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II. Research Projects

A. Cohort Studies

BABYDIAB study

The BABYDIAB study is the first prospective cohort study that examines the natural history of islet autoimmunity in children of patients with type 1 diabetes. Several other birth prospective studies examining islet autoimmunity and type 1 diabetes were initiated since the BABYDIAB study started in 1989.

BABYDIAB aimed to determine when islet autoantibodies first appear, which genetic and environmental factors influence their development, and what islet autoantibody characteristics were most associated with progression to type 1 diabetes. Recruitment began in 1989 and ended in 2000. Families were eligible if one or both parents had type 1 diabetes. Recruitment was facilitated by advertisements in pediatric and adult journals and in pediatric and neonatal clinics. Cord blood was obtained in obstetric departments from eligible families that consented to participation. During follow-up, venous blood samples from children are obtained at pediatric outpatient departments. Venous blood samples and questionnaires are obtained from children at study visits scheduled at age 9 months, 2, 5, 8, 11, 14, 17 and 20 years. Islet autoantibodies against insulin (IAA), GAD (GADA), IA-2 (IA-2A) and zinc transporter 8 (ZnT8-A) are measured in all collected samples. If children
have a positive autoantibody result, visit frequencies and islet autoantibody measurements are subsequently performed at 6 to 12 month intervals. The study is coordinated centrally from Munich and conducted from this site by directly contacting the participating families and their family pediatricians. The BABYDIAB cohort contains 1650 offspring followed from birth to last sample for a median of 10.7 years (range 0.75–20.5 years). 1515 offspring participated in the 2-year follow-up visit, 1370 in the 5-year follow-up visit, 1211 in the 8-year follow-up visit, 899 in the 11-year follow-up, 411 in 14-year follow-up, 69 in 17 year follow-up and 12 in 20 year follow-up. The cumulative dropout rate is 20.9% by the age 8 of years. The primary outcome is the development of persistent autoantibodies to one or more of the antigens insulin, GAD, IA-2, or ZnT8. The secondary outcome is the development of type 1 diabetes according to the criteria drawn up by the American Diabetes Association (ADA) (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997). Thus far, 152 offspring developed persistent islet autoantibodies, and 56 offspring progressed to type 1 diabetes.

Findings of BABYDIAB could show that islet autoimmunity in people developing type 1 diabetes in childhood is often initiated within the first two years of life and that insulin is often the first target autoantigen of this early autoimmune response in infants.

TEDDY Consortium (The Environmental Determinants of Diabetes in the Young)

The TEDDY consortium comprises of six clinical centers located in the USA and Europe: Washington (Seattle), Colorado (Denver), and Georgia (Augusta); Finland (Turku); Sweden (Malmo); and Germany (Munich, Forschergruppe Diabetes), and a data coordinating center in Tampa, Florida. The primary objective of this multicenter, multinational, epidemiological study is the identification of infectious agents, dietary factors, or other environmental exposures that are associated with increased risk of autoimmunity and type 1 diabetes. Factors affecting specific phenotypic manifestations such as early age of onset or rate of progression or protection from the development of type 1 diabetes will also be identified. Identification of such factors will lead to a better understanding of disease pathogenesis and result in new strategies to prevent, delay, or reverse type 1 diabetes.

Newborns were eligible if they were younger than 4.5 months and had high-risk human leukocyte antigen alleles (HLA-DR,DQ) in the general population or had first degree relatives (FDRs) affected by type 1 diabetes. From 2004-2010, TEDDY screened more than 420,000 newborns from both the general population and families already affected by type 1 diabetes and identified 21,577 children with high-risk HLA-DR,DQ genotypes. Of those, 8,668 (917 first-degree relatives and 7,751 newborns from the general population) are enrolled in the prospective follow-up beginning before the age of 4.5 months. The German clinical center screened 36,105 newborns (1,535 first degree relatives and 34,570 newborns from the general population). Of those, 593 are enrolled in the follow-up in Germany (219 first degree relatives and 374 from the general population).

Participants are seen every 3 months up to 4 years of age, with subsequent visits every 6 months until the subject is 15 years of age. Blood samples are collected at each visit for detection of islet autoantibodies, candidate infectious agents and
nutritional biomarkers; monthly stool samples are collected for infectious agents. Demographic data, information regarding the child’s diet, illnesses, vaccination, allergies and psychosocial factors are obtained by interviews and questionnaires.

The primary outcome is the development of persistent autoantibodies to one or more of the antigens insulin, GAD, IA-2. The secondary outcome is the development of type 1 diabetes according to the criteria drawn up by the American Diabetes Association (ADA), (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997).

As of December 31, 2010, 259 children developed persistent islet autoantibodies (26 from Germany) and 80 children developed type 1 diabetes (12 from Germany).

(www.teddystudy.org)

**TrialNet**

TrialNet is a network of known diabetes centers, founded in 2002 to develop and implement new strategies in the treatment of type 1 diabetes. TrialNet emerged from the clinical centers organizing the Diabetes Prevention Trial 1 (DPT-1) in the USA. TrialNet is sponsored by the National Institutes of Health (NIH), the Juvenile Diabetes Research Foundation (JDRF) and other medical organizations of the USA. One of the main objectives is to develop new immunological therapies to protect beta cells from further destruction before but also after diabetes manifestation. The network comprehends intervention trials as well as studies on the natural history and the genetics of type 1 diabetes. Also international centers (Melbourne, Bristol, Turku, Milan, Munich) participate in TrialNet.

Since November 2005, the Forschergruppe Diabetes e.V. has participated in the Natural History Study which analyzes the pathogenesis of type 1 diabetes by genetic, immunologic and metabolic markers in first degree relatives of subjects with type 1 diabetes aged 1-45 years and in second and third degree relatives aged 1-20 years. In 2010, 167 participants were recruited, totalling 1389 participants at the Munich site. In case of positivity of islet autoantibodies, subjects can enter phase 2 (for baseline risk assessment) and phase 3 (for follow-up risk assessment). In Munich, 9 participants decided to enter phase 2 or 3.

In April 2010, the site in Munich was informed that eligible subjects for the TrialNet Oral Insulin Study could be referred to the Trialnet Center in Milan. Up to now, none of the IAA positive individuals has been willing to travel to Milan, but meanwhile the site has fulfilled the qualifications for a participation in the Australian INIT trial.

**German Gestational Diabetes study**

The aim of the German Gestational Diabetes Study is to stratify risk for postpartum diabetes in women who have gestational diabetes. 306 women postpartum participate in the study. Recruitment was conducted from 1989 until 1999. The women were invited to a follow up after 9 months, 2, 5, 8, 11, 14 and 17 years. The visits included an oral glucose tolerance test, measuring the HbA1C and documentation of the Body mass index.
As a conclusion of this study, women with gestational diabetes have a high risk of developing diabetes postpartum. Women with overweight and insulin dependence have the highest risk. Prevention of the postpartal risk is evaluated in the first study for Germany PINGUIN (www.pinguin-studie.de)

**German Gestational Diabetes Offspring study**

The German Gestational Diabetes Offspring study prospectively has followed more than 300 offspring of mothers with gestational diabetes since 1989. Enrolled subjects are followed at the age of 9 months, 2, 5, 8, 11, 14, 17 and 20 years of age for islet autoantibodies (ICA, IAA, GADA, IA-2A) and environmental factors. Further more genetic risk markers (T1D and T2D related) are determined. One aim of the study was to assess the impact of GDM on overweight risk and insulin resistance in offspring. Data on the child’s BMI was collected at the age of 2, 8 and 11 years from 232 offspring of mothers with GDM (OGDM) and compared to 757 offspring of mothers with T1D (OT1D) and 431 offspring of non-diabetic mothers born between 1989 and 2000. Insulin resistance (HOMA-IR) was determined at the age of 8 and 11 years in 751 children (74 OGDM). Overweight was defined as BMI percentile ≥90; insulin resistance was defined by HOMA-IR. Overweight prevalence was increased in OGDM as compared to OT1D and to offspring of non-diabetic mothers throughout childhood (age 11 years: 31.1%, 15.8%, 15.5%, p=0.005). Maternal obesity was an important predictor of overweight risk in children (age 11 years OR 7.0, 95%CI 1.8-27.7, p=0.006); birth size and maternal smoking during pregnancy were inconsistently associated, and treatment of GDM during pregnancy did not affect overweight risk. HOMA-IR was increased in OGDM compared to offspring of non-GDM mothers (p=0.01, adjusted for sex and age), and was associated with the child’s BMI (p=0.004).

Based on these results we conclude that overweight and insulin resistance in children is increased in OGDM compared to OT1D or offspring of non-diabetic mothers. The finding that overweight risk is mainly associated with maternal obesity suggests that familial predisposition contributes to childhood growth in these offspring. These results have been published in 2010.

**Postpartum outcome in mothers with Gestational diabetes and their Offspring (POGO-study)**

Offspring of mothers with Gestational Diabetes Mellitus (GDM) are at increased risk of childhood obesity and insulin resistance. Maternal pregravid overweight was identified as a strong predictor for the development of overweight and insulin resistance in the offspring of mothers with GDM. Maternal Body Mass Index (BMI) and weight gain during pregnancy have been reported to affect the gut microbiome in the offspring and recent studies indicate that the gut microbiota play a role in the development of obesity and type 2 diabetes by increasing dietary energy harvest, promoting fat deposition, and triggering systemic inflammation. In addition, microbiota transplantation studies in murine models and humans have shown that by transplantation of obese-type gut flora total body fat is increased and that by transplantation of feces from lean donors into obese patients, insulin sensitivity is improved in obese patients. Based on these results the hypothesis is that offspring of
mothers with GDM show changes in the composition of gut microbiota that are affected by maternal pregravid BMI and correlate with offspring BMI, glucose homeostasis and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR). To test this hypothesis, we initiated a new study addressing the following aims:

1.) To determine whether the gut microbiome differs significantly between children at risk of obesity and children not at risk (risk factors being maternal GDM status of the mother, maternal pregravid obesity and birth size of the child) and

2.) To determine whether the gut microbiome is different in obese children and in insulin resistant children compared to normal weight children and whether the gut microbiome is associated with higher levels of inflammation markers and leptin.

The expected outcome of the project is to provide fundamentally new insight to the underlying mechanisms of the development of overweight and insulin resistance in high-risk children and in the next step, open a new research field of developing intervention/prevention strategies.

Ethical approval for the study has been obtained in December 2010, the study will start in 2011.

TEENDIAB

The TEENDIAB study is part of the TREPPYD Consortium within the German Competence Network Diabetes mellitus. The TEENDIAB study aims to investigate the period of puberty and adolescence in the natural course of type 1 diabetes development. Based on preliminary data, the study hypothesizes that the immune phenotype of children developing autoimmunity during puberty and adolescence differs from that in childhood, therefore implying that different genetic and environmental factors influence the development of autoimmunity in puberty and early infancy.

TEENDIAB is an observational cohort study in which up to 1500 children between 8 and 12 years of age who have a first degree relative with T1D will be enrolled. The follow-up will be continued until the age of 18. Analyses with respect to the phenotype of islet autoimmunity, genotypes of type 1 diabetes - and type 2 diabetes - associated genes, insulin resistance and beta cell function will be performed, as well as the collection of clinical information regarding growth, obesity, and physical exercise. The findings of this study will enhance the understanding of type 1 diabetes pathogenesis by providing answers to the poignant questions related to the increasing diabetes incidence in youth and the impact of obesity on diabetes development in this age period.

The TEENDIAB study is a two-center study in Germany. The study sites in Munich (Forschergruppe Diabetes, Klinikum rechts der Isar, Technische Universität München, A.-G. Ziegler) and Hannover (Kinderklinik auf der Bult; T. Danne and O. Kordonouri) recruit TEENDIAB participants from all over Germany. The first study visit and the visit at the age of fourteen years will take place in the study centers Munich or Hannover; remaining follow-up visits can be carried out either at the two study sites or as remote visits by local pediatricians or family doctors. Follow-up includes the collection of fasting samples for HOMA-IR, samples during IVGTT and OGTT, hormone profiles, metabolic and inflammatory markers, lipids, detailed
demographic data, physical examinations, dietary habits, and measurements of intima thickness and hypertension in all subjects.

The primary outcome is the development of persistent autoantibodies to one or more of the antigens insulin, GAD, IA-2, or ZnT8. The secondary outcome is the development of type 1 diabetes according to the criteria drawn up by the American Diabetes Association (ADA) (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997).

Recruitment began in November 2008, currently (12-2010), 233 children aged 8-12 years with a first degree family history of type 1 diabetes are recruited into the study.

Recruitment is facilitated by a network of collaborating centers (hospitals, diabetologists, pediatric general practitioners) advertising in diabetes newsletter, brochures, internet, lay journals, television, radio, and news articles as well as by self support groups.

German new onset diabetes in the young incident cohort study: DiMelli

Diabetes incidences in childhood and youth are increasing worldwide, including autoimmune and non-autoimmune cases. Recent findings indicate that there is a larger than expected proportion of type 2 diabetes in youth and potentially cases of intermediate diabetes phenotypes. Most pediatric diabetes registries focus on type 1 diabetes and reliable data on type 2 diabetes incidences in youth are missing. The DiMelli study aims to establish a diabetes incidence cohort of patients diagnosed with diabetes mellitus under the age of 20 years in Germany for the characterization of diabetes phenotypes using immunologic, metabolic and genetic markers. It will furthermore assess the contribution of obesity and sociodemographic factors in the development of diabetes in childhood and youth. Recruitment started in 2009 and is expected to be at a rate of 250 patients per year. Preliminary results of 216 recruited patients, classified 84% of the cases as autoimmune diabetes (multiple islet autoantibody positive), 4% as non-autoimmune diabetes (islet autoantibody negative), and 12% as intermediate cases (one islet autoantibody positive). Prevalence of multiple islet autoantibodies was highest in children below 15 years of age and non-autoimmune cases were more frequent in adolescents over age 10 years. Prevalence of IAA decreased with age at onset, and was highest in children below 4 years and lowest in adolescents aged over 15 years (96% vs. 29%; p<0.01). Frequencies of GADA, IA-2A and ZnT8A were similar in all age groups. Autoantibodies to tissue transglutaminase C are associated to celiac disease and were positive in 11%, and autoantibodies to thyroid peroxidase that are associated to autoimmune thyroiditis were detected in 6% of the patients. Patients with multiple autoantibody positivity were younger (median age 10.0 vs. 14.1 years; p<0.01) and had lower fasting c-peptide levels (median c-peptide 1.2 nmol/l vs. 2.1 nmol/l; p<0.01) than patients classified as autoantibody negative patients. Fasting c-peptide levels were age-dependent and increased with age at onset (p<0.01). Patients with autoimmune diabetes had a lower BMI percentile at onset than patients with intermediate or non-autoimmune diabetes (median BMI percentile 18 vs. 43 vs. 69; p<0.01). The DiMelli study will help to generate new hypotheses on the etiology of diabetes and the contribution of genetic predisposition and environmental risk factors to the different types of diabetes. Establishing a biobank of sera and peripheral blood mononuclear cells of a large cohort of diabetes patients will facilitate future
hypothesis testing. The DiMelli study is supported by the Kompetenznetz Diabetes mellitus (Competence Network Diabetes mellitus) funded by the Federal Ministry of Education and Research (FKZ 01GI0805), and is a cooperation between the Forscherguppe Diabetes and the Kassenaerztliche Vereinigung Bayerns (KVB), the Association of Statutory Health Insurance Physicians of Bavaria.

B. Intervention studies

Babydiet study

BABYDIET is a German wide primary intervention study, which was initiated in order to determine whether primary intervention through delayed introduction of dietary gluten is feasible and could reduce the incidence of islet autoimmunity, celiac disease autoimmunity and type 1 diabetes in high risk first degree relatives of patients with type 1 diabetes. Another aim of the study is the identification of environmental agents which could be triggers of islet autoimmunity and the development of a biobank for future research projects. BABYDIET prospectively follows high risk offspring or siblings of patients with type 1 diabetes from birth. Newborn children were eligible if they had been younger than 3 months and had a high diabetes risk HLA genotype (DRB1*03-DQA1*0501-DQB1*0201/DRB1*04-DQA1*0301-DQB1*0302; DRB1*04-DQA1*0301-DQB1*0302/DRB1*04-DQA1*0301-DQB1*0302 or DRB1*03-DQA1*0501-DQB1*0201/ DRB1*03-DQA1*0501-DQB1*0201). To recruit a total of 150 children, 1162 newborns were screened for HLA-eligibility-genotypes between 2000 and 2006 from all over Germany. HLA class II alleles HLA-DRB1, HLA-DQA1 and HLA-DQB1 were determined using polymerase chain reaction-amplified DNA and nonreactive sequence-specific oligonucleotide probes. Thereof 171 (14.7 %) offspring met the inclusion criteria and 150 (87.7 %) families decided to participate in the study. Children participating in BABYDIET were randomized to one of two dietary intervention groups that introduced gluten-containing cereals either at age 6 months as recommended by the German National Committee for the Promotion of Breastfeeding or at age 12 months (intervention group). 73 children were randomised into the late gluten exposure and 77 children to the control group. Children are monitored intensively by 3 monthly collections of venous blood, urine and stool and 3-day records of weighed food intake for 3 years and yearly thereafter. Infections, medication and the introduction of new food groups are recorded daily until the age of 3 years. Additional demographic and family history questionnaires are collected at 3, 12, 24 and 36 month of age. Of the 150 participating children, 120 children completed follow-up to at least the age 3 years or reached the study endpoint (persistent islet autoantibody positive) before the age of 3 years. All children will be followed until the age of 10 years. Blood samples are collected to determine islet autoantibody profiles (IAA, GADA, IA2A, titer and epitope pattern), gliadin and tissue transglutaminase antibodies, tetanus and rubella antibodies, food antibodies, cytokine pattern of reacting T cells after tetanus stimulation, and T regulatory cells. The trial was completed in 2010 and the results submitted for publication.
PINGUIN-study (Postpartal Intervention at women with gestational diabetes and under insuline therapy)

Since December 2007 the randomized, placebo-controlled, double-blind, clinical phase-2 study with DPP4 Inhibitor vildagliptin has been conducted; overall 140 women will be included in the study. PINGUIN is the first type 2 diabetes prevention study in Germany in a cohort of women, who had gestational diabetes treated with Insulin. The purpose of the study is to prevent or delay the onset of type 2 diabetes in this group. During 24 months 50 mg vildagliptin is given twice a day; and another 12 months follow up. Primary endpoint of the study is the development of type 2 Diabetes according to the criteria of the ADA 1997. Secondary endpoints are improvement of ß-cell function. Improvement of further parameters indicating the metabolic syndrom and to check the lasting clinical value of a 24 months intake of 100mg vildagliptin daily. Further secondary endpoints are reduction of the risk to develop GDM during a following pregnancy and the reduction of insulin resistance.

Inclusion criteria are: age > 18 years, insulin dependent GDM during the preceding pregnancy, complete remission of GDM after delivery, date of delivery < 9 months before. Exclusion criteria are: pregnant or breastfeeding women, GADA or IA-2A pos. women or diagnosed diabetes. Up to now 70 patients were screened, 47 of them could be included in the study. The first 30 months visits are completed.

Immunointervention with DiaPep277® in recently diagnosed Type 1 Diabetes

Already in the 1990s, T-cells associated with islet autoimmunity were shown to react also with the 60 kDA human heat shock protein hsp60. These T-cells identify the amino acid sequence at position 437-460 (p277). DiaPep277 is a synthetic peptide with 24 amino acids in the sequence of p277, which proved to be cross-reactive with the native p277. It is injected subcutaneously.

First results of a treatment with DiaPep277 were published in November 2001. Ten months after the first injection of DiaPep277, the secretion of C-peptide was little changed compared to study inclusion shortly after diagnosis, whereas it had decreased to less than a third in placebo treated subjects. Until now, no side effects occurred which were clearly caused by DiaPep277.

Therefore, these results of the pilot study are now verified in a double-blind, placebo-controlled trial in 11 countries (Europe, Israel, South Africa). In Germany, three centers are involved (Gießen, Munich, Hannover). The study drug is given 9 times in 2 years and the secretion of C-peptide (fasted, mixed meal or glucagon stimulated) is determined several times during the course. In September 2009, the last of 457 participants was randomized; at the Forschergruppe Diabetes e.V., a total of 41 subjects were screened and of these, 38 were randomized. Two interim analyses showed promising results.

Immunointervention with DiaPep277® in recently diagnosed type 1 diabetes subjects – Phase III

Based on the phase II results, the aim of this double-blind, placebo-controlled, phase III trial is to demonstrate the treatment efficacy of DiaPep277® in preserving beta-cell
function in Type 1 diabetes patients. This new study is a global clinical trial, which will be conducted in Europe, USA, Israel and Latin America with approximately 450 patients being recruited at more than 100 clinical study sites. In Germany 5 centers are involved: Düsseldorf, Giessen, Hannover, München and Münster. The trial lasts up to 27 months and the study drug will be administered in total 10 times. Inclusion criteria are the following: age of 20-45 years old, diagnosis of Type 1 diabetes for up to 5 months at screening, beginning of insulin therapy within a month of the diagnosis of T1D, fasting C-Peptide levels ≥ 0.22nmol/l and <0.8nmol/l, presence of at least 1 of the diabetes-related autoantibodies and body mass index ≥ 17kg/m² and <30kg/m² at screening. The secretion of C-peptide (fasted, mixed meal or glucagon stimulated) will be determined several times during the trial. In our center in Munich the protocol is already approved and the recruitment has started.

AIDA (Anti-Interleukin-1 in Diabetes Action)

Since April 2009, the Forschergruppe Diabetes e.V. has been participating in AIDA, a randomized, double-blind, placebo-controlled phase IIa multicenter trial in subjects with recently diagnosed type 1 diabetes aged 18-35 years. The agent is anakinra (Kineret®), a synthetic interleukin-1-receptor antagonist which is injected subcutaneously in a daily dose of 100 mg over a period of 9 months.

Interleukin-1β, a proinflammatory cytokine, is a known effector molecule of inflammatory β-cell destruction. It lowers β-cell function, leads to apoptosis and possibly to induction of type 1 diabetes. The natural interleukin-1-receptor antagonist is a competitive inhibitor and prevents human β-cells from loss of function caused by glucotoxicity and apoptosis. The aim is to maintain β-cell function in patients with recently diagnosed type 1 diabetes by immunomodulation with anakinra and to assess safety and efficacy of the treatment. A total of 80 participants in eleven European countries will be included. Principal Investigator is Thomas Mandrup-Poulsen from the STENO Diabetes Center in Gentofte, Denmark which is also the coordinating center. In Munich 13 patients were screened and of these, 11 were randomized by the end of 2010.

Pre-POINT study

The aim of this trial is to induce a protective immune response to islet autoantigens by oral administration of insulin prior to the development of autoimmunity in children with high risk for type 1 diabetes. Pre-POINT will determine the feasibility of performing a primary autoantigen vaccination trial in high risk children and will determine the dose of oral insulin administration that is safe and is bioavailable to the immune system that will be used in the phase II POINT trial aimed at determining efficacy.

Type 1 diabetes results from a destruction of insulin-producing beta cells in the pancreas by the body’s immune system. Children who develop diabetes have autoantibodies to insulin and other beta cell antigens prior to clinical disease, and it is considered that the autoimmunity to these antigens is the underlying cause of beta cell destruction. Previous studies in the NOD mouse have indicated that early mucosal administration of insulin induces protective immunity and prevents diabetes
onset. A study in man performed in autoantibody positive individuals showed that oral administration of comparatively low doses of insulin was safe, but the study was inconclusive with respect to efficacy. We have shown that neonates having a >50% risk to develop type 1 diabetes can be identified, thereby allowing mucosal administration of insulin to be attempted prior to the initiation of autoimmunity. This study will aim to find a dose of oral insulin administration that could be used in these children to provide protection against type 1 diabetes.

The Diabetes POINT study will give oral insulin to high risk children who have not yet developed the autoantibodies in order to provide protection before the disease process starts. This will be performed in the context of a multi-center, placebo-controlled, double-blind,double-masked, intervention trial. Using information about other family members with diabetes and genetic typing, children with a >50% risk to develop diabetes will be identified. Initially (Pre-POINT), a dose-finding phase of the POINT study will be performed. Up to 25 children will be randomized to increasing doses of insulin administered orally (2.5, 7.5, 22.5, or 67.5 mg per day) to determine a dose that is safe and bioavailable to the immune system. Children will be monitored for the development of islet autoantibodies and diabetes, and blood samples will be taken to investigate whether the study drug has induced a protective immune response to insulin. Depending upon the outcome of Pre-POINT, the study will continue to the phase II POINT study which will determine the efficacy of oral insulin administration in autoantibody-negative high risk children.

The findings of the Pre-POINT dose-finding study will determine whether the continuation of the study to determine efficacy is feasible and if so which dose and route of administration will be used.

If the study is successful, the results of this trial are of high relevance for type 1 diabetes and could lead to a primary type 1 diabetes vaccination for all genetically at risk children.

CORDY

Autologous stem cell transplants have already been successfully used as a treatment option for autoimmune disorders such as multiple sclerosis (MS) and Evans syndrome as well as for some types of cancer. In recent animal studies bone marrow transplantation has resulted in the prevention of hyperglycemias.

The specific aim of the current study is to regenerate pancreatic islet insulin producing beta cells and also improve blood glucose control through the transfusion of autologous cord blood into children with newly diagnosed type 1 diabetes. As secondary aims, we attempt to study the potential changes in metabolism and immune function that lead to islet regeneration. The study is an open controlled study. The aim is to include 20 patients for transfusion or natural follow-up.

Potential participants are children older than 1 year, whose type 1 diagnosis doesn’t date back more than 12 months. For the treatment group the umbilical cord blood should be stored in the private German cord blood bank Vita34.

The therapy consists of one transfusion at the beginning of the study, but the subjects will be observed and examined during the next 2 years. In total 23 children (5-10 in Germany) will undergo a transfusion. In our centre 5 children were already
transfused and 5 followed for natural follow-up. This study is part of an international study, which is conducted in USA since April 2005.

MuKiS (mother-child-sport) - a study to evaluate the impact of exercise on maternal metabolism and fetal development in women with gestational diabetes

The number of pregnant women with gestational diabetes is increasing worldwide. Increased maternal and fetal morbidity and an increased long-term risk for obesity and type 2 diabetes are a direct consequence. There are hardly any studies on the influence of exercise on the child's metabolic status and on child development in the womb. MuKiS (mother-child-sport) is a pilot study and examines the feasibility and the efficiency of exercise therapy for women with gestational diabetes. 60 women with gestational diabetes should be included in the study. These must be between 24th and 30th week of pregnancy. The women are then randomized into an intervention and control group (n = 30 / n = 30). Women in the intervention group received 10 weeks physical activity. The physical activity program takes place two times a week for 45 minutes instead. If a positive influence of exercise to the mother's metabolic status and to the child development is shown by MuKiS, the efficiency and durability of this lifestyle intervention in a Phase II-III study will be evaluated in a subsequent study. So far 14 women have been included in the study, of which 7 were randomized to intervention and 7 to control group.

INIT II

The INIT II is a randomized, double-blind, placebo-controlled trial of intranasal insulin in children and young adults (age 4-30 years) at risk of type 1 diabetes. Subjects of the TrialNet Natural History Study with confirmed serum antibodies to two or more islet antigens and a normal oral glucose tolerance test can participate and receive insulin or placebo intranasal on seven consecutive days and then once a week for 12 months. The funding body of the study, which is sponsored by Melbourne Health, Australia, is the Australian Diabetes Vaccine Development Centre (DVDC). The primary objective of the study is to determine whether intranasal administration of insulin to children and young adults at risk for type 1 diabetes will reduce the rate of development of diabetes. Secondary objective is to determine if intranasal administration of insulin to children and young adults at risk for T1D will: 1) prevent expected loss of pancreatic β-cell function, 2) improve insulin action, 3) stimulate immune responses consistent with the induction of immune tolerance to insulin. Therefore, the team of Anette Ziegler reviewed the study protocol and its amendments, the SOPs, the IMPD, the DSMB charta, the safety report and the monitoring plan. They translated diaries and patient information into German and submitted the study documents to the local Ethics Committee in April, the amendment in August 2010. The documents were also submitted to the regulatory authority (BfArM). At the same time, database training was completed and suggestions were made to improve the database with respect to German requirements. Finally, the local database in Munich was checked for potential study participants, and the visit schedule was discussed within the team, so candidates can be invited for screening in the very near future.
C. Specific projects

Staging and monitoring pathogenesis and intervention in type 1 diabetes

The aim of the following project is to identify peripheral blood markers of the adaptive immune response that can be used to stage pre-clinical type 1 diabetes, and as secondary markers of outcome in intervention trials.

Autoreactive T and B cells form part of the adaptive immune response to islet autoantigens that almost invariably precedes type 1 diabetes onset. In theory they are the specific markers of the autoimmune pathogenesis that can be utilized to monitor pathogenesis and intervention. We have demonstrated that specific characteristics of the humoral autoimmune response can stratify progression from single to multiple islet autoimmunity and from antibody positivity to diabetes. It is not known whether these and other markers of the adaptive immune response can be used for monitoring purposes.

In the following project the overall hypothesis of this grant to be tested is that measurable characteristics of the humoral islet autoimmune response and of the immune regulatory T cell response may be used to stage and monitor disease progression in type 1 diabetes. Our novel markers that stratify progression to type 1 diabetes as well as markers of immuno-regulatory T cell phenotype will be tested for their ability to stage and respond to intervention in ongoing natural history studies and primary intervention studies performed in Munich, as well as an international cohort and oral antigen intervention study (DPT-1). Specifically, the project will 1. determine the most accurate models for stratifying progression to diabetes using islet antibody characteristics; 2. determine whether the models and markers can stage progression to diabetes; 3. develop novel assays for stratification of risk; 4. determine whether assays that measure immune-regulation of cell-mediated responses are useful for monitoring intervention; and 5. determine whether oral insulin treatment given as a primary intervention can modify the development of autoimmunity in high risk neonates (The Diabetes POINT study).

It is expected that markers or a marker ‘phenotype’ will be identified that progressively changes during progression to type 1 diabetes which can therefore be used for monitoring disease and intervention.

This study is of relevance for type 1 diabetes and will directly contribute to our ability to monitor progression to diabetes and therefore have validated surrogate markers, which can be used in clinical intervention trials.

This project was supported by JDRF Early-Career-Patient-oriented-Diabetes-Research-Award to Dr. Peter Achenbach

GAD autoantibody affinity in LADA patients

The DIAMYD clinical pilot trial tested whether GAD65 antigen-specific immune intervention could preserve endogenous insulin secretion in patients with latent autoimmune diabetes in adults (LADA). Forty-seven LADA patients received 2 subcutaneous injections of alum-formulated recombinant human GAD65 (4 µg, 20
µg, 100 µg or 500 µg) or placebo at intervals of 4 weeks and were followed thereafter for 30 months with respect to metabolic outcome. Here, we asked whether GAD autoantibody (GADA) affinity is affected by vaccination with rhGAD65 and associated with fasting C-peptide levels in LADA patients. The study was done in collaboration with Drs Ake Lernmark and Carl-David Agardh (Malmö, Sweden) and Drs Jadwiga Furmaniak and Michael Powell (Cardiff, UK). Sera of 46 participants of the DIAMYD trial were available with sufficient volume for affinity testing. GADA affinity was measured at baseline (before first injection) and 20 weeks after the second injection of study drug (week 24) by competitive binding experiments with [125I]-labeled and unlabeled recombinant human GAD65 (RSR Ltd., Cardiff, UK). At baseline, GADA affinity varied from 2 x 10^7 to 5 x 10^12 L/mol (median 3.6 x 10^10 L/mol), was correlated with GADA titer (r = 0.4727; P = 0.0009), and was not significantly associated with islet autoantibody status among the 46 LADA patients. Although, 10 of 33 single GADA-positive patients had relatively lower affinities (<2 x 10^9 L/mol) as compared to 1 of 13 patients positive for GADA plus IAA, IA-2A and/or ZnT8A (P = 0.1). With respect to the intervention, patients receiving 4 µg rhGAD65 had higher baseline GADA affinity (median 9.3 x 10^11 L/mol; n = 9) than patients receiving placebo (2.3 x 10^10 L/mol; P = 0.03; n = 12), or 20 µg (6.3 x 10^10 L/mol, n = 8), 100 µg (1.2 x 10^10 L/mol; n = 9) or 500 µg rhGAD65 (1.8 x 10^10 L/mol; n = 8). No significant changes in affinity were observed from baseline to week 24 for all intervention groups. Fasting C-peptide correlated with GADA affinity (r = -0.3704; P = 0.02) and GADA titer (r = -0.3169; P = 0.03). Patients with affinity <2 x 10^9 L/mol had better preserved fasting C-peptide levels at baseline than patients with higher affinity (mean 1.02 vs. 0.66 nmol/L; P = 0.007), and kept higher levels on follow-up (month 2: 1.22 vs. 0.62, P = 0.001; month 6: 1.10 vs. 0.71, P = 0.03; month 12: 1.32 vs. 0.76, P = 0.1; month 18: 1.21 vs. 0.76, P = 0.08; month 24: 1.28 vs. 0.75, P = 0.04; month 30: 1.26 vs. 0.61 nmol/L, P = 0.02).

In conclusion, intervention with alum-formulated rhGAD given twice subcutaneously to LADA patients at intervals of 4 weeks had no effect on GADA affinity. Our data suggest that patients with low GADA affinity and low GADA titer have better metabolic outcome reflected by preservation of mean fasting-C-peptide levels >1 nmol/L over a time course of 30 months.

**GAD autoantibody affinity in schoolchildren**

In collaboration with Dr Michael Schlosser (Greifswald) GADA affinity and epitope specificity was tested in follow-up samples from 102 GADA-positive children and adolescents of the general population who have been prospectively followed in the Karlsburg Schoolchildren study. We found GADA profiles and associated T1D risks very similar to our previously published findings in children with a first-degree T1D family history (Diabetes 56: 1527-33) suggesting that the same mechanisms of GAD65 autoimmunity acting in both groups of GADA-positive children.
**A simplified method to assess affinity of insulin autoantibodies**

Insulin autoantibodies (IAA) precede type 1 diabetes, but not all IAA-positive children develop other islet autoantibodies and disease. Diabetes risk can be stratified by laborious IAA affinity measurement using competition with multiple ligand concentrations. A simplified method to assess IAA affinity was developed and established in our lab on IAA-positive samples from prospectively followed first-degree relatives of T1D patients, and subsequently tested in sera from Australian relatives who participated in the screening for the INIT-2 study. This was done in collaboration with Dr Peter Colman (Melbourne, Australia).

We identified a single competitor concentration that discriminates low- and high-affinity IAA. Discrimination was achieved among 122 IAA-positive sera using 7.0 nM competitor which is 54-fold that of the assay radioligand concentration. Relative-binding <60% at this competitor concentration identified all 85 sera with affinities ≥1.0 x 10⁸ L/mol and none with lower affinities (P<0.0001), and 45 (96%) of 47 multiple islet autoantibody-positive sera (P<0.0001). IAA competition was further tested in a second set of 119 IAA-positive sera from Australia. Of these, 99 fulfilled high-affinity competition criteria of <60% relative-binding at 7.0 nM competitor including 89 (94%) of 95 sera with multiple islet autoantibodies (P<0.0001). Thus, increased IAA specificity can be achieved with simple modification to existing assays.

**Autoantibodies to CCL3**

Recently, autoantibodies against the inducible chemokine CCL3 were reported to be associated with T1D, and a commercial kit for the measurement of anti-CCL3 autoantibodies is now available. We had the opportunity to evaluate this commercial kit (MT-CCL3-IFU; Micromedic Technologies, Ramat Gan, Israel) using sera from 54 patients with new or recent onset of T1D (median age 10 years), 40 controls (median age 11.2 years), 33 first-degree relatives of patients with T1D (median age 10.5 years) and 17 participants with other autoimmune diseases (median age 12.5 years). We found no association between anti-CCL3 autoantibodies and T1D. Instead, we found that the level of anti-CCL3 autoantibodies correlated with the length of storage of the serum sample assayed. Thus, we would not recommend that the ELISA-based anti-CCL3 autoantibody kit be used to aid the prediction or diagnosis of T1D.

**Modelling Type 1 diabetes pathogenesis**

Progression to type 1 diabetes (T1D) is not uniform. Based on individual genetic background and environment children may develop islet autoimmunity at different ages, show different autoantibody profiles (e.g. intensity and autoantigen specificity / spreading), and progress to T1D rapidly, slowly, or not at all. In this project, we aim to develop mathematical algorithms that consider multiple T1D-associated factors in order to analyse the complex T1D pathogenesis, explain immune pattern, and identify clusters that are associated with different progression of islet autoimmunity. The project is done in collaboration with the group of Dr zu Castell from the Department of Scientific Computing at Helmholtz Center Munich.
For a first analysis, we used data from 142 children who have been followed from birth in the BABYDIAB study and developed persistent autoantibodies against insulin (IAA), glutamate decarboxylase (GADA), insulinoma-associated antigen 2 (IA-2A) and/or zinc transporter 8 (ZnT8A). Data were analysed using similarity measures that considered qualitative changes of the four autoantibodies on follow-up and association studies on genetic background considering HLA and INS VNTR alleles and SNPs of 9 other T1D-associated genes.

We developed an algorithm that was used for hierarchical clustering of children based on similarities in autoantibody profiles over time. Clusters distinguished between children who differed with respect to age and sequence of IAA, GADA, IA-2A and ZnT8A appearance, and provided good discrimination with respect to T1D development ranging from 0-100% among individual clusters. Children within each cluster were then analysed with respect to genetic background in association studies. A second algorithm was developed, which could link clusters to combinations of T1D-associated alleles/gene SNPs.

In conclusion, mathematical modelling of data from prospective cohorts can identify groups of children with distinct progression of islet autoimmunity to T1D and may provide insight into complex disease mechanisms. Cluster analysis will further be refined.

DASP 2010 workshop

The Diabetes Antibody Standardization Program (DASP) is a collaboration between the Immunology of Diabetes Society (IDS) and US Centers for Disease Control and Prevention (CDC), set up to evaluate and improve assays for diabetes-associated autoantibodies. The DASP Committee has organized and run the DASP 2010 workshop and presented data at the IDS meeting in Incheon, South Korea (see program attached). Peter Achenbach is chairing the committee since 2008. Laboratories from 19 countries participated with a total of 194 assays. Workshop data are currently being analyzed in detail.

Immunomodulating effect of adjuvant therapy with 1α,25-dihydroxyvitamin D3 on dendritic cells of new onset type 1 diabetes patients

Several studies have suggested a protective effect of vitamin D3 on the development of type 1 diabetes. The active form of this vitamin (1α,25(OH)2D3; Calcitriol) affects the differentiation, maturation, and function of dendritic cells (DCs). In this study, we investigated whether patients with new-onset type 1 diabetes who received adjuvant therapy with 1α,25(OH)2D3 showed an immunological effect on DC subpopulations. The study was done in collaboration with Paolo Monti and Ezio Bonifacio from Dresden University of Technology.

Within a double-blind randomised placebo-controlled phase II clinical study 40 new-onset type 1 diabetes patients were randomly assigned to receive either 0.25µg oral calcitriol (n=22; median age ± SD, 31.4 ± 6.8 yrs; 16 male) or oral placebo (n=18; 24.0 ± 6.0 yrs; 13 male) daily over a nine-month period, and were followed for a total of 18 months. Mononuclear cells were isolated at 0, 3, 6, 9, 12 and 18 months from peripheral blood. The number of DCs and the ratio of the plasmacytoid and myeloid
DC subpopulations (PDC, MDC1, MDC2) was determined before treatment, and at 9, 12 and 18 months by FACS analysis and compared between the two groups. A decrease in the number of DCs from baseline to month 9 was detected among calcitriol-treated patients (p=0.03). This was not observed for placebo-treated patients. At month 9, the proportion of DCs among mononuclear cells was lower in calcitriol-treated patients (median 0.71%, IQR 0.49-0.93) compared to the placebo group (0.96%, IQR 0.67-1.17; p=0.04). Furthermore, calcitriol-treated patients had a lower proportion of PDCs (median 0.34%, IQR 0.22-0.48; vs. 0.49%, IQR 0.34-0.82, in placebo group; P=0.03). No difference between the treatment groups was observed with respect to the MDC1 and MDC2 subpopulations. Six calcitriol-treated patients decreased in PDCs by >50% of their baseline numbers (potential "responder"). After stopping the intervention (at month 12 and 18) there were no longer differences in the number of DCs or its subpopulations between patients from both treatment groups. In conclusion, during an adjuvant therapy with daily 0.25µg calcitriol the number of DCs is decreasing, especially among the PDC subpopulation. These data suggest an immune modulating effect of 1α,25-dihydroxyvitamin D3 in new-onset type 1 diabetes patients.

**IA-2 autoantibody affinity and epitope specificity in children at risk for Type 1 diabetes**

Autoantibodies to insulinoma-associated protein 2 (IA-2A), insulin (IAA), glutamate decarboxylase (GADA) and zinc transporter 8 (ZnT8A) are features of pre-clinical type 1 diabetes (T1D) in children. For IAA and GADA, antibody affinity is related to epitope specificity and identifies children who are more likely to develop multiple islet autoantibodies and diabetes. In this study, we asked whether affinity and epitope binding of IA-2A are associated and may stratify progression to T1D in IA-2A-positive children.

From 50 children who were prospectively followed from birth in the BABYDIAB study (median observation time 8.6 years) the first available IA2-A positive serum sample was analyzed (median age at IA-2A seroconversion 3.6 years). IA-2A positive follow up samples were available from 30 of these children. IA-2A affinity was measured by competitive binding experiments using a constant amount of [125I]-labelled (0.02 nmol/L) and 5 increasing concentrations of unlabeled recombinant human IA-2ic (5.1x10^-7 – 5.1x10^-11 mol/L) or TBST buffer, respectively. Affinity was determined by non-linear regression analysis using GraphPad Prism 3 program and expressed as reciprocal Kd value (L/mol). Epitope specificity of IA-2A was determined using radiobinding assays on [35S]methionine-labelled in vitro translated constructs of IA-2ic (JM601-682 and PTP682-979) and the homologue protein IA-2β.

At first IA-2A appearance, at least one additional autoantibody (IAA, GADA, ZnT8A) was detectable in 49 (98%) children. IA-2A affinity ranged from 107 to 1011 L/mol (median 5.5x10^9 L/mol) and was high (≥1x10^9 L/mol) in 41 (82%) children. Affinity was not significantly correlated with IA-2A titer at IA-2A seroconversion. Antibody binding to IA-2-PTP epitopes and to IA-2β was detected in 60% of samples, respectively, 38% bound to IA-2-JM, and 52% to multiple IA-2 epitopes. There was no significant association between IA-2A affinity and epitope specificity.

On follow-up, IA-2A affinity remained relatively constant and high. All three children with affinities <1x10^8 L/mol in the first IA-2A positive sample increased to high affinity.
Epitope spreading to IA-2-PTP and IA-2β was common. Three children did not develop antibodies to the PTP region and remained at lower IA-2A affinity; among them the only child with single and transient IA-2A. So far 33 out of 50 (66%) children developed T1D at median age of 6.9 years (median 2.1 years after IA-2A seroconversion). Affinity could not stratify T1D risk. Our data support the notion, that autoimmunity against multiple islet antigens is associated with the occurrence of high-affinity autoantibodies and that single IA-2A are rare. Consequently, affinity does not improve T1D prediction among IA-2A positive children. Spreading of IA-2A reactivity against epitopes within the IA-2-PTP region and IA-2β indicates a mature, T1D-relevant autoimmune response.

Islet autoantibody profiles in young patients with recently diagnosed diabetes

As part of the Competence Network Diabetes we have provided core measurements of islet autoantibodies for patients with recent-onset diabetes participating in the DPV project (Prof. Holl, Ulm). DPV is a German-wide registry for patients with all types of diabetes, particularly teenagers and children but also adults. The centralized high-quality measurement of all major T1D-associated autoantibodies (IAA, GADA, IA-2A, ZnT8A) improves diabetes classification and allows determination of autoantibody phenotypes at diabetes onset. Furthermore, it allows direct comparison of antibody results between different KKNDM studies and, in case of GADA and IA-2A, large NIH-funded international studies (e.g. TEDDY) because of the use of harmonized autoantibody detection methods. The project also represents an unprecedented German-wide expert diagnostic service in the field of diabetes and is now well accepted among paediatricians and doctors treating diabetic patients. We currently receive about 50-60 blood samples from young patients with newly diagnosed diabetes per month. As of today, about 1500 samples were screened for islet autoantibodies. In a first analysis, we looked at autoantibody profiles in the sera of 619 young DPV patients with recent-onset diabetes (median time from diagnosis 1 day, IQR 5.3-13.1; age range 0.7-18.9 years). Autoantibodies to GAD, IA-2 and COOH-terminal constructs of the R325 or W325 variants of human ZnT8 were measured in all samples. Insulin autoantibodies were measured in samples obtained within the first two weeks of diagnosis. Of all patients, 78% had at least two of the autoantibodies, 11% had a single autoantibody, and 12% were autoantibody-negative suggesting that the diabetes of these patients is not autoimmune. This fact strongly supports the disease relevance of the 4 autoantibody markers used for screening and suggests that autoimmune diabetes is usually associated with multiple antibodies. Differences between patients can be seen with regard to autoantibody status and age at diagnosis. Autoantibody-negative patients were older than autoantibody-positive patients (median age 11.8 years vs. 9.4 years; p=0.01). There was no difference in age at diagnosis between single and multiple autoantibody-positive patients (median age 9.8 vs. 9.2 years, p=0.3). However, single GADA-positive patients were older at diabetes onset than single IAA-positive patients (median age 11.6 vs. 7.4 years, p=0.03). Differences were also seen in the prevalence of the four autoantibody-specificities with respect to autoantibody status. Within single autoantibody-positive patients, GADA prevalence was highest (46%), followed by IAA (26%), IA-2A (18%), and ZnT8A (15%). Within multiple autoantibody-positive patients, the prevalence was high and similar for all four antibodies (71-84%).
ZnT8A were detected in 397 (64%) patients, among them 387 of 537 (72%) with positive GADA, IA-2A and/or IAA, and 10 of 82 (12%) who were negative for these autoantibodies (P<0.0001). Among the 397 ZnT8A positive patients, 97 (24%) had antibodies that only bound the ZnT8 R325-variant, 33 (8%) had antibodies that only bound the ZnT8 W325-variant, and 267 (67%) had antibodies that bound with both ZnT8 R325W-variants. The appearance of ZnT8A restricted to one of the ZnT8 variants was not associated with age at diagnosis (P=0.3). Overall, ZnT8A prevalence increased with age at diagnosis (P=0.01). ZnT8A were more often found in patients who already had autoantibodies against two or more islet autoantigens other than ZnT8: 66 of 122 (54%) patients previously classified as single autoantibody positive were ZnT8A-positive, compared to 321 of 415 (77%) patients previously classified as multiple autoantibody-positive (P<0.0001).

In summary, a precise distinction of autoimmune and non-autoimmune diabetes in a young cohort with recent-onset diabetes is possible by screening for the current set of autoantibody-markers (IAA, GADA, IA-2A, ZnT8A) suggesting that they are strongly associated with autoimmunity that leads to young onset T1DM.

**International harmonization of GAD- and IA-2 autoantibody assays for NIDDK consortia**

Autoantibodies to IA-2 (IA-2A) and GAD (GADA) are markers for diagnosis, screening and measuring outcomes in NIDDK consortia studies. A harmonization program was established to increase comparability of results within and among these studies.

Large volumes of six working calibrators were prepared from pooled sera with GADA 4.8-493 WHO units/ml and IA-2A 2-235 WHO units/ml. Harmonized assay protocols for IA-2A and GADA using $^{35}$S-methionine-labelled in vitro transcribed and translated antigens were developed based on methods in use in three NIDDK laboratories. Antibody thresholds were defined using sera from patients with recent onset type 1 diabetes and healthy controls. To evaluate the impact of the harmonized assay protocol on concordance of IA-2A and GADA results, two laboratories retested stored TEDDY study sera using the harmonized assays.

The harmonized assays gave comparable but not identical results in the three laboratories. For IA-2A, using a common threshold of 5 DK units/ml, 549 of 550 control and patient samples were concordantly scored as positive or negative, specificity was >99% with sensitivity 64% in all laboratories. For GADA, using thresholds equivalent to the 97th percentile of 974 control samples in each laboratory, 1051 (97.9%) of 1074 samples were concordant. On the retested TEDDY samples discordance decreased from 4% to 1.8% for IA-2A (n=604 samples; P=0.02) and from 15.4% to 2.7% for GADA (n=515 samples; P<0.0001).

Harmonization of GADA and IA-2A is feasible using large volume working calibrators and common protocols, and is an effective approach to ensure consistency in autoantibody measurements.
Insulin autoantibodies with high affinity to the bovine milk protein alpha casein

Food introduction into the human diet varies between countries and ethnicity, but general principles are exclusive breast milk or formula feeding during the first 4 to 6 months of life, with solid foods such as cereal, vegetables and fruit being introduced between 17 and 26 weeks of age. Exposure to food components such as the wheat protein gluten, bovine insulin from cow’s milk, as well as the bovine milk component casein have been discussed as causes of type 1 diabetes, and in the case of bovine insulin as the primary immunizing antigen giving rise to antibodies that are reactive with human insulin. Insulin autoantibodies (IAA) can appear in children within months of introducing solid foods to the diet and before clinical type 1 diabetes.

The aim of this study was to determine whether infant dietary antigens could be immunizing agents of IAA. IAA binding to [125I] insulin was competed with food preparations and extracts of foods encountered in the infant diet (milk formulas, bovine milk, wheat flour, fowl meal). Bovine milk powder extracts inhibited IAA-positive samples from 6 of 53 children (age 0.3-14.0 years) participating in German prospective cohorts. Inhibition in these sera ranged from 23% to 100%. Competition was abolished when hydrolyzed milk powder was used. Competition with protein components of bovine milk found that two of the 6 milk-reactive sera were strongly inhibited by alpha- and beta-casein; none were inhibited by the milk proteins bovine serum albumin or lactoglobulins. The two casein-reactive sera had high affinity to alpha-casein (1.7x10^9 ; 3.1x10^9 L/mol), and lesser affinity to beta-casein (4.0x10^8 ; 7.0x10^7 L/mol) and insulin (2.6x10^8 ; 1.6x10^8 L/mol). No children with milk-reactive IAA developed autoantibodies to other islet autoantigens or diabetes (median follow-up 9.8 years). These results suggest that autoimmunity to insulin can infrequently occur via cross-reactivity to food proteins, but this form of IAA immunization does not appear to be associated with progression to diabetes. This study is funded by grants from the Deutsche Forschungsgemeinschaft (ZI 310/12-6, ZI 310/14-4, FZ 111), the Juvenile Diabetes Research Foundation (1-2006-665, P. Achenbach: 11-2005-1117), and the NIH/DFG Research Career Transition Award Program (K. Adler: KO 3418/1-1), and is a cooperation between the Forschergruppe Diabetes and A. K. Heninger and E. Bonifacio from the Center for Regenerative Therapies, Dresden University of Technology.

The effect of gestation on the development of autoimmune diabetes in non-obese diabetic mice

The impact of gestation and fetal-maternal interactions on pre-existent autoimmune beta cell destruction is widely unknown. Pregnancy is a condition in which insulin demand is increased and which is associated with an expansion of beta cell mass. In some cases, this leads to glucose intolerance and gestational diabetes which resolves after delivery. However, in cases where there is underlying autoimmunity, as identified by islet autoantibody positive mothers, diabetes often persists throughout life with typical characteristics of type 1 diabetes, including life-long insulin requirement. The onset of diabetes during gestation in these women is hypothesized to be a result of the sudden increase in insulin demand which is not met by a limited islet reserve and an acceleration of immune mediated beta cell destruction. This is contrasted by reports of amelioration of autoimmune diseases during pregnancy
through establishing a privileged state of tolerance potentially by shifting immune responses towards a lower or less inflammatory state.

The aim of this study was to investigate the influence of gestation per se and via half and fully mismatched male mates on the onset of autoimmune diabetes in non-obese diabetic (NOD) mice. Using a litter-matched experimental design, we examined cumulative diabetes frequencies of NOD dams mated to genetically identical NOD, haploidentical CByB6F1/J and fully mismatched C57BL/6J male mice. Splenocytes of NOD dams after pregnancy via haploidentical mates were analysed for fetal microchimerism by flow cytometry measuring MHC H2 molecules. Pregnancy from NOD males did neither increase nor accelerate the diabetes onset of NOD dams, demonstrating that gestation per se has no adverse effects. In contrast, pregnancy initiated at 10 weeks of age via haploidentical male mice resulted in significantly (p=0.028) and via fully genetically mismatched male mice in slightly delayed diabetes onset (p=0.048). This finding supports the described reversal of diabetes in NOD mice after infusion of adjuvant plus haploidentical male mouse splenocytes. However, we found no evidence of persistent chimeric lymphocytes from haploidentical paternal origin within the dams’ splenocytes. Therefore, we can only assume that fetal microchimerism is involved in the observed amelioration of the beta cell-directed autoimmune attack in our NOD dams.

In conclusion, gestation has no enhancing effects on pre-existent autoimmune beta cell destruction, and pregnancy via haploidentical mates has delaying impact on autoimmune diabetes development in NOD mice. The data help to elucidate the understanding of gestational effects on type 1 diabetes, but the mechanism on the maternal diabetes development remains to be elucidated.

This study is funded by grants from the NIH/DFG Research Career Transition Award Program (K. Adler: KO 3418/1-1), and is a cooperation between the Forschergruppe Diabetes and Y. F. Fuchs, P. Monti and E. Bonifacio from the Center for Regenerative Therapies, Dresden University of Technology.

Phenotypic characterization of leukocytes in NOD mice in the development of diabetes: subset dynamics and its relationship to diabetic outcome

In human type 1 diabetes, T cells play a major role in the autoimmune pathogenesis. In NOD mice, autoreactive T cells are detectable in peripheral blood at an early age. Therefore, they can be used as predictors for diabetes development. Furthermore, a CD25 expressing subset of CD4+ T cells (regulatory T cells) is able to prevent the onset of diabetes. Also the NOD B cell compartment and its antibody production correlate with the development of diabetes, and specific B cell subsets expand in the process. Thus, the dynamics of such surface expression patterns of activation- and homing markers, and of regulatory T cells and B cells during diabetes development have a high potential to reflect underlying processes, which result in autoreactive inflammation and might have a predictive value for the development of diabetes. Recording these parameters during diabetes development will allow us to discern patterns and develop testable models that correlate with type 1 diabetes development. A mouse cohort was generated assembled by spontaneous autoimmune diabetic NOD mice and genetically closely related NOR mice that do not develop diabetes. Peripheral blood was drawn starting at age 4 weeks for every second week from 54 NOD and 22 NOR mice for flow cytometric and insulin
autoantibody analysis over a period of 36 weeks per mouse. 13 age-matched NOD and 18 NOR mice were additionally followed to address possible effects of the frequent blood sampling on weight development and diabetes onset.

Using the immunology screen at the German Mouse Clinic polychromatic flow cytometry on peripheral blood has been performed. A wide range of T cell and B cell subsets have been analysed, including the novel surface molecule ‘GARP’, which is expressed on a subset of regulatory T cells. Mathematical methods for analysing and integration of multivariate datasets, based on concepts of non-parametric, multivariate statistics and kernel based machine learning have been developed and implemented. Preliminary tests have been carried out to derive a proof of principle. The methods have been adapted to cope with the compositional data from flow cytometry.

Milestones and deliverables after one year:

1st year:

a) Mathematical methods from machine learning have been developed for the interpretation of T and B cell subset patterns and adapted using existing data of wildtype and mutant mice.
b) A female NOD mouse cohort has been generated. Peripheral blood was drawn according to the scheme mentioned above.
c) The blood draw and lymphocyte surface marker staining routines are established.

2nd year:

d) Upon exit of the study, immunohistological organ analysis will be performed to be correlated with finding within the peripheral blood.
e) The mathematical tools developed in 1.a) will be applied and adjusted as the analysis of the data generated in 1.b) and c) progresses.
f) Using the patterns found, the algorithms will be refined and fed back into a data analysis loop towards the aim of elucidating dynamics and parameters in peripheral blood leukocytes during the development of an autoreactive T cell response.
g) The findings will be correlated with immunohistological analysis of secondary lymphoid organs and pancreas target organ.

This study is a collaboration between Adler K, Foertsch K, Ziegler AG (Forschegruppe Diabetes), Adler T, Verschoor A, Busch DH (Institut für Mikrobiologie, Immunologie und Hygiene der TU München), Hense B (Institut für Biomathematik und Biometrie, Helmholtz Zentrum München), and zu Castell W (Abteilung Scientific Computing, Helmholtz Zentrum München).

Antigens and epitopes leading to autoimmune diabetes in RIP-CD80+GP+ mice

Several beta-cell autoantigens have been implicated in the beta-cell directed autoimmune attack leading to type 1 diabetes. In order to identify diabetes-relevant autoantigens and their immune-relevant epitopes we conducted immunization studies in the bitransgenic RIP-CD80xRIP-LCMV-GP mouse model for CD8+ T cell mediated autoimmune diabetes.
Mice were immunized with antigen encoding mammalian plasmids vectors (100 µg DNA per mouse) or with peptide-loaded dendritic cells and followed for 140 days or until overt diabetes developed.

As a positive control, mice immunized with the LCMV-GP-DNA model antigen developed diabetes within median 18 days (n=17). As a negative control, we immunized 16 mice with Hepatitis-B-Surface-Antigen-DNA and one developed diabetes. All mice immunized with the mutated insulin-DNA, A21-A developed diabetes at a median time of 18 days post immunization and 8 of 12 mice immunized with islet-specific glucose-6-phosphatase catalytic subunit-related protein (IGRP)-DNA developed diabetes within median 56 days (P<0.001 vs. negative control). Immunizing the mice with insulinoma-associated protein 2 (IA-2 and IA-2beta), glutamic acid decarboxylase 67kD (GAD67), amylin (IAPP) and chromogranin A (ChgA) induced diabetes in 25-33% of mice within median 63-103 days, whereas immunization with GAD65-DNA and SGNE1-DNA induced diabetes in 2 and no mice, respectively.

To further identify relevant epitopes, we immunized mice with selected peptides (10 µM) loaded onto mature dendritic cells. The murine IGRP_{225-233} peptide induced diabetes in 67% of the treated mice (n=12) within median 91 days (P=0.05 vs. the negative control peptide LCMV-NP_{396-404}), IGRP_{265-273} in 36% of mice, and the FNL9 peptide in 42% of mice. We conclude that this mouse model of antigen specific autoimmune diabetes identified antigens that induce rapid disease onset (insulin), moderate disease kinetics (IGRP and IGRP_{225-233} peptide) and delayed onset (IA-2) and that the model can be used for studying experimental autoimmune diabetes and its immune modulation. This study is funded by grants to Kerstin Adler from the NIH/DFG Research Career Transition Awards Program (DFG KO 3418 1-1) as well as the German Diabetes Association, and is a cooperation between Adler K, Balke H, Foertsch K, Mortler-Hildebrandt LF, Ziegler AG (Forschergruppe Diabetes), Fuchs Y, Spanner A, Bonifacio E (Center for Regenerative Therapies, Dresden University of Technology, Dresden, Germany), and Pechhold K, Harlan DM (Diabetes Center of Excellence, University of Massachusetts, Worcester, MA, USA).

D. EU-Projekt: DIAbetes type 1 PRediction, Early Pathogenesis and Prevention (DIAPREPP)

The group of Prof. Anette-G. Ziegler is part of the collaborative project DIAPREPP and specifically addresses the call FP7 Cooperation Work Programme: Health-2007-2.4.3-1 Early processes in the pathogenesis of type 1 diabetes and strategies for early prevention.

The earliest currently identifiable process in the pathogenesis of type 1 diabetes is the development of autoimmunity to islet beta cells in the form of autoantibodies. Hindering attempts to prevent autoimmune T1D, the aetiology and pathogenesis of the islet auto-immunization, including whether it is preceded by metabolic abnormalities and cell-mediated autoimmunity, is still poorly understood. To overcome this, DIAPREPP will focus on the early auto-immunization against islet antigens, in particular to disclose events preceding current autoantibody markers. The concept is that events prior to auto-immunization govern the likelihood and 'signature' of immunization, which in turn determines progression to disease. The overall objective is to determine mechanisms of islet autoantigen immunization. In a
truly collaborative manner, and through five work packages plus three dedicated to dissemination, training, and management, DIAPREPP will provide an unique set of clinical material that includes a case-control cohort representative of the world's largest studies of pre-T1D, with follow-up and samples from birth, and pancreatic islets and lymph nodes from patients, investigate the effects of environmental exposure to infections on islet cells and immune cells, perform extensive metabolomic analysis of pre-autoimmune samples and in relevant animal models to test mechanistic hypotheses of auto-immunization, carry out detailed analyses of early autoimmune responses with a special focus on autoreactive CD8+ T cells, apply findings to ongoing prevention studies. Together with the group of Merja Roivianen (National Institute for Health and Welfare THL) and within work package 2, 343 stool samples of 104 children at type 1 diabetes risk participating in the BABYDIET dietary intervention trial were tested for the presence of enterovirus by using highly sensitive real-time PCR assay. The analysis showed that 24% of the children were positive for enterovirus and 96% of the stool samples of these children. Altogether, 32 enterovirus serotypes were isolated from the stool samples of the BABYDIET study children. There was no association of the exposure to dietary gluten at either 6 or 12 months of age (dietary intervention), maternal T1D, breastfeeding duration (<4 or ≥4 months) and the presence of enterovirus infections in the children. Children who were enterovirus-positive had not a higher risk to develop islet autoantibodies and transglutaminase autoantibody compared to children who were enterovirus-negative. There was also no association of enterovirus infections on clinical symptoms such as gastrointestinal and respiratory symptoms. Further analyses of the frequency of enterovirus infections in autoantibody positive and negative children are in progress with respect to enterovirus subtypes. Since 11 of 343 fecal specimens were collected from children with acute gastrointestinal symptoms, they were analyzed, in addition to enteroviruses, for the presence of other intestinal RNA viruses (norovirus, astrovirus, rotavirus, sapovirus). Highly sensitive virus specific real-time RT-PCR methods revealed that altogether 45.5 % of stool samples were positive regarding different enteric viruses (9.1 % for enterovirus, 9.1 % for sapovirus, 27.3 % for norovirus). Another project within work package 3 and in cooperation with Matej Orešič focuses on events that occur prior to the development of islet autoimmunity. We examined whether serum metabolite profiles differ between children with respect to islet autoantibody status and the age of islet autoantibody development. Twenty-nine metabolites of the amino acid metabolism and 511 lipids assigned to 12 lipid clusters were analyzed in children with a type 1 diabetic parent who first developed autoantibodies at the age of 2 years or younger or at the age of 8 years or older, or remained autoantibody-negative and were matched for age, date of birth, and HLA genotypes. Metabolites and lipids were measured using ultra performance liquid chromatography and mass spectroscopy. Differences in the metabolite profiles were observed relative to age and islet autoantibody status. Independent of numerous age-related differences, autoantibody-positive children had higher levels of odd-chain triglycerides and polyunsaturated fatty acid containing phospholipids compared to autoantibody-negative children and independent of age at first autoantibody appearance. Children who developed autoantibodies within the first two years of life had a two-fold lower concentration of methionine compared to those who developed autoantibodies in late childhood or remained autoantibody-negative.
E. Competence Network Diabetes mellitus (CNDM) (Technische Universität München)

The German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung [BMBF]) agreed to fund a diabetes competence network – the first diabetes mellitus project to be funded by the ministry’s new “Health Research – Research for People” program. The aim of the new network is to improve healthcare provision by generating and integrating new insights into the development, prevention and treatment of diabetes mellitus. Optimum healthcare is especially important in the early stages of the disease, when complications and their impact on healthcare budgets are easier to prevent. A key focus of the new Diabetes Competence Network will be to improve the translation of research results into everyday medical practice. This competence will be available not only to national and international experts, but also to doctors, patients and the public at large.

The network integrates seven consortia including 25 research projects at different institutions throughout Germany. These consortia were chosen through an international peer-review selection process. The leader and deputy of each of the seven consortia comprise the network for the Executive Board of the Competence Network Diabetes. The Executive Board is the main decision making body.

The network has a Speaker who represents the network in public and towards the German Ministry for Education and Research. The Speaker is elected for a three year period by the Executive Board of the Competence Network Diabetes. The elected Speaker for the first three years is Anette-Gabriele Ziegler. The Network and Speaker are supported by the Central Office of the Competence Network Diabetes, situated in Munich, at the institution of the speaker. The Central Office comprises the managing director (Dr. Volker Hammen, an assistant Lydia Henneberger), as well as public relations with a press office (Cordula Falk). The office should support the speaker and Executive Board. The office assists in the organization of national and international symposia, congresses, phone conferences, and meetings of the scientists working for the network. The office controls the central financial administration for these activities. It prepares and distributes internal reports for the network members, the interim reports and final reports for the BMBF. Further obligations of the central office are the production of the network newsletter, the creation of network flyers and the network homepage http://www.kompetenznetz-diabetes-mellitus.net.

The network has a Scientific Advisory Board (SAB) with a chair and 7 members representing different areas of diabetes research. The function of the SAB is to act as an independent advisory body to both the scientists and the BMBF with respect to the quality, content and direction of the diabetes network research and activities. The SAB is invited to an executive board meeting once a year. In addition, an exchange should take place once per year within a phone conference. The network integrates four expert committees (working groups) to support horizontal and vertical networking within the consortia.

The four working groups are:

- Working group meta-database (Wolfgang Rathmann, Düsseldorf)
- Working group Epidemiology, Biometrics, and Health Economics (Wolfgang Rathmann, Düsseldorf / Rolf Holle, Munich / Andrea Icks, Düsseldorf)
• Working group Mental aspects (Johannes Kruse, Giessen / Frank Petrak, Bochum)
• Working group Biomarker and Central measurements (Ezio Bonifacio, Dresden)

The network is linked to the Competence Network Obesity and to the Telematic (TMR) platform. Together, the Diabetes and Obesity networks establish a Metabolomics platform and a Central laboratory platform which provide network partners with central measurements of specialized biomarkers for diabetes and obesity. The aim of this project will be the development of Standard Operating Procedures SOPs (sampling, processing, storage and preparation of samples) for harmonization of laboratory measurements in projects of both networks. The TMF platform, of which the Competence Network Diabetes is a member, is an overhead structure which supports the exchange of information with other medical competence networks, and special technology platforms.

Currently the network includes 62 members who represent the scientific components of each project (members list in appendix). The members may participate in Executive Board meetings, but are not eligible to vote.

Central and Internet communication tools:
A homepage and communication platform of the Competence Network Diabetes was established. A two-monthly newsletter summarizing recent findings of individual research projects is distributed through this communication platform to national and international experts as well as physicians, patients and the public at large. Patients can register and receive information on research studies as well as other diabetes studies in Germany through the Competence Network Diabetes. A strong collaboration exists between the Competence Network Diabetes and the German Diabetes Association (DDG) and diabetes.De.

The use of registries for recruitment into clinical trials:
The DiMelli registry is currently used to recruit for prevention and intervention studies such as Pre-POINT and a cord blood transfusion trial performed in collaboration with the University of Florida. All physicians who register their patients receive the results of islet autoantibody and metabolic testing together with an invitation for the child or the sibling to contact the network to discuss participation in suitable clinical trials. This activity is expected to be extended to patients in the DPV registry.

Statements of the competence network:
Two position statements were written in collaboration with the German Diabetes Association (DDG) and diabetes.DE. One about the use of the biomarker HbA1c to diagnose diabetes (“Stellungnahme der Deutschen Diabetes Gesellschaft, diabetesDE und des Kompetenznetzes Diabetes mellitus zur Verwendung des HbA1c-Wertes als Biomarker zur Diabetesdiagnose“) and one about the XCell-Center, a private clinic for regenerative medicine, in combination with a research review of today’s knowledge of stem cell therapy to treat diabetes.

Interactions with international organisations and studies:
International cooperations with the NIDDK-SEARCH, EURO-DIAB, ISPAD (International Society for Pediatric and Adolescent Diabetes), DIAPREPP EU-consortium, CDC antibody standardization program (DASP), IMIDIA, KORA-study, PREPOINT study, and the Recall study are ongoing. As a specific example, joint projects with the TEDDY-consortium (prevalence of DKA at onset of type 1 diabetes)
and the SEARCH-for diabetes in youth project from the US (comparison of adolescents classified as type 2 diabetes from central European and north American descent) were initiated.

Scientific Advisory Board evaluation:
The network projects and year 1 report were presented to the SAB in October 2009 at a meeting with all scientists. The SAB discussed progress and directions with the individual consortia and the steering committee.

Pediatric Biobank
Immunologic and genetic research on diabetes depends on biomaterials from well-characterized patients. For the investigation of either multigenetic traits, or rare monogenetic forms of diabetes, large sample sizes are required. In the past, research on pediatric aspects of diabetes in Germany was negatively affected by the lack of multicenter biobanks. Therefore, a central Pediatric biobank for Germany should be provided by the office of the competence net. The competence of the already existing DPV network for Germany and Austria should be used for this. DPV is an EDP-based documentation programme for patients with all diabetes types, for adults as well as for children and youngsters. The importance of immunology for type-1-diabetes, as well as for other types of diabetes, is indisputable. In order to test new markers of this disease, serum samples from a large number of newly diagnosed children with diabetes (< 3 month diagnose of diabetes), recruited from both the DPV initiative in Germany/Austria and the TREPPYD-DiMelli register in Bavaria, will be analysed for islet autoantibodies (GADA, IA2-A, ZnT8R-A, ZNT8W-A, IAA) at the laboratory of Prof. Ziegler.

Central measurements for the Competence Network Diabetes
Initiated by the Workgroup Biomarker and in collaboration with the Competence Network Obesity a harmonization working group was founded to establish, organize and manage a central high quality analytical platform for the benefit of all consortia of both networks. The goal of using central laboratory platforms is to harmonize methods and the measurement of biomarkers as well as to ensure a continuous quality control.

The work plan has been developed in collaboration with the Competence Network Obesity. A Harmonization Committee has been established to accomplish this specific task which was awarded additional funding by the BMBF. Funding includes a scientific position (Kerstin Adler) to oversee the activities. The Harmonization Working Group has identified a series of markers that have relevance to both, the Diabetes and Obesity networks (Cholesterol, LDL Cholesterol, HDL Cholesterol, Small dense LDL, Free fatty acids, polyunsaturated fatty acids, Insulin, Proinsulin, C peptide, HbA1c, Leptin, Adiponectin, Retinol binding protein 4 (= RBP4), diabetes-associated islet-antibodies, C reactive protein (hsCRP), monocyte chemoattractant protein 1 (MCP-1; CCL2), Interleukin-8, Interleukin-6, Nampt (Visfatin), Type-1- and Type-2-diabetes associated genes). A specific call for central laboratories within Germany for measurement of these markers was announced and 16 applications were received and are currently under review: Five applications from central laboratories of university hospitals, five applications from laboratory companies and six applications from research laboratories. It is expected that from this laboratories, a core will be contracted to act as central laboratories for measurements of samples that are from cohorts included in network projects and registries. This will include the provision of standard operating procedures for sample collection, storage and shipping, the establishment of network specific quality control programmes and the
identification of contact persons for the Competence Networks. A Metabolomics Platform was established and is used by two Networks, Diabetes and Obesity.

TREPPYD

Consortium Leader: Anette-Gabriele Ziegler, TU Munich.

Diabetes in childhood and adolescence is largely autoimmune in phenotype, but growing trends in obesity have complicated both diagnosis and treatment. It now seems plausible that both immuno-modulating therapies and therapies that improve insulin action could delay diabetes onset. Long-term TREPPYD objectives are to determine how obesity and insulin action can be targeted to reduce diabetes incidence in youth in Germany; identify different phenotypes of type 1 diabetes and islet autoimmunity for individualized therapy options; develop novel autoantigen-directed strategies of immune regulation that specifically control the aberrant autoimmunity found in young onset diabetes, and develop sophisticated tools and methods of autoimmune profiling that will improve assignment of pre-diabetic subjects to appropriate intervention trials and monitoring efficacy.

TREPPYD has 5 funded subprojects (1, 2, 4, 5, 6) to address these objectives in an interactive manner.

Project 1 executes a novel prospective German-wide cohort study in pubertal children to identify etiological factors associated with islet autoimmunity that initiates during adolescence. (TEENDIAB, Ziegler)

Project 2 draws on clinical research strengths to perform a Bavarian-wide incident cohort study and biobank collection innovatively and jointly executed through the public/private health insurance infrastructure and the scientific sector. Of strategic importance, this is closely linked to the Bavarian DMP (disease management programme) and the DPV (Diabetes Prospective Documentation Initiative) which will allow registry-based follow-up of diabetes management the cohort. (DiMelli, Munte)

Project 4 exploits technological know-how in autoimmunity and immune assays to phenotype humoral autoimmune responses preceding diabetes onset. (Islet Autoantibody-Project, Achenbach)

Projects 5 and 6 bring two recent entries to German science with outstanding track records to develop drug-based and autologous cell-based antigen-specific immunotherapy to cure diabetes. (Treg-Projekt, Kretschmer; DiaCord, Bonifacio)
III. Publications 2010

Original Papers


Winkler C, Bonifacio E, Grallert H, Henneberger L, Illig T, Ziegler AG. BMI at age of 8 years is influenced by the type 2 diabetes susceptibility genes HHEX-IDE and CDKAL1. Diabetes: 59(8):2063-7. 2010

Ziegler AG, Mollenhauer U, Achenbach P, Bonifacio E. Anti-CCL3 autoantibodies are not markers of type 1 diabetes when measured by a commercial ELISA method. Diabetologia. Epub ahead of print. 2010

Bookchapters, Abstracts, Letters, Proceedings


Hummel M. Reisen, Berufswahl, Führerschein, Sport – Optionen und Empfehlungen. Der niedergelassene Arzt 59 (2) 54-56 . 2010


Hummel M. Sekundäre Diabetesformen. Diabetologie und Stoffwechsel 5: R47-R64. 2010


Hummel M. Pharmakotherapie des Gestationsdiabetes. Congress report 5: 8-12. 2010


Wallner M, Thümer L, Hummel M, Ziegler AG. Treatment of type 1 diabetes is changing-breakthrough in immune intervention. submitted Diabetes und Stoffwechsel. 2010


Warncke K, Ziegler AG. Prävention des Diabetes mellitus. Submitted 2010


Abstracts/Congressartikles


Hausmann S. "GAD autoantibody affinity in LADA patients". Diaprepp Meeting 2010


Peissner W, Wallner M, Bunk M, Ziegler AG, Koletzko B. Metabolomics reveals differential metabolic regulation at the catabolic-anabolic switchpoint during oral glucose challenge testing in women after recent gestational diabetes. EASD 2010 in Stockholm (Poster)


Wallner M, Bunk M, Ziegler AG. Diabetesrisiko postpartum - Update der Deutschen prospektiven Gestationsdiabetesstudie (DDG 2010)


Winkler C, Bonifacio E, Grallert H, Lauber C, Trovesi E, Illig T, Ziegler AG. Novel Type 1 and Type 2 Diabetes susceptibility genes influence development of islet autoimmunity and Type 1 Diabetes in children of parents with Type 1 Diabetes. Diabetologia 53 (Suppl. 1): S120: 275, 2010, EASD 2010 in Stockholm

IV. Diploma Thesis/ PhD Projects 2010

Dipl. Ing. Christine Bender
Diploma Thesis: 1,0
Title: „Charakterisierung von Typ-1 Diabetes assoziierten Autoantikörper bei gesunden Schulkindern: Affinität und Epitopspezifität von Glutamatdecarboxylase (GAD) Autoantikörper“

Dr. oec. troph. Daniela Bettina Müller
PhD project: magna cum laude
Title: „Nahrungsbestandteile und deren Einfluss auf die Pathogenese von Autoimmundiabetes von Mensch und Maus“

Dr. rer. nat. Maren Pflüger
PhD project: magna cum laude
Title: „Frühkindliche metabolische und immunologische Prägung bei Kindern mit erhöhtem Typ 1 Diabetesrisiko“
V. Third-party funds 2010

EP7-HEALTH-2007, DIAPREPP N202013
Project: Diabetes type 1 prediction, early pathogenesis, and prevention
Period: 2008-2010
Funding around 180.000,- Euro yearly
Principal investigator

NIH (National Institute of Health, USA)
Consortium: The Environmental Determinants of Diabetes in the Young (TEDDY) Study
October 2002 – September 2013
Per year: 1.000.000,- US$
Principal Investigator

NIH (National Institute of Health, USA)
Consortium: The Environmental Determinants of Diabetes in the Young (TEDDY) Study - Nutrition
October 2002 – September 2013
Per year: 80.000,- US$
Principal Investigator

JDRF (Juvenile Diabetes Research Foundation, USA)
Project: 1-2003-646
BABYDIAB-German multicenter study to evaluate risk- and protective factors for the development of islet autoimmunity and type 1 diabetes in offspring of parents with type 1 diabetes
August 2006 – July 2009
Per year: US $ 0,-
Principal Investigator

NIH (National Institute of Health, USA)
Type 1 Diabetes TrialNet
Natural history Study in type 1 diabetes
Laufzeit: Mai 2004 – 2010
40.000,- US$ in 2010
Principal Investigator für Deutschland
Juvenile Diabetes Research Foundation (JDRF)
Type 1 Diabetes TrialNet
Januar 2009 – Dezember 2011
Funding in 2010: 71.500,- US$
Principal Investigator

JDRF (Juvenile Diabetes Research Foundation, USA)
JDRF File# 8-2006-313)
Primary intervention with mucosal insulin for prevention of type 1 diabetes in infants at high risk to develop diabetes: Diabetes Pre-POINT trial
Per year: 75.000,- US$
Co-Investigator

JDRF (Juvenile Diabetes Research Foundation, USA)
The Anti-Interleukin 1 in Diabetes Action trial (AIDA)
Präventionsstudie beim Typ 1 Diabetes
Period: 2008-2011
Ca 14.081,- Euro per Jahr
Co-Investigator

Adromeda Biotech Ltd.
Multinationale, randomisierte Doppelblindstudie in Phase III zur Untersuchung der klinischen Wirksamkeit und Sicherheit von DiaPep277™ bei Patienten mit frisch diagnostiziertem Typ 1 Diabetes
period 2007 - 2011
Funding for 2010: 30.000 Euro
Co-investigator

JDRF (Juvenile Diabetes Research Foundation, USA)
Early Career Patient-oriented Diabetes Research Award
For coworker Dr. Peter Achenbach
Grant: 11-2005-1117
Project: Staging and monitoring of pathogenesis and intervention in Type 1 diabetes
Period: 2005 - 2010
Funding: 150.000,- US$ yearly

**NIH-DFG Research Career Transition Award Programme (4 Jahre)**
For coworker Dr. Kerstin Koczwara
Period: 2004-2010
Post-doc position for 4 years

**University of Florida – Dr. Schatz**
Projekt: Cord Blood Therapies
Period: 2008 - 2010-02-03
Funding: 40.000 US$ yearly

**Diverse klinische Studien (General Hospital Boston, MSD Sharp, University of Glasgow, Novartis)**
Einnahmen 2010: ca. 12.500 Euro

**BMBF - Krankheitsbezogenes Kompetenznetz Diabetes mellitus:** Translational Research on the early pathogenesis and prevention of young-onset diabetes (TREPPYD)

**Projekt: TP Netzkoordination: Geschäftsstelle, Metadatenbank, IT-Plattform und TP Harmonisierungskomitee, TP Pädiatrische Biobank**
Period: 2008 - 2011
Funding 2010: 409.236,- Euro
Sprecherin Prof. Dr. med. A.-G. Ziegler
Principal investigator
Durchführung: Technische Universität München, vertreten durch das Klinikum rechts der Isar

**TP 1: TEENDiab-Kohortenstudie**
Period: 2008 - 2011
Funding 2010: 326.416,- Euro
For coworker Prof. Dr. med. A.-G. Ziegler
Durchführung: Technische Universität München, vertreten durch das Klinikum rechts der Isar

**TP 2: DiMelli – Cohort Study (ehemals Noddy)**
Period: 2008 - 2011
Funding 2010: 71.684,- Euro
Dr. Axel Munte, KVB
Co-Investigator
Durchführung: Technische Universität München, vertreten durch das Klinikum rechts der Isar

**TP 4: Islet autoantibody high-end characterisation for pathogenetic and therapeutic monitoring of autoimmune diabetes**
Funding 2010: 69.084,- Euro
For coworker Dr. Peter Achenbach
Durchführung: Technische Universität München, vertreten durch das Klinikum rechts der Isar

**BMBF Klinische Studien**
Primary intervention with mucosal insulin for prevention of type 1 diabetes in infants at high risk to develop diabetes: Diabetes Pre-POINTand POINT trial
Per year: 21.219,- Euro
Period: 2008-2011
Co-Investigator
Durchführung: Technische Universität München, vertreten durch das Klinikum rechts der Isar

**Diverse klinische Studien TUM (Vita34)**
Spende für Nabelschnurprojekt
Einnahmen 2009: 0 Euro

Stiftung DHFG
Einnahmen: 20.000 Euro

EFSD – Albert Renold Travel Fellowship for Young Scientists for a 4weeks stay in Finland: (3500€)
VI. Guest Speakers 2010

Beta cell meets immunity – Symposium (Tuesday, September 28, 2010)

Opening and Chair: Anette-Gabriele Ziegler, Munich, Germany

Marian Rewers, Aurora, USA, TEDDY und DAISY contributions to the etiology and natural history of type 1 diabetes
Maren Pflüger, Munich, Germany, Metabolomic profiles in autoantibody positive children
Peter Achenbach, Munich, Germany, Mathematical modelling of autoantibody natural history

Chair: Jochen Seißler; Munich, Germany

Lorenzo Piemonti, Milan, Italy, Intrabone islet transplantation - mouse and man
Eckhard Wolf, Munich, Germany, Xenotransplantation
Heiko Lickert, Munich, Germany, Models for beta cell development
Stephan Speier, Dresden, Germany, Models for in vivo beta cell imaging

Chair: Anette-Gabriele Ziegler, Munich, Germany

Bart Roep, Leiden, Netherlands, Autoreactive T cells in type 1 diabetes
Anne Heninger, Dresden, Germany, Naïve and memory autoreactive T cells in neonates
Anne Eugster, Dresden, Germany, B-cell repertoires of pancreatic lymph nodes
Vito Lampasona, Milan, Italy, Identification of antigen specific B cells

Chair: Ezio Bonifacio, Dresden, Germany

Peter Colman, Melbourne, Australia, INIT II - Intranasal insulin for secondary prevention of type 1 diabetes
Dick Insel, New York, USA, 40 years of JDRF - where to go
Ezio Bonifacio, Dresden, Germany, An abbreviated history of the Oktoberfest

Fortbildungsveranstaltung Typ 1 Diabetes und Insulintherapie (Saturday, November 27, 2010)

Begrüßung: Anette-Gabriele Ziegler, Munich, Germany

Grundlagen:

Moderation: Michael Hummel, Munich, Germany

Anette-Gabriele Ziegler, Munich, Germany, Was haben wir die letzten 10 Jahre zur Entstehung des T1D gelernt?
Peter Achenbach, Munich, Germany, Prävention T1D – der klinische Einsatz naht
Roman Iakoubov, Munich, Germany, Glukagon & GLP-1 – auch bei T1D von Bedeutung?
Jochen Seißler, Munich, Germany, Insulinresistenz bei T1D – Pathogenese und Therapie des Double-Diabetes
Christine Milz, Munich, Germany, Dimelli — Kurz-Vorstellung des neuen bayerischen Diabetesregisters

**Komplikationen der Insulintherapie**

**Moderation:** Johannes Erdmann, Munich, Germany

Oliver Schnell, Munich, Germany, Neue Aspekte zum Insulin — endotheliale Effekte —mitogene Effekte

Karin Lange, Hannover, Germany, Hypoglykämien — die Komplikation der Insulintherapie: psychische und physische Aspekte

Michael Hummel, Munich, Germany, Hypoglykämien — der ungewöhnliche Fall aus der Praxis

**Praktische Durchführung der Insulintherapie**

**Moderation:** Bernd Ruhland, Munich, Germany

Katharina Warncke, Munich, Germany, Kontinuierliches Glukosemonitoring — praktisches Vorgehen zur Optimierung der Diabetestherapie

Hans Hauner, Munich, Germany, Ernährungsempfehlungen bei Insulintherapie

Martin Füchtenbusch, Munich, Germany, Gewichtsmanagement unter Insulintherapie

Martin Halle, Munich, Germany, Sport unter Insulintherapie

**Podiumsdiskussion mit allen Referenten**

**Moderation:** Hellmut Mehnert, Munich, Germany

Hellmut Mehnert, Munich, Germany, Schlusswort und Ausblick „Der Diabetesstandort München“

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**DASP 2010 workshop session, October 31, 9.00-11.00**

**VENUE:** Songdo Convensia, Incheon, Korea

**Moderator:** Peter Achenbach

1. Welcome and Introduction
   - Peter Achenbach (Germany)

2. Results of the DASP 2010 workshop on standard autoantibodies: GADA, IA-2A, IAA, ICA
   - Pat Mueller (USA)

3. New developments
   3.1. The Islet Autoantibody Assay Harmonization Program
   - Alistair Williams (UK)
   3.2. ELISA methods for detection of GADA
   - Michael Schlosser (Germany)
3.3. Experiences with autoantibody assays based on LIPS technique
Bill Hagopian (USA)

3.4. Results of LIPS assays in DASP 2010
Vito Lampasona (Italy)

4. Results of the DASP 2010 ZnT8A workshop
Vito Lampasona (Italy)

5. Combined appearance of GADA, IA-2A, IAA, and ZnT8A in DASP 2010 samples
Michael Schlosser (Germany)

6. Summary and Outlook
Peter Achenbach (Germany)

VII. Press work and Public Relations 2010

Since the end of the year 2004 press and public relations work exists. This expansion of operations aims among other things the support of recruiting members for the ongoing studies and faster publishing of the results of the studies.

Single operations of the press work

- All-the-year announcements
  - in magazines for parents like KIDSgo!, Eltern, Mein Kind, Baby und Familie
  - in diabetes and pharmacy magazines for laymen like Diabetes Journal, feelfree, Befund Diabetes, Diabetes Ratgeber, Insuliner; Subkutan, Diabetes aktuell, Inbalance, Kontakt
  - in magazines for professionals like Deutsche Hebammenzeitschrift, Deutsche Zeitschrift für Klinische Forschung, Kinderärztliche Praxis, Diabetes, Stoffwechsel und Herz, Diabetesforum, Pädiatrix
  - in the daily press like Münchner Merkur, Dachauer Nachrichten and Ruhr Nachrichten
  - in newsletters like curado, Diabetes-Deutschland, MRI, Helmholtz Zentrum München
  - in other magazines like Ernährungsumschau, Zentralblatt,

- Announcements in the television: Quivive (RBB), Projekt Zukunft (Deutsche Welle), Rundschau (BR), Servicezeit Gesundheit (WDR), Alpha Campus (BR Alpha)
- Announcements in the radio: SWR Campus (SWR2)
Single operations of the public relation

- Mail and telephone operations for gynaecologists, paediatricians, diabetologists and self-help groups.
- Providing information materials for different events like midwives workshops, events of self-help groups, diabetic information days and the conference of the DDG.
- Placing of advertisements for different studies in magazines like Zwergerl Magazin, Diabetiker ABC and Mein Kind

Press work and public relations Competence Network Diabetes 2010

Since the beginning of 2010 press and public relations work exists. Since spring 2010 the website has been changed for technical, visual and content reasons. Because of the improved structure, users can find information more quickly. In addition to the separation of content from experts and stakeholders, in the stakeholders section we involved an area of studies.

There, the interested persons get information about current clinical studies. A press section with downloadable press releases and useful graphics now also offers important content for journalists. One focus of innovation is the optimized registry for patients, doctors and journalists. The registered users receive a bimonthly newsletter. In order to place the highest possible position on Google, we started to link the website to the most important diabetes websites and other health websites around Germany and Europe. We also created a homepage for the study “TEENDIAB”, which is a project of TREPPYD (www.teendiab.de).

Single operations of the press work

All-the-year announcements
- in magazines for parents like jung & gesund, Diabetes-Eltern-Journal
- in diabetes and pharmacy magazines for laymen like stixi, Diabetes Journal, feelfree, Befund Diabetes, Diabetes Ratgeber, Insuliner; Subkutan, Diabetes aktuell, Inbalance, Accu Chek Diabetes Live, Bolus, Kontakt
- in magazines for professionals like Kinderärztliche Praxis, Diabetes, Stoffwechsel und Herz, Bayerisches Ärzteblatt, Diabetesforum, Pädiatrix, Medizinische Welt
- in magazines of health insurance companies like BKK Gesundheit and KKH aktiv
- in newsletters like curado, Diabetes-Deutschland, Ärztezeitung, MRI and Springer
- in other magazines like Gesund in Bayern, DGE Info
Single operations of the public relation

- Releasing newsletter (website, print).
- Providing information materials (flyer etc.) for different purposes
- Supporting events and workshops of the Competence Network Diabetes or events, Members of the KKNDm took part (Psychodiabetologie 2010, DGKJ-Jahrestagung 2010)
2. Arbeitsgruppe Prof. Standl

I. Bericht 2010

Die Arbeiten am Schwabinger Herzinfarkt- und Schlaganfallregister wurden gemeinsam mit der Arbeitsgruppe von Prof. Schnell durchgeführt (siehe dort). Weiter ausgebaut wurde die Mitarbeit bei mehreren großen randomisierten Langzeit-Multizenter-Interventionsstudien mit verschiedenen Konzepten zur Blutzucker senkenden Therapie mit Blick auf die Prävention von kardiovaskulären Endpunkten in Kooperation mit der Oxford Trial Unit, United Kingdom sowie der Duke University, United States:

1) Steering-Committee TECOS Trial (Trial Evaluating Cardiovascular Outcomes with Sitagliptin in Patients with Type 2 Diabetes). In Tecos sollen ca. 14 000 Patienten mit Typ-2-Diabetes unter üblicher Versorgung bei niedergelassenen Ärzten eingeschlossen und über mindestens vier Jahre beobachtet werden. Hauptendpunkte sind Herz-Kreislauf-Tod, nichttödliche Herzinfarkte und Schlaganfälle. In speziellen Strata wird der Inkretin-Enhancer Sitagliptin on Top einer Therapie mit Metformin, bzw einer Therapie mit einem Sulfonylharnstoff, Pioglitazon oder Insulin untersucht. Zum Jahresende 2010 waren ca. 5000 Patienten weltweit eingeschlossen.


Die Kontroversen und Debatten über die richtige Zielsetzung für die Blutzuckersenkende Therapie nach der Veröffentlichung der enttäuschenden Studienergebnissen von ACCORD, ADVANCE und VADT im Kontext mit kardiovaskulären Ereignissen wurden in eigenen Arbeiten analysiert und veröffentlicht (siehe Literaturverzeichnis).

Bzgl. der komplexen Situation zur Frage der Primärprävention mit Aspirin bei allen Diabetikern wurde die aktuelle Studienevidenz evaluiert und in Diabetes Care publiziert (siehe Literaturverzeichnis).

II. Veranstaltungen


III. Funktionen und Ehrungen


IV. Veröffentlichungen

(1) O. Schnell, KF Braun, M Müller, E Standl, W Otter
The Munich Myocardial Infarction Registry: impact of C-reactive protein and kidney function on hospital mortality in diabetic patients
Diabetes & Vascular Disease Research 2010 XX(X) 1-6
dvr.sagepub.com DOI 10.1177/1479164110372641

(2) The Navigator Study Group, under inclusion of E. Standl, Data Safety Monitoring Committee. Effect of nateglinide on the incidence of diabetes and cardiovascular events.


(7) E. Standl, O. Schnell, A. Ceriello. Postprandial Hyperglycemia and Glycemic Variability – Should We Care? Diabetes Care (2011) 34, Suppl.2, accepted

(8) A. Nicolucci, E. Standl. Anti-Platelet Therapy for Every Diabetic Person? Diabetes Care (2011) 34, Suppl.2, accepted
3. Study group of Prof. Dr. O. Schnell

I. Progress report 2010

Diabetes and the heart

We continued to analyze the data of the “Silent Diabetes Study”. The results were presented at the Congress of the European Society of Cardiology (ESC) (1) and the annual meeting of the “Diabetes and Cardiovascular Disease EASD Study Group in Belgrade. The aim of the study was to compare isolated glycated hemoglobin (HbA1c) sampling with the results of an oral glucose tolerance test (OGTT) for early detection of silent diabetes mellitus (DM) in routine cath lab patients with known or suspected coronary artery disease (CAD). 1015 pts, 696 male (69%), 319 female (31%), mean age 68 + 9 yrs (45 - 89 yrs), who were referred for coronary angiography (CA) from May 2007 until May 2009, were included in the study. Patients with a history of DM or abnormal glucose regulation were excluded from the study. In all patients, and also in both subgroups with either elective CA (n = 866) or acute CA (n = 149), no correlation was found between HbA1c levels and angiographically determined signs of presence or progression of CAD. In contrast to HbA1c sampling, a significant correlation was found between glucometabolic state determined by OGTT and progression of CAD. In the entire group, newly detected DM was revealed in only 4.1% by HbA1c testing, but in 14.1% by OGTT results. Isolated sampling of glycated hemoglobin (HbA1c) was found to be not suitable for early detection of silent DM in routine catheterisation laboratory patients without a history of DM or abnormal glucose regulation. No correlation was detected between HbA1c levels and angiographically determined presence or progression of CAD. The OGTT remains the gold standard for early detection of silent DM in pts referred for elective CA or CA in ACS. The results have been submitted to an international peer-reviewed journal and are currently prepared for submission in the revised version. Additional analyses including adiponectin, hs-CRP and NT-pro BNP are currently being undertaken.

Another study aimed at the recognition of abnormal glucose metabolism and its impact on treatment in patients with acute myocardial infarction in Germany (SWEETHEART registry) (2). Since 2007, 1773 consecutive patients with STEMI or NSTEMI were enrolled into the MI-registry SWEETHEART. Out of 1,773 consecutive patients with MI, 919 (52.3%) presented with STEMI and 837 (47.7%) with NSTEMI. Diabetes was already known in 33.0% of patients. Oral glucose tolerance tests identified another 16.1% of patients with manifest diabetes and 22.4% with impaired fasting glucose or impaired glucose tolerance (pre-diabetes). In summary, there was a high prevalence of newly diagnosed diabetes and pre-diabetes in consecutive patients with myocardial infarction in Germany.

New analyses of the Munich Myocardial Infarction Registry were also published (3). The aim of the study was to analyze hospital mortality with regard to the presence of diabetes, elevation of C-reactive protein (CRP) levels and impaired kidney function (IKF) on admission. All patients of the Munich Myocardial Infarction Registry (1999 – 2004, n = 2015) were assessed. In both D (n= 770, 38,%) and ND (n= 1245, 61,2%), CRP and kidney function on admission were analyzed with regard to hospital outcome. In diabetic patients, both a CRP level > 7 mg/l and a glomerular filtration rate (GFR) < 60 ml/min were an independent risk factor for mortality (OR 3.5, 95%
CI: 1.8-6.9; OR 4.4, 95% CI: 2.4-8.3). In non diabetic patients with CRP levels equal or below the median and absence of impaired kidney function, hospital mortality was 0.7 % whereas the presence of the triad diabetes, CRP levels above the median and impaired kidney function increased hospital mortality to 23.5 %. The registry demonstrates that the presence of the triad diabetes, elevated CRP levels and reduced glomerular filtration rate on admission is associated with an excessive hospital mortality. Optimized early interventions are to be initiated to potentially overcome the unfavourable prognosis.

An experimental study investigated the effect of intermittent hypoxia on pathological changes in the left ventricular (LV) myocardium due to PPG in lean mice, and evaluated the influence of acarbose, an alpha-glucosidase inhibitor (4). Male C57BL/6J mice aged 8 weeks were exposed to intermittent hypoxia (8 h/day during the daytime) or kept under normoxia. PPG was caused by restriction of feeding to 1-h periods twice a day, with the restricted-diet (RD) mice receiving either standard chow or chow containing 0.02% acarbose. Treatment with acarbose inhibited oxidative stress and TNF-alpha mRNA expression, and preserved the histological architecture of the LV myocardium.

For the occurrence of cardiovascular complications in diabetes, endothelial dysfunction plays an important role. Alterations of the endothelial-dependent coronary flow reserve have been shown to be based on the reduced bioavailability of nitric monooxide (NO). As compared with other nitrates, the long-acting nitrate pentaerythritol tetrannitrate (PETN) displays characteristics, which may be beneficial for the treatment of endothelial dysfunction. The current view on the topic was summarized focussing on treatment with pentaerythritol tetrannitrate (PETN) may be advantageous in diabetic patients, who frequently present with endothelial dysfunction (5).

The current status of clinical trials assessing diabetes and cardiovascular disease was summarized in a review article, which also focussed on the current ESC / EASD Guidelines on Diabetes, Pre-Diabetes and Cardiovascular disease (6). Furthermore, cardiovascular effects of glitazones and potential differences within the group of glitazones were also summarized in a review article (7).

**Self-monitoring of blood glucose in diabetes**

Several articles of the group focussed on self-monitoring of blood glucose (8-11). Prof. Schnell chaired a group of European diabetologists to develop a consensus statement on clinical cases of self-monitoring of blood glucose. The document was published in two parts. The background of the consensus document was as follows: advanced international guidelines and recommendations on self-monitoring of blood glucose (SMBG) had recently been published. They support the structured implementation of the SMBG in diabetes. Individualized strategies are required to apply optimized and efficacious treatment approaches.

The Consensus of European experts, therefore, focussed on 9 clinical case, which address aspects of the daily clinical practice: 1. Paediatric patient with type 1 diabetes, 2. Patient with gestational diabetes, 3. Type 2 diabetic patient with elevated postprandial blood glucose levels, 4. Type 2 diabetic Patient with lack of motivation and adherence, 5. Type 2 diabetic patient at risk of hypoglycaemia or with hypoglycaemia unawareness, 6. Type 2 diabetic patient with coronary artery disease, Type 2 diabetic patient with nephropathy, 9. Elderly Type 2 diabetic patient (≥ 80
years of age). The 9 clinical cases aimed at presenting typical clinical settings, in which self-monitoring of blood glucose could be useful and recommended. With this, the document presents a new step in recommendations for the use of self-monitoring of blood glucose and supports the aim to implement structured self-monitoring of blood glucose in the daily clinical care.

II. Educational activities, symposia

Two highly-scientific symposia were organized as educational activities. The meetings were supported by the "Verein zur Förderung der internationalen wissenschaftlichen Kommunikation im Bereich der Diabetologie e.V." and they were held under the auspices of the Diabetes Research Group e.V.

The first symposium was organized in cooperation with the Study Group “Diabetes and Cardiovascular Disease in Barcelona on the occasion of the Congress of the European Society of Cardiology. The attendance was excellent and more than 400 participants joined the meeting. The second meeting was held in Berlin on the occasion of the annual meeting of the "Stiftung der herzkranke Diabetiker". More than 250 diabetologists and cardiologists attended the meeting.

Programme ESC Congress, Stockholm

Diabetes and Cardiovascular Disease: Effects of Insulin and GLP-1

A symposium of the Munich Diabetes Research Institute and the Diabetes & Cardiovascular Disease EASD Study Group
31st August 2010, ESC Congress 2010 Stockholm, 2:00 p.m. – 3:30 p.m.

Chair: A. Ceriello, E. Standl

14:00 – 14:05 Introduction
A. Ceriello (Barcelona, ES), E. Standl (Munich, DE)

14:05 – 14:30 Insulin and cardiovascular disease: the reality
S. Del Prato (Pisa, IT)

14:30 – 15:00 The physiological role of GLP-1
M. Diamant (Amsterdam, NL)

15:00 – 15:30 Cardiovascular effects of GLP-1 analogues
O. Schnell (Munich, DE)
Programm X. Jahrestagung. Der herzkranke Diabetiker
Glukosemanagement und CV-Risiko: präprandial, postprandial, Variabilität

3. Dezember 2010, X. Jahrestagung. Der herzkranke Diabetiker 16.00 - 17:00
Chair: O. Schnell, D. Tschöpe

16:00 - 16:20 Silent Diabetes bei Herzkatheter-Patienten: HbA1c oder OGTT?
R. Dörr, Dresden

16:20 - 16:40 Glykämische Variabilität – ein wichtiger Risikofaktor für endotheliale und myokardiale Funktionsstörungen
M. Hanefeld, Dresden

16:40 - 17:00 Diabetes – (k)ein KHK-Risikoäquivalent?
E. Standl, München

III. Literature

Abstracts


Original articles


Review articles


Dissertations in 2010:

Mr. Michail Vavelidis; Topic: The Munich Myocardial Infarction Registry: Hospital and 3-year mortality in patients with and without diabetes.
4. Arbeitsgruppe Prof. Schaaf

I. Bericht 2010

Psychiatrische und neuropsychologische Komorbiditäten bei Patienten mit Diabetes mellitus

Fördermittel: Max-Planck-Gesellschaft, Kooperationsprojekt der Arbeitsgruppe Neuropsychologie und Klinische Neuroendokrinologie des Max-Planck-Instituts für Psychiatrie sowie der Klinik für Endokrinologie, Diabetologie und Suchtmedizin des Klinikums München Schwabing


Die im Jahr 2009 initiierte und im Frühjahr 2010 abgeschlossene Studie zu kurzfristigen Effekten einer Antidepressiva-Einnahme (Mirtazapin) bei gesunden

II. Literatur:

(1) Zihl, J; Schaaf, L; Zillmer, E
The relationship between adult neuropsychological profiles and diabetic patients’ glycaemic control

(2) Ising, M; Grautoff S.; Pollmächer T; Himmerich; Schaaf L
Glucose tolerance in depressed patients and under antidepressant treatment

(3) Kloiber S; Roeske D; Müller-Myhsok B; Hennings J; Holsboer F; Lucae S
Genome-wide association study ob body weight in patients with major depression
Insitutssymposium des Max-Planck-Instituts für Psychiatrie, 2010
5. Arbeitsgruppe Prof. Haslbeck

I. Zusammensetzung der Arbeitsgruppe 2010

Prof. Dr. M. Haslbeck, Angelika Ruf, (Funktions- und Dokumentationsassistentin)

II. Bericht 2010

Diabetische Neuropathie


III. Literatur


6. Arbeitsbeitrag Prof. Mehnert 2010

I. Aktivitäten 2010

24 Editorials zu aktuellen Diabetesfragen in der Ärzte Zeitung 2010
Zahlreiche Leserfragen, kurze Statements und Interviews, Vorträge und Moderationen

II. Veröffentlichungen 2010

(1) Walle, H., Becker, C., Liebermeister, H., Mehnert H:
Journal für Pharmakologie und Therapie 1/2010, S. 3 - 9

(2) Mehnert H. et al.:
Inkretinbasierte Diabetestherapien, wissenschaftlich und Praktisch diskutiert. Teil 1
Diabetes, Stoffwechsel und Herz. 19, Heft 4, S. 285 – 291

(3) Mehnert H. et al.:
Inkretinbasierte Diabetestherapien, wissenschaftlich und Praktisch diskutiert. Teil 2
Diabetes, Stoffwechsel und Herz. 19, Heft 5, S. 371 – 378

(4) Mehnert H:
Wann soll mit einer Insulintherapie begonnen werden?
Diabetes, Stoffwechsel und Herz. 19, Heft 3, S. 214 – 215

(5) Mehnert H:
Ernährungs- und Bewegungstherapie – aktueller denn je.
Diabetes, Stoffwechsel und Herz. 19, Heft 4, S. 296 - 299