from 9.6 years up to 19.7 years. Interestingly, a significant positive correlation between the number of patients treated at a center and the mean age at which patients left the center was encountered ($r = +0.46$, $p < 0.005$). No information on the reason why patients had left the center was

PII: S0168-8227(99)00018-2

available. In younger children, moving home or dissatisfaction with the center are likely involved. Therefore, transferral to adult care is better reflected by the upper age-limit at which patients are still seen at a center. Based on the 95th percentile, again a wide spread between centers ranging from 15.1 years to 29.7 years was encountered.Summary: Even in one country, the age at which patients with type-1 diabetes leave pediatric care differs widely between centers. In Germany, larger centers tend to care for a considerable proportion of patients up to adulthood. Therefore, the mean age of the patient population is relevant when treatment policies and outcome indicators are compared between different institutions. Future research should include a questionnaire on the reasons for leaving a center as well as a follow-up of the patients.

## O3

**Quality of life and hope in young adults with childhood onset type 1 diabetes**

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The aim of this study was to investigate quality of life and hope for the future in young adults with prepubertal onset type 1 diabetes. Seventy adults aged 18–26 years (mean 21.7) were assessed for psychological morbidity using the Symptom Checklist 90-Revised (SCL-90-R) and for quality of life using the DQOL (from the DCCT). Future impact of diabetes and hope were measured using the Hunter Opinions and Personal Expectations Scale (HOPES) [1] and the Future Impact of Diabetes Scale (FIDS), an 80 item semi-structured interview developed for this study.

The median $HbA_{1c}$ was 8.4% [5.2-13%] and the mean BMI was 25 [18%31]. Two had had laser treatment for severe retinopathy and microalbuminuria was present in 12 (17%). Overall 96% subjects scored highly for QOL and 87% for Hope, 75% rated as non-cases for psychological morbidity.

| Measure | Result | Male (n = 35) | Female (n = 34) | $HbA_{1c}$ < 8.4% | $HbA_{1c}$ > 8.5% |
|---|---|---|---|---|---|
| DQOL | High QOL | 34 (97%) | 32 (94%) | 36 (97%) | 30 (94%) |
| HOPES | High Hope | 30 (86%) | 30 (88%) | 33 (89%) | 27 (84%) |
| SCL90R | Non Case | 29 (82%) | 23 (68%) | 30 (81%) | 22 (69%) |

However, preliminary analysis from the FIDS indicates 82% worry about future complications. In terms of current diabetes management 63% were happy, 55% felt their diet and bgl monitoring was suboptimal and 64% believe future management will improve with age, perceiving a more structured adult lifestyle. Ninety percent want to have children, 76% believe diabetes will effect this and 72% are greatly concerned. 77% believe no-one understands what it is like to have diabetes but 23% feel close friends and family do understand. 24% have seriously considered or attempted suicide.

Results from the questionnaires indicate a well-adjusted and hopeful group of young adults. However, preliminary data from the FIDS illuminates specific concerns and risk factors, as illustrated in the domains of parenting and suicide, faced by this cohort. This highlights the imperative need for qualitative and quantitative investigation.

[1] Nunn KP, Lewin TJ, Walton JM, Carr VJ, 1996, Psych Med, 26, 531-545.

*This study was supported by a grant from Diabetes Australia.*

## O4

**Centre differences in the quality of life**

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To study the relationship between metabolic control and quality of life for adolescents, an internationally adapted diabetes quality of life (DQOL) questionnaire, with parental and professional assessment was combined with a central determination of $HbA_{1c}$ (HPLC, Biorad Variant) in 20 centres of 17 countries. A total number of 2103 adolescents (median age 14 (range 10–18) years, median $HbA_{1c}$ concentration 8.5% (4.8–17.4%) participated. As in the previous study in 1995 $HbA_{1c}$ varied significantly between centres (range $7.7 \pm 1.0\% - 9.6 \pm 1.8\%$) with 6 centres being significantly above and 6 significantly below the grand mean. There was significant variation among centres ($p < 0.0001$) in the quality of life scores from $93.3 \pm 20.1$ to $115.8 \pm 25.6$. These centre differences on quality of life perceptions were present in all subscales (impact, worries, satisfaction and health perception) of the patient questionnaire as well as in the parental and professional assessment of burden. While there was a clear association between good metabolic control and better quality of life scores for each centre no differences between the centres significantly above or below the average $HbA_{1c}$ were apparent in the overall quality of life scores. Thus cultural differences between centres appear to have a significant influence on the quality of life perceptions of patients, parents and health professionals between different paediatric diabetes centres independent from that of the prevailing glycaemic control.

## O5

**Does $HbA_{1c}$ (1995) predict quality of life in 1998? A study of 1023 adolescents from 17 countries**

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From the total number of 2873 children & adolescents included in an International Study in 1995, 1023 adolescents were restudied in 1998 with a further determination of $HbA_1C$ (measured centrally), clinical and demographic data, completion of the Diabetes Quality of Life Questionnaire (DQOL) and by multidimensional questionnaires for parents & professionals. The young people attended 20 paediatric departments in 17 countries in Europe, Japan and North America.

There were 514 boys and 509 girls, mean age $14.8 \pm 2.2$ yrs and mean diabetes duration $7.5 \pm 3.3$ yrs in 1998. Mean $HbA_1C$ ($9.0 \pm 1.6\%$) did not differ significantly from the 1995 $HbA_{1c}$ level for adolescents aged 11-–8 years ($n = 1902$). As in 1995 $HbA_{1c}$ varied significantly ($p < 0.001$) between centres. The 20 centres were subdivided into those significantly below; those significantly above; or those not statistically significant different from the mean $HbA_{1c}$ value. Three centres had a better ranking compared to 1995; three had a poorer; 14 centres did not change their ranking over this time period.

A low $HbA_{1c}$ level in 1995 was a good predictor for better QOL scores in 1998 in the subscales measuring impact, worries and health perception. Adolescents with lower $HbA_{1c}$ had better QOL scores. Likewise younger patients had better QOL scores. Moreover, high burden of the disease, as rated by parents and health care providers, was associated with higher $HbA_{1c}$ levels.

Lower $HbA_{1c}$ in early adolescence seems to predict better QOL in older adolescents. The nature of the relationship between QOL, the impact of diabetes on families and measures of metabolic control needs continuing careful evaluation.

## O6

**Is metabolic control related to quality of life? A study of 2103 children / adolescents with IDDM from 17 countries**

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An international study was conducted involving 17 countries in Europe, Japan and North America to determine the relationship between metabolic control and quality of life (QOL) for children/adolescents. $HbA_{1c}$ (measured centrally), clinical and demographic data were collected. QOL was assessed in young people using the Diabetes Quality of Life Questionnaire (DQOL), and multi dimensional questionnaires were constructed for parents and health professionals. 2,103 young persons provided blood samples, median age 14 yrs (range 10–18), median diabetes duration 5 yrs (range 0–17), median $HbA_{1c}$ 8.5% (4.8–17.4) and 1979 young persons, parents and professionals completed questionnaires.

The $HbA_{1c}$ increased with age and duration of diabetes for both sexes. The incidence of hypoglycemia resulting in unconsciousness was 16.2/100 patient years. Lower $HbA_{1c}$ levels were statistically related to lower DQOL scores indicating better QOL perceptions.

| HbA1c % | N | DQOL | |
|---|---|---|---|
| | | Mean | Range |
| > 8 | 748 | 98.3 | 55–188 |
| 8–9.5 | 701 | 102.0 | 59–174 |
| > 9.5 | 530 | 105.2 | 59.3–187.0 |

The mean DQOL score for the three subgroups was significantly different ($p = 0.0001$). Younger people (< 15yrs) had lower HbA1c levels, more positive health perceptions, and both parents and health professionals perceived the burden of disease as greater than on older (> 15 yrs) adolescents. High burden, as rated by parent and health professional, was associated with higher HbA1c ($p = < 0.0001$). Older females (> 15 yrs) had both poorer metabolic control and QOL measures than males. Professionals, but not parents, saw burden of disease as higher for this group. This is the first major international evidence that better metabolic control is associated with a better QOL for adolescents and their parents.

## O7

**Complications and health care: Six years post-diagnosis in an incident IDDM cohort in NSW**

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This is a follow-up study of an incident cohort of childhood IDDM, six years after diagnosis. The aims are to determine health care utilisation and complications status and any possible relationships. Between 1990–1992 in NSW, 361 new cases of IDDM under the age of 15 years were identified by two methods of ascertainmenta. 66 cases were identified only by date of birth and region, one had died, 11 had moved interstate and 10 were untraceable.

206 (75% of those contactable) participated in an assessment of diabetes complications and/or health care utilisation. From the total cohort, participants were younger than nonparticipants (14.4 vs. 17.5 yrs, $p = 0.0001$) but were not more likely to come from a rural or urban area.

The median $HbA_{1c}$ was 8.7% [7.9–9.8]. Retinopathy was present in 24% (by stereoscopic fundal photography) and AER > 7.5$\mu$g/min in 21%: total 34% with either or both complications. Multiple logistic regression for either/both complications showed that significant risk factors were older age: OR 1.15 [CI 1.03, 1.29], and higher diastolic blood pressure: OR 1.06 [CI 1.02, 1.10].

At diagnosis, 94% were admitted to hospital, 6% were only seen by a primary care physician. Since diagnosis, 45% had severe hypoglycaemia. In the last 12 months, 25% had been admitted to hospital (78% due to diabetes), 51% had taken time off school due to diabetes and 36% had ketosis.

Those complication-free were more likely to have seen a psychologist at diagnosis ($p = 0.01$), seen a doctor recently ($p = 0.003$), identified high bgl in last 12 months ($p = 0.017$), but spoken to a diabetes educator less frequently in the last 12 months ($p = 0.03$).

34% had evidence of early microvascular complications, but this is likely an underestimate due to the age bias. Complication status was associated in part with less health care utilisation.

[a]Verge CF, Silink M, Howard NJ. 1994, ''Diabetes Care''; 17: 693–696.

*This study was supported by a regional grant from Novo-Nordisk.*

## O8

**Early Onset Type 2 Diabetes (MODY 4)**

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Mutations in genes that regulate development and/or functioning of pancreatic beta cells may be a cause of Type 2 Diabetes Mellitus occurring at a relatively early age and in an auto dominant transmission (MODY). IPF-I is a pancreatic homeodomain transcription factor that regulates early pancreatic development and the expression of beta cell specific genes. Disruption of the IPF-1 in mice results in pancreatic agenesis. We have found in an infant with pancreatic agenesis homozygosity for an inactivating mutation in the exon of the coding sequence of IPF-I (Pro63fsdelC). Both parents have early onset Type 2 diabetes and are obligate heterozygotes for the mutation. The extended family pedigree of the proband has been examined for the mutation. At least one consanguineous loop has been identified. We genotyped 26 family members from 5 generations, 8 of whom had the allele. Of those eight, six had been diagnosed previously with diabetes, and were being treated with diet and/or oral hypoglycemic agents. The average age of onset of their diabetes was 35 years (range 17 to 67 yrs). None of these persons have shown ketosis or required insulin therapy.

We hypothesized that IPF-I mutations could result in abnormal beta cell growth, decreased glucose induced insulin gene expression and/or abnormal expression of GLUT2 and/or glucokinase. Insulin secretion was quantitated with a six-step hyperglycemic glucose clamp. Eleven family members (5 with normal IPF-I genotype and 6 with the mutation) were studied. Subjects with the IPF-I mutation had significantly higher basal glucose levels but similar insulin levels. At each step of the clamp subjects with the IPF-I mutation had significantly reduced insulin responses compared to those with normal IPF-I. We concluded that the IPF-I mutation is associated with severe impairment of insulin secretion and that this mutation segregates with early onset Type 2 diabetes — MODY 4.

## O9

**Maturity-onset diabetes of the young (MODY): A Norwegian experience**

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Maturity-onset diabetes of the young (MODY) is a type of diabetes with autosomal dominant inheritance, onset usually before the age of 25, absence of ketosis, and no absolute insulin requirement. The condition shows clinical and genetic heterogeneity, and at present five genetic subtypes are known, designated MODY1–5. Genetic testing may have practical implications, since the different subtypes vary with respect to late complications. MODY3 (mutation of hepatocyte nuclear factor (HNF)-1$\alpha$) may thus give rise to a more severe phenotype than MODY2 (mutation of the glucokinase gene). We have recently started a research program focusing on the genetic epidemiology of MODY in Norway. By means of a network of interested physicians we have per January 1999 registered some 25 families with clinical MODY. Molecular genetic analyses have so far identified one family with MODY2, three families with MODY3, and one family with MODY5. MODY2 represents a mild diabetes which can be managed without insulin during long periods (Acta Paediatr Scand 1998; 87: 853–856). In one family with MODY3 and a hot-spot mutation of HNF-1$\alpha$ (Diabetologia 1998; 41: 607–608) there was a high prevalence of severe eye complications. A unique family with MODY5 showed the additional findings of severe urogenital malformations, with oligomeganephronia and vaginal aplasia. MODY5, showing mild diabetes or glucose intolerance, represents a novel syndrome with mutation of the transcription factor HNF-1$\beta$.

*Conclusion*: In the course of one year some 25 families with clinical Mody have been registered in Norway. This condition may thus be more common than previously thought. Genetic analyses have so far revealed families with MODY2, 3 and 5.

## O10

**Body composition predicts both insulin secretion and insulin sensitivity (assessed by minimal model) in patients with cystic fibrosis**

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*Background:* The pathophysiology of diabetes mellitus in cystic fibrosis (CF) is still not completely understood, insulin resistance is likely to be involved.

*Methods:* 28 patients with cystic fibrosis (mean age 18.2 years, range 10.3–33.2 years) and 23 control subjects (mean age 22.5 years, range 6–27) were evaluated. Body composition was measured by bioimpedance analysis (RJL Systems, Detroit), insulin secretion and peripheral insulin sensitivity were quantitated by minimal model analysis based on a frequent-sampling tolbutamide-modified intravenous glucose tolerance test (31 simultaneous determinations of insulin and glucose; insulin measured by radioimmunoassay, Pharmacia, Freiburg, Germany). Glucose tolerance was quantitated according to WHO criteria based on a standardized oral glucose tolerance test (1.75 g glucose per kg).

*Results:* Body mass index was significantly lower in CF patients ($18.1 \pm 3$ kg/m$^2$) compared to controls ($22.3 \pm 3$ kg/m$^2$, $p < 0.0001$). The percentage of body fat averaged $15.5 \pm 9\%$ in CF compared to $22.4 \pm 9\%$ in controls ($p < 0.02$). Both basal insulin concentration ($r = 0.51$, $p < 0.005$) as well as insulin release in response to intravenous tolbutamide ($r = 0.50$, $p < 0.01$) were significantly related to body fat content. In addition, body fat was inversely related to insulin sensitivity: $r = -0.61$, $p < 0.001$. This relationship was present irrespective of the degree of glucose intolerance: 15 CF-patients with normal glucose tolerance: $r = -0.56$, $p < 0.03$; 5 patients with impaired glucose tolerance: $r = -0.71$) and 8 patients with diabetes mellitus($r = -0.39$, $p = 0.07$). Insulin sensitivity was significantly lower in CF-patients with impaired glucose tolerance ($8.2 \pm 4.4$) or diabetes ($9.0 \pm 6.1$) compared

to CF-patients with normal glucose tolerance ($14.4 \pm 11.7$) or healthy control subjects ($16.2 \pm 11$; $p < 0.05$). Insulin-independent glucose disposal, $S_G$, was also significantly lower in CF-patients with abnormal carbohydrate metabolism, however this parameter was not related to body fat content or body-mass-index. BMI, body fat content and tolbutamide-stimulated insulin release were not different between CF patients with normal, impaired or diabetic glucose tolerance.

*Conclusions:* These data demonstrate that a high body fat content predicts good insulin secretion in response to sulfonylurea, but low insulin sensitivity. The pathophysiology of diabetes in patients with cystic fibrosis is therefore similar to adults with type-2 diabetes. These findings support the hypothesis that impaired glucose tolerance and diabetes in CF are due to regulatory abnormalities of insulin release in conjunction with reduced insulin sensitivity.

## O11

**Phenotype/genotype correlation and cystic fibrosis related diabetes (CFRD)**

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A genotype/phenotype correlation between the early onset CFRD and N1303K mutation was previously identified in a small series of 28 CFRD patients (pts), attending the Genoa Cystic Fibrosis (CF) Centre (Cotellessa et al, Arch Dis Child, 1996;75:546). In order to confirm the observation, data regarding 141 CFDR pts out of 1229 CF pts attending 14 Italian CF Centres were collected. All the pts were older than 10 years (yrs) and had been genotyped. Mean age at CF diagnosis in the 141 CFRD pts was 6.4 yrs and mean age at diabetes onset was 18.7 yrs. Pancreatic insufficiency was recognised in 135/141 pts. On the basis of WHO criteria we identified two groups of diabetic patients: group A) 75/141 pts (mean age 17.4; range 10–25 yrs) with classic symptoms of diabetes (polyuria, polydipsia, glycosuria and fasting glucose $> 140$ mg/dl); group B) 66/141 pts (mean age 21.1; range 11–42 yrs) with two following abnormal OGTTs. Mean age at diabetes onset was statistically different between group A and B ($p < 0.001$). Gene mutations analysis in the 141 CFRD pts showed that ▲F508 was the most frequent mutation (147/282 alleles: 52%; mean age diabetes onset 17.8 yrs) and N1303K the second most frequent mutation (18/282 alleles: 6.3%; mean age diabetes onset 18.3 yrs), without difference as compared with non-diabetic CF pts (52%vs 48.6% and 6.3% vs 5.1% respectively). W1282X was the third most frequent mutation in CFRD pts (mean age diabetes onset 18.7 yrs), more frequent than in non-diabetic CF pts (5.3% vs 2%; $p < 0.001$). No significant difference was found in mutation frequency between Group A and B. Nearly all identified mutations in our CFRD pts belong to functional classes I, II and III (Welsh et al, Cell 1993; 73:1251): only four alleles with classes IV and V mutations have been identified. Unlike our previous study we did not find a higher frequency of N1303K mutation in CFRD pts or any correlation between N1303K and early onset of CFRD. Data referring to this large CF series showed a significantly higher frequency of W1282X in CFRD pts than in non-diabetic CF pts, without correlation with early onset DM. According to other recent reports, CFRD was associated with classes I, II, III mutations.

## O12

**Strain dependent difference in sensitivity of islets of langerhans to IL-1β — relation to promoter polymorphisms in the inos gene?**

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*Background*: Nitric oxide (NO) may be a necessary but not sufficient mediator of cytokine mediated selective $\beta$-cells destruction. Previously, we have described a NO correlated difference of IL-1$\beta$ sensitivity *in vivo* and *in vitro* of islets from two rat strains, Brown Norway (BN) being more resistant than Wistar Kyoto (WK). This difference was associated with islet NO synthesis. The aim of the study was to i) examine the time-response of IL-1$\beta$ effects *in vitro* of isletsfrom both strains and ii) sequence the iNOS promoter region of these rat strains for polymorphisms.

*Methods*: 150 islets from 5–7 day-old rats of both strains were set up in 300$\mu$l RPMI 1640 + 0.5% HS with 0–150 pgIL-1$\beta$/ml (dose-response) for 2–48 hours (time-response). The incubation media were examined for insulin and nitrite accumulation. Semi-quantitative iNOS mRNA analusis were performed and the iNOS promoter region cloned and sequenced from both strains.

*Results*: *Dose-response* experiments (24 hours IL-1$\beta$ exposure) showed that insulin and nitrite responses to be dose and strain dependent (all $p < 0.02$, 2 way ANOVA). At 15 pgIL-1$\beta$/ml higher nitrite accumulation was seen for WK vs BN ($370 \pm 68{,}1$ vs $284 \pm 102$% of ctr) ($p < 0.05$). *Time-response* (15 pgIL-1$\beta$/ml): Insulin and nitrite responses were correlated significantly with time and strain (all $p < 0.03$, 2 way ANOVA). After 12 hrs of IL-1$\beta$ incubation nitrite was only detected from WK islets vs BN islets ($p < 0.02$). The iNOS mRNA content, expressed as ratio of a house-keeping mRNA ( $\beta$-glycoronidase), was determined after 4, 12 and 24 hours of IL-1$\beta$ incubation with a peak value at 12 hrs for both strains. iNOS mRNA response was significantly correlated to time and strain ($p = 0.0002$ and 0.01, resp., 2 way ANOVA). *Genetic screening*: 2042 bp of the promoter region and exon 1 were cloned from BN and WK. In the 5' end of the cloned promoter region a deletion of 10 bp (WK) and a 'T' (BN) → 'C' (WK) substitution were identified in the same GT-repeat structure. Finally, a 'A' (BN) → 'G' (WK) polymorphism was seen in exon 1 (the 5'UTR of the iNOS gene).

*Conclusion*: BN and WK respond with a different sensitivity to IL-1$\beta$ evaluated *in-vitro* by dose-response and time-re-

sponse. The genetic differences, especially 5' in the iNOS promoter, may have functional implications.

## O13

**HLA-DR, DQ genotype and heterogeneity of Japanese children with IDDM**

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*AIM:* The incidence of IDDM is much lower in Japanese children than Caucasian. Moreover, heterogeneity of IDDM is existed in Japanese, that is many Japanese IDDM children are detected by urine glucose screening at school when they are asymptomatic and progression of symptoms is slow, and is called slowly progressing IDDM. I would like to analyse the heterogeneity of IDDM from the point of HLA genes.

*Materials and methods:* 162 children with diabetes and 97 control are subjects of this study. Diabetic children are divided into 3 groups, that is, A: abrupt and over 5 years of age at onset (n = 102), B: abrupt and less than 5 years at onset (n = 36), S: slowly progressing IDDM (n = 24), and C: controls (n = 97) .HLA-DQA and DQB genes are analysed be direct sequence and DRB gene was analysed using DRB sequencing-based typing kit.

*Results and conclusions*: HLA-DQA-DQB-DRB genotype in group A and B were significantly different from that of control, however, group S were not significantly different from controls. HLA-301-303-901 (R.R. = 4.15), 301-401-405 (R.R. = 3.2), 301-302-803 in group A and 301-303-901 in group B were significantly increased and 102-602-1501, 103-601-1502 were significantly decreased. HLA-DQA-DQB-DRB genotypes in group A and B were either DQA(R)-DQB(nD)-DR(D) or DQA(R)-DQB(D)-DRB(nD). HLA genotype in group S was some what different from abrupt onset type and age dependent HLA genotypes exist in abrupt onset.

## O14

**Antibodies to tissue transglutaminase predict latent coeliac disease in children with diabetes mellitus**

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*Background*: Tissue transglutaminase (tTG) has been recently identified to be the main endomysial autoantigen of coeliac disease (CD). We studied the clinical significance of the determination of antibodies to tTG for the prediction of latent CD in patients with diabetes, since the association of these disorders is well documented.

*Methods* Five hundred and twenty diabetes patients (age: 14 (2–27) years; diabetes-duration: 4 (0–24) years) without IgA-deficiency were tested for IgA antibodies to tTG (ELISA) and to endomysium (EmA, indirect immunofluorescence). Patients with elevated anti-tTG antibodies were additionally tested for IgA and IgG antibodies to gliadin (AGA).

*Results*: The prevalence of anti-tTG antibodies among patients with diabetes was 4.4% (23 of 520). Positive EmA were found in 18 of 520 patients (3.5%). None of anti-tTG negative patients was positive for EmA. Three of 23 tTG positive patients had a known CD. Ten of the remaining patients without clinical symptoms of CD underwent small bowel biopsy: Six of them had CD (one patient was negative for EmA and AGA), while classical histological findings for CD could not be found in 4 cases (two patients EmA negative, two EmA positive, all AGA negative).

*Interpretation*: These data show that antibodies to tissue transglutaminase are a helpful tool for screening latent coeliac disease in patients with type 1 diabetes mellitus. Small bowel biopsy, however, remains necessary to confirm the diagnosis, as some patients may be false positive.

## O15

**Elimination of transplacentally transferred antibodies associated with type 1 diabetes in infants of affected families**

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To study the elimination of transplacentally transferred antibodies we enrolled 101 mothers and their newborn infants from families with type 1 diabetes; the infants had in addition an increased HLA-defined risk for the disease. Thirty-five of the 101 infants (34.7%) had disease-associated antibodies in their cord blood. Follow-up samples were taken at the ages of 3, 6, 9, 12, 18 and 24 months. Eighteen of the 35 newborn infants tested positive for islet cell antibodies (ICA) in cord blood with a median of 12.5 JDF units (range 5–130), 15 for GAD antibodies (GADA) with a median of 40.3 RU (range 5.57–303), 14 for IA-2 antibodies (IA-2A) with a median of 6.58 RU (range 0.48–89.1), and 25 for insulin antibodies (IA) with a median of 0.66 RU (range 0.16–28.1). The mean elimination time for ICA was 3.6 months (range 1.5–10.5), for GADA 5.1 months (range 1.5–15.0), for IA-2A 4.3 months (range 1.5–9.0) and for IA 3.1 months (range 1.5–7.5). The initial levels of ICA, GADA, IA-2A and IA in cord blood correlated closely with the elimination time ($r = 0.77 - 0.94$; $p < 0.001$). At the age of 3, 6 and 9 months seven, four and one of the infants had ICA with levels corresponding to 19.1%, 6.1% and 0.3% of the initial level. The corresponding numbers of GADA-positive infants up to the age of 12 months were nine, four, three, and one with antibody levels accounting for 34.0%, 13.0%, 2.8%, and 1.1% of the initial titer. IA-2A positivity was detected at the age of 3 and 6 months in nine and three infants with antibody levels amounting to 18.2% and 6.0% of the initial ones. Nine infants tested positive for IA at 3 months and four at 6 months with antibody titers comprising 22.4% and 7.0% of the initial levels. A higher proportion of ICA was eliminated at the age of 3, 6 and 9 months than that of GADA ($p < 0.02$ or less) and IA ($p < 0.04$ or less). In addition the eliminated ICA proportion was higher than that IA ($p < 0.005$ or less) at 6 and 9 months of age. There was no statistical difference in the elimination

rate between other antibodies. GADA seemed to persist longer, and the only antibody still detectable at the age of 1 year was GADA (3.2 RU) in one infant with one of the highest initial levels (212 RU). We conclude that most of the transplacentally transferred antibodies associated with type 1 diabetes are eliminated from the peripheral circulation of the infant before the age of 9 months, but occasionally they might persist up to the age of 1 year, which has to be taken into account when planning strategies for screening infants for signs of beta-cell autoimmunity.

## O16

**The first signs of beta-cell autoimmunity appear in infancy in the general population: The Finnish Dipp study**

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To monitor the appearance of diabetes-associated autoantibodies and the development of type 1 diabetes in young children we observed from birth 2448 infants with increased genetic risk for the disease (high risk: HLA DQB1*02/0302, n = 548; moderate risk: DQB1*0302/x, x other than *0301 or *0602, n = 1900) at intervals of 3–6 months. Islet cell antibodies (ICA) were used as the primary screening tool in this population-based study. If an infant seroconverted to ICA positivity, all his/her samples were analyzed also for autoantibodies to insulin (IAA), GAD65 (GADA) and the IA-2 molecule (IA-2A). Transplacentally transferred antibodies were excluded from this analysis. Fifteen infants (2.7%) tested positive for ICA at least once during the period of follow-up among those who carried the high risk genotype, while 23 (1.2%; $p = 0.019$) of those with the moderate risk genotype had ICA. Altogether 694 children were observed up to the age of 2 years, and 15 of them (2.2%) tested positive for ICA at that age. Six of those 38 children (16%) who tested positive for ICA developed type 1 diabetes before November 1998, and all of them tested positive for at least two autoantibodies 0.1–1.5 years before the diagnosis. The first autoantibodies were detected at the age of 0.5–2.3 years (mean 1.2 yr.). Two thirds of those who tested positive for ICA (25/38) had at least two antibodies detectable during the observation period. In this group IAA appeared earlier than ICA ($p = 0.002$), GADA ($p = 0.019$) and IA-2A ($p < 0.001$), and both ICA ($p = 0.007$) and GADA ($p = 0.049$) appeared earlier than IA-2A. Eight of the 38 antibody-positive children reconverted to antibody negativity; all of them had tested positive for ICA only. These data indicate that carriers of the high risk genotype identified from the general population show signs of beta-cell autoimmunity in infancy proportionally more often than those having the moderate risk genotype. The diabetes-associated autoantibodies emerge in no predetermined order, but IAA appear first more commonly than the other antibody specificities

## O17

**Feasibility of a randomized double-blind trial aiming at avoidance of cow's milk in infancy: the TRIGR project**

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The overall aim of the project is to determine whether avoidance of nutritional cow's milk proteins (CMPs) for at least the first 6 months of life reduces the incidence of type 1 diabetes in children at high risk of developing the disease. Here we report about the feasibility of the second pilot study performed in 15 hospitals in Finland. Genetically high risk newborn infants (first degree relative with type 1 diabetes and positive for HLA DQB1*0302 and/or DQB1*02, but negative for DQB1*0602,*0603, and *0301) were randomized to the intervention (n = 114) and control groups (n = 120). After full breast-feeding the intervention group received a casein hydrolysate and the control group a CM containing formula until the age of 6–8 months. Out of 234 infants who started the study 34 (15%) had dropped out from the study by the age of 8 months. Right after the birth of the child the families received both written and oral advice to avoid CM products and beef in the diet of the child until the age of 6–8 months. The advice was repeated during the visits to the clinic at the ages of 3 and 6 months. The maternal diet both during pregnancy and lactation was studied by a validated food frequency questionnaire. Child's diet was assessed by 3-day food record and a structured questionnaire at the ages of 6, 12, and 24 months. The families recorded deviations from the advised diet and age at introduction of new foods. The duration of total breast-feeding was longer in the intervention group than in the control group (8.1 vs. 7.2 mo, $p < 0.01$). The age at introduction of supplementary milk feeding was higher in the intervention group (3.3 vs. 2.2 mo, $p < 0.01$). On the average the children in the intervention group had used formula for 4.0 months compared to 4.7 months in the control group ($p < 0.05$). Twelve percent were not exposed to the study formula at all, and 5% had used it for less than 2 months. Of the families, 19% reported deviations from the advised diet on an average 1.7 times. To conclude, the study gave a realistic picture of the requirements of a dietary intervention study in infants and provided valuable guidance for the planning and the sample size estimation in the study proper.

## O18

**Eating disorders (ED) are more common in adolescent females with type 1 diabetes (DM)**

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Available data suggest that eating disturbances are common and persistent in adolescent females with DM, are associated

with poor metabolic control and early onset of microvascular complications. Controversy remains whether the presence of DM is associated with an increased frequency of ED because previous studies have lacked statistical power to detect clinically important differences between teens with and without DM.

We conducted a cross-sectional study to determine the prevalence of clinical (DSM-IV) and sub-threshold ED in 361 adolescent females with DM from 3 centers (Toronto, Ottawa and Hamilton, ON) and 1123 age-matched controls recruited from local schools. ED status was determined by self-report measures and a standardized diagnostic interview, the Eating Disorders Examination. Metabolic control was assessed in the DM group by HbA1c levels (mean ± SD 8.9 ± 1.7%). Mean ± SD age of the total cohort was 15 ± 2 yr.

DSM-IV ED were significantly more prevalent among subjects with DM (10.2%) than in the controls (4.8%, p = 0.0001). Sub-threshold ED were also more common in the DM adolescents (12.4%) than controls (6.5%, p = 0.0001). Subjects with DM had a higher mean BMI than controls (22.7 ± 3.8 vs 20.6 ± 3.3, p = 0.0001). DM subjects with either clinical or sub-threshold ED were older at diagnosis of DM (p = 0.002) and at the time of study (p = 0.003) than the nonED DM subjects. HbA1c was higher in those with clinical ED than in the nonED DM group (9.5 ± 2.1 vs 8.8 ± 1.7%, p = 0.05). Insulin omission or underdosing to control weight was reported in 11.4% of those with DM, similar to that reported previously in this age group.

We conclude that (i) both clinical and sub-threshold ED are significantly more common in adolescent females with DM than in their nondiabetic peers; and (ii) metabolic control is impaired in those with a clinical ED. These data suggest that DM or its management plays a role in either the initiation or maintenance of eating disturbances in susceptible adolescent females.

## O19

**Relationship between ambulatory and conventional blood pressure readings in adolescents with type 1 diabetes**

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*Background*: 24-hour ambulatory blood pressure monitoring (ABPM) is increasingly used for detecting hypertension in patients with diabetes, and assessing the efficacy of treatment. It allows identification of patients with ''white coat'' hypertension and can also provide additional information about diurnal variation in blood pressure (BP) and heart rate variability. It has been suggested that ABPM predicts end organ damage better than conventional measurements. However its full benefits are still being studied, in particular whether it has advantages over standards readings preformed in the clinic.

*Aim of this study*: To compare BP readings using a sphygmomanometer with Dinamap readings and daytime readings obtained using ABPM.

*Methods*: The group studied comprised 20 normotensive, normotensive patients with type 1 diabetes and 30 patients with microalbuminuria matched for age, sec and duration of diabetes. Each subjects had a standard clinic sphygmomanometer reading recorded under normal clinic conditions by their usual physician. Dinamap readings were recorded as the mean of 5 readings after 5 minutes supine rest. Each subject underwent 24 hr ABPM with mean daytime readings used for comparison.

*Results*: Clinic systolic BP readings were lower than both Dinamap and daytime ABPM readings. Clinic diastolic BP readings were also lower than ABPM readings, but Dinamap diastolic readings were lower than both. These trends in BP readings were identical for both normoalbuminuric patients and those with microalbuminuria, although the latter group had higher mean BP readings as would be expected.

| | Clinic BP | Dinamap | ABPM | p |
|---|---|---|---|---|
| SystBP (mmHg) | 120.4 ± 16.3 | 126.4 ± 13.0 | 127.2 ± 8.8 | 0.03 |
| DiastBP (mmHg) | 71.8 ± 2.2 | 67.6 ± 2.7 | 74.7 ± 2.0 | < .001 |

*Conclusions*: Clinic BP readings using a sphygmomanoneter appear to underestimate blood pressure. Dinamap readings underestimate diastolic BP. ABPM may provide a more accurate picture of BP burden, as well as allowing detection of loss of diurnal variation. This information is particularly important when deciding to treat patients with microalbuminara.

## O20

**NAT2 polymorphism, smoking and Type 1 diabetic nephropathy**

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*N*-acetyltransferase (NAT2) polymorphism has been suggested to be related to diabetic microvascular complications. To study the distribution of *NAT2* genotypes in Caucasian Type 1 diabetic patients with and without diabetic nephropathy, 214 adult Type 1 diabetic patients and 53 healthy subjects were genotyped by PCR-RFLP. In addition, 75 young Type 1 diabetic patients were genotyped, and 70 of them also phenotyped by caffeine. Of the adult patients, 83 had normal albumin excretion, 58 had microalbuminuria, and 73 had overt diabetic nephropathy. *NAT2* allele frequencies were similarly distributed between the diabetic patients and healthy controls: 0.29/0.25 (*NAT2*4*), 0.03/0.04 (*NAT2*7B*), 0.25/0.27 (*NAT2*6A*), and 0.43/0.44 (*NAT2B*), and also within the diabetic subgroups. Because smoking is a known risk factor for diabetic nephropathy, non-smoking and smoking patients were analysed separately. NAT2 allele frequencies differed significantly between the non-smoking normoalbuminuric, microalbuminuric and nephropathic patients: 0.18/0.41/0.30 (NAT2*4), 0.04/0.00/0.02 (NAT2*7B), 0.35/0.18/0.17 (NAT2*6A), 0.43/0.41/0.50 (NAT2*5B), $p = 0.013$, Chi-Square test. In non-smoking fast acetylators the odds ratio for microalbuminuria and nephropathy was 3.1 (95% CI 1.36–7.05), $p = 0.007$ by logistic regression. In smokers a

non-significant odds ratio was found [0.31 (95% CI 0.08–1.2), $p = 0.09$]. Smoking is a strong confounding factor in relation to *NAT2* analyses and diabetic nephropathy. According to our data, in non-smoking Type 1 diabetic patients a fast acetylation capacity implies an increased risk for diabetic nephropathy.

## O21

**Microalbuminuria: Experience from the Danish nation-wide studies**

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In 1989 a nation-wide screening for microalbuminuria was performed in 22 paediatric departments with participation of 957 Danish children and adolescents with Type 1 diabetes, age 2 to 19 years and mean diabetes duration of 6 years. Median $HbA_{1c}$ was 9.6% and the prevalence of persistent microalbuminuria was 4.3%. Microalbuminuria was extremely rare before puberty and in our study only two girls were diagnosed.

Several previous reports have suggested a relationship between poor blood glucose control and increased urinary albumin excretion. We found that only females with microalbuminuria had significantly elevated $HbA_{1c}$ values compared to diabetic patients with normoalbuminuria. The normal range for diastolic blood pressure in diabetic boys and girls aged 8 to 18 years with normoalbuminuria was determined. Sixty percent of adolescents with microalbuminuria had diastolic blood pressure in the upper quartile for normoalbuminuria.

A cohort of 353 children, included in the nation-wide investigation in 1989 has been followed for 6 years with assessment of metabolic control and development of diabetic nephropathy in 1995. Median $HbA_{1c}$ was 9.7% and elevated AER ($> 20\mu g/min$) was diagnosed in 12.8% of these patients, mean age: $20.7 \pm 3.3$ years and mean diabetes duration: $13.2 \pm 3.2$ years. Risk-factors for elevated AER (1995) were high AER ($p < 0.001$) (1989) and high $HbA_{1c}$ (1989) ($p < 0.001$). Raised urinary albumin was not markedly dependent on diabetes duration .In the period 1989 to 1995 11.4% of the normoalbuminuric patients developed elevated albumin excretion rate ($> 20\mu g/min$), corresponding to an annual incidence of microalbuminuria of 1.4%. Of the patients with microalbuminuria in 1989 40% were still microalbuminuric in 1995 while 60% had returned to normal albumin excretion rate and half of the macroalbuminuric patients were still macroalbuminnuric in 1995 while the other half had returned to normal albumin excretion rate. None of the patients received anti-hypertensive medication.

During the past 9 years a declining incidence of microalbuminuria has been observed in children and adolescents in Denmark. In 1998 results from the Danish Registry of Childhood Diabetes (covering 211 children, approximately 35% of all aged 9–18 years) showed that median $HbA_{1c}$ was reduced to 8.7% and only two patients had microalbuminuria (0.9%).

The prevalence of elevated AER seem to decrease in young Danish patients, presumably due to improved metabolic control in this age-group. The simultaneous remittance rate of micro- and even macroalbuminuria seems to be high and long-term follow up studies are required to evaluate whether intervention at an early stage with ACE-inhibitors is indicated in children with elevated AER.

## O22

**Outcome measures while on continuous subcutaneous insulin infusion (CSII) in pediatrics**

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The purpose of the present study was to determine outcome of 89 pts who have been placed on CSII; mean age $15.9 \pm 3.6$ yrs, mean duration of diabetes was $7.8 \pm 4.3$ yrs. Reasons for insulin pump initiation include diabetes control, flexibility/lifestyle change, insulin regimen mis-matching, insulin resistance, dawn phenomenon, complications, pregnancy and recurrent hypoglycemia. The computerized outcome system in our center has been designed to manage physical health/control, risk factors/complications, education/function, psychosocial/behavioral, resource utilization/cost and satisfaction parameters. Each domain is further analyzed through the use of an Outcome Research Model (descriptions → associations → intervention research → risk profiling/prediction modeling) with subsequent strategies to advance practice. Physical health and diabetes control showed that mean annual $HbA_{1C}$ prior to CSII was $8.3 \pm 1.6$ and $7.9 \pm 1.2$ after initiation ($p < 0.05$). Associations with improved $HbA_{1c}$ included age ($p < 0.01$), knowledge ($p < 0.001$), integration ($p < 0.05$) & family behavior ($p < 0.02$). Risk factors/complications since initiation of CSII yielded 8 recurrent DKA hospitalizations (0.02 events/pt/yr), 2 ER visits (0.005 events/pt/yr) and 1 severe low blood glucose events (0.002 events/pt/yr). Education/function showed that mean competencies of pump pts was 6.9 (0–8 score) and mean knowledge score of 87% ± 11. Psychosocial/behavioral measures administered included adherence (mean $78 \pm 9$, NS), integration (mean $88 \pm 11$ $p < 0.05$), family behavior (mean $69 \pm 10$, $p < 0.02$), and quality of life (mean 4.0, NS). Significant changes in measures before and after CSII were in satisfaction ($p = 0.02$) and knowledge ($p = 0.04$). Resource utilization/cost for 1998 included mean of $3.0 \pm 0.5$ clinic visits/yr, $3.0 \pm .05$ nursing visits/yr and $1.0 \pm 0.25$ dietary visits/yr. Incidences of DKA, ER visits and severe low BG events (above) are below national and center benchmarks. 82% of pts used the phone/FAX service. Mean satisfaction score was 4.6 (0–5 scale). These data suggest that CSII can decrease HbA1C in pediatric type 1 pts. Knowledge and satisfaction increase with CSII; adherence is not as critical with CSII. Behavioral programs geared to improve integration of diabetes along with advanced home management education programs should be developed and evaluated to advance diabetes outcome in pediatric pts with CSII.

## P1

**Carnitine and myocardial functions in diabetic children**

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It is well known that carnitine may have an effect on