ABSTRACT SERVICE

ETIOLOGY AND EPIDEMIOLOGY

Primary pancreatic beta-cell secretory defect caused by mutations in glucokinase gene in kindreds of maturity onset diabetes of the young.

Velho G; Froguel P; Clement K; Pueyo ME; Rakotoambinina B; Zouali H; Passa P; Cohen D; Robert JJ: Lancet. 1992; 340 : 444-8.

Maturity-onset diabetes of the young (MODY), characterized by NIDDM with an early age of onset, is a genetically heterogeneous disorder. In most MODY kindreds described in France, chronic hyperglycaemia is caused by mutations in the gene encoding pancreatic beta-cell and liver glucokinase (GCK). We here report the beta-cell secretory profiles of nine patients from four GCK-linked MODY kindreds. First-phase insulin secretion assessed by an intravenous glucose test was comparable in patients and seven controls. However, beta-cell secretory response to continuous glucose stimulus during a hyperglycaemic glucose clamp was significantly reduced: mean plasma insulin values of 12 (SD 7) vs 40 (11) mU/l ($p = 0.0001$) and mean plasma C-peptide values of 1.20 (0.30) vs 2.61 (0.37) ($p = 0.0001$). This secretory profile is different from those for NIDDM with late age of onset or MODY not linked to GCK. Fasting plasma insulin and C-peptide levels in patients were inappropriately low in relation to, concomitant plasma glucose level. Furthermore, during a hyperinsulinaemic euglycaemic clamp, endogenous insulin secretion at euglycaemia (5 mmol/l) was suppressed in patients but not in controls. These results suggest that mutant GCK may lead to chronic hyperglycaemia by raising the threshold of circulating glucose level which induces insulin secretion. These data provide the first demonstration of a primary pancreatic secretory defect associated with a form of NIDDM.

Close linkage of glucokinase locus on chromosome 7p to early-onset non-insulin-dependent diabetes mellitus

Froguel P; Vaxillaire M; Sun F; Velho G; Zouali H; Butel MO; Lesage S; Vionnet N; Clement K; Fougerousse F; et al. Nature. 1992; 356 : 162-4.

NIDDM is a major health problem affecting 5°~6 of the world population. Genetic factors are important in NIDDM but the mechanisms leading to glucose intolerance are unknown. Genetic linkage has been investigated in multigeneration families to localize and ultimately identify the gene(s) predisposing to NIDDM. Here we report linkage between the glucokinase locus on chromosome 7p and diabetes in 16 French families with maturity-onset diabetes of the young, a form of NIDDM characterized by monogenic autosomal dominant transmission and early age of onset. Statistical evidence of genetic heterogeneity was significant, with an estimated 45-95% of the 16 families showing linkage to glucokinase. Because glucokinase is a key enzyme of blood glucose homeostasis, these results are evidence that a gene involved in glucose metabolism could be implicated in the pathogenesis of NIDDM.

An increased level of antibodies to beta-lactoglobulin is a risk determinant for early-onset type-I (insulin-dependent diabetes mellitus independent of islet cell antibodies and early introduction of cow's milk.

Dahlquist G; Savilahti E: Landin-Olsson M: Diabetologia. 1992; 35; 980-4.

Using a case-control design we have studied whether antibodies to cow's milk proteins are risk determinants for childhood-onset type-I (insulin-dependent) diabetes mellitus independent of early exposure to cow's milk formula and islet cell antibodies. Sera from 116 recent-onset diabetic children and 112 age- and sex-matched control children were analysed for cow's milk protein IgA, IgG and IgM antibodies, beta-lactoglobulin IgA and IgM antibodies, and islet cell antibodies. The titres were compared to questionnaire data on duration of breast-feeding and introduction of formula feeding. Most antibody levels tended to be increased among diabetic compared with control children. This was statistically significant for cow's milk protein IgA antibodies ($p < 0.001$) and beta-lactoglobulin IgA antibodies ($P < 0.01$) as well as for islet cell antibody-positivity which was found among 92% of the diabetic and 3% of the control children. The differences in cow's milk protein antibodies as well as beta- lactoglobulin antibodies were more pronounced arnong children with an early onset of type-I diabetes. Breast-feeding duration was significantly inversely related to the log of beta-lactoglobulin IgG ($r=-0.16$, $p < 0.04$) and the log of cow's milk protein IgA antibodies ($r=-0.17$, $p < 0.001$). A positive correlation was found between formula feeding the logarithm of beta-lactoglobulin IgG antibodies ($r=0.22$, $p=0.01$) and the log of cow's milk protein IgA antibodies ($r=0.16$, $p = 0.04$). In a multiple logistic regression analysis it was found that IgA antibodies to beta-lactoglobulin and cow's milk protein were significantly related to the risk of type-I diabetes independent of islet cell antibodies. When introducing formula feeding before the age of 4 months as a variable in the regression it was shown that islet cell antibodies and betalactoglobulin IgA antibodies were still significantly and independently related to an increased risk of diabetes whereas cow's milk protein IgA antibodies did not add further to the regression. It is concluded that beta-lactoglobulin IgA antibodies are significantly associated with an increased risk of diabetes at a young age independent of islet cell antibody status and of an early weaning to cow's milk formula. In genetically susceptible children early exposure to beta-lactoglobulin might be one trigger in the autoimmune process leading to development of type-I diabetes.

Has the process causing non-insulin-dependent diabetes started at birth? Evidence in neonates from a population with a high prevalence of diabetes

Simmons D; Baker J; James A; Roberts A. N.Z. Med. J. 1992; 105:326- 8.

The present study was carried out to investigate whether differences in the glucose-insulin axis are present at birth in neonates from ethnic groups at high risk of diabetes. Fructosamine samples were taken from Maori, European and Pacific Island expectant mothers at their 28-week appointment at the public outpatients' clinic at the National Women's Hospital, Auckland. Umbilical cord samples for

insulin, C-peptide and fructosamine assay were taken at delivery and babies had their subscapular skinfold fat thickness measured by callipers. The mean maternal 28-week fructosamine was similar in the three populations in spite of a higher prevalence of gestational diabetes among Pacific Islanders. Of the 1066 deliveries, cord samples were available for 207 Europeans, 81 Maoris and 113 Pacific Islanders. Both Pacific Island and Maori babies had higher cord fructosamine concentrations than European babies. However, Pacific Island babies were also heavier and had higher cord insulin concentrations and subscapular skinfold thickness than European babies. The elevated cord fructosamine concentrations suggest that Maori and Pacific Island babies, who share a high risk of NIDDM later in life, are hyperglycaemic at birth. The paradoxical insulin results and the cause for the relative neonatal hyperglycemia warrant further investigation.

Childhood diabetes, insulin and Africa. DERI (Diabetes Epidemiology Research International) Study Group

Makame MH. Diabetic Med. 1992; 9:571-3.

Mortality associated with type-I (insulin-dependent) diabetes has perceptually declined with the identification and widespread use of insulin. In the pre-insulin era, over 80% of all individuals developing diabetes died each year, now less than one in 200 die. Sadly, this remarkable achievement has not reached the children who develop diabetes in sub-Saharan Africa where the onset of childhood diabetes is the equivalent of a death sentence. Two major issues of importance related to type-I diabetes in African and other developing countries are missed diagnosis and unavailability of insulin, issues which cannot be ignored.

A genetic marker at the glucokinase gene locus for type-II (non-insulin-dependent) diabetes mellitus in Mauritian Creoles

Chiu KC; Province MA; Dowse GK; Zimmet PZ; Wagner G; Serjeantson S; Permutt MA. Diabetologia. 1992; 35:632-8.

The prevalence of type-II (non-insulin-dependent) diabetes mellitus is high in Mauritius, a multi-ethnic island nation in the southwestern Indian Ocean. Evaluation of candidate genes in the different ethnic groups represents a means of assessing the genetic component. As glucokinase is known to be a key regulator of glucose homeostasis in liver and pancreatic betacells, the human gene was isolated and a dinucleotide repeat (CA)n marker was identified at this locus. A polymerase chain reaction assay was developed and alleles differing in size were observed in individuals, according to the number of repeats in the amplified fragment. Eighty-five Creoles and 63 Indians of known glucose tolerance status were typed by amplification of genomic DNA for this dinucleotide (CA)n repeat marker. Four different alleles were observed including Z, the most common allele and Z + 2, Z + 4 and Z + 10, which differed from Z by 2,4 and 10 nucleotides, respectively. In Mauritian Creoles, the frequency of the Z + 2 allele was greater in type-II diabetic subjects than in control subjects (23.8 vs 8.9%, P=0.008), and the frequency of the Z allele was lower in type-II diabetic subjects (60 vs 75.6%, p=0.03). Analysis with univariate logistic regression models indicated that the Z+2 allele had the highest odds ratio, 3.08 (95% CI 1.14-8.35, p=0.0416), among the other risk factors (age, sex, BMI and waist/hip ratio). The multivariate odds ratio for type-II diabetes was 2.88 (95% CI 0.98-8.50, p=0.0551).

A case-control study of group B Coxsackie virus immunoglobulin M antibody prevalence and HLA-DR antigens in newly diagnosed cases of insulin-dependent diabetes mellitus

D'Alessio DJ. Am. J. Epidemiol. 1992; 135: 1331-8.

From July 1984 through June 1987, we sought referral of all newly diagnosed cases of IDDM aged 0-29 years in a 14-county area of southern Wisconsin. Each case was asked to identify an age- and sex-matched friend control. Blood specimens were obtained for group B Coxsackie virus immunologlobulin M (IgM) neutralizing antibody titer on cases and controls and HLA-DR typing of cases. There were 225 cases referred, of whom 194 participated. Of these, 134 had both HLA-DR typing and an initial serum specimen drawn within 59 days of diagnosis. Only two of 50 IDDM cases < 9 years of age had positive (≥1:16) group B Coxsackie virus IgM titers. Fifteen of 84 cases aged 10-29 years (17.8%) were group B Coxsackie virus IgM-positve, compared with five of 71 controls (7.0%). However, group B Coxsackie virus IgM antibody positivity was concentrated in HLA-DR3-positive cases (10 of 39, OR = 4.55, 95% CI 1.26-18.27, p < 0.01). HLA-DR3-negative cases were not different from controls in group B Coxsackie virus IgM prevalence. Eighty-three percent of the cases and 86% of the group B Coxsackie virus IgM-positive cases were referred in the first 24 months of study. These data demonstrate an association between group B Coxsackie virus infections and onset of IDDM only in HLA-DR3-positive persons aged 10 years or older. The data also suggest that diabetogenic group B Coxsackie virus strains may circulate only periodically; however, a longer period of study is needed to examine this possibility.

Diabetes mellitus, impaired glucose tolerance and mortality among elderly men: the Finnish cohorts of the Seven Countries Study

Stengard JH; Tuomilehto J; Pekkanen J; Kivinen P; Kaarsalo E; Nissinen A; Karvonen MJ. Diabetologia. 1992; 35:760-5.

We studied the association of glucose intolerance with total and cause-specific mortality during a 5-year follow-up of 637 elderly Finnish men aged 65-84 years. Total mortality was 276 per 1000 for men aged 65-74 years and 537 per 1000 for men aged 75-84 years. Five-year total mortality adjusted for age was 364 per 1000 in diabetic men, 234 per 1000 in men with IGT and 209 per 1000 in men with NGT. The relative risk of death among diabetic men was 2.10 (95% CI 1.26-3.49) and among men with IGT 1.17 (95% CI 0.71- 1.94) times higher compared with men with NGT. Cardiovascular disease was the most common cause of death in every glucose tolerance group. The multivariate adjusted relative risk of cardiovascular death was increased (1.55) in diabetic patients, albeit non-significantly (95% CI 0.84-2.85). Diabetes resulted in an increased risk of cardiovascular mortality among men aged 65-74 years but not among the 75-84-year-old men. Relative risk of death from non-cardiovascular causes was slightly increased among diabetic subjects. In conclusion, diabetes mellitus is a significant determinant of mortality among elderly Finnish men.

PATHOLOGY AND DIAGNOSIS

Heterogeneous glycaemic and insulinaemic responses to oral glucose in non-diabetic men: interactions between duration of obesity, body fat distribution and family history of diabetes mellitus

Lemieux S; Despres JP; Nadeau A; Prud'homme D; Tremblay A; Bouchard C. Diabetologia. 1992; 35:653-9.

The interaction between environrnental and genetic factors in the alterations of glucose-insulin homoestasis was studied in 104 non-diabetic men. Family history of diabetes mellitus was used as an index of genetic predisposition to diabetes. Body composition was measured by underwater weighing whereas subcutaneous and visceral adipose tissue areas were measured at the abdominal and femoral levels by computed tomography. The sample was first divided into two groups. The first group included subjects with 'normal' glycaemic and insulinaemic responses during a 75 g OGTT. The second group was composed of subjects either with a high glucose response or high insulin response or both. Men included in the second group were different from the 'normal' subjects for almost all body fatness variables. They also presented a prevalence of a positive family history of diabetes which was significantly higher than 'norrnal' subjects. The second group was then divided into three distinct subgroups based on insulin and glucose responses of the subjects during the OGTT. Subjects with high insulin but 'normal' glucose responses were characterized by significantly higher levels of total body fat and deep abdominal adipose tissue when compared with the `normal' group ($p < 0.05$). Men with both high insulinaemic and high glycaemic responses displayed higher body fatness values and higher deep and subcutaneous abdominal adipose tissue areas ($p < 0.05$) in comparison with 'normal' subjects. They also had a higher BMI at age 20 years than control subjects and subjects with high insulin but 'normal' glucose responses.

Abnormalities in the ultradian oscillations of insulin secretion and glucose levels in type-II (non-insulin-dependent) diabetic patients

Sturis J; Polonsky KS; Shapiro ET; Blackman JD; O'Meara NM; van Cauter E. Diabetologia. 1992; 35:681-9.

To investigate the temporal organization of insulin secretion and glucose concentration during fasting in type-II (non-insulin- dependent) diabetes mellitus, we studied seven patients with type-II diabetes, eight obese non-diabetic control subjects and eight normal-weight non-diabetic subjects. Blood sampling for glucose, insulin and C-peptide was performed at 15-minute intervals during a 24-hour period of fasting for the diabetic and the obese control subjects and during an 8-hour fasting period for the normal subjects. Insulin secretion rates were calculated from the peripheral C-peptide concentration profiles. Ultradian oscillations of glucose levels and .insulin secretion rates were evident during fasting in all subjects. An additional study with blood sampling at 2-minute intervals for 8 hours further indicated that this ultradian periodicity is expressed independently of rapid 10-15 minutes' insulin oscillations. There were no differences between diabetic and non-diabetic subjects in the frequency of the ultradian oscillations of insulin secretion (which averaged 12-15 oscillations per 24 hours) and in the rate of concornitancy of oscillations of insulin secretion with oscillations in glucose levels, which averaged 63-65%. The relative amplitudes of both the insulin and glucose oscillations were also similar in diabetic and non-diabetic subjects. The major abnormality in patients with type-II diabetes was evidenced by spectral analysis and confirmed by calculations of the distributions of inter-pulse intervals. It consisted of a slowing of the glucose oscillations, without a similar slowing of the oscillations in insulin secretion.

Vascular endothelial cell antibodies in diabetic patients. Association with diabetic retinopathy

Jones DB; Wallace R; Frier BM. Diabetes Care. 1992; 15:552-5.

A study consisting of 70 IDDM subjects, NIDDM subjects and 40 non-diabetic control subjects was set up to determine the incidence of antiendothelial cell antibodies in diabetic patients with and without retinopathy. Blood samples were obtained from diabetic patients and control subjects, and patients with background and proliferative retinopathy were identified. Vascular endothelial cell (VEC) antibodies were examined in the sera of 36 NIDDM subjects, 70 IDDM subjects and 40 nondiabetic control subjects by indirect immunofluorescence. VEC antibodies were present in five of 40. (12%) control subjects, seven of 23 (30%) newly diagnosed IDDM patients, six of 17 (35%) IDDM patients without retinopathy, 12 of 18 (67%) IDDM patients with background retinopathy ($p < 0.05$) and nine of 12 (75%) IDDM patients with proliferative retinopathy ($p < 0.01$). Three of 13 (23%) NIDDM patients with retinopathy and six of 23 (26%) without retinopathy were VEC antibodypositive. No associations were observed between the presence of VEC antibodies and either the quality of glycaemic control or the duration of diabetes. A significant association between VEC antibodies and large-vessel disease was found in IDDM patients with retinopathy ($P < 0.05$). It is concluded that antibodies directed against vascular endothelial cells may play a role in the development of microvascular and possibly macrovascular, disease in diabetes.

Urinary excretion of IGF-1 and growth hormone in children with IDDM

Quattrin T, Albini CH; Reiter EO; Mills BJ; MacGillivray MH. Diabetes Care. 1992: 15:490-4.

A study was set up to compare the urinary output of IGF-1 and GH in prepubertal and pubertal children with IDDM vs nondiabetic subjects, and to analyze the relationship between the urinary excretion of these peptides and degree of metabolic control. Group 1 included 30 IDDM patients who had diabetes for 4.9 ± 0.7 years and had normal renal function (mean age 11.6 ± 0.9 years); group 2 consisted of 31 control subjects (mean age 9.2 ± 0.6 years). Sensitive radioimmunoassays were used to measure IGF- 1 and GH in urine aliquots from 12-hour timed overnight collections that had been dialyzed, concentrated 50-fold and lyophilized. Significantly lower- IGF-1 and GH outputs per kg body weight per 12 hours were observed in IDDM subjects compared with control subjects. When data were expressed per kg of body weight, no difference was observed between the urinary output of IGF-1 and GH between prepubertal and pubertal subjects within group 1 or group 2. The prepubertal children had significantly lower HbA_1 than the pubertal population; however, no correlation was found between

urinary output of IGF-1 or GH and HbA_1. A positive correlation was observed between urinary IGF-1 and GH ($r=0.85$, $p < 0.001$). It is concluded that patients with long-standing IDDM excrete significantly lower urinary levels of IGF-1 and GH compared with normal subjects. Serial rneasurements of these peptides from onset of IDDM are needed to define whether the changes observed are present at diagnosis or are secondary to duration of disease.

Non-invasive glucose monitoring in diabetic patients: a preliminary evaluation

Robinson MR; Eaton RP; Haaland DM; Koepp GW; Thomas EV; Stallard BR; Robinson PL - Clin. Chem. 1992; 38: 1618-22.

Non-invasive monitoring of blood tissue glucose concentrations has been successfully accomplished in individual diabetic subjects by using near-infrared (NIR) spectroscopy coupled with chemometric methods. Three different spectrometer configurations were tested: a) a Fourier-transform infrared spectrometer with an indium antimonide detector; b) a grating monochromator equipped with a silicon (Si) array detector, without fiber optics; and c) a grating monochromator equipped with an Si detector, with fiber-optic sampling. NIR spectra were obtained from diabetic subjects by transmission through the finger during a meal tolerance test. The maximum range of observed plasma glucose concentrations obtained from blood samples was 2.5-27 mmol/l. The NIR spectra were processed by using the chemometric multivariate calibration methods of partial least squares and principal component regression. The best calibration yielded a cross validated average absolute error in glucose concentration of 1.1 mmol/l. This predictive ability suggests that non-invasive glucose determinations by NIR/chemometrics is a viable analytical method.

Ambulatory blood pressure in type-I diabetes mellitus. Comparison to presence of incipient nephropathy in adolescents and young adults

Moore WV; Donaldson DL; Chonko AM; Ideus P; Wiegmann TB. Diabetes. 1992; 41: 1035-41.

AMBP measurements were obtained at 20-minute intervals during the day and at 60-minute intervals during the night in 38 adolescents and young adults (12-25 years old) with type-I diabetes and in 36 healthy, non-diabetic control subjects of comparable age. The group of patients with elevated AER (>l5ug/min) had higher mean 24-hour sBP, dBP and BPB (defined as the prevalence of systolic readings >130 mm Hg or diastolic readings >85 mm Hg) compared with both the group of patients with type-I diabetes and AER <15 and the control group. The normal diurnal variation in BP and BPB was observed in the control group and the group with type-1 diabetes and AER < 15, whereas the nocturnal decrease observed in the group with type-I diabetes and AER >15 was not statistically significant. Elevations in AMBP of the patient group with AER >15 were reflected in random BP measurements. Even though the mean random BP measurements of all groups were within the normal range for age, the mean random sBP and dBP of the type-I diabetes patients with AER >15 was higher than both the control group and the group with type-I diabetes and AER <15. The GFR, determined by the clearance of ^{99}Tc-DTPA, was associated negatively with measures of AMBP and AER in the group with AER >15.

Further defects in counterregulatory responses induced by recurrent hypoglycemia in IDDM

Davis MR; Mellman M; Shamoon H. Diabetes. 1992; 41: 1335-40.

We evaluated the effect of previous experimental hypoglycemia on counterregulatory responses to hypoglycemia in 13 IDDM patients. These patients had defects in counterregulatory responses to hypoglycemia compared with seven non-diabetic control subjects. Plasma EPI and glucagon responses to hypoglycemia in IDDM patients were 60% of levels in non-diabetic subjects ($p < 0.02$ and $p < 0.001$ respectively). Hepatic glucose output (3-[^{3}H]glucose) was reduced by 60% of normal ($p < 0.005$), and the glucose infusion rate required to maintain plasma glucose was correspondingly greater in people with IDDM ($p < 0.001$). With a modified glucose clamp (plasma insulin 330 pM), the diabetic subjects underwent two sequential .120-minute periods of hypoglycemia (3.0 mM) with an intervening 60-minute euglycemic recovery period. In the IDDM patients, there were 30-50% decreases in plasma GH ($p < 0.005$) and cortisol ($p < 0.001$) responses during the second hypoglycemic period compared with the first. In addition, glucose output, already defective compared with that in non-diabetic subjects, was further reduced by 33% ($p = 0.03$) during the second period of experimental hypoglycemia. There was no effect of repeated hypoglycemia on the responses of plasma glucagon, EPI or NE, though plasma EPI was correlated directly with glucose output ($p < 0.001$) and inversely with glucose uptake ($p < 0.05$). There was no correlation between the rise in glucose output during hypoglycemia and antecedent glycemic control as measured by HBA_1. We conclude that in IDDM patients with pre-existing defects in counterregulatory responses to hypoglycemia, recurrent, mild hypoglycemia is associated with additional reductions in pituitary adrenocortical hormonal secretion and further impairment of hepatic glucose production.

Recombinant glutamic acid decarboxylase (representing the single isoform expressed in human islets) detects IDDM-associated 64,000 M(r) autoantibodies

Karlsen AE; Hagopian WA; Petersen JS; Boel E; Dyrberg T; Grubin CE; Michelsen BK; Madsen OD; Lernmark A. Diabetes. 1992; 41: 1355- 9.

GAD is an autoantigen in IDDM. Molecular cloning and specific antibodies allowed us to demonstrate that only the lower M(r) GAD64 isoform is expressed in human islets, in contrast to human brain, rat islets and rat brain, all of which express both GAD64 and GAD67. Expression of the human islet GAD64 isoform in COS-7 and BHK cells resulted in an enzymatically active rGAD64, which is immunoreactive with diabetic sera comparable with that of the islet 64,000 M(r) autoantigen. Immunoprecipitation analysis showed that 21/28 (75%) IDDM sera had rGAD64 antibodies compared with only 1/59 (1.7%) of the healthy control sera. In immunoblot analysis, an SMS serum-but only 1/10 randomly selected IDDM sera- recognized the blotted rGAD64 without relation to immunoprecipitation titers. In conclusion, only the GAD64 isoform is expressed in human islets, in contrast to

rat islets, which also express the GAD67 isoform. The immunological properties of human rGAD64 are comparable with the native 64,000 M(r) islet autoantigen, allowing further studies of the immunopathogenesis of IDDM.

Lp(a) concentrations in NIDDM

Haffner SM; Morales PA; Stern MP; Gruber MK - Diabetes. 1992; 4 1: 1267- 72.

NIDDM patients have a two-to fourfold increased risk of coronary heart disease relative to non-diabetic subjects. This excess risk is explained only partially by increased levels of standard risk factors. We compared the plasma concentrations of Lp(a) in NIDDM patients (n = 260) and non diabetic subjects (n = 336) who participated in a population-based study (San Antonio Heart Study). Lp(a) was measured using a monoclonal anti-Lp(a) antibody. NIDDM patients and non-diabetic subjects had similar Lp(a) concentrations for both men (13.6 ± 1.5 vs 16.1 ± 1.4 mg/dl) and women (12.6 ± 0.8 vs 15.9 ± 1.3 mg/dl) (p=0.361). Duration of diabetes and level of fasting glycemia were not significantly related to Lp(a) concentrations. Lp(a) levels were significantly higher in patients who had higher total and LDL- cholesterol levels. We conclude that in a large population-based study, Lp(a) levels are not increased in NIDDM patients.

Postprandial thermogenesis at rest and postexercise before and after physical training in lean, obese and mildly diabetic men

Segal KR; Blando L; Ginsberg-Fellner F; Edano A. Metab. Clin. Exp. 1992; 41:868-78.

To determine the independent impact of physical training on postprandial thermogenesis at rest and after 1 hour of cycling at 100 W, 10 lean (15 ± 1% body fat), 10 obese (33 ± 2% fat) and six obese diet-controlled, type-II diabetic men (34 ± 4% fat) underwent 12 weeks of vigorous cycle ergometer training (4 h/week at approxirnately 70%) of maximum oxygen consumption while maintaining body weight and composition. Body weight was held constant by refeeding the energy expended in each training session. Cardiorespiratory fitness increased by approximately 27%, but body weight and fat did not change. Before and at least 4 days after the last exercise session, energy expenditure was dmeasured for 3 hours under four conditions: 1) rest, no meal; 2) rest, after a 720 kcal mixed meal; 3) postexercise after 1 hour's cycling, no meal; and 4) postexercise, meal after exercise. The thermic effect of food was calculated as postprandial minus post- absorptive energy expenditure at rest and postexercise (kcal/3 h). Before and after training, the thermic effect of food during rest was lower in obese than in lean men and lower in diabetic than in obese men ($p < 0.05$). Thermogenesis was improved after short-term exercise in obese and diabetic men compared with that at rest, but was not normalized ($p < 0.05$ for lean vs obese, diabetic men). A significant effect of training on thermogenesis was due to a srnall but significant increase after training for diabetic men under the postexercise condition. Thus, while short- term exercise enhances but does not normalize thermogenesis in obese and diabetic men, long-term exercise leading to increased cardiorespiratory fitness, in the absence of changes in body composition, leads to a small increase in thermogenesis in diabetic men, which manifests only after a short period of exercise.

The effect of chronic hyperglycaemia on the islet B-cell responsiveness in newly diagnosed type-II diabetes

Gjessing HJ; Reinhold B; Pederson O. Diabetic Med. 1992; 9:601-4.

The aim of the present study was to evaluate the effect of chronic hyperglycaemia on the pancreatic B-cell response to stimulation with a standard mixed meal or intravenous glucagon in seven subjects with newly diagnosed type-II diabetes. Stimulation was performed at mean chronic fasting hyperglycaemia of 11.8 ± 0.7 (SEM) $mmol^{-1}$ and at normoglycaemia obtained by an intravenous infusion of regular insulin followed by an insulin wash-out period. The incremental plasma C-peptide AUC after stimulation with the meal was similar at normo- and hyperglycaemia. In contrast, prestimulatory plasma C-peptide and the incremental plasma C-peptide AUC after stimulation with glucagon were significantly higher at chronic hyperglycaemia than at normoglycaemia ($p < 0.01$ and $p < 0.05$). In conclusion, chronic hyperglycaemia as seen in newly diagnosed type-II diabetes is associated with a complete lack of potentiation of postprandial islet B-cell secretion but a partly preserved potentiation of basal and postglucagon islet B-cell secretion.

MPO activity and generation of active 0_2 species in leukocytes from poorly controlled diabetic patients

Sato N; Shimizu H; Suwa K; Shimomura Y; Kobayashi I; Mori M. Diabetes Care. 1992; 15: 1050-2.

This study was undertaken to determine which part of ROI generation is reduced in the neutrophils from patients with NIDDM, Superoxide anion ($O_{2\$AM}$) production, LDCL activity in response to opsonized zymosan and MPO activity were measured in leukocytes of poorly controlled NIDDM patients (FBG > 8.89 mM. HbA_1 > 10%). In diabetic subjects, both $O_{2\$AM}$ production and LDCL activity assessed with initial slope gradient and peak value were significantly reduced. MPO activity was also decreased in diabetic subjects and there was a significant correlation between HbA_1 levels and MPO activity of diabetic subjects. This study demonstrated that every step in leukocyte ROI generation should be reduced in the leukocytes from poorly controlled diabetic patients.

Blood ketone bodies in NIDDM: relationship with diabetic control and endogenous insulin secretion

Suzuki M; Kosegawa I; Miura S; Negishi K; Itabashi A; Katayama S; Ishii J; Kamata S; Fujita C. Diabetes Res. Detect. Ther. 1991; 18: 11- 7.

To evaluate the relationship of blood ketone bodies with diabetic control and endogenous insulin secretion, fasting plasma glucose (FPG), HbA_{1c}; fasting serum C-peptide (CPR), blood total ketone- bodies (TKB), blood acetoacetate (AcAc) and blood 3- hydroxybutyrate (3-OHB) were compared in 78 outpatients with NIDDM treated with diet (n = 13), sulfonylurea (n = 52) and insulin (n = 13). TKB, AcAc and 3-OHB in patients treated with insulin were significantly higher than in patients treated with diet or sulfonylurea. In patients given diet therapy, log 3-OHB showed significant

negative correlations with FPG, HbA_{1c} and CPR. In patients treated with sulfonylurea, log 3-OHB showed significant positive correlations with FPG and HbA_{1c}, but not with CPR. In patients treated with insulin, there were no correlations of log 3-OHB with FPG, HbA_{1c} and CPR. For evaluation of the metabolic state in diabetes mellitus, measurement of blood ketone bodies is useful and moreover necessary, in addition to diabetic control or determination of the endogenous insulin level.

Impaired insulin-mediated skeletal muscle blood flow in patients with NIDDM

Laakso M; Edelman SV; Brechtel G: Baron AD - Diabetes. 1992; 41: 1076- 83.

Patients with NIDDM exhibit decreased rates of skeletal muscle insulin-mediated glucose uptake (IMGU). Because IMGU is equal to the product of the arteriovenous glucose difference (AVG delta) across and blood flow (F) into muscle (IMGU = AVG delta x F), reduced tissue permeability (AVG delta) and/or glucose and insulin delivery (F) can potentially lead to decreased IMGU. The components of skeletal muscle IMGU were studied in six obese NIDDM subjects (103 ± 9 kg) and compared with those previously determined in six lean (weight 68 ± 3 kg) and six obese (94 ± 3 kg) with NGT. The insulin dose-response curves for whole body and leg muscle IMGU were constructed using the combined euglycemic clamp and leg balance techniques during sequential insulin infusions (range of serum insulin 130-80.000 pmol/l). In lean, obese and NIDDM subjects, whole body IMGU, femoral AVG delta and leg IMGU increased in dose-dependent fashion over the range of insulin with an ED_{50} of 400-500 pmol/l inlean, 1000-1200 pmol/l in obese and 4000-7000 pmol/l in NIDDM subjects ($p < 0.01$ lean vs obese and NIDDM). In lean and obese subjects, maximally effective insulin concentrations increased leg blood flow approximately twofold from basal with an ED_{50} of 266 pmol/l and 957 pmol/l, respectively ($p < 0.01$ lean vs obese). In contrast, leg F did not increase from the basal value in NIDDM subjects (2.7 ± 0.1 vs 3.5 ± 0.5 dl/min. ns).

Assessment of glucose tolerance test criteria for diagnosis of diabetes in Chinese subjects

Cockram CS: Lau JT. Chan AY: Woo J: Swaminathan R - Diabetes Care. 1992; 15: 988-90.

The relationship between fasting plasma glucose (FPG) and 2hour glucose were examined in 680 OGTTs with a quadratic regression model and ROC analysis to examine and compare WHO diagnostic criteria for diabetes mellitus. Simultaneous measurements of HbA_1 and fructosamine were also compared with multiple linear regression. Two hundred eighteen subjects (32%) had 2-hour glucose ≥11.1 mM, of which only 86 had FPG ≥7.8 mM. Only two subjects had FPG > 7.8 mM and 2hour glucose < 7.8 mM. Of subjects with 2-hour glucose < 7.8 mM (n = 332), only nine had FPG > 6.0 mM. From the quadratic model, the predicted FPG corresponding to 2-hour glucose = 11.1 mM was 5.7 mM, whereas the predicted 2-hour glucose corresponding to FPG = 7.8 mM was 15.2 mM. ROC analysis showed that, with 2-hour glucose ≥11.1 mM as indicating diabetes, an FPG of 5.6 mM gave an intersect for sensitivity and specificity of 87%. HbA_1 and fructosamine correlated more closely with 2-hour glucose and area under the OGTT curve than the FPG. Given that a 2-hour glucose cut-off of 11.1 mM can be justified from other studies, our results suggest that the FPG cut-off of 7.8 mM when used for screening purposes should be reduced. At a suggested value of 7.0 mM, specificity remain 98.5%, whereas sensitivity increases to 57%.

Twenty-four-hour energy expenditure in Pima Indians with type-II (non-insulin-dependent) diabetes mellitus

Fontvieille AM; Lillioja S; Ferraro RT; Schulz LO; Rising R; Ravussin E. Diabetologia. 1992; 35:753-9.

To assess the impact of type-II (non-insulin-dependent) diabetes mellitus on energy metabolism, 24-hour energy expenditure, basal metabolic rate and sleeping metabolic rate were measured in a respiratory chamber in 151 Pima Indians, 102 with NGT (67 male/35 female, [mean ± SD] 28 ± 7 years, 99 ± 24 kg, 32 ± 9% body fat) and in 49 with type-II diabetes (22 male/27 female 35±11 years, 107 ± 33 kg, 39 ± 7% body fat), after at least 3 days on a weight- maintaining diet. After adjustment for differences in fat-free mass, fat mass, age and sex, 24-hour energy expenditure, basal metabolic rate and sleeping metabolic rate were significantly higher in diabetic patients than in control subjects (72 kcal/day, $p < 0.05$; 99 kcal/day, $p < 0.005$; 99 kcal/day, $p < 0.001$ respectively). Spontaneous physical activity was similar in both groups whereas the thermic effect of food, calculated as the mean energy expenditure corrected for activity through-out the day above sleeping metabolic rate and expressed as a percentage of energy intake, was significantly lower in type-II diabetic patients (17.1 ± 7.1 vs 19.8 ± 5.6% $p < 0.05$). Adjusted values of 24-hour energy expenditure, basal metabolic rate and sleeping metabolic rate were correlated with hepatic endogenous glucose production ($r = 0.22$, $p < 0.05$; $r = 0.22$, $p < 0.05$; $r = 0.31$, $p < 0.01$, respectively). Therefore, increased basal and sleeping metabolic rates, resulting in increased 24hour sedentary energy expenditure may play a role in the weight loss so often observed in type-11 diabetic subjects in addition to the energy loss from glycosuria.

Hypertension in newly diagnosed non-insulin-dependent diabetic subjects.

Bergomi M; Vinceti M; Rovesti S; Benedetti P; Pacchioni C; Beneduce M; Vivoli G. Diabetes Res. Clin. Pract. 1992; 17:61-7.

Medical records of newly diagnosed NIDDM patients attending a diabetic centre in Modena, northern Italy, during the period 1985-88 were reviewed to analyze the prevalence of hypertension at age of diagnosis of diabetes and its association with selected risk factors. The prevalence of hypertension was also determined in a representative sample of control subjects. In the muitivariate analysis, greater BMI and older age, but not smoking, were strongly associated with increased rates of hypertension both in control and in diabetic subjects. In diabetic patients, family history of diabetes, defined as presence of diabetes in close relatives, was not significantly associated with hypertension, while rates of hypertension were significantly lower in patients who reported at least one parent affected by diabetes. After adjustment for age and BMI, newly diagnosed NIDDM was not an independent risk factor for hypertension. These findings seem to be consistent with the hypothesis that

diabetes and hypertension are not linked by a common genetic background.

TREATMENT : GENERAL ASPECTS

Telephone modem access improves diabetes control in those with insulin-requiring diabetes.

Ahring KK; Ahring JP; Joyce C; Farid NR. Diabetes Care. 1992; 15:971- 5.

Forty-two patients participated in the study and were followed for 12 weeks to assess whether modem access improves diabetes control in IDDM patients. The patients were randomly divided into two groups at baseline, a modem group and a control group. There were no significant differences between HbA_{1c} random blood glucose and weight between the groups at the beginning of the study. Patients were asked to perform five blood glucose determinations/day (before breakfast, before lunch, afternoon [15:00 h], before dinner and at bedtime) twice/week. The modem group transferred their data over the phone once/week. The control group would bring in their results on their regular visits every 6 weeks. Patients in the modem group were counseled every week over the telephone after transferring results to adjust insulin and food intake if necessary. In the modem group, HbA_{1c} improved from 0.106-0.092 (13.20%). The control group improved from 0.112-0.102 (8.9%). There was no significant change in weight, random blood glucose or insulin. It is concluded that the use of telephone modem-based patient-monitoring systems in diabetes clinical research seems to stimulate the patient to keep closer control of blood glucose levels. It might be especially useful in rural settings, for which this study was designed.

Nasal glucagon in the treatment of hypoglycaemia in type-I (insulin-dependent) diabetic patients.

Rosenfalck AM; Bendtson I; Jorgensen S; Binder C. Diabetes Res. Clin. Pract. 1992; 17:43-50.

The aim of this study was to compare the effect of nasally administered glucagon in doses of 1 (A) and 2 mg (B), with 1 mg glucagon administered intramuscularly (C) in 12 C-peptidenegative IDDM patients. Spontaneous recovery (D) from insulin- induced hypoglycaemia in the same patients was used as reference. The mean age was 31.1 (21-48) years, diabetes duration 10.8 (2.7- 31) years and HbAic 7.7 (6.5-9.8)%. Hypoglycaemia was induced by i.v. insulin infusion. When blood glucose (BG) reached about 2 mmol/l either glucagon was administered or the patients recovered spontaneously. BG nadir was 1.6 (1.1-2.3) mmol/l. BG increments during the first 15 minutes after glucagon administration were: (A) 1.9 ±.0.7 (0.4-3.0); (B) 2.5 ± 0.7 (1.5-3.5); (C) 2.5±1.0 (1.2-4.7); and (D) 0.3±0.4 (0-1.0) mmol/l, respectively. All treatments were more effective, measured as increments in BG, than spontaneous recovery, $p < 0.00001$. There was no difference between nasal treatment with 2 mg (B) and i.m. treatment (C), both being more effective than 1 mg (A) nasal treatment, $p < 0.1$. BG continued to increase up to 10 mmol/l 90 minutes after i.m. glucagon administration, whereas it stabilized at a level of 4.6- 6 mmol/l, 30-45 minutes after nasal administration. Eighty percent of the patients had side effects to nasal adminstration - local irritation, rhinitis or sneezing. Half of the patients sneezed, without correlation with the delivered dose of glucagon. None of the patients had side effects which would preclude further treatment.

Glycemic control in early IDDM. The Wisconsin Diabetes Registry

Allen C; Zaccaro DJ; Palta M; Klein R; Duck SC; D' Alessio DJ. Diabetes Care. 1992; 15:980-7.

A cohort (n = 277) was followed from diabetes diagnosis to evaluate longitudinal glycemic control, urinary C-peptide levels and certain features of diabetes of self-management. Unselected cases with IDDM, who were < 30 years of age, were identified at diagnosis from a 28-county area in Wisconsin. Subjects were asked to submit blood every 4 months for GHb testing, to report aspects of diabetes self-management every 6 months and to collect a 24- hour urine specimen 4 months after diagnosis. In the first year of diabetes, the rate of increase (0.23%/month) in GHb was significant for the cohort ($p < 0.001$) and for almost all age and sex subgroups. In the second year, there was no significant rate of increase for the cohort as a whole ($p > 0.10$). Adolescent males (10-19 years of age) had a mean GHb level for year 2 higher than males of other age groups and higher than female adolescents ($p < 0.001$). Adolescent males had a significant rate of increase in GHb for year 2 ($p = 0.02$); unlike all other age and sex subgroups. Adolescents had higher initial 24-hour urine C- peptide levels than children <10 years of age ($p < 0.01$). During the second year of diabetes, the percentage of adolescent males reporting three or more insulin injections/day was lower than any other subgroup. These data suggest that glycemic control stabilizes during the second year of IDDM, except in adolescent males, and that this may be due partly to aspects of self management.

INSULIN THERAPY : GENERAL ASPECTS

Hormonal counterregulation, symptom awareness and neurophysiological function in type-I diabetes during insulin- induced hypoglycaemia.

Lingenfelser T; Buettner UW; Plonz C; Steffen J; Eggstein M; Jakober B. Diabetic Med. 1992; 9:528-35.

To evaluate a putative differential impact of human (HI) and porcine (PI) insulin on human brain function we examined 10 type- I (insulin-dependent) diabetic patients without any signs of sensory or autonomic neuropathy. The glucose clamp technique was applied to achieve stable glycaemic plateaus of 5.6, 3.3, 2.2 and 1.7 mmol l^{-1} on two occasions with randomized and blinded allocation of either HI or PI. At each of the plateaus, symptom awareness, hormonal counterregulation and neurophysiological functions (primary sensory information processing of the auditory and somatosensory system) were recorded. The effect of both types of insulin on glucose metabolism and counterregulatory hormone response was almost identical. Catecholamines increased (adrenaline $p < 0.05$; noradrenaline $p < 0.02$) during hypoglycaemia, independent of the type of insulin being used. Symptom awareness increased significantly during the fall of blood glucose concentration. This effect was more pronounced (total symptom score 26 vs 2, $p < 0.05$) with PI, but only during developing hypoglycaemia (3.3 mmol l^{-1} plateau). For brainstem auditory evoked potentials and somatosensory

evoked potentials, all individual and averaged latencies and corresponding amplitudes were within the normal range. No effect of insulin type or blood glucose concentration on neurophysiological measures could be detected. Our results suggest a differential impact of HI and PI on human brain function with regard to symptom awareness, but not hormonal counterregulation. This direct effect of insulin on central nervous function does not involve the afferent transmission in the auditory and somatosensory system.

Symptomatic and hormonal hypoglycaemic responses to human and porcine insulin in patients with type-I diabetes mellitus.

Ferrer JP; Esmatjes E; Gonzalez-Clemente JM; Goday A; Conget 1; Jimenez W; Gomis R; Rivera F; Vilardell E. Diabetic Med. 1992; 9:552- 7.

In recent years there has been great concern that human insulin (HI) may induce fewer hypoglycaemic warning symptoms than porcine insulin (PI). We addressed this issue in eight patients aged 25.6 ± 3.3 (SEM) years with type-I (insulin-dependent) diabetes mellitus of 15.1 ± 3.7 years' duration who complained that hypoglycaemia unawareness had appeared after transferring from PI to HI. Acute induction of hypoglycaemia was induced on two occasions with semisynthetic HI and purified PI under double- blind conditions. Blood glucose was first clamped for 2 hours at 4.4-6.7 mmol l^{-1} with an intravenous infusion of HI or PI at 50 mU $kg^{-1}h^{-1}$ and 20% glucose at a variable rate. Thereafter, insulin infusion alone was maintained for 100 minutes. Heart rate, arterial pressure, reflex times, autonomic and neuroglycopenic signs and symptoms were assessed every 10 minutes. Arterialized venous blood samples were taken to measure blood glucose every 10 minutes and catecholamines, insulin, glucagon, GH and cortisol every 20 minutes. Autonomic symptoms first appeared at a plasma glucose level of 2.92 ± 0.21 mmol l^{-1} with HI vs 2.92 ± 0.48 mmol l^{-1} with PI (ns). There were no significant differences between the two studies concerning any of the above-mentioned clinical parameters or the counterregulatory hormone responses. A differential effect of insulin species on the ability to perceive hypoglycaemia in patients who ascribed diminished perception of hypoglycaemia to the use of HI was thus not observed.

C-peptide profiles in patients with non-insulin-dependent diabetes mellitus before and during insulin treatment

Lindstrom T; Arnqvist HJ; Ludvigsson J; von Schenck HH. Acta Endocrinol. 1992; 126:477-83.

The objective of the study was to evaluate the effect of insulin treatment on insulin secretion in patients with NIDDM. Ten patients with NIDDM were first investigated while still taking oral hypoglycemic agents and then randomized to a crossover study with two 8-week periods of insulin treatment (oral treatment having been stopped) given either as mainly intermediate-acting insulin twice daily (two-dose) or as prepandial regular insulin and intermediate-acting insulin at bedtime (four-dose). In the patients treated with oral agents the 24hour C-peptide AUC was similar to that in the controls, but the profile was different with a rise at breakfast but with almost absent meal peaks during the rest of the day. Insulin treatment improved glycemic control markedly, lowered urinary C-peptide excretion and the serum C- peptide concentrations being reduced by more than 50%. The shape of the C-peptide profiles was unaltered and there were no significant differences between the two insulin regimens. The decrease in serum C-peptide concentration during insulin treatment correlated with the change in blood glucose. Fasting serum C-peptide concentrations correlated closely with the 24- hour C-peptide AUC. In conclusion, insulin treatment of NIDDM patients with secondary failure to oral agents greatly reduces the insulin secretion, probably owing to the reduction in blood glucose.

INSULIN THERAPY: DELIVERY AND PHARMACOKINETICS

Comparison of peripheral and portal (via the umbilical vein) routes of insulin infusion in IDDM patients

Shishko PI; Kovalev PA; Goncharov VG; Zajarny IU. Diabetes. 1992; 41: 1042-9.

Twelve subjects with IDDM were treated using continuous subcutaneous insulin infusion (CSII) and intraportal insulin infusion (IPII) via the umbilical vein for 4 months. Glucose control improved in both CSII and IPl1 groups, but a decrease in glucose and HbA_{1c} was more rapid and more significant in the IPII group than in CSII, even though insulin requirement was lower during IPII than CSII (40 ± 2 vs 50 ± 2 U/day, $p < 0.05$). The insulin plasma fasting levels were different (88 ± 10.7 in the IPII group vs 263 ± 23 pM in CSII, $p < 0.001$). High plasma levels of lactate, pyruvate, alanine, cortisol and GH were decreased in both groups, with their full normalization only in the IPII group. Glucagon concentrations were low in both groups at the beginning of the study (30.0 ± 4.1 in the CSII group and 32.3 ± 1.8 ng/l in IPII); they were equalized to control values in the IPII group and were low in the CSII group at the study's end (46.0 ± 3.7 in IPII vs 31.7 ± 3.1 ng/l in CSII, $p < 0.05$). We conclude that intraportal administration of insulin via the umbilical vein at rates of 0.01-0.05 $U.kg^{-1}.h^{-1}$ reduces plasma levels of glucose, three carbon precursors, cortisol and GH by a direct action on the liver, and the hepatic action of peripherally administered insulin is manifested only when the infusion rate is increased to 0.1-0.3 $U.kg^{-1}.h^{-1}$.

Conventional and sprinkler needle injection of magnesium insulin

Colagiuri S; Bryson J; Keating S; Tan L; King J; Eigenmann C; Jorgensen KH. Diabetic Med. 1992; 9:616-21.

Currently available short-acting insulin preparations fail to mimic the postprandial insulin profile of non-diabetic individuals. The activity of a novel insulin designed for faster absorption has been tested after subcutaneous injection. Magnesium insulin (50 U ml^{-1}) given by sprinkler needle was compared with unmodified human insulin (100 U ml^{-1}) given by conventional needle and unmodified human insulin (50 U ml^{-1}) given by sprinkler needle in normal volunteers using a euglycaemic clamp. Magnesium insulin had a significantly faster onset of action resulting in a higher exogenous insulin level by 15 minutes; peak level was reached after 60 minutes compared with 75 minutes for the unmodified insulins, and duration of action was significantly shorter than both unmodified insulins. No significant differences were observed between the unmodified insulins for the first 5 hours after injection, indicating that the observed differences to mag-

nesium insulin could not be attributed to the insulin concentration or the type of needle used for insulin administration. Injection of magnesium insulin prior to a test breakfast in people with type-II diabetes resulted in significantly lower total and 0-120 minute areas under the glucose curve, and earlier rise in exogenous insulin levels, and a higher area under the insulin curve from 0-120 minutes compared with unmodified 100 U ml^{-1} human insulin.

ORAL HYPOGLYCEMIC AGENTS

Is combination of sulfonylurea and insulin therapy useful in NIDDM patients? A metaanalysis

Pugh JA; Wagner ML; Sawyer J; Ramirez G; Tuley M; Fried- berg SJ. Diabetes Care. 1992; 15:953-9.

A study was carrred out to assess the efficacy of combination therapy with insulin and sulfonylurea in the treatment of NIDDM. Studies published between January 1966 and January 1991 were identified through a computerized Medline search and by hand searching the bibliographies of identified articles. We identified 17 eligible randomized, controlled trials of combination therapy in NIDDM. These trials had a minimum duration of 8 weeks and at least one of three outcome measures (fasting glucose, HbA_1 or C-peptide) with SD or SE of the mean reported to do metaanalysis. With standardized forms, three independent reviews abstracted measures of study quality and specific descriptive information about population, intervention and outcome measurements. We calculated effect size and weighted mean changes of the three outcome measures for control and treatment groups. In the treatment group, fasting plasma glucose decreased from a mean of 11.4 mM (206 mg/dl) at baseline to a mean of 9.16 mM (165 mg/dl) post-treatment, whereas the control group decreased from 11.3-10.8 mM (204-194 mg/dl) (effect size 0.39, $p < 0.0001$). For HbA_1, the treatment group decreased from a baseline of 11.0- 10.2% compared with 11.0 and 11.2% in the control group (effect size 0.43, $p < 0.0001$). For fasting C-peptide, the treatment group increased from 0.49-0.58 nM (1.45-1.75 ng/ml) compared with 0.47 and 0.43 (1.42 and 1.30) for the control group (effect size 0.26, $p < 0.017$). Combined insulin-sulfonylurea therapy leads to modest improvement in glycemic control compared with insulin therapy alone. With combined therapy, lower insulin doses may be used to achieve similar control. Obese patients with higher fasting C-peptides may be more likely to respond than others.

Comparison of combined therapies in treatment of secondary failure to glyburide

Trischitta V; Italia S; Mazzarion S; Buscema M; Rabuazzo AM; Sangiorgio L; Squatrito S; Vigneri R. Diabetes Care. 1992; 15:539- 42.

A crossover study was carried out to compare the effectiveness of alternative combined treatments in patients with NIDDM with secondary failure to sulfonylureas. Sixteen NIDDM patients were randomly assigned to a combined treatment with the addition of either a single low-dose bedtime injection of 0.2 U/kg body weight NPH insulin or an oral three times a day administration of 1.5 g/day metformin to the previously ineffective glyburide treatment. Both combined therapies significantly ($p < 0.01$) reduced fasting plasma glucose (FPG), postprandial plasma glucose (PPPG) and percentage of HbA_1. The addition of metformin was more effective than the addition of insulin ($p < 0.01$) in improving PPPG in the eight patients with higher postglucagon C-peptide levels. In contrast, the efficacy of neither combined therapy was related to patient age, age of diabetes onset, duration of the disease, percentage of ideal body weight and FPG. The addition of insulin but not metformin caused a significant ($p < 0.01$) increase of mean body weight. Neither combined treatment. caused changes in serum cholesterol and triglyceride levels. No symptomatic hypoglycemic episode was reported in any of the 16 patients. The addition of bedtime NPH insulin or metformin was effective in improving glycemic control in most NIDDM patients with secondary failure to glyburide. The combination of metformin and sulfonylurea was more effective in reducing PPPG and did not induce any increase of body weight.

DIET AND NUTRITION

Comparison of effects of high and low carbohydrate diets on plasma lipoproteins and insulin sensitivity in patients with mild NIDDM

Garg A; Grundy SM; Unger RH. Diabetes. 1992; 41: 1278-85.

Previous. studies indicate that diets rich in digestible carbohydrates improve glucose tolerance in non-diabetic individuals,. but may worsen glycemic control in NIDDM patients with moderately severe hyperglycemia. The effects of such high-carbohydrate diets on glucose metabolism in patients with mild NIDDM have not been studied adequately. This study compares responses to an isocaloric high-carbohydrate diet (60% of total energy from carbohydrates) and a low-carbohydrate diet (35% of total energy from carbohydrates) in eight men with mild NIDDM. Both diets were low in saturated fatty acids, whereas the low-carbohydrate diet was rich in monounsaturated fatty acids. The two diets were matched for dietary fiber content (25 g/day). All patients were randomly assigned to receive first one and then the other diet, each for a period of 21 days, in a metabolic ward. Compared with the low-carbohydrate diet, the high-carbohydrate diet caused a 27.5% increase in plasma triglycerides and a similar increase in VLDL-cholesterol levels; it also reduced levels of HDL cholesterol by 11%. Plasma glucose and insulin responses to identical standard breakfast meals were studied on days 4 and 21 of each period and these did not differ significantly between the two diets. At the end of each period, a euglycemic hyperinsulinemic glucose clamp study with simultaneous infusion of [3-^{3}H] glucose revealed no significant changes in hepatic insulin sensitivity; and peripheral insulin- mediated glucose disposal remained unchanged (14.7 ± 1:4 vs 16.5 ± 2.3 $\mu M.kg^{-1}.min^{-1}$ on the high and low carbohydrate diets, respectively). We conclude that in patients with mild NIDDM, high carbohydrate diets do not improve glycemic control nor insulin sensitivity and they raise plasma triglyceride and VLDL cholesterol concentrations and reduce HDL-cholesterol levels, which may not be desirable.

Day-to-day variation of blood glucose and insulin responses in NIDDM subjects after starch-rich meal

Rasmussen OW; Gregersen S; Dorup J; Hermansen K. Diabetes Care. 1992; 15:522-4.

Ten NIDDM subjects attending the outpatient clinic at Aarhus Kommune-hospital were followed to study day-to-day variation of postprandial blood glucose and insulin increments in NIDDM subjects and to analyze intra-and interperson variance of response. The subjects ate three meals of 90 g of white bread, with 7 days between tests. Mean ± SD areas under the blood glucose response curve (above basal) over a 3-hour period were 557 ± 60, 569 ± 74 and 565 ± 67 mM x 180 min (ns) and areas under the insulin response curve were 3350 ± 448, 2815 ± 359 and 3551 ± 679 mU/I x 180 min (ns) on each of the three occasions. The 95% Cls of blood glucose and insulin areas for the test meal repeated three times were 564 ± 120 mM x 180 min and 3240 ± 1645 mU/I x 180 min, respectively. Intra-and interperson components of variance were 25 vs 75% (glucose) and 78 vs 22% (insulin) of the total variance. The intraperson components of variance included all sources of variation other than between-person variation. There was no significant correlation between blood glucose and insulin response areas. It is concluded that a valid estimate of the glycemic response in a single patient is obtained after a single meal. Because of the large between-person variation, paired data should preferably be used when comparing glycemic responses to different foods.

PREGNANCY

Oral contraceptive use and the risk of type-II (non-insulindependent) diabetes mellitus in a large prospective study of women

Rimm EB; Manson JE; Stampfer MJ; Colditz GA; Willett WC; Rosner B; Hennekens CH; Speizer FE. Diabetologia. 1992; 35:967 72.

We examined the association between oral contraceptive use and incidence of type-II (non-insulin-dependent) diabetes mellitus among 115,117 female nurses free of diabetes, cardiovascular disease and cancer in 1976, and followed-up for 12 years. During 1,237,440 person-years of follow-up, 2276 women who provided information on oral contraceptive use were clinically diagnosed with type-II diabetes. Women who used oral contraceptives in the past had only a slight.and marginally increased relative risk of 1.10 (95% CI 1.01, 1.21) compared with those women who had never used oral contraceptives after controlling for known risk factors of disease. We found no evidence of increased risk with longer duration of use or with shorter interval since last use. Current users did not have an increased risk of type-II diabetes (relative risk = 0.86, 95% CI 0.46, 1.61) when compared with women who had never used the drug. There was no effect modification by obesity, family history of diabetes or physical activity. These data suggest that past or current oral contraceptive use does not substantially influence subsequent risk of type-II diabetes.

Sonographic estimation of fetal weight in diabetic pregnancy.

Pedersen JF; Molsted-Pedersen L. Br. J. Obstet, Gynaecol. 1992; 99:475-8.

A retrospective study was carried out to investigate whether fetal weight estimation by ultrasound in diabetic pregnancy might be based upon fetal abdominal circumference (AC) alone. Study subjects comprised 86 diabetic pregnant women who had an ultrasound within 2 days before delivery. We assessed in 73 fetuses various formulas based upon biparietal diameter and AC against formulas based upon AC alone and these were only marginally less effective than the more complex ones. In 86 fetuses an AC was available. These fetuses were divided into a study population and a test population. The linear model was customized for the study population. Evaluation on the test population showed that the relative error (error as a percentage of birthweight) in predicting birthweight had a standard deviation of 7.8%. The efficacy of AC in detecting fetuses > 4000 g was examined in the test population: if AC > 36.0 cm was chosen as a criterion for macrosomia the positive and negative predictive values were 80% (8/10) and 91% (30/33), respectively. It is concluded that formulas for estimating fetal weight in diabetic pregnancy based on AC alone are almost as effective as more complex ones. We recommend a simple linear formula of fetal weight as a function of AC.

Predictive factors for the development of diabetes in women with previous gestational diabetes mellitus.

Damm P; Kuhl C; Bertlsen A; Molsted-Pedersen L. Am. J. Obstet. Gynecol. 1992; 167:607-16.

The purpose of this study was to determine the incidence of diabetes in women with previous dietary-treated gestational diabetes mellitus (GDM) and to identity predictive factors for development of diabetes. Two to 11 years postpartum, glucose tolerance was investigated in 241 women with previous dietary- treated GDM and 57 women without previous GDM (control group). Diabetes developed in 42 (17.4%) women with previous GDM (3.7% IDDM and 13.7% NIDDM). Diabetes did not develop in any of the controls. Predictive factors for diabetes development were fasting glucose level at diagnosis (high glucose, high risk), preterm delivery, and an OGTT result that showed diabetes 2 months postpartum. In a subgroup of previous patients with GDM in whom plasma insulin was measured during an OGTT in late pregnancy a low insulin response at diagnosis was found to be an independent predictive factor for diabetes development. Women with previous dietary-treated GDM have a considerably increased risk of later having diabetes. Follow-up investigations are therefore important, especially in those women with previous GDM in whom the identified predictive factors are present.

Diabetic ketoacidosis. A rare complication of gestational diabetes

Maislos M; Harman-Bohem I; Weitzman S. Diabetes Care. 1992; 15: 968- 70.

We describe 2.5 years of close follow-up of a Bedouin woman who was hospitalized for diabetic ketoacidosis (DKA) while pregnant with her llth child. Plasma glucose returned to normal levels immediately after delivery of a dead conceptus. Four months later, while normoglycemic, the patient became pregnant again. During the subsequent pregnancy, GDM was diagnosed at week 20 of gestation. Tight plasrna glucose control was achieved with an insulin regimen and the patient delivered a healthy girl at term. Plasma glucose again returned to normal and remained so to date, 18 months postpartum. An OGTT and a euglycemic hyperinsulinemic clamp were performed between pregnancies; another OGTT was performed at week 14 of the

last pregnancy. Plasma glucose, insulin and C-peptide were measured in blood samples during the procedures. We established beyond doubt that the patient developed GDM and returned to essentially NGT after her last (l2th) delivery. During the 11th pregnancy, gestational diabetes was complicated by severe DKA: GDM is a common abnormality of glucose metabolism during pregnancy, which affects fetal development and leads to peripartum complications. Our report stresses that under certain circumstances, gestational diabetes can be complicated by DKA and become life-threatening to the mother and fetus.

Fetal surveillance in pregnancies complicated by insulin-dependent diabetes mellitus

Landon MB; Langer O; Gabbe SG; Schick C; Brustman L. Am. J. Obstet, Gynecol. 1992; 167:617-21.

Our objective was to determine whether maternal vascular disease and/or glycemic control can be related to tests of fetal condition in diabetic pregnancies. A total of 114 women with IDDM who used a memory-based glucose reflectance meter were prospectively evaluated. Non-stress testing was begun weekly at 28-30 weeks and twice weekly at 32 weeks. A non-reactive non- stress test was followed by a biophysical profile in all cases. A total of 1676 non-stress tests were performed (14.7 ± 3.2 tests per patient). Eight percent (n = 134) were non-reactive, necessitating a bio-physical profile. A comparison of ambulatory glucose profile data, including mean blood glucose level, variation and excursions from the median, revealed no significant differences in patients with reactive vs non-reactive non-stress tests. Ten patients, including eight with vascular disease, were delivered because of abnormal test results of fetal condition. Nephropathy or hypertension was associated with intervention for fetal wellbeing in eight of 20 women (40%) with these risk factors. Only two of 94 patients (2%) without nephropathy or hypertension required delivery because of abnormal results of fetal testing ($p < 0.001$). One fetal death occurred. No significant differences in the various glycemic parameters were found in women delivered for suspected fetal jeopardy vs the non- intervention group. Pregnancies complicated by vascular disease are at greatest risk for abnormal results of fetal testing that necessitate early delivery. Women without vascular complications and with maintenance of good glycemic control rarely have fetal compromise.

COMPLICATIONS : GENERAL ASPECTS

The risk of foot ulceration in diabetic patients with high foot pressure: a prospective study

Veves A; Murray HJ; Young MJ; Boulton AJ. Diabetologia. 1992; 35: 660- 3.

Foot ulceration results in substantial morbidity amongst diabetic patients. We have studied prospectively the relationship between high foot pressures and foot ulceration using an optical pedobarograph. A series of 86 diabetic patients, mean age 53.3 (range 17-77) years, mean duration of diabetes 17.1 (range 1-36) years, were followed-up for a mean period of 30 (range 15-34) months. Clinical neuropathy was present in 58 (67%) patients at baseline examination. Mean peak foot pressure was higher at the follow-up compared with baseline (13.5 $kg.cm^{-2}$ ± 7.1 SD vs 11.2±5.4, $p < 0.001$), with abnormally high foot pressures (> 12.3) being present in 55 patients at follow up and 43 at the baseline visit (p = ns). Plantar foot ulcers developed in 21 feet of 15 patients (17%), all of whom had abnormally high pressures at baseline; neuropathy was present in 14 patients at baseline. Non-plantar ulcers occurred in eight (9%) patients. Thus, plantar ulceration occurred in 35% of diabetic patients with high foot pressures but in none of those with normal pressures. We have shown for the first time in a prospective study that high plantar foot pressures in diabetic patients are strongly predictive of subsequent plantar ulceration, especially in the presence of neuropathy.

Relation of skin capillary pressure in patients with insulindependent diabetes mellitus to complications and metabolic control

Sandman DD; Shore AC; Tooke JE. New Engl. J. Med. 1992; 327: 760- 4.

Microvascular disease is a major problem in patients with diabetes mellitus. It has been suggested that diabetic microangiopathy may result from an increase in capillary blood flow and capillary hypertension, but direct evidence of capillary hypertension in such patients is lacking. We measured capillary pressure at the summit of the capillary loop by direct microcannulation of skin nailfold capillaries and a dynamic method of pressure measurement in 29 patients with insulin dependent (type-I) diabetes and 29 normal subjects matched for age and sex. Among the diabetic patients, seven had had diabetes for <1 year, 12 had incipient nephropathy (albumin excretion 20- 200 µg per min) and 10 had overt nephropathy (albumin excretion >200 µg per min). In addition, seven patients with no evidence of nephropathy were studied before and after 3 months of improved glycemic control. The median capillary pressure in the diabetic patients was 20.4 mm Hg (range 13.6-25.3), as compared with 16.7 mm Hg (range 12.8-22.8, $p < 0.001$) in the normal subjects. The values were higher in each subgroup of diabetic patients than in the corresponding group of normal subjects, but the values did not differ among the three subgroups of diabetic patients. In the seven patients who were studied before and after 3 months of improved glycemic control, the median capillary pressure fell from 20.0 mm Hg (range 18.5-21.7) to 17.8 mm Hg (range 14.1-20.3, p = 0.02). Nailfold capillary hypertension may develop early in the course of diabetes, before the emergence of microvascular disease and may be influenced by changes in metabolic control.

Trends in diabetes and diabetic complications, 1980-1987

Wetferhall SF,- Olson DR; DeStefano F: Stevenson JM; Ford ES; German RR; Will JC; Newman JM; Sepe SJ; Vinicor F. Diabetes Care. 1992; 15:960-7.

Although diabetes is a major source of morbidity and mortality in the United States, only recently has a unified national surveillance system begun to monitor trends in diabetes and diabetic complications. We established a diabetes surveillance system using data for 1980-1987 from vital records, the National Health Interview Survey, the National Hospital Discharge Survey, and the Health Care Financing Administration's records to examine trends in the prevalence and incidence of diabetes, diabetes mortality, hospitalizations and diabetic complications. From 1980 through 1987, the number of individuals known to have

diabetes increased by 1 million to 6.82 million. Age-standardized prevalence for diabetes increased 9% during this period, from 25.4-27.6/1000 US residents ($p = 0.03$). The incidence of diabetes increased among women ($p = 0.003$), particularly among those >65 years old ($p = 0.02$). Age-standardized mortality rates (for diabetes as either an underlying or contributing cause) per 100,000 individuals with diabetes declined 12%, from 2350-2066. Annual mortality rates from stroke (as an underlying cause and diabetes as a contributing cause) and diabetic ketoacidosis declined 29% ($p = 0.003$) and 22% ($p < 0.001$), respectively. During these 8 years, hospitalization rates for major cardiovascular disease and stroke (as the primary diagnosis, and diabetes as a secondary diagnosis) increased 34% ($p = 0.006$) and 38% ($p = 0.01$), respectively. Also during this period, hospitalization rates increased 21% for diabetic ketoacidosis ($p = 0.01$) and 29% for lower-extremity amputations ($p = 0.06$). From 1982 through 1986, treatment for end-stage renal disease related to diabetes increased >10% each year ($P < 0.001$). The prevalence of diagnosed diabetes was nearly twice as high in blacks as in whites ($p = 0.04$). Blacks also had increased rates of lower-extremity amputation ($p = 0.02$), diabetic ketoacidosis ($p < 0.001$) and end-stage renal disease ($p = 0.01$). Diabetes surveillance data will be useful in planning, targeting and evaluating public health efforts designed to prevent and control diabetes and its complications.

CARDIOVASCULAR COMPLICATIONS

Morbidity, mortality and albuminuria in type-II diabetic patients: a three-year prospective study of a random cohort In general practice.

Stiegler H; Standl E; Schulz K; Roth R; Lehmacher W. Diabetic Med. 1992; 9:53.

In a 3-years prospective study, the prevalence of albuminuria and its relationship to macrovascular disease, pre-existing vascular risk factors and mortality rate were studied in a random cohort of 290 patients with type-II diabetes mellitus in general practice. Newly occurring micro- or macro-albuminuria was associated with significantly ($p < 0.05$) higher systolic blood pressure: median (IQ range) 157 (140-170) vs 150 (130-160) mm Hg, in addition to higher serum triglycerides: median (IQ range) 2.71 (1.84-4.25) vs 1.84 (1.35-3.14) mmol l^{-1} and C-peptide levels: median (IQ range) 1.30 (0.98-2.16) vs 1.10 (0.82-1.58) nmol l^{-1}, at 3-year follow-up. Patients with macroalbuminuria at final examination had significantly higher systolic and diastolic blood pressure, serum triglyceride and beta2-microglobulin levels, decreased HDL- cholesterol and a significantly higher prevalence of carotid artery stenoses and peripheral vascular disease. Patients dying from vascular causes showed significantly higher urinary albumin levels at entrance as compared with the surviving patients: median (IQ range) 42.2 (11-249.7) vs 10.4 (4.6-28.0) mg l^{-1}, $p < 0.008$, and overall mortality rate was significantly linked with the presence of macroalbuminuria (26 vs 5% in normoalbuminuric patients). A comparison between the results of the initial and the final examination indicated an overall worsening of renal variables (albuminuria; median [IQ range] female 9.5 [4.5-21] vs 13.4 [5.1-39.7] mg l^{-1}, $p < 0.05$; male 13.8 [4.7-34.1] vs 32.6 [8.1-78.7], $p < 0.001$), despite a significant improvement in metabolic variables.

Asymptomatic hyperglycemia and atherosclerotic vascular disease in the elderly

Mykkaenen L; Laakso M; Pyoeraelae K. Diabetes Care. 1992; 15: 1020- 30.

A representative cross-sectional population sample of 1431 subjects (511 men, 920 women: 65-74 years old) was taken to investigate the relationship between asymptomatic hyperglycemia (IGT or newly diagnosed NIDDM) and atherosclerotic vascular disease. Altogether, 312 men and 515 women had NGT, 84 men and 158 women had IGT, 33 men and 59 women had newly diagnosed NIDDM, and 82 men and 188 women had previously diagnosed NIDDM. The participation rate was 71%. Main outcome measures were prevalence rates of coronary heart disease, stroke and intermittent claudication. There was no difference in the prevalence of definite or possible myocardial infarction verified in hospital between subjects with asymptomatic hyperglycemia and NGT (15.5 vs 13.3% in men, 6.3 vs 5.3% in women). Men with asymptomatic hyperglycemia had 1.5X higher prevalence of angina pectoris (29.4 vs 19.3%, $p < 0.05$), major QQS changes (21.1 vs 12.0%, $p < 0.05$), ischemic ECG changes (59 vs 45%, $p < 0.05$) and silent myocardial infarction on ECG (14.8 vs 7.9%, $p < 0.05$) compared with men with NGT. Women with asymptomatic hyperglycemia had more often ischemic ECG changes compared with women with NGT (48.3 vs 39.7%, $p < 0.05$). There was no difference (ns) in the prevalence of verified stroke (3.5 vs 4.6% in men, 2.7 vs 2.5% in women) or claudication (7.0 vs 7.7% in men, 4.6 vs 4.3% in women) between subjects with asymptomatic hyperglycemia and NGT. In multiple logistic regression analyses, the association between risk factors and myocardial infarction or ischemic ECG changes in subjects with asymptomatic hyperglycemia was not consistent. Elderly subjects with asymptomatic hyperglycemia (particularly men) tended to have an increased prevalence of coronary heart disease. Thus, asymptomatic hyperglycemia in the elderly is not a benign phenomenon but is associated with cardiovascular morbidity.

Aspirin effects on mortality and morbidity in patients with diabetes mellitus. Early Treatment Diabetic Retinopathy Study report 14

ETDRS Investigators. JAMA. 1992; 268: 1292-300.

This report presents information on the effects of aspirin on mortality, the occurrence of cardiovascular events and the incidence of kidney disease in the patients enrolled in the Early Treatment Diabetic Retinopathy Study (ETDRS). This multicenter, randomized clinical trial of aspirin vs placebo was sponsored by the National Eye Institute. Patients (n = 3711) were enrolled in 22 clinical centers between April 1980 and July 1985. Men and women between the ages of 18 and 70 years with a clinical diagnosis of diabetes mellitus were eligible. Approximately 30% of all patients were considered to have type-I diabetes mellitus, 31% type-II and in 39% type-I or II could not be determined definitely. Patients were randomly assigned to aspirin or placebo (two 325 mg tablets once per day). Mortality from all causes was specified as the primary outcome measure for assessing the systemic effects of aspirin. Other outcome variables included cause-specific mortality and cardiovascular events. The estimate of relative risk for total mortality for aspirin-treated patients compared with placebo-treated patients for the entire study period was

0.91 (99% CI 0.75-1.11). Larger differences were noted for the occurrence of fatal and non-fatal myocardial infarction; the estimate of relative risk was 0.83 for the entire follow-up period (99% CI 0.66-1.04). The effects of aspirin on any of the cardiovascular events considered in the ETDRS were not substantially different from the effects observed in other studies that included mainly non-diabetic persons. Furthermore, there was no evidence of harmful effects of aspirin. Aspirin has been recommended previously for persons at risk for cardiovascular disease. The ETDRS results support application of this recommendation to those persons with diabetes at increased risk of cardio-vascular disease.

EYE COMPLICATIONS

Progression of non-proliferative diabetic retinopathy and visual outcome after extracapsular cataract extraction and intraocular lens implantation

Jaffe GJ; Burton TC; Kuhn E; Prescott A; Hartz A. Am. J. Opthalmol. 1992; 114:448-56.

Twenty-one patients with symmetric non-proliferative retinopathy who underwent extracapsular cataract extraction and intraocular lens implantation were followed up postoperatively for an average (±SD) of 18±7 months to determine the incidence of progression of diabetic retinopathy, the final visual acuity and factors predictive of progression of retinopathy and final visual acuity. Progression of retinopathy, defined as the development of clinically significant macular edema, an increase in intraretinal hemorrhages or hard exudate, or the development of proliferative diabetic retinopathy, was assessed in both eyes of 19 patients; in two remaining patients, dense preoperative cataract in the fellow eye precluded comparison of retinopathy progression in the operated on eye to progression in the fellow eye. Overall, retinopathy progressed in 14 of 19 operated-on eyes (74%). Cataract extraction was highly associated with asymmetric progression of non-proliferative retinopathy; it progressed only in the operated-on eye in seven of 19 patients (37%), but in no patients did progresion occur in the fellow eye alone (p=0.0078). Women had a significantly increased risk of progression of retinopathy in the operated-on eye compared with men (p=0.005). Visual acuity improved in 19 of 21 operated-on eyes (86%); however, only 11 eyes (52%) achieved a visual acuity of 20/50 or better and only six eyes (14%) achieved a visual acuity of 20/25 or better. In only five eyes was the final visual acuity in the operated-on eye more than two lines better than the final visual acuity in the fellow eye. The visual acuity measured preoperatively by the Potential Acuity Meter was highly correlated with the final visual acuity ($p = 0.0046$). Patients treated with oral hypoglycemic agents had a worse visual prognosis than those treated with insulin ($p = 0.035$). Overweight women also had a significantly worse visual outcome than those patietns wiih normal body weight ($p = 0.021$). The results of this study have important implications for the preoperative and postoperative management of diabetic patients undergoing extracapsular cataract extraction and intraocular lens implantation.

High systolic blood pressure increases prevalence and severity of retinopathy In NIDDM patients

Cignarelli M; De Cicco ML; Damato A; Paternostro A; Pagliarini S; Santoro S; Cardia L; De Pergola G; Giorgino R. Diabetes Care. 1992; 15: 1002-8

Ophthalmoscopy and FAG were conducted among a group of NIDDM patients with either an sBP above (n = 54) or below (n = 55) 140 mm Hg, to determine whether the severity of retinopathy was higher in the former. The groups were matched according to diabetes duration, metabolic control (HbA_{1C}) and AER. Patients with an sBP > 140 mm Hg had a higher prevalence of retinopathy, established according to a rating scale (4.9 ± 3.8 vs 3.2 ± 3.3, $p < 0.02$); furthermore, their BMI values were higher (28.1 ± 4.5 vs 24.9 ± 4.1 kg/m^2, $p < 0.001$). The group of normotensive subjects showed the highest rate of low grading (0-2) values. However, the highest prevalence rates of 8-10 grading values (proliferative retinopathy) were found in the hypertensive group. These data suggest that sBP values > 140 mm Hg favor the onset of retinopathy in NIDDM patients during the first 10 years of disease.

GENITOURINARY AND RENAL COMPLICATIONS

Microalbuminuria in type-I diabetic patients. Prevalence and clinical characteristics

Microalbuminuria Collaborative Study Group. Diabetes Care. 1992: 15:495-501

The purpose of this study was to estimate the prevalence of microalbuminuria, overnight UAE rate (AER) ≥30 and ≤250µg/min, in a large sequential sample of non-hypertensive insulin- dependent (type-I) diabetic patients attending hospital diabetic clinics, to identify micro- and normoalbuminuric patients in this sample for subsequent intervention and natural history follow-up studies, and to compare the clinical characteristics of micro- and normoalbuminuric patients identified. Screening was conducted in two phases. In phase I, all eligible patients were asked to provide an early morning urine specimen for measurement of albumin concentration and albumin-creatinine ratio. In phase 2, all patients with an albumin concentration ≥15 mg/l and/or an albumin-creatinine ratio ≥3.5 mg/mmol, and a random sample of those with an albumin concentration <15 mg/l and an albumin-creatinine ratio <3.5 mg/mmol, were asked to collect a timed overnight urine specimen for determination of AER. Among 1888 patients (16-60 years old, diabetes onset < 40 years and duration of diabetes <35 years) who were screened, the prevalence of microalbuminuria was approximately 3.7% (95% CI 2.7-7.6%). Duration of diabetes was significantly longer in micro- than in normoalbuminuric patients (20 vs 15 years, respectively; $p < 0.001$), and in no patient with microalbuminuria was the duration of diabetes <5 years. Systolic and diastolic blood pressures, higher in micro- than in normoalbuminuric patients (132 vs 122 mm Hg, $p < 0.01$; 77 vs 72 mm Hg, $p < 0.01$), were strongly associated with AER. It is concluded that microalbuminuria in type-I diabetes, which appears to represent an earlier phase in the development of clinical nephropathy, is associated with elevated blood pressure and a longer duration of diabetes.

Does increased glomerular filtration rate or disturbed tubular function early in the course of childhood type-I diabetes predict the development of nephropathy?

Lervang HH; Jensen S; Brochner-Mortensen J; Ditzel J Diabetic Med. 1992; 9:635-40.

To clarify whether glomerular hyperfiltration or disturbances in renal tubular function may be early markers of the later development of nephropathy a follow-up study was performed in 34 young type-I diabetic patients, who had originally been investigated 12 years previously. The initial median age was 14 (range 7-18) years and median diabetes duration 7 (2-14) years. At initial examination only one of the 34 diabetic patients exhibited increased UAE rate. The median glomerular filtration rate was increased (136 vs 107 rnl min^{-1} 1.73 m^{-2}, $p < 0.0001$) and median threshold concentration of phosphate per litre of glomerular filtrate was decreased (1.27 vs 1.76 mmol l^{-2}, $p < 0.0001$) in the diabetic group as compared with that of 28 healthy children. At follow-up 17 patients showed increased UAE rate and the median glomerular filtration rate in this group was significantly lower than that of 17 patients with normal UAE rate (108 vs 125 ml min^{-1} 1.73 m^{-2}, $p < 0.05$). However, no relationships were found between the increased UAE (incipient and/or overt diabetic nephropathy) at follow-up to either the initial glomerular filtration rate 134 vs 137ml min^{-1} 1.73 m^{-2}, $p > 0.05$) or to renal tubular function assessed from urinary excretion rate of beta -microglobulin (0.059 vs 0.069 µg min^{-1}, $p > 0.05$) and the renal threshold concentration of phosphate per litre of glomerular filtrate (1.29 vs 1.22 mmol l^{-2}. $p > 0.05$).

Increased incidence of end-stage renal failure secondary to diabetes mellitus in Asian ethnic groups in the UK

Burden AC; McNally PG; Feehally J; Walls J. Diabetic Med. 1992; 9:64 1- 5

Diabetic renal disease is more common in patients of Asian ethnic origin than white Caucasians in the UK. This study determines whether a disparity in the incidence of end-stage renal failure secondary to diabetes mellitus exists between these ethnic groups. The incidence of treated end-stage renal failure was estimated using the person-time at risk incidence rate for patients receiving renal replacement therapy secondary to diabetes mellitus in the country of Leicestershire from 1979-1988. The incidence rate of end-stage renal failure expressed for the estimated population of patients with diabetes mellitus in patients of Asian ethnic origin was 486.6 (95% CI 185.1-788.1) cases per million person- years per year, compared with 35.6 (17-54.2) in white Caucasians. All patients of Asian ethnic origin developing end-stage renal failure had NIDDM. The high incidence of end-stage renal failure secondary to diabetes mellitus in patients of Asian ethnic origin in the UK imparts significant public health implications for resource planning and allocation and the need to initiate strategies to ameliorate renal disease in this ethnic group.

NEUROLOGICAL COMPLICATIONS

Glycemic control and peripheral nerve conduction in children and young adults after 5-6 months of IDDM. Wisconsin Diabetes Registry

Allen C; Duck SC; Sufit RL; Swick HM; D'Alessio DJ. Diabetes Care. 1992; 15:502-7

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A cohort of people (n = 86) was examined in the first few months after IDDM diagnosis to evaluate the effect of hyperglycemia on nerve conduction velocities and latencies. Unselected cases with IDDM, who were 6-29 years of age, were identified at diagnosis from a large, geographically defined area of southern Wisconsin. Peripheral nerve conduction was measured on a sample for this cohort. Peroneal nerve conduction velocity was significantly inversely related to glycosylated hemoglobin ($p < 0.05$, age and height adjusted). All other nerve conduction velocities and latencies (median motor, median sensory and sural) showed the same tendency, but the associations were not statistically significant. Twenty-four-hour urine C-peptide and duration of diabetes (3-11 months) were not consistently related to nerve conduction parameters after controlling for age and height. These findings suggest that as early as 5-6 months after diabetes diagnosis and at a time frequently characterized by partial remission of IDDM, hyperglycemia has a role in the acute slowing of nerve conduction velocity. Other factors such as residual endogenous insulin production do not appear to influence these early changes.

PHYCHOSOCIAL ASPECTS / EDUCATION / MOTIVATION

Smokers with IDDM experience excess morbidity. The Colorado IDDM Registry

Gay EC; Cai Y; Gale SM; Baron A; Cruickshanks KJ; Kostraba JN; Hamman RF. Diabetes Care. 1992; 15:947 52.

The purpose of this study was to determine whether there is an association between smoking and the self-reported morbidity of people with IDDM and to evaluate the nature of a possible interaction between smoking and IDDM in increasing the risk of morbidity among smokers with IDDM. Subjects were non-Hispanic whites aged 18-28 years who participated in the Colorado IDDM Registry Follow-up Survey (case subjects, n = 24) or the 1985 NHIS (control subjects, n = 5876). Assessments of self-reported morbidity included any hospitalization in the past year; bed days; sick days and limited-activity days in the past 2 weeks; and ratings of poor health. The criteria outlined by Saracci were used to determine whether smoking was associated with greater morbidity among IDDM case compared with control subjects (smoking by IDDM interaction). Age- and sex-adjusted ORs, estimated from logistic regression, showed that people with IDDM reported excess morbidity compared with control subjects, regardless of smoking status. Smokers with IDDM reported morbidity 3-10 times as often as non-smoking control subjects and were two to three times more likely to report morbidity that non-smokers with IDDM. The smoking by IDDM interaction was more than multiplicative for all morbidity measures. 50 to 75% of excess morbidity in young smokers with IDDM over simple additive effects was related to the interaction between smoking and IDDM. There was excess reported morbidity among people with IDDM who smoked, greater than that expected from the combined effects of smoking and IDDM. Smoking cessation in young people with IDDM may alleviate some of this excess, but more study is needed to determine whether smoking serves as an indicator of poor IDDM care practices or has a physiological impact that compounds the morbidity experienced by people with IDDM.