# Abstract Service

## EPIDEMIOLOGY

### Long-term instability of fasting plasma glucose, a novel predictor of cardiovascular mortality in elderly patients with non-insulin-dependent diabetes mellitus: the Verona Diabetes Study.

*Muggeo M, Verlato G, Bonora E, Zoppini G, Corbellini M, de Macro R. Circulation 1997; 96(6) : 1750-4.*

BACKGROUND: We recently reported that long –term fasting plasma glucose (FPG) instability predicts all-cause mortality in elderly patients with non-insulin-dependent diabetes mellitus (NIDDM). The aim of the present study was to evaluate whether glucose instability, as represented by the coefficient of variation of FPG concentrations (CV-FPG) measured during a 3-year period, can predict specific causes of death in the subsequent 5 years.

METHODS AND RESULTS: Five hundred and sixty-six elderly patients with NIDDM were followed up for 5years to assess mortality and causes of death. All FPG determination of the 3 years preceding the follow-up available in the clinical records were collected and analyzed. Patients were grouped in tertiles of mean FPG, CV-FPG, and the slope of FPG. These parameters of glucose control, as well as sex, age, duration of diabetes and insulin treatment, cigarette smoking , hypertension, and total cholesterol, were included in a multivariate analysis of mortality. During the follow up, 63 men and 128 women died. Diabetes- and malignancy related mortality were not independently associated with any parameter of glucose control, whereas cardiovscular-related mortality was independently associated with CV-FPG (P= 0.07) but not with the mean or the slope of FPG. In particular, the relative risk of cardiovascular mortality in subjects in tertile III versus tertile I of CV-FPG was 2.40 (95% CI, 1.28 to 4.53).

CONCLUSIONS: These results indicate that FPG instability is a predictor of cardiovascular-related mortality in elderly patients with NIDDM and suggest that glucose stability might be a goal in the management of these patients.

### Rising incidence of insulin dependent diabetes in children aged under 5 years in the Oxford region: time tend analysis. The Bart's-Oxford study Group.

*Gardner SG. Bingley PJ. Sawtell PA. Weeks S. Gale EA. BMJ. 1997; 315(7110) : 713-7.*

OBJECTIVES: To monitor incidence of insulin dependent diabetes in children in Oxford health region since 1985, and to look for any evidence of disproportionate increase in children aged under 5.

DESIGN: Primary ascertainment of cases of childhood diabetes was by prospective registration of all patients with insulin dependent diabetes diagnosed before age 15 years between 1985 and 1996 and resident in Oxford region at time of diagnosis. This was supplemented by examination of centralised hospital discharge records and death certificates. Secondary case ascertainment was by postal surveys of general practitioners in1987 and 1996.

SETTING: Area formerly administered by Oxford Regional Health Authority.

SUBJECTS: 1037 children presenting with insulin dependent diabetes under age of 15 years.

MAIN OUTCOME MEASURES: Incidence of insulin dependent diabetes in children aged to 0-4, 5-9 and 10-14 years during 1985-95

RESULTS: Overall incidence of diabetes in children aged 0-15 was 18.6 cases/100000/year and showed an annual increase of 4% from 1985 to 1996. This was mainly due to a rapid increase in children aged 0-4 years, in whom there was an annual increase of 11% (95% confidence interval 6% to 15%, $P < 0.0001$), while the annual increase in those aged 5-9 was 4% (0 to 7%, $P= 0.55$).

CONCLUSION: Incidence of insulin dependent diabetes in children aged under 5 years has risen markedly in the Oxford region over the past decade. The cause of the increase is unknown, but environmental influences encountered before birth or in early postnatal life are likely to be responsible.

### Prevalence of NIDDM and impaired glucose tolerance in a rural and an urban population in Cameroon.

*Mbanya JC, Ngogang J, Salah JN, Minkoulou E, Balkau B. Diabetologia 1997; 40(7) : 824-9.*

The adoption of Western lifestyles is known to lead to increasing prevalence of non-insulin-dependent diabetes mellitus in Africa, yet epidemiological studies using standardized methods are rare. The prevalence of diabetes and impaired glucose tolerance was determined in arural and an urban community in Cameroon using the 75-g oral glucose tolerance test and World Health Organization diagnostic criteria in 719 rural (292 men, 427 women) and 1048 urban (458 men, 590 women) subjects aged 24-74 years. The response rate was 95 and 91% for the rural and urban population, respectively. The age-standardized prevalence of diabetes in the rural and urban population was respectively 0.9% (95% confidence interval (0.2-2.7) and 0.8% (0.2-1.8) for men and 0.5% (0.1-1.6) and 1.6% (0.7-3.1) for women, and that of impaired glucose tolerance was 5.8% (3.3-9.4) and 1.8% (0.9-3.2) for men, and for women, 2.2% (1.0-4.0) and 2.0% (0.6-4.5). Although for both men and women the body mass index was higher at all ages in the urban than in the rural area, the 2-h plasma glucose, even after the adjustment for age and body mass index, was significantly higher in the rural than urban area ($p < 0.005$, $p < 0.002$ for men and women, respectively). There was a female excess of diabetes in the urban area and an equal sex distribution in the rural area. In the rural area 67% (4 of 6) of diabetic subjects were unknown before the survey, compared with 57% (8 of 14) in the urban area. These data indicate a low prevalence of diabetes in Cameroon; however, the prevalence of impaired glucose tolerance suggests an early stage of a diabetes epidemic.

## ETIOPATHOLOGY

### Autoantibodies to IA-2 and IA-2 beta in insulin-dependent dia-betes mellitus recongnize conformational epitopes: location of the 37- and 40-kDa fragments determined.

*Xie H, Zhag B, Matsumoto Y, LiQ. Notkins AL, Lan MS. Journal of Immunology 1997; 159(7) : 3662-7.*

A-2 and IA-2 beta are major autoantigens in insulin-dependent dia-betes mellitus (IDDM) and the precursors, respectively, of a 40- and 37-kDa tryptic fragment that reacts with IDDM sera. In the present study, by amino acid sequencing of recombinant IA-2 and IA-2 beta, we determined the tryptic cleavage sites involved in the generation of these fragments. Both cleavage sites are immediately after an arginine residue at position 653 for IA-2 and position 679 for IA-2 beta. The resulting tryptic fragments are 326 and 307 amino acids in length and retain their ability to react with IDDM sera. In contrast to IA-2 and IA-2 beta, other members of the protein tyrosine phosphatase (PTP) family (i.e., RPTP kappa, RPTPmu, NU-3, SHP, and 3CH134) are completely susceptible to digestion by trypsin. Sequence analysis revealed five conserved five conserved cysteine residues in IA-2 and IA-2 beta that are not present in other PTPs. Reduction and alkylation of IA-2 and IA-2 beta recombinant proteins resulted in loss of both resistance to digestion by trypsin and reactivity with antoantibodies in IDDM sera. It is concluded that disulfide bond formation plays a critical role in the maintaince of antigenic structure and that the auto-antibodies to IA-2/IA-2 beta in IDDM sera recognize conformation epitopes.

**Inhibition of diabetes in non-obese diabetic mice by nicotinamide treatment for 5 weeks at the early age.**

*Kim JY, Chi JK, Kim EJ, Park SY, Kim YW, Lee SK. Journal of Korean Medical Science 1997; 12(4) : 293-7.*

To know the effects of nocotinamide (NCT) treatment for 5 weeks at the early age on insulitis and development of diabetes in non-obese diabetic (NOD) mice, this experiment was performed. Ten ICR (Institute of Cancer Research) and 15 female NOD mice at 4 weeks of age were used. Mice were assigned to ICR and NOD groups, and NOD mice were randomly divided to control and NCT-treated groups. NCT was administered to mice orally as a solution and in a dose of 500 mg / kg body weight a day from the age of 4 to 8 weeks. Diabetes onset was 18 weeks of age in control group, and 22 weeks of age in NCT-treated group. Cumulative incidences of diabetes at 25 weeks of age in control and NCT-treated NOD mice were 63 and 29%, respectively. Insulitis occurred in all NOD mice. Incidence of insulitis in total islets was decreased by NCT treatment in diabetic NOD mice, but intesity of insulitis was not improved by NCT treatment. Blood glucose level was increased markedly, and plasma insulin level was decreased by diabetes development in NOD mice. Plasma triglycerides and total cholesterol levels were increased in diabetic mice than in non-diabetic mice. In conclusion, these results suggest that NCT treatment for 5 weeks at the early age in NOD mice inhibits development of diabetes and insulitis in diabetic NOD mice.

**A missense mutation in the hepatocyte nuclear factor 4 alpha gene in a UK pedigree with maturity-onset diabetes of the young.**

*Bulman MP, Dronsfield MJ, Frayling T, Appleton M, Bain SC, Ellard S, Hattersley AT. Diabetologia 1997; 40(7) : 859-62.*

Maturity-onset diabetes of the young (MODY) is a monogenic sub-group of non-insulin dependent diabetes mellitus (NIDDM) characterised bylan early age of onset (< 25 years) and an autosomal dominant mode of inheritance. MODY is genetically heterogeneous with three different genes identified to date; hepatocyte nuclear factor 4 alpha (HNF-4alpha) [MODY1], glucokinase [MODY2] and hepatocyte nuclear factor 1 alpha (HNF-1 alpha) [MODY3]. A nonsense mutation in the HNF-4 alpha gene has recently been shown to cause MODY in a single large North American pedigree (RW). We screened a large UK Caucasion MODY family which showed weak evidence of linkage to the MODY1 locus on chromosome 20g (lod score for ADA 0.68 at theta = 0) for mutation in the coding region of the HNF-4 alpha gene by direct sequencing. A missense mutation in the substitution of glutamine for glutamic acid was identified in exon 7 (E276Q). The mutation was present in all of the diabetic members of the pedigree plus two unaffected subjects and was not detected in 75 normal control subjects or 95 UK Caucasian subjects with late-onset NIDDM. This is the first missense mutation to be described in the HNF-4 alpha gene.

**Infact insulin stimulation of skeletal muscle blood flow, its heterogeneity and redistribution, but not of glucose uptake in non-insulin-dependent diabetes mellitus.**

*Utriainen T, Nuutila P, Takala T, Vicini P, Ruotsalainen U, Ronnemaa T, Tolvanen T, Raitakari M, Haaparanta M Kirvela O, Cobelli C, Yki-jarvinen H. Journal of clinical investigation 1997; 100(4) : 777-85.*

We tested the hypothesis that defects in insulin stimulation of skeletal muscle blood flow, flow dispersion, and coupling between flow and glucose uptake contribute to insulin resistance of glucose uptake in non-insulin-dependent diabetes mellitus (NIDDM). We used positron emission tomography combined with 150jH2O and [18F]-2-deoxy-glucose and a Bayesian iterative reconstruction algorithm mean muscle blood flow, flow heterogeneity, and their relationship to glucose uptake under normoglycemic hyper insulinemic conditions in 10 men with NIDDM (HbA 1c 8.1+/-0.5%, age 43+/-2 yr, BMI 27.3+/-0.7 kg/m2) and in 7 matched normal men. In patients with NIDDM, rates of whole body (35+/-3 vs. 44 +/-3 micromol/kg body weight. min, $P < 0.05$) and femoral muscle (71+/-6 vs. 96+/-7 micromol/kg muscle . min, $P < 0.02$) glucose uptake were significantly decreased. Insulin increased muscle blood flow similarly in both groups, from 1.9+/-0.3 to 2.8+/0.4 ml/ 100g muscle. Min in the patients with NIDDM, $P < 0.01$, and from 2.3+/0.3 to 3.0+/0.3 ml/100g muscle. Min in the normal subjects, $P < 0.02$. Pixel-by-pixet analysis of flow images revealed marked spatial heterogeneity of blood flow. In both groups, insulin increased absolute but not relative dispersion of flow, and insulin-stimulated but not basal blood flow colocalized with glucose uptake. These data provide the first evidence for physiological flow heterogeneity in human skeletal muscle, and demonstrate that insulin increase absolute but not relative dispersion of flow, Furthermore, insulin redirects flow to areas where it stimulates glucose uptake. In patients with NIDDM, these novel actions of insulin are infact, implying that muscle insulin resistance can be attributed to impaired cellular glucose uptake.

**Autoantibodies associated with presymptomatic insulin-dependent diabetes mellitus in women.**

*Whittingham S, Byron SL, Tuomilehto J, Zimmet PZ, Myers MA, Vidgren G, Rowley MJ, Feeney SJ, Koskela P, Tuomilehto-Wolf E, Mackay IR. Diabetic Medicine 1997; 14(8) : 678-85.*

Presymptomatic autoantibodies markers of insulin-dependent (Type 1) diabetes mellitus (IDDM) are less well characterized in adults that in children. We quantitated anti-GAD, anti-ICA512 and ICA by titration to endpoint and compared frequencies and levels in 139 Finnish women from whom 390 serum samples had been archived during antecedent pregnancies for 10 years' before and up to 1 year after diagnosis of diabetes. Also, we compared the autoantibody status in adults with IDDM with that of children with newly diagnosed IDDM. Of the 35 women seropositive for 1 or more autoantibodies, 77% developed IDDM, 11% non-insulin-dependent (Type 2) diabetes mellitus (NIDDM), 9% gestational diabetes mellitus requiring insulin (GDM-ins) and 3% GDM controlled by diet. The frequency of antibodies during the 10-year presymptomatic period was 83% for anti-glutamic acid decarboxylase (GAD), 52% for anti-ICA512 and 41% for islet cell antibodies (ICA) for those who developed IDDM, 25%, 17%, and 0% for NIDDM, 12%, 4%, and 8% for GDM-ins and 1%, 0%, and 1% for GDM-diet. Anti-GAD was found most consistently in early samples; 13 of 15 with a single autoantibody at their first test had anti-GAD. Among those who developed IDDM, the frequency of anti-GAD was constant, anti-ICA512 increased threefold, and ICA increased slightly before diagnosis. Levels of the autoantibodies varied between subjects, but were relatively stable in individual subjects. Comparison of tests on the women, and children after diagnosis of IDDM, showed the frequencies and levels to be the same for anti-GAD but lower for anti- ICA512 and ICA in adults. Our observations show in women the long latency of seropositively before overt IDDM, the predominance of anti-GAD among these three serological markers, and the presence of these markers in NIDDM presumably representing a NIDDM phase of autoimmune insulitis.

**Prediction of type 1 diabetes postpartum in patients with gestational diabetes mellitus by combined islet cell autoantibody screening; a prospective multicenter study.**

*Fuchtenbusch M, Ferber K, Standl E, Ziegler AG. Diabetes 1997; 46(9) : 1459-67.*

Women with gestational diabetes mellitus (GDM) have a considerable risk of developing diabetes later in life. To determine the predictive value of autoantibody markerss in gestational diabetic pregnancy for the development of type 1 diabetes postpartum, we tested 437 patients with GDM (289 women treated with diet only [GDM-A] and 148 requiring insulin treatment during pregnancy [GDM-B] for antibodies to islet cells (ICAs), GADAs), and tryosine phosphatase ICA512/IA-2 (IA2As). We prospectively followed them with repeated oral glucose tolerance tests and antibody determination for up to 7 years postpartum (mean, 1.6 years; range, 0-7.2 years). The cumulative risk of diabetes up to 5 years postpartum was 17% (95% Cl 12-22%). The risk of type 1 diabetes was 3% (2-5%) by 9 months and 7% (4-9%) 2 years after delivery. At delivery, 8.5% of all patients were ICA+, 9.5% were GADA+, 6.2% were IA2A+, and 18.1% were positive for at least one antibody (12.6% for GDM-A vs. 30.4% for GDM-B, P < 0.0001). During follow-up, GADAs persisted in 75%, ICAs in 35%, and IA2As in 30% of the subjects positive for the respective marker at delivery. By 2 years postpartum, 29% (19-39%) of patients positive for at least one antibody developed type 1 diabetes, compared with 2% (1-4%) of antibody-negative patients (P < 0.0001). Thereby, the risk for type 1 diabetes 2 years postpartum increased with the number of antibodies present at delivery from 17% (6.28%) for one antibody, to 61% (30.91%) for two antibodies, and to 84% (55-100%) for 3 antibodies. Risk of progression to type 1diabetes postpartum was also associated with the status of parity. Women with one or more pregnancies before the index pregnancy had a higher risk for type 1 diabetes 2 years after delivery (14.7% [4.9.-24.5%]) than women having their first (i.e, index) pregnancy (5% [2.9-7%]) (P < 0.006). A comparison of different prediction strategies showed that single antibody screening with GADA yielded the highest sensitivity of 63% (45-75%), compared with ICA (48% [31-65%]) and IA2A (34% [13-47%]). Combined screening with two autoantibodies increased sensitivity to 74% (60-92%) when using GADA plus ICA or GADA plus IA2A, respectively. Screening with all three markers improved sensitivity further to 82% (67-100%). Beta-cell autoantibodies determined at delivery in women with GDM are highly predictive for the development of type 1 diabetes postpartum. Autoantibody screening in pregnant women with GDM from populations at high risk for type 1 diabetes should therefore be considered to allow early diagnosis and appropriate therapy.

**Pathophysiology of Type 2 diabetes and modes of action of therapeutic interventions. [Review] [181 refs]**

*Dagogo-jack S, Santiago JV. Archives of internal Medicine. 1997; 157(16): 1802-17.*

At least 90% of the 12 to 15 million persons with diabetes mellitus in the United State, half of whose condition remains undiagnosed, have type 2 diabetes. Type 2 diabetes is preceded by a long period of impaired glucose tolerance of macrovascular complications. Thus, at the time of diagnosis, long-term complications have developed in almost one fourth of patients. Susceptibility to type 2 diabetes requires genetic (most likely polygenic) and acquired factors, and its pathogenesis involves an interplay of progressive insulin resistance and beta-cell failure. The ideal treatment of type 2 diabetes should reverse insulin resistance and beta-cell dysfunction in most treated patients and prevent, delay, or reverse long-term complications. Current strategies are aimed at amelioration of insulin resistance (diet, exercise, weight loss, and metformin and trogitazone therapy), augmentation of insulin supply (sulfonylurea and insulin therapy), or limitation of postprandial hyperglycemia (acarbose therapy). Future therapies probably will target (1) insulin resistance, using a multifaceted approach; (2) hepatic glucose production, using gluconeogenesis inhibitors; (3) excess nonesterfied fatty acid production, using lipolysis inhibitors; and (4) fat oxidation, using carnitine palmitoyltransferase I and II inhibitors. Attempts also could be made to stimulate energy of beta 3-adrenoceptor agonists. One promising strategy is an attack on multiple pathophysiological processes by combining antidiabetic agents with disparate mechanisms of action. Thus, we now have unprecedented resources for drug therapy for diabetes, with great opportunity for innovative combinations. It is hoped that these expanded choices will provide the tools necessary for a more efficient management of type 2 diabetes and prevention of its long-term complications. [References: 181]

## TREATMENT – EXERCISE

**Chromium and exercise training: effect on obese women.**

*Grant KE, Chandler RM, Castle AL, Lvy JL. Source Medicine & Science in Sports & Exercise 1997; 29(8) : 992-8.*

Chromium supplementation may affect various risk factors for coronary artery disease (CAD) and non-insulin-dependent diabetes mellitus (NIDDM), including body weight and composition, basal plasma hormone and substrate levels, and response to an orla glucose load. This study examined the effects of chromium supplementation (400 micrograms.d-1), with or without exercise training, on these risk factors in young, obese women, Chromium picolinate supplementation resulted in significant weight gain in this population, while exercise training combined with chromium nicotinate supplementation resulted in significant weight loss and lowered the insulin response to an oral glucose load. We conclude that high levels of chromium picolinate supplementation are contraindicated for weight loss in young, obese women. Moreover, our results suggest that exercise training combined with chromium nicotinate supplementation may be more beneficial than exercise training alone for modification of certain CAD and NIDDM risk factors.

## COMPLICATIONS - GENERAL

### Polyol pathway activation and glutathione redox status in non-insulin-dependent diabetic patients.

*Bravi MC, Pietrangeli P, Laurenti O, Basili S, Cassone-Faldetta M, Ferri C, De Mattia G. Metabolism: Clinical & Experimental 1997; 46 (10): 1194-8.*

The current study aimed to evaluate whether nicotinamide adenine dinucleotide phosphate (NADPH) alteration in erythrocytes from patients with non-insulin-dependent diabetes mellitus (NIDDM) is responsible for the impaired glutathione (GSH) redox status, and to assess if shor-term inhibition of the polyol pathway normalizes NADPH levels and GSH redox status via an amelioration of the NADPH/total NADP ( tNADP) ratio. For this purpose, erythrocyte NADPH and GSH levels were measured in 18 NIDDM patients at baseline and then after 1 week of random double-blind assignment to treatment with either rolrestat (an aldose-bline assignment to treatment with either tolrestat (an aldose reductase inhibitor, 200 mg daily) (n = 12) or placebo (n = 6). A group of 16 healthy volunteers served as the control. In the basal condition, mean GSH (P < .0001) and NADPH (P < .0001) levels and NADPH/tNADP (P < .0001) and GSH/glutathione disulfide (GSSG) (P < .005) ratios were lower in NIDDM patients than in control subjects. Tolrestat treatment increased GSH levels (P < .05 v placebo and baseline) and the NADPH/tNADP ratio (P < .05 v placebo and baseline). Interestingly, tolrestat-induced chagnes in GSH and NADPH levels and in GSH/GSSG and NADPH/tNADP ratios were significant only in patients who showed a decreased NADPH/tNADP ratio at baseline (n = 8). In these latter patients, we also found a direct correlations between percentage increments in GSH levels and NADPH/tNADP ratios after tolrestat treatment (r = .71, P < .05). In conclusion, our findings support the hypothesis that polyol pathway activation decreases NADPH and GSH levels. Accordingly, short-term inhibition of this enzymatic route increased both the GSH level and the NADPH/tNADP ratio. These changes were observable only in the subgroup of patients with an abnormal NADPH/tNADP ratio at baseline. Polyol pathway inhibition could be useful for decreasing oxidative stress in NIDDM.

### Macrovascular disease and hyperglycaemia: 10-year survival analysis in Type 2 diabetes mellitus: the Belfast Diet Study.

*Hadden DR, Patterson CC, Atkinson AB, Kennedy L, Bell PM, McCance DR, Weaver JA, Diabetic Medicine 1997; 14(8) : 663-72.*

The relationship between macrovascular disease and blood glucose control in long-term follow-up of Type 2 (non-insulin-dependent) diabetes mellitus is difficult to study because of the gradual rise in fasting plasma glucose due to ongoing beta-cell failure. We used time-dependent convariates in Cox's proportional hazards model to allow variables measured annually during a 10-year prospective follow-up to be related to risk of myocardial infarction or cerebrovascular accident. Data for 432 newly diagnosed diabetic patients were available, 112 of whom suffered myocardial infarction (fatal or non-fatal). Analysis of baseline measurements only gave relative hazards (95% CL) of 1.04 (0.99, 1.09) per mmol l(-1) increase in fasting plasma glucose, 1.43 (1.12, 1.83) per decade increase in age and 1.07 (0.98, 1.17) per 10% increase in percentage of ideal weight. Analysis incorporating ongoing measurements gave corresponding figures of 1.07 (1.02, 1.12) for fasting plasma glucose, 1.64 (1.23, 2.20) for age and 1.06 (0.95, 1.18) for percentage of ideal weight. The risk of myocardial infarction while on insulin treatment 1.09 (0.58, 2.06) or oral agents 1.41 (0.86, 2.31) was not significantly elevated relative to dietary treatment. Baseline smoking status, systolic blood pressure and previous myocardial infarction were also significant predictors of myocardial infarction. Similar relationships were found for cerebrovascular accident and total mortality. Increasing fasting plasma glucose is a significant independent predictor of macrovascular disease in diabetes.

### Increased serum levels of advanced glycation end products (AGEs) in children and adolescents with IDDM.

*Berg TJ, Dahl-Jorgensen K, Torjesent PA, Hanssen KF. Diabetes Care 1997; 20(6) : 1006-8.*

OBJECTIVE: To investigate whether the serum levels of advanced glycation end products (AGEs) are increased in IDDM children and adolescents and to study the effect of puberty on serum levels of AGEs (S-AGEs).

RESEARCH DESIGN AND METHODS: A total of 68 children and adolescent IDDM patients (age, 13.3+/-04.0 years; duration of diabetes, 5.0 +/-3.6 years; HbA 1c, 8.2+/-2.0%; Tanner stage [public hair], 1vs. 2.5, 24/42) recruited from the pediatric outpatient clinic at Aker University Hospital subjects. S-AGEs were measured by a fluorometric immunoassay.

RESULTS: S-AGEs were significantly elevated in the diabetic group when compared with the control group (14.4 +/-3.5 vs. 11.7 +/-3.0 U/ml, P < 0.002). A significant correlation (r = 0.26, P <0.04) was found between S-AGEs and HBA 1c in the diabetic group but not in the control group. No significant correlation was found between S-AGEs and the duration of diabetic group or S-AGEs and blood glucose concentration or age in either group. We found no difference between S-AGEs in boys and girls and in prepubertal and pubertal diabetic or control subjects.

CONCLUSIONS: S-AGEs are increased in young patients with diabetic before puberty. Since AGEs Are linked to the pathogenesis of vascular complications, this obsevation suggest that the pathological processes leading to diabetic late complications start even before puberty.

**Cumlative glycemic exposure and microvascular complications in insulin-dependent diabetes mellitus. The glycemic threshold revisited [see comments].**

*Orchard TJ, Forrest KY, Ellis D, Becker DJ. Archives of internal medicine 1997; 157(16) : 1851-6.*

BACKGROUND: The development of microvascular insulin-dependent diabetes mellitus (IDDM) complications has been shown to be related to both duration of dibates and the degree of glycemic exposure, However, controversy exists as to whether there is a threshold of glycemic exposure, below which there is minimal risk. Furthermore, there are few describing the relationship of total glycemic exposure (duration X degree) to complications rates-a potentially useful research and clinical tool.

OBJECTIVE: To determine a cumulative glycemic exposure variable that combines the effect of both degree and duration of hyperglycemia and to evaluate variable in terms of its relation to microvascular complications. The association between cumulative glycemic exposure and complication risk was also examined to evaluate whether there was a threshold effect.

METHODS: A total of 353 patients with IDDM who had completed the first 6 years of follow-up in the Pittsburgh Epidemiology of Diabetes Complications Study were included in this analysis. These subjects had a mean age of 27.9 years, and the mean duration of the disease was 19.4 years, Subjects were examined at baseline (cycle 1) and then biennially (cycle 2, cycle 3, and cycle 4) for diabetes complication. Total glycosylated hemoglobin (HBA1) was measured at each cycle. A cumulative glycemic exposure variable, named A 1months, was calculated by multiplying the number of HBA1 units above normal at each cycle by the number of months between the midpoints of the preceding and succeeding cycle intervals.

RESULTS: The mean number of A1 months experienced at the time of diagnosis of proliferative retinopathy (914), microalbuminuria (952), overt nephropathy (1043), and symmetrical polyneuropathy (1043) did not vary by duration of diabetes, Thus approximately 1000 A1months were needed (on average) for the advanced complications to develop. Although the risk for developing proliferative retinopathy rose gradually as A1months increased, a more abrupt increase in the risk was seen (again at approximately 1000 A1months) for micoralbuminuria (odds ratio, 6.9; 95% confidence interval, 2.5-19.1), overt nephropathy (odds ratio, 6.5; 95% confidence interval, 2.5- 19.1), overt nephropathy (odds ratio, 6.5; 95%, confidence interval, 2.0-21.7), and distal symmetrical polyneuropathy (odds ratio, 6.5; 95 confidence interval, 2.4-17B). Nonetheless, complications developed in the majority of cases at glycemic exposures below 1000 A1months. The cumulative glycemic exposure variable A1months does not predict complication any better than its component variables (duration and HbA1). Furthermore, formal statistical testing failed to show a definitive threshold for any complication.

CONCLUSIONS: Although A1months does not enhance prediction of complications, it may be a useful summary measure of glycemic exposure for both patients and physicians. However, although subjects with 1000 A1months or more appear to be at increased risk of developing most microvascular complications, because the majority of complications arise in subjects with less than this exposure, this threshold value should only be considered a minimal goal. For example, our data suggest that for most microvascular complications to develop, it would take, on average, 83 years with an HbA1 unit at 1% above normal, 42 years at 2% above normal, 28 years at 3% above normal. 21 years at 4% above normal, and 18 years at 5% above normal.

**24-h blood pressure and autonomic function is related to albumin excretion within the normoalbuminuric range in IDDM patients.**

*Poulsen PL, Ebbehoj E, Hansen KW, Mogensen CE, Diabetologia 1997; 40(6) : 718-25.*

Significant changes in both blood pressure, autonomic function and kidney ultrastructure are observed in insulin-dependent diabetic (IDDM) patients with microalbuminuria. Intervention strategies are evaluated at even earlier stages of disease. Identification of patients at risk of developing microalbuminuria must be based of patients at risk of developing microalbuminuria must be based on a thorough knowledge of the relations between key pathophysiological parameters in patients with normoalbuminuria. The aim of the present study was to characterize the interactions of urinary albumin excretion (UAE), 24-h ambulatory blood pressure (AMBP), and sympathovagal balance in a large group of normoalbuminuric IDDM patients. In 117 normoalobuminuric (UAE < 20 micrograms/min) patients we performed 24-h AMBP (Spacelabs 90207), with assessment of diurnal blood pressure and heart rate (HR) variation, and short-term (three times 5 min) power spectral analysis of RR interval oscillations, as well as cardiovascular reflex tests (HR variation to deep breathing, postural HR and blood pressure response). Patients with UAE above the median (4.2 micrograms/min) had significantly higher 24-h systolic and diastolic AMBP (125 +/-10.1/76+/-7.2 mmHg) compared to the low normolbuminuric group (120+/-8.4/74=/-5.1 mmHg), $p < 0.01$ and 0.02, respectively. Patients with UAE above the median had significantly reduced short-term RR interval variability including both the high frequency component (5.47 +/-1.36 vs 6.10 +/-1.43 In ms2), and low frequency component (5.47 +/- 1.36 vs 6.10 +/- 1.43 In ms2), and low frequency component (5.48 +/-1.18 In ms2 compared to 5.80 +/-1.41 In ms2), $p < 0.02$ and $p = 0.04$ (ANOVA). In addition, patients with high-normal UAE had reduced mean RR level (faster heart rates) 916+/-108 compared to 963 +/-140ms, $p < 0.04$. These differences were not explained by age, duration of diabetes, gender, level of physical activity, or cigarette smoking HbA1c was significantly higher (8.6 +/-1.0%, $p = 0.03$) in the group with high normal UAE. Comparing normoalbuminuric IDDM patients with UAE above the below the median value, we found significantly higher AMBP in combination with significant differences in sympathovagal balance and significantly poorer glycaemic control in the group with high-normol albumin excretion. Our data demonstrate interactions between albumin excretion, blood pressure, autonomic function, and glycaemic status, already present in the normoalbuminuric range and may describe a syndrome indicative of later complications.

## COMPLICATIONS-IHD

**Factors influencing LVM in hypertensive type-1 diabetic patients.**

*Gerdts E, Myking OL, Lund-Johansen P, Omvik P, Blood Pressure 1997;6(4) : 197-202.*

Diabetes mellitus is associated with a high prevalence of hypertension and left ventricular hypertrophy (LVH), and a causative relationship with abnormal sodium metabolism in diabetic patients has been suggested. Factors influencing left ventricular mass (LVM) were assessed in 30 hypertensive type-1 diabetic patients, mean age 46 +/-9 (range 24-67) years, with a mean duration of diabetes and hypertension of 19 +/-10 and 6+/-5 years, respectively. In the total study population, casual blood pressure was 163/94+/-24/10 mmHg and 24 h blood pressure was 155/87 +/- 17/8 mmHg. Twenty-four-hour urine samples were obtained to measure daily albumin excretion (0.77 +/- 1.06 g) and dietary sodium intake was assessed as 24 h sodium excretion (173 +/- 77 mmol). Creartinine clearance averaged 1.41 +/- 0.53 ml/s. LVM determined by echocardiography was 221 +/- 74 g (range 104-408 g) and 33% of the patients had LVH, Multiple regression analysis identified dietary sodium intake and plasma atrial natriuretic peptide as independent predictors of LVM (R2 = 0.52, p <0.001). No significant assoication was found between LVM and blood pressure or albuminuria. The results propose dietary sodium intake as an important factor in the development of LVH in hypertensive type-1 diabetic patients.

**Quantitative comparison of angiographic characteristics of coronary artery disease in patients with non-insulin-dependent diabetes mellitus compared with matched nondiabetic control subjects.**

*Pajunen P, Nieminen MS, Taskinen MR, Syvanne M. American journal of Cardiology 1997 ; 80(5) : 550-6)*

The angiographic characteristics of coronary artery disease (CAD) in non-insulin-dependent diabetes mellitus (NIDDM) patients were studied by quantitative coronary angiography (QCA). Fifty-seven consecutive NIDDM patients undergoing clinically indicated elective coronary angiography and 57 nondiabetic coronary artery disease (CAD) patients were individually matched for sex, age, and body mass index. Technically adequate coronary angiograms, available for 55 subjects in each group, were analyzed with third-generation QCA software. To evaluate the anatomic severity and extent of CAD, several QCA-derived parameters were incorporated into indexes describing various per-patient features of CAD. These measures reflect CAD severity, extent, and overall "altheroma burden", and were calculated separately for different coronary segments (i.e., left main, proximal, mid, and distal segments), for the different coronary arterial territories (i.e., left main, left anterior descending, left circumflex, and right), and for the entire coronary tree. No significant differences were found between the NIDDM and nondiabetic groups (global severity index, 51 +/- 14 vs. 54 +/- 13, p = NS; global extent index, 34 +/- 13 vs. 32 +/-12, p = NS; global atheroma burden index, 27 +/-16 vs. 24 +/-12, p = NS). We also found no between-group differences in proximal, mid, or distal segments, in separate vessel territories, or in left ventricular function. Our data suggest that CAD patients, with and without NIDDM, who have similar symptoms at a given age, have similar severity and extent of CAD.

## COMPLICATIONS-RETINOPATHY

**Diabetic papillopathy: two case reports in individuals with adult onset diabetes mellitus.**

*Keely KA, Yip B. Journal of the American Optometric Association. 1997; 68(9):595-603.*

BACKGROUND: Diabetic papillopathy is a benign unilateral or bilateral optic neuropathy with transient optic disk edema and minimal reduction in visual function. The optic disk edema typically resolves in a few months with no resulting optic atrophy and minimal or no decrease in acuity. The exact etiology of the disk edema is unknown, but theories retinal vascular leakage into and surrounding the optic nerve and disruption of axoplasmic flow resulting from microvascular disease of the optic nerve head vasculature.

CASE REPORT: Two adult patients receiving insulin for type II diabetes mellitus manifested disk and minimal visual dysfunction. Both patients showed funduscopic evidence of mild-to-moderate nonproliferative diabetic retinopathy O. D. and O.S., and one patient had clinically significant macular edema in both eyes. The diagnosis in both cases was diabetic paillopathy. Both patients had significant resolution of their disk edema in 3 to 6 months, with stable acuities and no signs of optic atrophy.

CONCLUSIONS: Although diabetic papillopathy is a well-known clinical entity in patients with type 1 diabetes, the clinical profile can be expanded to include individuals with type II diabetes.

## COMPLICATIONS – NEPHROPATHY

**Renal function in the noninsulin-dependent diabetic rat: effects of unilateral nephrectomy.**

*Mozaffari MS, Warren BK, Russell CM, Schaffer SW. Journal of Pharmacological & Toxicological Methods 1997; 37(4) : 197-203.*

A new model of non insulin-dependent diabetic (NIDD) is described which exhibits more prominent defects in renal function than does the standard neonatal NIDD model. To produce this model, 2-day-old neonatal male Wistar Kyoto (WKY) rats were injected intraperitoneally with streptozotocin (90 mg/kg; NIDD), while their correspoding nondiabetic controls were administered vehicle (citrate buffer, pH: 4.5; control). At 3 weeks of age, the animals were weaned, and 1 week later, under ether anesthesia, the animals underwent a right nephrectomy or a sham operation. Diabetes was confirmed by intraperitoneal administration of a glucose load (2g/kg), which resulted in significantly higher blood glucose concentration in the NIDD, compared to the non-diabetic rats. Surgical reduction of renal mass had no effect on the glycemic response to a glucose tolerance test in either group. Intraenous administration of an isotonic saline load resulted in a similar patern of enhanced sodium and fluid excretion in the two-kidney sham-operated nondiabetic and NIDD rats. These responses were significantly higher than those observed in their counterparts with one remaining kidney. Yet the natriuretic and diuretic responses to the saline load were significantly lower in the nephrectomized NIDD, compared to the nephrectomized nondiabetic rats. The glomerular filtration rate was similar in the sham-operated (two kidneys) NIDD and non-diabetic rats. In contrast, both the basal and saline-stimulated glomerular filtration rate was lower in the nephrectomized NIDD rats compared to the nephrectomized nondiabetic group. Mean arterial pressure was similar between the two nephrectomized groups, thereby ruling out a significant contribution from the pressure-diuresis-natriuresis mechanism to the reduction in sodium and fluid excretion in the nephrectomized NIDD rats. Thus, unilateral nephrectomy is an effective method of accelerating the manifestation of

NIDD-related renal alterations. The mild, but progressive, nature of diabetes in this model should facilitate the investigation of temporal changes in renal function in NIDDM.

**Deletion insertion polymorphism of the angoiotensin converting enzyme gene and progression of diabetic nephropathy.**

*Bjorck S, Blohme G, Sylven C, Mulec H. Nephrology, Dialysis, Trnasplantation 1997; 12 Suppl 2 : 67-70.*

BACKGROUND: The activity in the renin angiotensin system is important for the progression of diabetic nephropathy. Genetic abnormalities in this system have been suggested as a risk factor for the development and progression of diabetic nephropathy. The homozygous DD (deletion) genotype of the angiotensin-converting enzyme gene has been associated with increased circulating angiotensin converting enzyme and a more rapid progression of lqA nephritis. The aim of the present study was to investigate the relationship between the DD genotype and rate of decline in kidney function in-patients with type 1 diabetes and nephropathy in relation to other risk factors for loss of renal function.

METHODS: The insertion-deletion polymorphism was determined in-patients with type 1 diabetes mellitus and diabetic nephropathy. Retrospective data were collected in 86 patients. The patients were stuided by determining glomerular filtration rate during a mean (+/-SD) of 8.5 +/- 4.0 years (range 1.3-14.5 years) using the clearance of 51Cr EDTA. Measurements for glycaemic control, urinary albumin excretion, blood pressure, and serum lipids were available for the study period.

RESULTS: The mean decline in glomerular filtration rate was 3.2 +/- 3.6 ml/min/year in all patients. Patients with the DD, ID and II genotype showed a rate change in glomerular filtration of –3.5 +/- 3.5, -3.1 +/- 4.4 and –2.6 +/- 2.3 ml/min/year respectively. The tendency towards a more rapid decline in kidney function in the DD genotype was nonsignificant. The decline in renal function was significantly correlated to systolic and diastolic blood pressure, HbAlc and serum triglycerides. Serum cholesterol was nearly significantly correlated to the decline in glomerular filtration rate (P = 0.057). Of these variables, glycaemic control and blood pressure control remained significant in multivariate analysis (P = 0.02 and P = 0.04, respectively). The patients with the DD genotype weighted significantly less. The body weight in patients with the DD genotype was 67.1 +/- 11.4 kg vs. 74.9 +/- 9.2 kg in patients with the II genotype (P = 0.018).

CONCLUSION: In this study, poor glycaemic and blood pressure control were associated with a more rapid loss of renal function in diabetic nephropathy while polymorphism of the angiotensin converting enzyme gene was not.

**The relationship between microalbuminuria in first generation diabetic and non-diabetic subjects and microalbuminuria and hypertension in the second generation (a population based study).**

*Vestbo E, Damsgaard EG, Mogensen CE. Nephrology, Dialysis, Transplantation 1997; 12 Suppl 2 : 32-6.*

BACKGROUND: Predisposition to hypertension has been proposed as a risk factor for development of diabetic nephropathy and hypertension. The aim of this study was to examine a possible relation between microalbuminuria (urinary albumin excretion (UAE) 20-200 micrograms/min) in diabetic and non-diabetic subjects and microalbuminuria as well as hypertension in the next generation.

METHODS: We examined 280 non-diabetic subjects in a cross sectional study (mean age 47-48 years). 136 were first born off-spring of non insulin dependent diabetic (NIDDM) patients and 144 were first born offspring of non-diabetic controls. Hypertension was defined as systolic blood pressure > 140 mmHg, and/or diastolic blood pressure > 90 mmHg, and/or the presence of antihypertensive medications. Data was analysed by multiple logistic regression.

RESULTS: We found that parental microalbuminuria was not predictive for microalbuminuria in the second generation in this population at the time of follow-up. However, microalbuminuria was predictive for hypertension in the second generation of diabetic patients, Odds ratio (OR) = 2.5, P = 0.05 when adjusted for age, gender, smoking, and obesity. In offspting of non-diabetic persons parental microalbuminuria also increased the risk of hypertension in the offspring generation, OR = 3.7, P = 0.02. Obesity was the strongest predictor for microalbuminuria and for hypertension in offsping of diabetic patient and of non-diabetic persons.

CONCLUSION: We found a significant relation between microalbuminuria in the parental generation and hypertension in the offspring both of a diabetic population and of a non-diabetic population.

**Expression of glutamic acid decarboxylase in nervous tissue structures targeted by autoantibodies in patients with diabetic autonomic neuropathy.**

*Zanone MM, Petersen JS, Vergani D, Peakman M. Journal of Neuroimmunology 1997; 78(1-2) : 1-7.*

We have previously identified an association between symptomatic diabetic autonomic neuropathy (DAN) and autoantibodies to sympathetic and parasympathetic nervous structures. The antigens identified by these autoantibodies are not known, but glutamic acid decarboxylase (GAD) has been suggested as a candidate target, since anti-GAD autoantibodies are present in patients with long-term diabetes and GAD is expressed in a variety of cell types and structures in the nervous system. The aim of this study was to examine GAD expression in sympathetic ganglia and vagus nerve and to compare the distribution of GAD within these tissues with that of anti-sympathetic ganglia and anti-vagus nerve autoantibodies from patients with DAN, using single and double indirect immunofluorescence on tissue sections. The monoclonal antibody GAD-6, specific for GAD65, gave a granular, peripheral cytoplasmic staining pattern in sympathetic ganglion cells. Dual immunofluorescene demonstrated that serum from a patient with anti-sympathetic ganglion autoantibodies stained the same cells, but homogeneously throughout the cytoplasm. In the vagus nerve, patient's serum stained the fibers only; GAD-6 stained the cytoplasm of parasympathetic ganglion cells but only occasional fibers. In addition, GAD enzymatic activity was detectable in both sympathetic ganglia and vagus nerve. Incubation of sera or GAD-6 overnight with a crude homogenate of human brain as an antigen source abolished staining of the nervous tissues by GAD-6, but not by patients' sera. The different localisation of GAD and the autopantigens

targeted by patients' sera indicates that GAD is not the target of the autoantibodies characteristic of DAN. Moreover, absorption studies using human brain homogenate suggest that the targets of ani-sympathetic ganglion and anti-vagus nerve autoantibodies are absent or represented only at low levels in the central nervous system and may be confined to the periphery.

**Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria. The EUCLID Study Group [see comments].**

*Anonymous, Lancet 1997; 349(9068) : 1787-92.*

BACKGROUND: Renal disease in people with insulin-dependent diabetes (IDDM) continues to pose a major health threat. Inhibitors of angiotensin-converting enzyme (ACE) slow the decline of renal function in advanced renal disease, but their effects at earlier stages are unclear, and the degree of albuminuria at which treatment should start is not known.

METHODS: We carried out a randomised, double-blind, placebo-controlled trial of the ACE inhibitor lisinopril in 530 men and women with IDDM aged 20-59 years with normoalbuminuria or microalbuminuria. Patients were recruited from 18 European centers, and were not on medication for hypertension. Resting blood pressure at entry was at least 75 and no more than 90 mm Hg diastolic, and no more than 155 mm Hg systolic. Urinary albumin excretion rate (AER) was centrally assessed by means of two overnight urine collections at baseline, 6, 12, 18, and 24 months.

FINDINGS: There were no difference in baseline characteristics by treatment group; mean AER was 8.0 micrograms/min in both groups; and prevalence of microalbuminuria was 13% and 17% in the placebo and lisinopril groups, respectively. On intention-to-treat analysis at 2 years, AER was 2.2 micrograms/min lower in the lisinopril than in the placebo group, a percentage difference of 18.8% (95% CI 2.0-32.7, p = 0.03), adjusted for baseline AER and center, absolute difference 2.2 micrograms/min. In people with normoalbuminuria, the treatment difference was 1.0 microgram / min (1207% [-2.9 to 26.0], p = 0.1). In those with microalbuminuria, however, the treatment difference was 34.2 micrograms/min (49.7% [-14.5 to 77.9], p = 0.1; for interaction, p = 0.04). For patients who completed 24 months on the trial, the final treatment difference in AER was 38.5 micrograms/min in those with microalbuminuria at baseline (p = 0.001), and 0.23 microgram/min in those with normoalbuminuria at baseline (p = 0.6). There was no treatment difference in hypoglycemic events or in metabolic control as assessed by glycated hemoglobin.

INTERPRETATION: Lisinopril slows the progression of renal disease in normotensive IDDM patients with little or no albuminuria, though greatest effect was in those with microalnbuminuria (AER > or = 20 micrograms/min). Our results show that lisinopril does not increase the risk of hypoglycemic events in IDDM.

**Rental functional response to protein loading in type 1 (insulin-dependent) diabetic patients on normal or high salt intake.**

*Lopes de Faria JB, Friedman R, de Cosmo S, Dodds RA, Mortton JJ, Viberti GC, Nephron. 1997; 76(4):411-7.*

Insulin-dependent diabetes mellitus (IDDM) patients may have an increased intrarenal angiotensin II activity. In diabetic patients, captopril increases the renal hemodynamic response to an amino acid infusion. We investigated the effects of two salt diets on arterial pressure and renal response to a protein load in 10 normotensive (blood pressure < 140/90 mm Hg) IDDM patients (aged 30 +/- 3 years) who had diabetes for 7 +/- 4 years and normoalbuminuria levels [albumin excretion rate 4.8 ( 2.5-19.1) micro/min]. After 1 week of normal (approximately 100 mmol/day; approdimately 100 mEq/l) and 1 week of high (approximately 300 mmol/day; approximately 300 mEq/l) salt intake, renal hemodynamic studies were performed at baseline and after a protein load (meat meal) of 100 g/1.73 m2. The mean 24-hour urinary sodium excretion levels were 99 +/- 27 and 293 +/- 80 mmol (mEq) with normal and high salt intake, respectively. No significant changes were seen in plasma sodium and glucose control with the normal and high salt diets, respectively: plasma sodium 135 +/- 3 vs. 137 +/- 1 mmol/l (mEq/l), (p = 0.08) and glycated hemoglobin 9.1 +/- 1.9 vs. 9.4 +/- 2.1% (p = 0.36). The body weight (70.9 +/- 12 vs. 71.8 +/- 13 kg; p = 0.015) was significantly higher with a high salt diet. The mean arterial pressure was similar with both diets (normal vs. high salt diet 91 +/- 9 vs. 89 +/- 6 mm Hg, p = 0.25). The plasma renin concentration [28 +/- 15 vs, 16 +/- 6 microU/ml(168 +/- 90 vs. 96 +/- 36 pmol/l), p = 0.013] and angiotensin II [8.8 +/- 4.4 vs. 6.4 +/- 3.5 pg/ml (0.052 +/- 0.025 vs. 0.038 +/- 0.021 nmol/l), p = 0.016] were significantly lower with the high salt diet. Following protein loading, the glomerular filtration rate increased with both diets: normal salt diet 114 +/- 26 vs. 128 +/- 30 ml/min/1.73 m2(1.9 +/- 0.43 vs. 2.13 +/- 0.50 ml/s/1.73 m2), p = 0.04; high salt diEt 118 +/- 23 vs. 127 +/- 29 ml/min/1.73 m2 (1.97 +/- 0.38 vs. 2.12 +/- 0.48 ml/s/1.73 m2), p = 0.13. The change in renal plasma flow was similar to that of the glomerular filtration rate with normal and high salt intake, respectively: 566 +/- 94 vs. 617 +/- 142 ml/min/1.73 m2 (9.44 +/- 1.57 vs. 10.29 +/- 2.37 ml/s/173 m2), p = 0.0017; 572 +/- 125 vs. 600 +/- 110 ml/min/1.73 m2 (9.54 +/- 10.00 +/- 1.83 ml/s/1.73 m2), p = 0.057. In this subject of normotensive normoalbuminuric IDDM patients, a high salt intake did not promote an exaggerated renal response to the protein load despite inhibition of the renin-angiotensin system.

## COMPLICATIONS – HYPOGLYCEMIA

**Preservation of physiological responses to hypoglycemia 2 days after antecedent hypoglycemia in-patients with IDDM [see comments].**

*George E, Marques JL, Harris ND, Macdonald IA, Hardisty CA, Heller SR. Diabetes Care 1997; 20(8) : 1293-8.*

OBJECTIVE: To assess the effects of short-term antecedent hypoglycemia on responses to further hypoglycemia 2 days later in patients with IDDM.

RESEARCH DESIGN AND METHODS: We studied eight type I diabetic patients without hypoglycemia unawareness or autonomic neuropathy during two periods at least 4 weeks apart. On day 1, 2 h of either clamped hyperinsulinemic (60 mU.m-2.min-1) hypoglycemic at 2.8 mmol/l or euglycemia at 5.0 mmol/l were induced. Hyperinsulinemic hypoglycemia was induced 2 days later with 40 min glucose steps of 5.0, 4.0, 3.5, 3.0, and 2.5 mmol/l. Catecholamine levels and symptomatic and physiological responses were measured every 10-20 min.

RESULTS: When compared with the responses measured following euglycemia, the responses of norepinephirine 2 days after hypoglycemia were reduced (peak, 1.4 +/- 0.4 [mean +/- SE] vs. 1.0 +/- 0.3 nmol/l [P < 0.05]; threshold, 3.4 +/- 0.1 vs. 3.6 +/- 0.1 nmol/l glucose [P < 0.01]). The responses of epinephrine (peak, 4.0 +/- 1.4 vs. 3.5 +/- 0.8 nmol/l [P = 0.84]; threshold, 3.8 +/- 0.1 vs. 3.6 +/- 0.1 mmol/l glucose [P = 0.38]), water loss (peak, 194 +/- 34 vs. 179 +/- 47 g-1.m-2.h-1 [P = 0.73]; thresold, 2.9 +/- 0.2 vs. 2.9 +/- 0.2 mmol/l glucose [p = 0.90]), tremor (peak, 0.28 +/- 0.05 vs.0.37 +/- 0.06 root mean square volts (RMS V) [P = 0.19]; threshold, 3.2 +/- 0.2 vs. 3.1 +/- 0.2 mmol/l glucose [P = 070]), total symptom scores (peak, 10.6 +/- 2.1 vs. 10.8 +/- 1.9 [P = 0.95]; threshold, 3.3 +/- 0.2 vs. 3.6 +/0 0.1 mmol/l glucose [P = 0.15]), and congnitive function (four-choice reaction time: threshold, 2.9 +/- 0.2 vs. 3.0 +/- 0.2 mmol/I glucose [P = 0.69]) were unaffeted.

CONCLUSIONS: The effect on hypooglycemic physipological responses of 2 h of experimental hypoglycemia lasts for 1-2 days in these patients with IDDM. The pathophysiological effect of antecedent hypolcemia may be of shorter duration in IDDM patients with IDDM. The pathophysiological effect of antecedent hypoglycemia may be of shorter duration in IDDM patients, compared with nondiabetic subjects.

## PREGNANCY IN DIABETES

### Outcomes of pregnancy in insulin dependent diabetic women: results of a five year population cohort study [see comments].

*Casson IF, Clarke CA, Howard CV, McKendrick O, Pennycook S, Pharoah PO, Platt MJ, Stanisstreet M, van Velszen D, Walkinshaw S. BMJ 1997; 315(7103) : 275-8.*

OBJECTIVE: To monitor pregnancies in women with pre-existent insulin dependent diabetes for pregnancy loss, congenital malformations, and fetal growth in a geographically defined area of north west England.

DESIGN: Population cohort study.

SETTING: 10 maternity units in Cheshire, Lancashire, and merseyside which had no regional guidelines for the management of pregnancy in diabetic women.

SUBJECTS: 462 pregnancies in 355 women with insulin dependent diabetes from the 10 centres over five years (1990-4 inclusive).

MAIN OUTCOME MEASURES: Numbers and rates of miscarriages, stillbirths, and neonatal and opostneonatal deaths; prevalence of congential malformations; birth weight in relation to gestational age.

RESULTS: Among 462 pregnancies, 351 (76%) resulted in a liveborn infant, 78 (17%) aborted spontaneously, nine (2%) resulted in stillbirth, and 24 (5%) were terminated. Of the terminations, nine were for congenital malformation. The stillbirth rate was 25.0/1000 total births (95% confidence interval 8.9 to 41.1) compared with a population rate of 5.0/1000, and infant mortality was 19.9/1000 live births (5.3 to 34.6) compared with 6.8/1000. The prevalence of congenital malformations was 94.0/1000 live births (63.5 to 124.5) compared malformations was 94.0/1000 live births (63.5 to 124.5) compared with 9.7/1000 in the general population. When corrected for gestational age, mean birth weight in the sample was 1.3 standard deviations greater than that of infants of non-diabetic mothers. Infants with congenital malformations weighed less than those without.

CONCLUSION: In an unselected population the infants of women with pre-existent insulin dependent diabetes mellitus have a 10-fold greater risk of a congenital malformation and a fivefold greater risk of being stillborn than infants in the general population. Further improvements in the management of pregnancy in diabetic women are needed if target of the St Vincent declaration of 1989 is to be met.