

### O-1

#### **Dietary patterns among infants in a dietary intervention trial for primary prevention of type 1 diabetes**

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**Introduction:** The present international, randomised, double-blinded trial tests the hypothesis whether weaning to a highly hydrolysed infant formula compared to cow's milk based formula decreases the risk of developing type 1 diabetes in children with increased genetic disease susceptibility.

**Aim:** Within the project we also collect information on breastfeeding and diet of the infants for future analyses when end points are available. Here we describe the dietary patterns in the infants during the first 6 months of life.

**Methodology:** During the first 6–8 months of life the infants are given study formula when additional milk is needed. Foods containing cow's milk and beef are avoided during this period. Otherwise the children follow national dietary recommendations. Dietary interviews are conducted every month during the intervention. The data collected by the end of March 2005 were used for this analysis (between 909 and 1196 subjects for each age point).

**Results:** At 2 weeks of age 98% of the children were breastfed and 34% exclusively breastfed, at 3 months 76% and 24%, and at 6 months 65% and 4%, respectively. Exclusive breastfeeding continued longer among European than North American participants ( $p < 0.001$ ). At 4 months of age 35% of the children received complementary foods in addition to breast milk and/or infant formula, and 88% at 6 months. At 6 months of age 73% of the children received vegetables, 72% fruit, 66% gluten-free cereals, 50% gluten-containing cereals, 32% meat and 11% fish. In Europe the first foods to be introduced were typically vegetables and fruits, whereas in North America gluten-free cereals were introduced first.

**Conclusion:** More than 60% of the subjects were breastfed for at least 6 months. Complementary foods were introduced earlier than currently recommended, and differences between European and North American participants were observed.

### O-2

#### **Predictive value of diabetes-associated autoantibodies in young children with increased HLA-conferred susceptibility to type 1 diabetes recruited from the general population**

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**Introduction:** This study aimed at assessing the predictive characteristics of autoantibodies in a cohort of young children recruited from the general population based on HLA-conferred susceptibility to type 1 diabetes (T1D).

**Aim:** See above.

**Methodology:** We observed from birth 7906 children (4391 boys) with HLA-defined predisposition to T1D at 3–12 months intervals for the appearance of signs of beta-cell autoimmunity with ICA as the primary screening tool. Follow-up continued for an average of 7.2 years. If a child seroconverted to ICA positivity, IAA, GADA and IA-2A were also measured in all previous samples. Persistent antibody positivity was defined as positivity in at least two consecutive samples including the last sample available.

**Results:** 757 children (9.6%) tested at least once positive for ICA, 236 (3.0%) for ICA + IAA, 220 (2.8%) for ICA + GADA and 197 (2.5%) for ICA + IA-2A. 215 (2.7%) had at least once three autoantibodies, and 124 (1.6%) all four antibodies. 348 (4.4%) were persistently positive for ICA and 271 (3.4%) for at least two antibodies. 163 (2.1%) had persistent positivity for at least three autoantibodies and 71 (0.9%) for all four autoantibodies. One hundred four children (50 boys, average age at diagnosis 5.5 years) progressed to T1D during the observation period. ICA had a sensitivity of 94.2%, a specificity of 91.6% and a positive predictive value (PPV) of 12.9% for T1D. Positivity for four antibodies had the highest specificity (99%) among antibody combinations, while ICA + IAA + GADA had the highest PPV (39%). For persistent autoantibody positivity the highest specificity was observed for positivity for all four antibodies (99.5%) and the highest PPV for positivity for ICA + IAA + IA-2A (46.9%).

**Conclusion:** More than 94% of future patients with T1D can be identified with ICA screening among young children with HLA-conferred disease susceptibility. Persistent positivity for all four autoantibodies is associated with the highest predictive sensitivity (99.5%), while persistent positivity for the combination of ICA + IAA + IA-2A provides the highest 5-year PPV (46.9%).

### O-3

#### **Glucose intolerance and diabetes mellitus in 1334 patients with cystic fibrosis (CF)**

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**Introduction:** Impaired carbohydrate metabolism is frequent in patients with cystic fibrosis, however few studies address the prevalence in a large-scale multicenter approach. In Germany and Austria, the CF-diabetes-study group recommends yearly screening by oral glucose tolerance test (WHO-criteria) starting age 10.

**Aim:** Evaluate the frequency of IGT and DM in CF patients.

**Methodology:** By April 2005, a total of 2646 OGT-tests in 1334 CF patients was available for analysis.

**Results:** Based on the most recent OGT-test, 945 patients displayed normal glucose tolerance (70.8%, mean age 19.8 years), 127 were classified as impaired glucose tolerance (9.5%, 21.7 years), 73 as impaired fasting glucose (5.5%, 20.9 years), 31 displayed both IFG and IGT (2.3%, 25.3 years) and 136 patients had a diabetic oral

glucose tolerance test (10.2%, mean age 21.9 years). 58.1% of diabetic patients were female, compared to 46.2% in NGT. CF patients with diabetes were significantly more underweight (SD-Score  $-1.32 \pm 0.11$ ) compared to the other groups (NGT:  $-0.91 \pm 0.04$ ,  $p < 0.05$ ). Kaplan-Maier-analysis revealed that the median age for the first pathologic OGT-test was 26.2 years (1st quartile: 17.3 years) with no difference between boys and girls. However, diabetes occurred significantly earlier in female patients compared to males: Two independent diabetic OGT-tests were present in a quarter of female patients by age 29.7, compared to 35.3 years in male subjects. By age 18, diabetes was diagnosed in 12.5% of female compared to 4.1% of male CF subjects based on two diabetic OGT-tests.

**Conclusion:** In summary, this prospective, large, multicenter study demonstrates that impaired carbohydrate metabolism and diabetes are common consequences of cystic fibrosis occurring during adolescence and adulthood. Girls are affected earlier in life compared to boys. Pediatric diabetologists have to be aware of the unique features of this secondary form of diabetes. These data represent the screening phase of a prospective intervention study comparing insulin therapy to oral repaglinide in CF diabetes.

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#### O-4

##### Kir6.2 mutations search in patients with permanent neonatal diabetes from a Polish population

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**Introduction:** Activating mutations in the KCJN11 gene encoding Kir6.2, the ATP-sensitive potassium-channel subunit have been recently described in patients with permanent neonatal diabetes (PND).

**Aim:** To examine the contribution of KCJN11 mutations to PND in patients from Poland.

**Methodology:** We sequenced the KCJN11 gene in 7 insulin treated, diabetic patients diagnosed before 6 months (range 1–26 weeks).

**Results:** We identified three patients with de novo heterozygous missense mutations. Two males, (Pol1 and Pol2) carried the previously described R201H mutation and one female (Pol3) diagnosed at 26 weeks was a carrier of novel mutation R50Q. All three subjects with Kir6.2 mutations presented with severe hyperglycemia at the diagnosis (30–50 mmol/l). There was evidence of clinical heterogeneity: the age of diagnosis was 2, 3 and 26 weeks in Pol1, Pol2, Pol3 respectively; all were born at term with birth weights of 2450, 2700 & 3000g and insulin requirements varied 0.25, 0.68, 0.1 U/kg. All three patients were successfully transferred to sulphonylurea therapy. In Pol1 and Pol2 case we used controlled-release glipizide GITS (gastrointestinal therapeutic system). For Pol1 5mg of glipizide was used, while Pol2 daily requirements was 30mg. Pol3 was well controlled on 0.5mg of glimepiride.

**Conclusion:** We summarize that Kir6.2 mutations are a common cause of PND in European Caucasians and provided the evidence of clinical heterogeneity between mutation carriers. The clinical results are consistent with the novel mutation R50Q being less severe than R201H although variation between patients with R201H suggest there may be other genetic or environmental moderators of phenotype. We report the first successful initial transfer of three patients from insulin to long-acting sulfonylureas (glimepiride and sustained-release glipizide).

#### O-5

##### Clinical and genetic heterogeneity in six Italian children with wolfram syndrome

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**Introduction:** Wolfram syndrome (WS) is an autosomal recessive neurodegenerative disorder characterized by juvenile, non autoimmune, diabetes mellitus, optic atrophy, diabetes insipidus and deafness also identified by the acronym 'DIDMOAD' (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness).

**Aim:** To evaluate clinical and genetic heterogeneity in six Italian children with WS.

**Methodology:** Wolfram gene (WFS1) mutation analysis was performed in 4 unrelated and 2 related Italian children without pathogenic mtDNA point mutations nor deletions. Clinical diagnosis of WS was sustained by the occurrence of juvenile-onset (age < 20 years) diabetes mellitus, optic atrophy and deafness. Mutation screening revealed a total of five distinct variants, including 4 novel mutations (1519del 16, S443I, IVS6 + 16G → A, T416I), one new neutral change (R708C) and one previously described variant (H611R).

**Results:** Case 1, a 18-year-old girl, with DM, OA, hydronephrosis, carried the homozygous 16-bp deletion (1519del 16), an out-of-frame deletion resulting in premature stop codon at residue 454, removing the last 437 amino acids and one neutral change (R708C). Case 2, a 20-year-old boy, with DM, OA and hearing loss, carried a compound heterozygous, a missense mutation (S443I) and an intronic mutation (IVS6 + 16G → A) which could result in abnormal splicing of messenger RNA and one previously described variant (H611R). Case 3, a 18-year-old boy, with DM, OA, hydronephrosis, cerebellar and brain stem atrophy, carried the homozygous 16-bp deletion (1519del 16). Case 4, a 16-year-old girl, with DM, OA, DI and hearing loss carried the homozygous deletion (1230del CTCT). Case 5, a 14-year-old girl and her sister, Case 6, a 11-year-old girl, both with DM, OA and hearing loss, carried the homozygous mutation (T416I).

**Conclusion:** All the mutations identified were allocated in the exon 8, corresponding to the transmembrane region of wolfram protein. In this location mutations recur most frequently. Each of these mutations has presumably pathogenic consequences for WFS1 structure and function protein, so explaining clinical heterogeneity.

#### O-6

##### HLA-DQ2 and TNF-alpha promoter G308A are associated with increased risk of celiac disease in type 1 diabetic children

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**Introduction:** The reason for the increased prevalence of celiac disease (CD) in individuals with type 1 diabetes mellitus (T1DM) is still incompletely understood. Apart from the influence of ongoing diabetic autoimmunity, the cause may lie in the genetic susceptibility factors shared by the two diseases. The overlap between CD and T1DM genetic susceptibility is not complete; therefore some

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genetic polymorphisms may significantly modify the risk of CD in diabetic subjects. Our aim was to investigate whether the susceptibility to CD in diabetic children is influenced by HLA-DQ2 and DQ8 positivity and by alleles of single nucleotide polymorphisms within the TGF-beta, TNF-alpha, IL-1, IL-10, and gamma-IFN genes.

**Methodology:** The genotypic data were compared between 141 cases (diabetic children with CD diagnosed using endomysium antibodies and confirmed by small bowel biopsy) and 252 controls (children with T1DM only, mostly two per case, matched for center, age-at-T1DM onset, and duration of diabetes). The subjects were recruited from ten major European pediatric diabetes centers where screening for CD is regularly performed. The polymorphisms were typed using PCR with sequence-specific primers, and the risk was assessed by building a stepwise conditional logistic regression model using variables which were significantly associated with CD in the univariate analysis.

**Results:** The best fitted model included HLA-DQ2 (OR = 2.74, CI 95% 1.43–5.24) and TNF-alpha -308 A (OR = 1.69, CI 95% 0.96–2.99), independently increasing the risk. Neither of the remaining investigated factors modified the risk.

**Conclusions:** The results indicate that the risk of CD disease in children with T1DM is significantly modified by positivity both for HLA-DQ2, and for a variant of another gene within the MHC, the TNF-alpha-308A. We decreased the likelihood of biases by matching for potentially confounding factors, particularly for the duration of diabetes, and by the large size of our multinational sample.

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### 0-7

#### There is a continuous increase of type 1 diabetes in Denmark

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**Introduction:** There is a worldwide increase of type-1-diabetes. In 1996 The Danish Childhood Diabetes Register was established. It is a nation-wide register collecting data from all Danish pediatric diabetes centers treating type-1-diabetic patients aged 0–15 years. All newly diagnosed type-1-diabetic patients <15 years have been enrolled since 1996.

**Aim:** To describe the incidence during the first 8 years.

**Methodology:** In the Danish health care system, all children aged 0–15 years with suspected type 1 diabetes are referred to a pediatric department. Since 1 January 1996, all hospitalized incident cases have been reported on a special form containing information about

the patient's personal identification number, sex, county of residence, place of birth, nationality, and date of diagnosis (i.e., date of first insulin injection). Data were validated against the national discharge register. Population data were obtained from Statistics Denmark.

**Results:** A total of 1661 children with diabetes before <15 years were diagnosed 1996–2003. There were 858 boys and 803 girls. The incidence level differed significantly across counties and there was a tendency towards a different increase in the different counties ( $p = 0.052$ ). The mean increase in incidence per year was 2.6% (CI 0.8–4.5%). However no statistical different increase per 5 year age group and between sexes were observed. Analysis of the increasing incidence showed no escape from linearity, thus period and cohort effect could not be separated.

**Conclusion:** There is a continuous increase of type-1-diabetes in Denmark and the increase seems to be steeper than reported earlier. The incidence level and the incidence increase vary between counties.

### 0-8

#### Multiple sclerosis and celiac disease patients similar to childhood type 1 diabetes have an abnormal seasonality of birth

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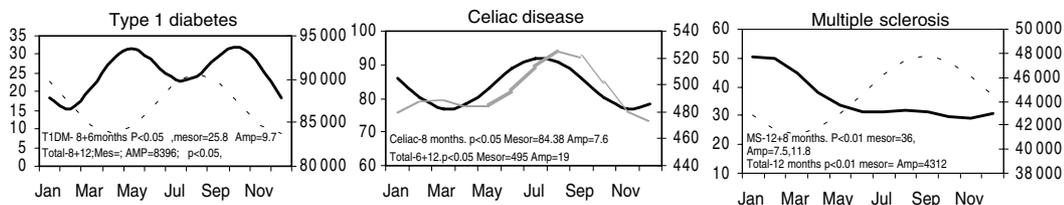
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**Introduction:** In the last 30 years a steep and almost parallel rise in the incidence of childhood Type 1 diabetes mellitus (CT1DM), multiple sclerosis (MS) and celiac disease (CD) was registered. This is attributed to environmental factors. All are auto-immune diseases.

**Aim:** As the association between CT1DM and CD or MS is frequent our aim was to find a common denominator.

**Methodology:** We studied the month of birth seasonality and rhythmicity in patients with CT1DM from Israel ( $n = 1865$ ), Europe ( $n = 11802$ ), USA ( $n = 4509$ ), Australia ( $n = 621$ ) and New Zealand ( $n = 275$ ); 966 patients with CD from the US and 2621 patients with MS from Israel and Sardinia. Data from the National Regional Bureau of Statistics of the respective countries served as controls. Statistical analysis was performed using the Cosinor fit and t-test between 4 yearly seasons.

**Results:** We found a different pattern of month of birth than that in the general population in young diabetics from ethnically homogeneous populations, in MS patients diagnosed below age 20 and in celiac patients without distinction of age.



**Conclusion:** The different seasonality of birth can be explained by a virus transmission from the mother to the fetus or newborn during viral epidemics and initiation of the autoimmune process in

utero or perinatally in the genetically unprotected individual. It remains to be found out whether the three diseases have the same viral trigger.

0-9

### The mortality of children and adolescence with diabetes in Denmark. A population based study

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**Introduction:** Childhood type 1 diabetes is increasing worldwide, and even though treatment has improved, there is still an excess in mortality. In former Danish studies a mortality of 0.9% was found, but there are no studies of mortality in Danish diabetic children based on a population based register. In 1996 a Danish Diabetes Register was established including all children with onset of diabetes before the age of 15, the results are reported in the EURO-DIAB study.

**Aim:** To determine the Standardised Mortality Ratio (SMR) amongst children and adolescence diagnosed with IDDM.

**Methodology:** In Denmark all individuals have a unique identity number, making it possible to combine information from several registers. Data from the diabetes register were combined with information from: 1. the centralised civil register which obtains information on death, disappearance and immigration, 2. The Danish death certificate register. From the Danish Statistics we obtained information about mortality, which was used to calculate the expected deaths in the different age groups.

**Result:** There were 2696 individuals included in the study, of whom 22 had died before December 2004. Four of the 22 died from diabetes, three of them at onset. The SMR were found to be 3.17 (CI 1.61–6.23), with the highest excess mortality in the age group of 0–4. The number of deaths was too small to detect any differences in mortality between genders at years of onset.

**Conclusion:** There is a 3 times higher mortality amongst children with IDDM in Denmark, compared to the childhood population mortality. The mortality seems to be somewhat higher than the countries we normally compare ourselves to.

0-10

### 'Sweet Talk' text messaging support to facilitate uptake of intensive insulin therapy

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**Introduction:** Intensive insulin therapy (IIT) is recommended to improve glycaemic control in young people with T1D. However, a substantial support package is necessary for successful implementation. Traditional support by health professionals is costly and time consuming.

**Aim:** 'Sweet Talk' is a text-messaging behavior intervention developed to support patients to increase self-efficacy, thereby increasing adherence to IIT and improving glycaemic control.

**Methodology:** Patients aged 8–18 years, on conventional insulin therapy (CIT) and with T1D for >1 year (n = 126) were invited to participate in the 'Sweet Talk' RCT. 92 patients were randomly allocated to Group 1 (control, n = 28), Group 2 (CIT and 'Sweet Talk', n = 33) or Group 3 (IIT and 'Sweet Talk', n = 31). Patients in Groups 2 +3 'contracted' self-management goals in clinic and these goals were reinforced with personalised daily text messages.

**Results:** 'Sweet Talk' combined with IIT was associated with significantly improved glycaemic control (mean HbA1c reduction of -1.1% after one year adjusted for baseline) compared with Groups 1 and 2, which showed a deterioration in glycaemic control (rise in HbA1c of 0.1 and 0.3%): p = 0.007. Self-Efficacy for diabetes increased in Groups 2 and 3 receiving the 'Sweet Talk'

intervention ( $\Delta$ : Group 1, -6.2; Group 2, +2.0; Group 3, +3.2, p < 0.003).

**Conclusion:** 'Sweet Talk' is an innovative, cheap strategy using text messages to provide 'push' support to adolescents with T1D, a notoriously difficult group to reach, engaging young people by using a medium integral to teenage culture. The high reach of our study (73%) compares favorably with other behavioral interventions. 'Sweet Talk' increased self-efficacy for diabetes and combined with IIT improved glycaemic control over the year of the study. This system could be adapted to a variety of health care settings including acute and chronic disease management and preventative strategies.

0-11

### Structure of pediatric diabetes care in Germany 1998–2003: increased centralization and qualification

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**Introduction:** German pediatric diabetes guidelines from 1995 recommend an integrated in- and outpatient pediatric diabetes care through a multidisciplinary team. The objective of this study was to analyze the recent changes in structure and process quality.

**Aim:** Analyze the changes in structure and process quality

**Methodology:** Two representative surveys were carried out within five years via a standardized questionnaire mailed to all pediatric units in Germany. Data with respect to personnel for diabetes care, educational programs, number of treated children in out- and inpatient pediatric diabetes care for the past year were collected.

**Results:** The response rate was 79% (n = 286 units) in 1998 and 80% (n = 298 units) for 2003. In 1998 a total of 1618 newly onset patients were reported, in 2003 this increased to 2274. While in 1998 only 44% of the newly onset patients were treated by a team with a certified pediatric diabetologist and a certified diabetes educator, this was the case in 64% in 2003. Such a team was present in 52 units in 1998 and in 94 units in 2003. In 1998 65% of the newly onset patients were treated in units with at least 10 new cases a year. This increased to 77.4% in 2003. In 1998 a total of 71% of the children were followed in centers with more than 60 patients in long-term care. In 2003 this had increased to 83% of the 14198 reported patients. An outpatient team of certified pediatric diabetologist, certified diabetes educator and other allied health professionals took care of 57% of the reported patients in 1998 and of 73% in 2003. On average the patients were seen 5.5 times per year.

**Conclusion:** This representative survey shows nearly a doubling in the number of pediatric units with a structure quality according to the national guidelines within five years.

0-12

### Reduction of parental worries in follow-up studies of children at risk for type 1 diabetes

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**Introduction:** Children with genetic risk for Type 1 Diabetes (T1D) are studied prospectively, which may be an emotionally trying task for parents. Parents' initial reactions to participation have been reported, but few have investigated reactions over longer time and none if fathers' and mothers' opinions differ.

**Aim:** DiPiS (Diabetes Prediction in Skåne) is a longitudinal study for exploring environmental factors in T1D. Children with genetic risk are studied annually for autoantibodies. Emotional reactions of parents are investigated in parallel.

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**Methodology:** Most newborns in southern Sweden (12000 births/year) are screened at birth for HLA T1D genetic risk. At two months of age, parents consent to participation and fill out questionnaires. At 2 years, 20% of the children are selected for annual follow up. Each year parents answer questions individually on psychosocial and other factors.

**Results:** At two years 2417/4138 invited families (58%) participated and in 90% both parents completed the questionnaire. A great majority were satisfied with the study information, but as observed at 2 months, fathers were more dissatisfied ( $p < 0.001$ ) and at 2 years had more unanswered study questions ( $p < 0.0001$ ). Both parents' satisfaction increased from 2 months to 2 years, but mothers thought about the study more often ( $p < 0.0001$ ). Parents satisfied with the study information reported less worries (mothers:  $p < 0.001$ ; fathers  $p < 0.001$ ). Less satisfied fathers reported more worries of chronic disease ( $p < 0.0013$ ). As observed at 2 months, mothers were more worried about future chronic disease in the child ( $p < 0.015$ ), but worries in relation to study participation did not differ between parents. At 2 years worries for chronic disease and study participation had decreased both in mothers and fathers ( $p < 0.001$  for all).

**Conclusion:** Worries had decreased after 2 years despite the fact that the child had been identified for T1D risk. Continuous study information and involvement of fathers could increase their study satisfaction and decrease worries in both parents.

### 0-13

#### Does DKA at diabetes onset in Ontario children represent missed or delayed diagnosis?

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**Introduction:** Delay in diagnosis of type 1 diabetes mellitus (T1DM) can lead to metabolic deterioration and diabetic ketoacidosis (DKA), the leading cause of morbidity and mortality in children with T1DM. We hypothesized that children presenting with DKA would have more medical encounters preceding the diagnosis than do those presenting without DKA. This may result from failure to recognize the early signs and symptoms of DM.

**Aim:** To evaluate the frequency of medical visits in the period prior to diagnosis of T1DM in children.

**Methodology:** Diagnostic coding data from the Canadian Institute for Health Information and the Ontario Health Insurance Plan were used to retrospectively identify all new cases of DM in children < 19y in the Province of Ontario, Canada from 1994 to 2000.

**Results:** 3947 children were diagnosed with DM during the study period; 735 (18.6%) presented with DKA. In those <3y of age, 39.7% presented with DKA. In the week prior to diagnosis, 48.7% of DKA children compared to 40.9% of those without DKA had at least 1 medical encounter ( $p = 0.0001$ ), with 22.4% of DKA and 13.5% of non-DKA children having exactly 1 medical encounter ( $p < 0.0001$ ). Similar observations were found for the two and four week period before diagnosis. There were no gender differences.

**Conclusion:** Children presenting with DKA had significantly more medical encounters in the period prior to diagnosis compared to those without DKA. These data support the hypothesis that, at least in some children, DKA at diagnosis may represent failure to detect the signs and symptoms of DM before metabolic deterioration to DKA occurs. Alternately, DKA may signify more fulminant disease and/or symptomatology that is difficult to recognize. This appears particularly true in the youngest children (<3yrs of age).

### 0-14

#### Long term differences in glycemic control across centers depend on the initial presentation at diagnosis. Results from the Hvidøre study group on childhood diabetes

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**Introduction:** As it has been established that between-center differences in glycaemic control are present soon after diabetes onset the Hvidøre Study Group decided to focus on the early course of the disease.

**Aim:** To investigate if differences in glycaemic control across centers depend on the degree of disease severity at onset.

**Methods:** Multicentre longitudinal investigation with 18 participating pediatric centers from 15 countries. 275 children and adolescents age < 16 years with newly diagnosed type 1 diabetes participated. Year of birth, sex, insulin dose and standard bicarbonate were recorded at onset. HbA1c, analyzed centrally, were determined at 0, 1, 3, 6, 12, 24, 36 and 48 months after diagnosis and serum for immunology was collected simultaneously.

**Results:** By stepwise multiple regression analyses the between center differences in HbA1c adjusted for sex and age appeared before diagnosis and persisted throughout the 4 years. P-values for center effects in HbA1c: 0 mths (onset): 0.03; 1 mth: 0.01; 3 mths: <0.0001; 6 mths: 0.01; 9 mths: 0.005; 12 mths: 0.0005; 18 mths: 0.02; 24 mths: <0.0001, 36 mths: 0.005; 48 mths: 0.016. If measures reflecting disease severity were included in the statistical model: ethnicity, initial HbA1c, standard bicarbonate and number testing positive for antibodies (GADA, ICA, IA2A) the between center difference in HbA1c was considerably less pronounced: 1 mth: 0.019; 3 mths: <0.0001; 6 mths: 0.056; 9 mths: 0.014; 12 mths: 0.11; 18 mths: 0.35; 24 mths: 0.006; 36 mths: 0.061; 48 mths: 0.41.

**Conclusion:** In conclusion the between center differences in glycaemic control are present before diagnosis and may explain differences between centers on the long term. This suggests that diabetes management is equally well performed in all centres by the professionals but that uncontrollable factors such as disease severity vary between centers affecting glycaemic control.

### 0-15

#### The PedPump survey: indication for CSII and number of daily boluses are associated with HbA1c in 1086 children with T1 DM from 17 countries

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Different indications lead to the use of CSII in children and adolescents with T1 DM. The PedPump survey aimed at analyzing current pediatric CSII practices in a large population of children and adolescents with T1 DM in pediatric diabetes centers in Europe and Israel. The survey was conducted in 30 centers from 17 countries. Clinical data including the primary indication for CSII and 90 day-pump memory downloads of patients treated with Medtronic MiniMed pumps were recorded using an electronic data collection

system. HbA1c was determined in a central laboratory with HPLC method (DCCT-standard). HbA1c and number of boluses per indication for CSII therapy were adjusted by age using the direct method. A total of 1086 pediatric patients (0–18 y) were included; mean age:  $11.9 \pm 4.2$ , diabetes duration:  $5.9 \pm 3.6$  (0.2–18 y), CSII duration:  $2.0 \pm 1.4$  (0.2–14.5 y), HbA1c:  $8.0 \pm 1.3\%$ . No significant differences were apparent in age-adjusted HbA1c between most of the different indication groups [(recurrent hypoglycemia ( $n = 388$ ,  $7.9 \pm 0.5\%$ ), flexibility/lifestyle ( $n = 292$ ,  $7.7 \pm 0.5\%$ ), dawn phenomenon ( $n = 131$ ,  $7.9 \pm 0.4\%$ ), needle phobia ( $n = 54$ ,  $7.9 \pm 1.0\%$ )], except when high HbA1c was the primary reason ( $n = 265$ ,  $8.8 \pm 0.5\%$ ,  $p < 0.01$ ). Children and adolescents giving more than 7 boluses/day had a significantly better HbA1c than those with fewer boluses ( $7.6 \pm 1.0$  vs.  $8.4 \pm 1.4\%$ ,  $p < 0.001$ ). Correspondingly, children with poor HbA1c had a slightly but significantly lower average age-adjusted daily bolus count (recurrent hypoglycemia:  $8.0 \pm 2.9$ , flexibility/lifestyle:  $7.2 \pm 3.4$ , dawn phenomenon:  $7.7 \pm 2.5$ , needle phobia:  $7.8 \pm 3.5$ , high HbA1c:  $6.5 \pm 2.7$ ,  $p < 0.01$  compared to other groups). Poor glycaemic control is associated with infrequent insulin application also under CSII. While most therapeutic regimens with injections feature three to four daily bolus doses, the average bolus number is higher in all indication groups even when a high HbA1c is the primary reason for CSII. This renders insulin pump therapy an adequate routine therapeutic option for children and adolescents with diabetes.

#### O-16

### Self-monitoring of capillary blood ketone 3beta-hydroxybutyrate, SMBK, is useful in detecting dawn phenomenon

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**Introduction:** We have demonstrated a statistically significant link between the morning rise in IGFBP-1 or morning level of free insulin like growth factor I (IGF-I) and dawn change in the plasma glucose (PG). The development of bed-side quantitative tests of capillary blood 3beta-hydroxybutyrate (beta-OHB) levels has recently been available for the support of diabetes diagnosis and management tools.

**Aim:** To clarify whether self measurement of capillary blood ketone (SMBK) of 3beta-hydroxybutyrate is useful to detect a dawn phenomenon.

**Methodology:** One hundred and twelve patients with T1DM (52 male and 60 female age;  $13.75 \pm 3.79$  years old, HbA1c;  $7.62 \pm 1.36\%$  normal range  $< 5.8\%$ ) were studied. Fasting plasma glucose (FPG) and fasting beta-OHB were measured. When fasting beta-OHB was above the reference range (0.0–0.5 mmol/l), diurnal changes were observed. Thirty-two patients with T1DM (15 male and 17 female, age;  $11.6 \pm 2.62$ , HbA1c;  $7.47 \pm 1.22\%$ ) were studied on nocturnal changes of plasma glucose, IGFBP-1 and free IGF-I.

**Results:** The difference in fasting beta-OHB level between the two groups (according to FPG, one of less than 250 mg/dl and the other of 250 mg/dl and more) was statistically significant ( $p < 0.001$ ). A change of IGFBP-1 between 2300 and 0700, delta IGFBP-1 (2300–0700), showed statistically a significant link with fasting beta-OHB ( $r = 0.414$ ,  $p < 0.05$ ). FPG at 0700 had a correlation with free IGF-I at 0700 ( $r = -0.498$ ,  $p < 0.005$ ). Furthermore delta free IGF-I (0500–0700) showed a good correlation with delta IGFBP-1 (2300–0700) ( $r = -0.372$ ,  $p < 0.05$ ). Fasting beta-OHB also had a

good correlation with delta free IGF-I (0500–0700) ( $r = -0.478$ ,  $p < 0.05$ ). In multiple regression analysis, beta-OHB = 0.270 ( $p < 0.0001$ ) +0.03 delta PG (0500–0700) ( $p < 0.05$ ) – 0.051 delta free IGF-I (0500–0700) ( $p < 0.05$ ) ( $r = 0.55$ ). Fasting high levels of beta-OHB in T1DM patients without any ill complaint were all resolved before lunch by the usual amount of insulin and breakfast.

**Conclusion:** We suggest that the morning level of capillary beta-OHB may be a useful clinical marker of the dawn phenomenon without measuring free IGF-I and IGFBP-1 in T1DM. We recommend SMBK if FPG  $> 250$  mg/dl. A supplemental insulin dose may not require in dawn phenomenon unless beta-OHB  $> 1.0$  mmol/l.

#### O-17

### Hydroxybutyrate near-patient testing to evaluate end-points for intravenous insulin therapy in the treatment of pediatric diabetic ketoacidosis

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**Aims:** To assess the clinical application of a near-patient testing (NPT) device for capillary blood hydroxybutyrate [HOB] measurement in evaluating a new end-point for intravenous [IV] insulin therapy in the treatment of pediatric diabetic ketoacidosis (DKA).

**Methods:** Children fulfilling the criteria for DKA (ketonuria, pH  $< 7.3$  and/or standard bicarbonate  $< 15$  mmol/L) were treated according to an integrated care pathway [ICP] with fluid replacement and insulin infusion [starting dose 0.03–0.05 units/Kg/h]. We measured capillary HOB hourly by NPT [Abbott Optium meter, analytical range 0–6.0 mmol/L], venous blood gases 4-hourly, venous HOB 4-hourly by laboratory enzymatic method, and tested all urine passed for ketones. Two possible ICP end-points were compared: [A] pH  $> 7.3$  followed by two successive NPT HOB measurements  $< 1$  mmol/L and [B] pH  $> 7.3$  and urine ketone-free [our current end-point].

**Results:** 35 patients aged 1–14 years completed the ICP [27 to negative ketonuria] without significant variation. Before treatment, median [range] laboratory HOB was 9.5 [4.6–15.70] mmol/L, pH 7.18 [6.98–7.38], standard bicarbonate 11.5 [4.3–18.6] mmol/L. During treatment, when pH reached 7.3, median NPT HOB was 1.1 [0.0–4.6] mmol/L and 5 patients were still markedly ketotic [NPT HOB  $> 3$  mmol/L]. ICP end-point A was reached after 18 [4–39] hours whereas end-point B was not reached until 28 [14–64] hours after starting treatment. The median lag was 11 [1–36] hours. For 59 paired venous samples [excluding samples with laboratory HOB  $> 6$  mmol/L], the relation between NPT [y] and laboratory [x] HOB was  $y = 0.92x - 0.05$ ,  $r^2 = 0.94$ , mean bias  $-0.25$  mmol/L.

**Conclusions:** [1] Serial measurement of NPT HOB allows evaluation of a new and earlier end-point for IV insulin therapy, free from the problems associated with urine collection and analysis in children with DKA. [2] Agreement between NPT and laboratory HOB was clinically acceptable for HOB levels within the meter's analytical range.

#### O-18

### Final stature in children with type 1 diabetes

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**Introduction:** The possible effects of an impaired metabolic control in children with type 1 diabetes on final stature are controversial, as puberty is a vulnerable period.

**Aim:** To evaluate, in a group of diabetic children: a) initial stature (IS), final stature (FS) and familiar stature (FaS); b) Initial and final BMI; c) age of puberty onset; d) to correlate these variables with the quality of metabolic control.

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**Methodology:** Sex, insulin therapy, age at diagnosis, diabetes duration, puberty onset, HbA1C (DCA 2000), IS-SDS, FS-SDS, FaS-SDS, initial and final BMI-SDS, were evaluated in a longitudinal study of 93 diabetic children (53 girls and 40 boys).

**Results:** Intensive insulin therapy was initiated at a mean age of  $13.1 \pm 2.1$  Y in 87 cases. Mean HbA1C between 0–4 Y, 5–9 Y and >10 Y was respectively  $8.1 \pm 1.7\%$ ,  $8.4 \pm 1.6\%$  and  $9.3 \pm 1.3\%$ , with a significant difference in the last 2 groups ( $p < 0.0001$ ). Comparing girls with boys: a) mean age of puberty onset was  $10.8 \pm 1.1$  Y vs  $12.1 \pm 0.97$  Y; b) mean HbA1C from 0–4 Y was  $9.0 \pm 1.3\%$  vs  $6.4 \pm 0.8\%$  ( $p = 0.006$ ), 5–10 Y  $8.6 \pm 1.5\%$  vs  $8.1 \pm 1.7\%$ , and >10 Y  $9.6 \pm 1.2\%$  vs  $8.9 \pm 1.2\%$  ( $p = 0.005$ ); c) mean IS-SDS  $-0.009 \pm 0.9$  vs  $-0.009 \pm 1.1$ ; d) mean FS-SDS  $-0.63 \pm 1.1$  vs  $-0.62 \pm 1.0$ ; e) mean FaS-SDS  $-1.03 \pm 0.9$  vs  $-0.92 \pm 0.8$ ; f) mean initial BMI-SDS  $0.28 \pm 1.0$  vs  $0.19 \pm 1.07$ ; g) mean final BMI-SDS  $1.1 \pm 0.7$  vs  $0.27 \pm 1.0$  ( $p < 0.0001$ ); h) in both sexes the FS-SDS was significantly inferior to the IS-SDS ( $p < 0.0001$ ), and significantly superior to the FaS-SDS ( $p = 0.01$  in girls,  $p = 0.02$  in boys); i) in girls, the final BMI-SDS was significantly superior to the initial ( $p < 0.0001$ ); j) comparing the group with FS-SDS superior to the FaS-SDS with the group with FS-SDS inferior to the FaS-SDS, HbA1C was significantly inferior in the former ( $9.1 \pm 1.3\%$  vs  $9.7 \pm 1.2\%$ ) ( $p = 0.02$ ).

**Conclusions:** a) FS-SDS was significantly superior to the FaS-SDS, but significantly inferior to the IS-SDS; b) in girls there was an excessive weight gain; c) during puberty, metabolic control deterioration seems to contribute to the lost of potential growth.

### 0-19

#### Tumor necrosis factor-alpha is a predictor of microalbuminuria in poorly controlled type 1 diabetes mellitus children

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**Introduction:** Microalbuminuria is a subclinical increase in urinary albumin excretion and represents an early stage of renal disease in Type 1 diabetes mellitus (DM) which tends to progress to clinically overt nephropathy. Despite the fact that numerous investigations on the nature of diabetic nephropathy were carried out, its pathomechanism remains unclear.

**Aims:** The aim of our study was to search for a relation between level of Tumor Necrosis Factor-alpha (TNF- $\alpha$ ) and N-acetyl-beta-D-glucosaminidase (NAG) enzyme in urine and the function of renal proximal tubule in children with Type 1 DM.

**Methodology:** Fifty six children (25 boys and 31 girls) age  $13.6 \pm 3.7$  years with Type 1 DM and 20 healthy children (8 girls and 12 boys) age  $12.4 \pm 4.9$  years were recruited from the Outpatient Diabetic Department at the Medical University of Gdańsk. In all children the level of TNF- $\alpha$  as well as NAG enzyme activity and A, B isoforms were measured in urine.

**Results:** The TNF- $\alpha$  serum level and activity of NAG, A and B isoforms in urine were significantly higher in the group of children with Type 1 DM in relation to the healthy control children. The patients with measurable microalbuminuria were characterized by a significantly higher TNF- $\alpha$  serum activity than the patients without diabetic nephropathy. Moreover, significantly positive correlation between serum TNF- $\alpha$  level and NAG with its A and B isoforms urine activity, and albumin excretion rate as well as HbA1c was found.

**Conclusion:** It seems that among analyzed parameters TNF- $\alpha$  serum activity is the strongest prognostic factor of the kidney damage preceding the increased activity of NAG and its isoforms in patients with no clinical sign of diabetic nephropathy. Conse-

quently it shall be pointed out that the presence and the levels of TNF- $\alpha$  in serum are not only markers of diabetic nephropathy but also indicators of diabetes metabolic control status.

### 0-20

#### Risk factors for arterial hypertension and microalbuminuria determined by ambulatory blood pressure profiles: a nationwide multicenter investigation in 1644 children and adolescents with diabetes mellitus type 1

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**Introduction:** Arterial hypertension is a key player in the development of diabetic complications. Blood pressure (BP) profiling is a widely accepted tool to evaluate BP regulation and is superior to single office BP measurement.

**Aim:** We used a nationwide database (DPV) to study the influence of risk factors for arterial hypertension and microalbuminuria in diabetes type 1.

**Methods:** Blood pressure profiles (24 hr) were performed in 1644 diabetic children (860 boys and 784 girls, mean age  $14.06 \pm 2.88$  years, mean diabetes duration  $5.18 \pm 3.99$  years, average HbA1c  $8.7 \pm 2.2\%$ ; mean insulin dosage  $0.85 \pm 0.29$  U/kg BW/d; mean  $\pm$  SD) and compared to a cohort of healthy German and Hungarian children. LMS transformed standard deviation scores (LMS) have been calculated for quantitative analysis of the BP profiles. The influence of age, gender, diabetes duration, HbA1c, BMI-SDS and insulin dose on BP regulation was tested by multiple linear regression, the determining factors for microalbuminuria by stepwise logistic regression analysis.

**Results:** BP was increased in the children with diabetes compared to controls, in particular the nocturnal BP (diurnal: LMS SBP  $0.09 \pm 0.83$ , LMS DBP  $-0.12 \pm 1.07$ , LMS MAP  $0.12 \pm 0.97$ ; nocturnal: LMS SBP  $0.63 \pm 1.1$ , LMS DBP  $0.68 \pm 1.07$ , LMS MAP  $0.89 \pm 1.2$ ;  $p < 0.0001$  vs. controls, t-test). Dipping was reduced in the diabetic patients (SBP  $9.8 \pm 5.6\%$  diab. vs.  $13 \pm 6\%$  controls;  $p < 0.0001$ , t-test) and DBP  $16.8 \pm 7.9\%$  diab. vs.  $23 \pm 9$  controls ( $p < 0.0001$ , t-test). Age, diabetes duration, gender, HbA1c, BMI and insulin dose exert a significant influence on blood pressure regulation during day and night. Dipping was only related to age. Microalbuminuria was associated with increased diurnal systolic and nocturnal diastolic BP and a reduced diastolic dipping.

**Conclusion:** To prevent arterial hypertension, it is necessary to optimize metabolic control, BMI and insulin treatment, as age, diabetes duration and gender cannot be influenced. Normalization of blood pressure is expected to reduce the risk of diabetic nephropathy.

### 0-21

#### Impact of hypoglycemic episodes on peripheral nerves function in children and adolescents with type 1 diabetes

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**Introduction:** Hypoglycemia is an acute disturbance of energy, especially impacted on the central nervous system, but direct influence on peripheral nervous function was not detected.

**Aim:** The aim of the study was to establish the influence of hypoglycemic moderate and severe episodes on peripheral nerve function.

**Methodology:** 97 children with type 1 diabetes (55 girls, 42 boys, mean age  $15.4 \pm 2.16$  years, mean duration of diabetes  $8.11 \pm 2.9$  years, mean age in onset  $7.16 \pm 2.96$  years, mean HbA<sub>1c</sub>  $8.58 \pm 1.06\%$ ) at least 10 years old and with at least 3 years duration of diabetes, were included in the study. Nerve conduction studies of the median, ulnar, tibial and peroneal motor nerves, and median, ulnar and sural sensory nerves were performed with standard surface stimulating and recording techniques. The motor and sensory amplitude, velocity, latency were detected. Moderate hypoglycemic episodes were defined as events of low glycemia requiring the help of another person but without loss of consciousness and/or convulsions, repeating frequently in at least one year. Severe hypoglycemia was defined as events with loss of consciousness and/or convulsions. Univariate ANOVA tests of significance were used.

**Results:** In the study population, 53 subjects had no history of hypoglycemic episodes, in 10 patients moderate hypoglycemic episodes had occurred. Twenty-eight patients have history of 1 or 2 severe hypoglycemic episodes, and 6 children had a history of more than two episodes of severe hypoglycemia. The subgroups with a history of hypoglycemic episodes had significant delay in all conduction parameters in sural nerve (amplitude  $p < 0.05$ , sensory latency  $p < 0.05$ , and velocity  $p < 0.005$ ), and in motor potential amplitude of tibial nerve ( $p < 0.005$ ).

**Conclusion:** The study showed the influence of hypoglycemic episodes on the function of all sural nerve parameters and tibial motor amplitude. Frequent moderate hypoglycemic episodes were a strong risk factor for damaging of peripheral, comparable with the impact of several severe hypoglycemia.

## 0-22

### Effects of $\alpha$ -lipoic acid on lipid and the erythrocyte metabolism in type 1 diabetes mellitus patients with cardiovascular autonomic neuropathy

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**Introduction:** The present study had examined the effect of  $\alpha$ -lipoic acid (ALA) on activity of acetylcholinesterase (ACE) in erythrocyte membrane, superoxide dismutase (SOD), glutathione peroxidase (GPO), catalase (CA), osmotic stability, levels of Na<sup>+</sup> and K<sup>+</sup> in erythrocytes, cholesterol (TC), low and high density lipoprotein-cholesterol (LDL-C, HDL-C), triglycerides (TG) in Type 1 diabetic patients (Type 1 DM) with cardiac autonomic neuropathy (CAN).

**Aim:** We had carried out an analysis of ALA effects on the above indices in Type 1 DM patients with CAN assessed by reduced heart rate variability (HRV).

**Methodology:** 41 patients ( $25 \pm 6$  years, 23 m/18 f) were allocated in two treatment groups. All patients were randomised to receive either a daily i/venous (2 weeks) and then per os dose of 600 mg ALA or placebo during 2 months.

**Results:** It is defined that ACE activity increases in erythrocyte membrane of Type 1 DM patients with CAN what testifies about the reconstruction of membranes, them penetration increasing, especially for Na<sup>+</sup> and K<sup>+</sup> (increased levels of Na<sup>+</sup> and K<sup>+</sup> in RBC's confirm it). High level of TC, LDL-C, TG ( $7.3 \pm 10.1$ ;  $4.5 \pm 0.2$ ;  $1.87 \pm 0.1$  mmol/l,  $p < 0.05$ ) and depressed enzymes activity were diagnosed in all of them. At the end of 2 months period TG and LDL-C levels were decreased and activity of SOD, GPO and CA ( $10.94 \pm 0.22$ ;  $321.7 \pm 19.2$  mcmol GSH/min 1 g Hb,  $p < 0.001$ ;  $1.76 \pm 0.23$  H<sub>2</sub>O<sub>2</sub>/min 1 g Hb,  $p < 0.05$ ), osmotic stability in erythrocytes significantly increases in patients from 1st group. Also, ALA promotes the decrease of ACE activity in erythrocyte membrane.

**Conclusion:** ALA may be used for prophylactic and treatment of cardiovascular autonomic neuropathy.

## 0-23

### Markedly increased risk of cardiovascular death in childhood-onset type 1 diabetes: a 24-year population based follow-up study

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**Introduction:** Type 1 diabetes implies an excess risk of mortality.

**Aims:** To examine the total and cause-specific mortality rates in childhood-onset type 1 diabetes in a nation-wide population-based Norwegian cohort.

**Methodology:** All individuals in Norway with childhood onset type 1 diabetes (0–14 years) from 1973 through 1982 were included (n = 1906). Mortality was recorded from diabetes onset until December 31<sup>st</sup> 2002, representing 46 147 person-years under observation. Highest attained age was 44 years and maximum diabetes duration 30 years. Cause of death was ascertained by review of death certificates, autopsy protocols and hospital records.

**Results:** During follow-up, 103 subjects died, 28 (27%) from cardiovascular disease (CVD). The overall standardized mortality ratio (SMR) was 4.0 (95% CI: 3.2–4.8) and no statistical sex differences could be established. The SMR for CVD was 23.1 (14.3–34.0) in men and 17.9 (7.1–33.6) in women. Acute metabolic complications of diabetes were the most common cause of death under the age of 30 years. CVD was responsible for the greatest proportion of deaths after age 30 years. At all ages deaths certified to CVD exceeded those certified to renal disease.

**Conclusion:** Childhood-onset type 1 diabetes carries a considerable increased risk of cardiovascular death in young adults when compared with the general population. To reduce these deaths attention should be directed to early detection and treatment of cardiovascular disease and associated risk factors.

## 0-24

### Early manifestation of arterial stiffness in newly diagnosed, untreated type 2 diabetic and impaired glucose tolerance (IGT) individuals

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**Introduction:** Macrovascular disease is a major complication of diabetic mellitus. Arterial stiffness is an independent predictor of macrovascular events. While microvascular disease starts to manifest late in diabetes, macrovascular disease may occur very early.

**Objective:** To investigate arterial stiffness among newly diagnosed untreated type 2 diabetic and impaired glucose tolerance (IGT) individuals.

**Methodology:** A cross sectional study involving newly diagnosed untreated diabetics and impaired glucose tolerance individuals was done. They were compared with age and sex matched normoglycaemics. Subjects were screened with the oral glucose tolerance test (OGTT) prior to recruitment into the study. Participants agreed to the following examinations: BP, BMI, fasting insulin, HbA<sub>1c</sub>, lipid profile and ECG. Arterial stiffness was measured by SphygmoCor<sup>®</sup> using pulse wave velocity (PWV) and augmentation index (AI) as indices of arterial stiffness. Thirty subjects per group were

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needed to demonstrate significant differences in arterial stiffness between groups at 80% power.

**Results:** Out of 1620 subjects, 644 agreed to have an OGTT. Of these 70 were diagnosed to have diabetes and 66 to have IGT. Of those newly diagnosed, 30 diabetics and 30 with IGT agreed to participate in the study. Diabetics and those with IGT had significantly higher BMI ( $p < 0.05$ ) compared to normoglycaemics ( $26.91 \pm 3.16$  vs.  $26.68 \pm 2.85$  vs.  $24.51 \pm 3.46 \text{ kg/m}^2$  respectively). Pulse wave

velocity was significantly greater ( $p < 0.05$ ) in the diabetics and those with IGT compared to normoglycemic ( $10.37 \pm 2.64$  vs.  $9.54 \pm 1.56$  vs.  $8.83 \pm 1.26 \text{ m/s}$ ). The augmentation index was greater in diabetics, compared to those with IGT and normoglycemics ( $134.53 \pm 17.32$  vs.  $132.02 \pm 16.11$  and  $129.43 \pm 11.57\%$ ).

**Conclusion:** This result shows that newly diagnosed diabetics and IGT have already demonstrated early preclinical manifestation of macrovascular disease.