

The figure displays the processed data 1985–1996 (Cx) and 1985–1995 (IDDM), both supposing a zero trend. The prediction was very good for Cx 1996 and sufficient for IDDM 1996 but failed for IDDM 1997 when all newly observed values were shifted over the prediction corridor. The IDDM curve lags behind that of Cx by 3 months (for 1-year rhythm), and by 1–5 years (3.5- to 10-year rhythm).

*In conclusion*, the tested periods alone explain the data for Cx while for IDDM the linear increasing trend is necessary since 1997 – the year of a boom increase of IDDM.

Support: Eurodiab Ace and Eurodiab Tiger projects.

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### Diabetes Incidence in Children of Different Nations in Germany

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Migration studies have been a classical epidemiological method to analyse the aetiological effect of genetic markers vs. environmental factors.

Baden-Württemberg is a federal state of Germany covering 10.0% of the country. Among 9.75 million inhabitants, 10.7% are foreigners; under the age of 15 years, 14.5% are foreigners.

Our incidence registry is based on 1,160 children who were analyzed retrospectively. In addition, data of 965 children were analyzed prospectively. The total incidence of childhood diabetes was reported to be 11.6/100,000 (95% CI, 10.9–12.2).

*Results:* (1) The incidence rate (IR) of German children is significantly higher than the IR of foreigners ( $\chi^2 = 25.31$ , d.f. = 1;  $p < 0.0001$ ). (2) The IR for German children alone is 12.2 (95% CI, 11.4–13.0), and for foreign children it is 7.1 (95% CI, 5.7–8.7). In detail: IR of Turkish children 5.2 (95% CI, 3.4–7.5), of Italian children 9.4 (5.6–14.6), of children from former Yugoslavia 5.5 (3.1–9.1), of children from Greece 5.0 (1.4–12.8). (3) The difference in the IR of children of different nations is highly significant ( $\chi^2 = 33.59$ , d.f. = 5,  $p < 0.0001$ ). (4) The IR of children from different nations corresponds to the IR reported for the particular home country of these children.

*Conclusion:* These results may point to a link between the genetic basis and the pathogenesis of diabetes mellitus. Further analysis will be done by evaluation of the prospective data.

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### Risk Factors for the Development of Microvascular Complications in Young Patients with Diabetes

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The DCCT showed a close relationship between metabolic control and diabetes-related complications in adolescents and adults with type 1 diabetes. Whether the same relation exists in younger

children is, however, less evident. A Danish nationwide cohort of children and adolescents with type 1 diabetes was followed for 9 years on three occasions (1987, 1989, 1995) with assessment of metabolic control and development of complications in kidneys, eyes and nerves. The aim of the 1995 follow-up study was to determine risk factors and prevalence of complications in young Danish patients with diabetes. Furthermore, the significance of the pre- and postpubertal diabetes duration was analyzed in relation to development of microvascular complications. Clinical information, HbA<sub>1c</sub>, AER, arterial blood pressure, fundus photos (central reading) and vibration perception threshold (VPT) was obtained from 353 patients (50% of the inception cohort), mean age: 20.7 ± 3.3 years and mean diabetes duration: 13.2 ± 3.2 years. HbA<sub>1c</sub> (normal range 4.3–5.8, mean 5.3%) and AER (upper normal limit (95%): 20 µg/min) in at least two timed overnight urine collections were analyzed centrally. Average HbA<sub>1c</sub> was 9.7 ± 1.7% (mean ± SD). Elevated AER (>20 µg/min) was diagnosed in 12.8% of the patients. Risk factors for elevated AER (1995) were high AER (1989) ( $p < 0.001$ ) and high HbA<sub>1c</sub> (1989) ( $p < 0.001$ ). Retinopathy was present in 58% and risk factors were long pre- ( $p < 0.01$ ) and postpubertal ( $p < 0.001$ ) diabetes duration and high HbA<sub>1c</sub> level (1989) ( $p < 0.0001$ ). Elevated VPT (>6.5 V) was shown in 60% and was related to male sex ( $p < 0.05$ ), older age ( $p < 0.001$ ) and elevated AER (1989) ( $p < 0.05$ ). The present study confirmed the close association between long-term metabolic control and the development of microvascular complications in young diabetic patients. The prepubertal diabetes duration contributes to the development of diabetic retinopathy but to a lesser extent than the postpubertal duration. There is a major need for the development of better management guidelines and quality assessment programmes for young people with diabetes.

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### The Oxygen Availability in Children with IDDM

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*Introduction:* Numerous studies have demonstrated that hypoxia is considered to be one of the main etiopathogenic factors in diabetic neuropathy. It is well known that hyperviscosity of blood, decrease of erythrocyte deformability, reduplication of the capillar basement membrane and increase of Hb-O<sub>2</sub> affinity may reduce the supply of O<sub>2</sub> to the nerves. The traditional parameters: oxygen tension, hemoglobin, and oxygen saturation may give misleading information. The computer program – ‘Oxygen Status Algorithm’ Siggaard-Andersen's and new parameters: px, cx, Qx shed more light on tissue hypoxia. Oxygen extraction tension –px defined as the oxygen tension which is required to extract 2.3 mmol O<sub>2</sub>/liter blood, reflects the integrated effects of changes in the arterial O<sub>2</sub>, oxygen capacity and Hb-O<sub>2</sub> affinity on the O<sub>2</sub> delivery to the tissue.

*Aim:* The analysis of the oxygen availability and determination of the risk factors of tissue hypoxia in children with IDDM.

*Material, Method:* 42 (25 girls, 17 boys) patients with IDDM have been examined. Average age 17.1 SD 2.6; diabetes duration 6.6 SD 3.37; average HbA<sub>1c</sub> 9.34 SD 2.41. Patients with ketoacidosis and hypoglycemia have been excluded. pO<sub>2</sub>, sO<sub>2</sub>, PCO<sub>2</sub>, pH, totHb, FhbcO, and FhbcMet were measured from arterial blood samples by cooximeter and hemoximeter and the next was introduced into

the Oxygen Status Algorithm program. Oxygen extraction tension, 2,3DPG, and p50 were calculated by this program. The results were presented as standardized values (SDS) with regard to the norms presented in the OSA program.

**Results:** 16.6% patients had oxygen extraction tension below 1 SDS; px significantly correlated with 2,3DPG ( $r = 0.89$ ,  $p < 0.05$ ), TotHb ( $r = 0.40$ ,  $p < 0.05$ ),  $sO_2$  ( $r = -0.80$ ,  $p < 0.05$ ), but not with duration of diabetes, HbA1c and method of insulin therapy. In the group with the reduced oxygen availability, the average value of HbA1c was higher than in the standard group, but not significantly.

**Conclusion:** The hypoxia may occur in diabetic children. Low values of 2,3DPG and Tot Hb are significant risk factors in tissue hypoxia. The Oxygen Status Algorithm program may be helpful in the treatment of diabetic children.

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### **Pyruvate Dehydrogenase Activity in Circulating Lymphomonocytes from Children with Maturity Onset Diabetes of the Young (MODY)**

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Pyruvate dehydrogenase (PDH), the rate-limiting enzyme for glucose oxidative breakdown, is a multimeric protein that in mammalian cells exists in a balance between a dephosphorylated active (PDHa) and a phosphorylated inactive (PDHb) form controlled by PDH kinase and PDHP phosphatase. The latter regulates the conversion of PDHb in PDHa, is activated by  $Ca^{2+}$  and  $Mg^{2+}$ , inhibited by NaF and constitutes the insulin target, so helping explain the control exerted by insulin over PDH. From the aforesaid enzyme activity assay performed with NaF and without  $Ca^{2+}$  and  $Mg^{2+}$  represents the amount of the enzyme in the active form (PDHa) whereas that with  $Ca^{2+}$  and  $Mg^{2+}$  (CaMg PDH) is representative of the efficiency of PDHP phosphatase in converting PDHb into PDHa. Previously, we showed that in circulating lymphomonocytes (LMC) from newly diagnosed IDDM children PDHa and CaMg PDH are comparable and significantly below normal, suggesting an unresponsiveness of PDHP phosphatase to  $Ca^{2+}$ - and  $Mg^{2+}$ -mediated activation, possibly due to insulinopenia affecting these individuals. Incubation of LMC from these children with insulin at 5  $\mu$ U/ml determines PDH activation even increased at 50  $\mu$ U/ml whereas in controls activation and inhibition, respectively, occur. In this study we evaluated basal and insulin-stimulated PDHa and CaMg PDH in LMC of 10 children (8 females, 2 males, mean age  $10 \pm 5$  years) with MODY and in 10 age-matched healthy individuals. MODY children were selected among hyperglycemic individuals for: (1) a family history of NIDDM; (2) fasting glycemia  $> 120$  mg/dl, abnormal glycemic curve under OGTT and normal insulinemic curve under IVGTT; (3) absence of autoantibodies against ICA, ICA512 and anti-GAD, as well as of HLA haplotypes specific for IDDM. In the enrolled patients both PDHa and CaMg PDH were significantly below normal (respectively,  $17 \pm 4$  and  $28 \pm 4$  vs.  $29 \pm 3$  and  $40 \pm 5$ ,  $p < 0.001$ ) but both recovered following in vitro stimulation with insulin at 5 and 50  $\mu$ U/ml. These alterations are comparable to those observed in IDDM children with the difference that in MODY chil-

dren CaMg PDH was significantly greater than PDHa whereas the two activities are comparable in IDDM children. These results support the view that the two groups can be differentiated in biochemical terms.

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### **Early Signs of Polyneuropathy in Adolescents with IDDM**

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Diabetic microvascular complications are rare before puberty, but start to manifest during and after puberty. Signs of polyneuropathy were studied in late prepubertal and pubertal IDDM patients with a disease duration  $> 2$  years in order to assess whether there is a relation between pubertal development and microvascular changes.

Seventy-eight adolescent patients with IDDM participated in the study. Twenty-one subjects (12 boys) were in late prepuberty, 49 (21 boys) pubertal and 8 (4 boys) postpubertal. The mean age of the patients was 13.5 years, the mean disease duration 7.5 years (range 2.1–15.6) and the mean GHbA1c 8.6% (range 5.3–13.0%). Forty-two age- and sex-matched nondiabetic adolescents served as controls, out of whom 7 (4 boys) were late prepubertal, 27 pubertal (16 boys) and 8 (3 boys) postpubertal. The neurological assessment comprised (1) motor (MCV) and sensory (SCV) nerve conduction velocity measurements; (2) vibration perception threshold (VPT) in the distal parts of the hands and feet; (3) autonomic nervous system (ANS) function tests: heart rate variability in rest (HRV), in response to deep breathing (DB) and active standing, as well as BP response to active standing.

MCV in the median and peroneal nerves ( $p < 0.001$ ) and SCV in the median and sural nerves were significantly reduced ( $p = 0.01$  or less) and the amplitude in the sural nerve was decreased ( $p < 0.001$ ) in patients with IDDM. There were no differences in HRV or in the heart rate response to DB or active standing or in BP response to active standing between patients with IDDM and nondiabetic adolescents after correction for height and basal heart rate. The VPT did not differ between the two groups after correction for height and skin temperature.

We conclude that although adolescent patients with IDDM had obvious signs of mixed sensorimotor polyneuropathy, we could not detect any clear differences in the ANS function tests between patients with IDDM and healthy adolescents. This implies that the ANS may be more resistant to diabetic neuropathy, or that factors other than those involved in the development of sensorimotor neuropathy may contribute to autonomic neuropathy.