ABSTRACT SERVICE

AETIOLOGY AND EPIDEMIOLOGY

The 'diabetic foot' syndrome. Association with other complications and the incidence of amputation.

Ratzmann KP, Drzimalla E, Raskovic M. Medizinische Klinik 1994; 89 : 469-72.

Background: Only few studies have investigated the incidence of foot lesions and amputation rate in diabetic patients.

Patients and Method: Thus, the 10- year incidence rates of first lower extremity amputation were studied in 560 diabetic patients, aged 35 to 55 years at baseline and followed up within the WHO-Multinational Study of Vascular Disease in Diabetes. Further more, we studied the frequency of other complications in 51 outpatients with 'the diabetic foot' syndrome.

Result: In Type 1 diabetic patients, the incidence rates (7.2/1,000 person-years for men and 7.6/1,000 person-years for women) were higher as compared with Type 2 diabetic patients (4.1/1,000 and 4.3/1,00 person-years for men and women, respectively). In multivariate analysis, duration of diabetes, hypertension, claudicatio intermittens, retinopathy and proteinuria emerged as potential risk factors. Outpatients with the 'diabetic foot' syndrome were characterized by an advanced age and a long duration of diabetes (59 years and 22.5 years , respectively). 30 patients (58%) had Type 1 diabetes and 21 (42%) had Type 2 diabetes mellitus. The proportion of complications was as follows: foot lesions due to diabetic neuropathy or peripheral ischaemic vessel disease in 45.1% and 25.5% and a combination of both in 29.4% . The majority of Type 2 diabetic patients had lesions due to peripheral ischaemic vessel disease (77%); these patients were 10 years older as compared with patients with neuropathic lesions. Proliferative retinopathy was 4 times as high in patients with neuropathic lesions as compared with patients ischaemic lesions(61% vs 15%).

Conclusion: The findings once again emphasize the importance of education and training programs in elderly diabetic patients.

Antibodies to glutamic acid decarboxylase and diabetes mellitus in the Multiple Risk Factor Intervention Trial.

Zimmet PZ, Shaten BJ, Kuller LH, Rowley MJ, Knowles WJ, Mackay IR. American Journal of Epidemiology 1994; 140: 683-90.

Diabetes mellitus is a heterogeneous disease. The better classification of types of diabetes mellitus among adults will improve epidemiologic studies of determinants of risk factors and genetic host susceptibilitiy. Recently, an antibody to a specific enzyme, glutamic acid decarboxylase, has been closely linked to insulin-dependent diabetes mellitus. Sera were collected at baseline between 1972 and 1974 from initially non-diabetic participants in the Multiple Risk Factor Intervention Trial. After approximately 18 years of frozen storage, the serum samples were tested for antibodies to glutamic acid decarboxylase (anti-GAD) in 175 men who developed diabetes and 352 matched controls who did not develop diabetes during the 6-year follow-up. Nine of the 527 samples tested had elevated (19 or more units) titers of anti-GAD. Six of the nine men with elevated anti-GAD subsequently developed diabetes and three of these six were ultimately placed on insulin therapy. These data suggest that elevated levels of anti-GAD may be a prospective marker for the subsequent development of insulin-dependent diabetes mellitus. The measurement of anti-GAD is relatively easy, can be performed in stored serum specimens and may be used in epidemiologic studies to enhance the understanding of the determinants of diabetes mellitus.

Incidence of diabetes mellitus in various population groups in Israel (1989 and 1990).

Laron Z, Mansour T, Slepon R, Karp M, Shohat T. Israel Journal of Medical Sciences 1994; 30 : 770-4.

A prospective survey of all newly diagnosed insulin-dependent diabetes mellitus (IDDM) children and adolescents aged 0-17 years in Israel was conducted for the years 1989 and 1990. All diabetic clinics in Israel treating young diabetic were contacted and they returned written reports to us. Each clinic was also visited regularly by a member of the team who reviewed the individual charts to obtain data on population origin as well as medical and demographic data. A total of 187 patients were identified (164 Jews and 23 Arabs), giving a total incidence rate of 5.46/ 10(5). Analysis of the incidence rates by population groups showed that Arabs and Jews originating in Asia had the lowest incidence (2.77 and 4.58/10(5) respectively), followed by Jews whose fathers were born in Israel (5.61 10(5)). The highest incidence was registered for Jews originating from Europe and North America (9.34/10(5)). The female-to-male preponderance ratio was higher in the Jews originating in Asia (2,1) than in Jews originating in Europe and North America (1.2). Comparing the present data with a survey performed for the years 1975-80 we found a statistically significant increase in incidence in all population groups. Our findings strongly suggest an influence of genetic factors on the incidence of childhood IDDM.

Antibodies to glutamic acid decarboxylase and p2-C peptides in sera from Coxsackie virus B4-infected mice and IDDM patients.

Hou J, Said C; Franchi D, Dockstader P. Chatterjee NK. Diabetes 1994; 43 : 1260-6.

The possible role of amino acid sequence and epitope homologies between a protein P2-C of Coxsackie virus B4 and human GAD in the development of host-specific immune response in insulin-dependent diabetes mellitus (IDDM) (molecular mimcry) was investigated. Peptide antibodies to the P2-C protein. GAD65 and GAD67 were raised to analyze their immunoreactivity by enzyme linked immunosorbent assay and immunoblotting with GAD purified from the brain and pancreas of mice that develop hyperglycaemia after the infection. Additionally, antibody reactivity to these peptide antigens was assessed in sera from the virus-infected mice and IDDM patients. All three peptide antisera reacted very strongly with homologous peptides; P2-C antiserum cross-reacted with GAD65 as efficiently as GAD 65 antiserum with P2-C, but no cross-reaction was detected between P2-C and GAD67 although cross-reaction between the twoo GADs was quite pronounced. P2-C antiserum immunocomplexed with GAD65 from mouse brain or pancreas, whereas GAD65 and GAD67 antisera both immunocomplexed with two GADs from these sources. Most of the sera from virus- infected mice were reactive to brain and pancreas GAD65 and peptides. A number of IDDM sera reacted with mouse GAD65 and also with P2-C and GAD65 peptides, whereas only a few reacted with GAD67 peptide. The immunoreactivity of the mouse and IDDM sera to P2-C and GAD 65 peptides was blocked by pre-adsorption with mouse GAD. The results suggest that molecular mimicry may play a role in the pathogenesis of the disease.

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Antibodies to islet 37 k antigen, but not to glutamate decarboxylase, discriminate rapid progression to IDDM in endocrine autoimmunity.

Christie MR, Genovese S, Cassidy D, Bosi E, Brown TJ, Lai M, Bonifacio E, Bottazzo GF. Diabetes 1994;43 : 1254-9.

Apart from islet cell antibodies (ICAs), antibodies to glutamate decarboxylase (GAD), insulin autoantibodies (IAAs) and a novel islet antigen (37k antigen) are potential markers for insulin-dependent diabetes mellitus (IDDM). GAD is also an antigen in the stiff-man syndrome (SMS) and both (SMS) and IDDM are associated with the ICAs and autoimmunity to other endocrine organs . We investigated possible links between antibody responses to islet antigens with autoimmunity to other endocrine organs and determined which specific antibodies can identify individuals who progress to IDDM. Antibodies to GAD were detected in ≥ 90% of both diabetic and non-diabetic patients with ICAs and other endocrine autoimmunity, in 59% of ICA-positive IDDM patients without endocrine autoimmunity, in all patients with SMS, but in only 1-3% of healthy (non-diabetic) and autoimmune disease control subjects. GAD antibody levels were increased in ICA-positive IDDM patients with polyendocrine autoimmunity compared to those without. In contrast, antibodies to 37k antigen were only detected in patients who developed acute-onset IDDM. IAAs were also associated with IDDM. Thus, certain factors enhance antibody responses to Gad in polyendocrine autoimmunity, but this does not necessarily lead to development of IDDM or SMS. Antibodies to 37k antigen are strongly associated with acute-onset IDDM and are useful serological markers for disease.

Quantitation of glutamic acid decarboxylase autoantibody levels in prospectively evaluated relatives of patients with Type 1 diabetes.

Yu L, Gianani R, Eisenbarth GS. Diabetes 1994; 43: 1229-33.

In this study, we demonstrate that levels of glutamic acid decarboxylase (GAD) autoantibodies (GAAs) by radioassay differ between relatives with GAD –absorbable and GAD-nonabsorbable islet cell antibodies (ICAs). Extremely high levels of GAAs are often found in relatives with GAD-absorbable ICAs (> 1,800 cpm, > 9 SD above normal control subjects; mean = 1,991 cpm) and lower levels (mean = 1,078 cpm) of GAAs were present in relatives with nonabsorbable ICAs (P < 10(-5)). The serum levels of GAAs were remarkably constant for relatives of both groups over time. The levels of GAAs were found to be inversely related to both the levels of insulin autoantibodies and the rate of loss of intravenous glucose stimulated insulin secretion (P < 10(-5) and P< 0.01 respectively). Relatives with low positive levels of GAAs had more rapid loss of insulin secretion and were at high risk to become diabetic (50% diabetic at 4 years) compared with relatives with higher levels (1,800 cpm) of GAAs (10% diabetic at 4 years; P < 0.05). These data suggest that high levels of GAAs are associated with a decreased risk of progression to Type 1 diabetes and extend the hypothesis that distinct subsets of ICAs and GAAs with differing prognostic significance can be identified.

Cellular immunity to a determinant common to glutamate decarboxylase and Coxsackle virus in insulin-dependent diabetes.

Journal of Clinical Investigation 1994; 94: 2125-9.

Insulin-dependent diabetes mellitus (IDDM) results from the autoimmune destruction of the insulin-producing pancreatic beta cells. Autoreactive T-lymphocytes are thought to play a pivotal role in the pathogensis of IDDM; however, the target antigens of these cells , as well as the inductive events in the disease, are unclear. PBMC in persons with or at increased risk for IDDM show elevated reactivity to the beta cell enzyme glutamate decarboxylase (GAD). To identify the T-lymphocyte reactive determinants of GAD, an overlapping set of synthetic peptides was used to stimulate the PBMC from these individuals, PBMC responsiveness to GAD peptides was not restricted to those with IDDM and a number of peptides elicited responses in PBMC. However, the major determinant of GAD recognized by persons at increased risk for IDDM was amino acids 247-279, a region which has a significant sequence similarity to the P2-C protein of Coxsackle B virus (47% of 15 increased risk [islet cell autoantibody-positive relatives]; 25 % of 16 newly diagnosed IDDM patients and 0 % of 13 healthy control subjects). Responses to tetanus and insulin antigens were not different between the study groups. In addition, PBMC from individuals responding to GAD peptides within 247-279 also responded to a Coxsackie viral peptide (i.e. P2-C amino acids 32-47), an observation supporting potential molecular mimicry in this immune response. Although the role of environmental agents in the pathogenesis of the disease remains unclear, these cellular immunological findings support the epidemiological evidence suggesting an inductive role for enteroviruses like Coxsackie B in the autoimmunity underlying IDDM.

Combined analysis of autoantibodies improves prediction of IDDM in islet cell antibody-positive relatives.

Bingley PJ, Christie MR, Bonifacio E, Bonfanti R, Shattock M, Fonte MT, Bottazzo GF, Gale EA. Diabetes 1994; 43: 1304-10.

Prediction of insulin-dependent diabetes mellitus (IDDM) is still largely based on islet cell antibodies (ICAs) , but it may improved by combined analysis with other humoral markers. We examined autoantibodies to insulin (IAAs), glutamic acid decarboxylase (GAD) and M(r) 37,000 and M(r) 40,000 fragments of islet antigens (37 and 40 kDa) together with ICA subtypes ins 101 family members with ICAs ≥ 10 Juvenlie Diabetes Foundation Units (JDF U) followed for up to 14 years , of whom 18 have developed IDDM. Life-table analysis showed a 43 % risk of IDDM within 10 years for those with ICAs ≥ 10 JDF U, rising to 53 % for those with ICAs ≥ 20 JDF U. The risk for ICAs ≥ 10 JDF U was 62% in the family members in the youngest age quartile (< 13.2 years) and fell with increasing age to 4 % in those > 40.7 years ofo age (P = 0.03). ICAs ≥ 10 JDF U combined with IAAs gave a risk of 84% (P = 0.03 compared with IAA-), and ICAs ≥ 10 JDF U combined with GAD antibodies gave a risk of 61 % (P = 0.018). The risk for ICAs ≥ 10 JDF U with antibodies to 37kDa antigen was 76 % (P < 0.0001). Risk increased with the number of autoantibodies, from 8 % for ICAs alone to 88 % with ≥ 3 autoantibodies (14 cases detected) (P < 0.001). The increased risk associated with multiple antibodies was observed independent of age.

Glutamic acid decarboxylase (GAD65) autoantibodies in prediction of beta-cell function and remission in recent-onset IDDM after cyclosporin treatment. The Canadian-European Randomized Control Trial Group.

Petersen JS, Dyrberg T, Karlsen AE, Molvig J. Michelsen B, Nerup J, Mandrup-Poulsen T. Diabetes 1994; 43: 1291-6.

We have investigated whether glutamic acid decarboxylase (GAD) autoantibodies (GAD65 Ab) were affected by cyclosporin therapy and were related to subsequent non-insulin requiring remission and loss of glucagonstimulated C-peptide response in 132 recent-onset insulin-dependent diabetes mellitus (IDDM) patients treated with cyclosporin or placebo for 12 months. GAD65 Ab were detected in a quantative radioligand assay using as tracer recombinant, in vitro translated, human islet [35S] methionine-labeled GAD65, GAD65 Ab were found at onset in 66% (87 of 132) of IDDM patients and in 1% (1 of 100) of healthy control subjects. The prevalence of

GAD65 Ab and median GAD65 Ab levels did not change in serum samples taken 3, 6,9 and 12 months after study entry in either the cyclosporin or the placebo treated goups. The presence or absence of GAD65 Ab at study entry did not predict non-insulin requiring remission in either cyclosporin or placebo treated patients. However the relative (compared with 0 months) glucagons-stimulated C-peptide response was more than 30 % lower in GAD65 Ab+ patients receiving placebo at 9 and 12 months compared with the GAD65 Ab- placebo patients ($P < 0.035$). Islet cell cytoplasmic antibody (ICA) and GAD65 Ab+ placebo treated patients showed no significant differences in stimulated C-peptide levels compared with those who were ICA- and GAD65 Ab+, suggesting that ICA was not independently associated with loss of beta-cell function.

Impaired glucose tolerance and diabetes mellitus in a rural population in South India.

Patandin S, Bots ML, Abel R, Valkenburg HA. Diabetes Research and Clinical Practice 1994; 24: 47-53.

In the present study the prevalence of impaired glucose tolerance and non-insulin-dependent diabetes mellitus in a rural population in South India was assessed and its associations with body mass index and a family history of diabetes mellitus. Data were obtained from inhabitants of two villages located in the North Arcot district of Tamil Nadu. After an overnight fast, 467 randomly selected subjects, aged 40 years or over, were given 75g glucose orally. After two hours the capillary glucose level was determined. The prevalence of impaired glucose tolerance (2 hour values $\geq$ 7.8 mmol/L and < 11.1 mmol/L) was 6.6 % (31 subjects). Non-insulin-dependent diabetes mellitus (2-hour value $\geq$ 11.1 mmol/L) was found in 23 subjects (4.9 %). Of these, 53 % were previously unknown. Age and sex adjusted mean body mass index was significantly higher among subjects with impaired glucose tolerance compared to subjects without glucose intolerance, with a mean difference of 1.4 kg/m^2 (95 % confidence interval (CI) 0.2, 2.6). A positive family history of diabetes non signigicantly higher in subjects with impaired glucose tolerance. Subjects with non-insulin-dependent diabetes mellitus had a higher mean body mass index compared to subjects with normal glucose levels with a mean difference of 1.9 kg/m^2 (95% CI 0.5, 3.3). A positive family history of diabetes was more common among diabetics with a difference of 20 % (95 % CI 10, 30). Our findings suggest that in a considerable proportion (11.5 %) of the rural South Indian population aged 40 years or over, glucose intolerance is present.

Childhood-onset diabetes in the White and South Asian population in Leicestershire, UK.

Gujrat JS, McNally PG, Botha JL, Burden AC. Diabetic Medicine 1994; 11: 570-2.

The prevalence of childhood-onset Type 1 diabetes mellitus is important for determining health care provisions. In Leicestershire 13.5 % of the childhood population (0-14 years) is of South Asian origin (census 1991). This study determined the prevalence of Type 1 diabetes in Whites and South Asians in Leicestershire, using a capture/recapture method to coincide with the 1991 Census day. Children (0-14 years) with Type 1 diabetes were captured from the central diabetic register. The health visitor and consultant records were used to recapture the cases.Total ascertainment of cases was 95-100 %. The prevalence of Type 1 diabetes in White children (107 cases) was 0.75/1000 children (95 % CI 0.61-0.89) compared with the South Asian prevalence (18 cases) of 0.77/1000 (95 % CI 0.41-1.13). The overall prevalence in White males was 0.82/1000 (0.61-1.03) compared with 0.68/1000 (0.48-0.87) in females. In South Asian males it was 0.59/1000 (0.15-1.03) compared with 0.96/1000 (0.39-1.53) in females . The prevalence of Type 1 diabetes in children of South Asian migrants to the United Kingdom cannot be said to be different from White children.

UK Prospective Diabetes Study (UKPDS). XI: Biochemical risk factors in Type 2 diabetic patients at diagnosis compared with age matched normal subjects.

Anonymous, Diabetic Medicine 1994; 11: 535-44.

A total of 507, newly diagnosed, white Caucasian Type 2 diabetic patients entered into UK Propective Diabetes Study, mean age 52 ± 9 (SD) years have been compared with 195 age matched normal subjects (fasting plasma glucose < 6 mmol/L) who had no known first degree relatives with diabetes. Diabetic patients were more obese BMI (kg/m^2) 30.1 ± 6.2 vs 26.2 ± 4.0 respectively, with female (F) diabetic patients more so than male (M). Fasting plasma glucose (mmol/L) was 12.2 ± 3.8 vs 5.0 ± 0.6 in diabetic and normal subjects and haemoglobin A_1 C (%) 9.3 ± 2.3 vs 5.4 ± 0.4. Hyperinsulinaemia (mU/L) was prevalent in both male and female diabetic patients, after adjustment for BMI [geometric mean ISD interval, M 12.1 (11.8 to 12.4) vs 8.3 (7.8 to 8.9) and F 13.3 (12.9 to 13.7) vs 7.4 (7.1 to 7.7)]. Plasma triglyceride (mmol/L) was higher in diabetic patients, 1.8 (1.1 to 2.9) vs 1.1 (0.6 to 1.8). Total cholesterol (mmol/L) was slightly elevated in diabetic patients, with females in both populations higher than males, M 5.5 ± 1.2 vs 5.2 ± 0.9 and F 5.8 ± 1.1 vs 5.5 ± 1.1 HDL-cholesterol (mmol/L) was slightly lower in male and markedly lower in female diabetic patients than in normal subjects , M 1.00 ± 0.26 vs 1.11 ± o.22 and F 1.12 ± 0.27 vs 1.42 ± 0.33. Urine albumin was raised in diabetic patients (mg/L) 16.3 (5.2 to 50.9) vs 7.2 (3.2 to 16.5) , as was urine N-acetylglycosaminidase (U/L 6.4 (3.5 to 11.7) vs 2.9 (1.9 to 4.5) and plasma N-acetylglycosaminidase (U/L) 11.5 ± 3.2 vs 10.2 ± 2.3. Normal subjects aged above 65 years had slightly higher haemoglobin A_1C, insulin, C-peptide, plasma and LDL-cholesterol, triglyceride, plasma and urine N-acetylglucosaminidase and lower HDL-cholesterol than younger subjects. The 2.5 and 97.5 percentiles for biochemical variables are presented for both population aged 25-65 years.

PATHOLOGY AND DIAGNOSIS

Glycated haemoglobin values: problems in assessing blood glucose control in diabetes mellitus.

Kilpatrick ES, Rumley AG, Dominiczak MH, Small M. BMJ 1994; 309 : 983-6.

Objective : To see whether two measures of glycated haemoglobin concentration – the haemoglobin A_1 (HbA_1) value and the haemoglobin A_1 C (HbA_1C) value assess blood glucose control differently in diabetes.

Design : Diabetic patients had glycaemic control assessed on the basis of HbA_1 and HbA_1C values measured by the same high performance liquid chromatography instrument and on the basis of HbA_1 measured by electrophoresis.

Setting: A diabetic outpatient clinic.

Subjects : 208 diabetic patients and 106 non-diabetic controls.

Main outcome Measures : Glycated haemoglobin concentrations classified according to European guidelines as representing good, borderline or poor glycaemic control by using standard deviations from a reference mean.

Results: Fewer patients were in good control (25; 12%) and more poorly controlled (157; 75%) as assessed by the HbA_1 C value compared with both HbA_1 assays (39 (19%) and 130 (63%)

respectively when using high performance liquid chromatography; 63 (30%) and 74 (36%) when using electrophoresis). The median patient value was 8.0 SD from the reference mean when using HbA_1C, 5.9 when using HbA_1 measured by the same high performance liquid chromatography method and 4.1 when using HbA_1 measured by electrophoresis.

Conclusion: Large differences exist between HbA_1 and HbA_1C in the classification of glycaemic control in diabetic patients. The HbA_1C value may suggest that a patient is at a high risk of long term diabetic complications when the HbA_1 value may not. Better standardiisation of glycated haemoglobin measurements is advisable.

Hyperinsulinaemia prevents prolonged hyperglycaemia after intense exercise in insulin-dependent diabetic subjects.

Sigal RJ, Purdon C. Fisher SJ, HalterJB, Vranic M, Marliss EB. Journal of ClinicalEndocrinology and Metabolism 1994;79 : 1049-57.

Hyperglycaemia with accomopanying hyperinsulinaemia occurs after brief, greater than 85% maximum oxygen consumption exercise to exhaustion in normal subjects and persists up to 60 mins of recovery. To determine the importance of endogenous insulin secretion during and after intense exercise, responses to exercise of lean fit male post-absorptive insulin-dependent diabetes mellitus (IDDM) subjects , aged aged 18-34 yr, were compared with those of control subjects (C; n=6). Three IV insulin protocols were employed: hyperglycaemic (HG; n = 7) and euglycaemic (EG1; n = 6) with constant insulin infusion and euglycaemic with doubled insulin infusion during recovery (EG2; n = 6). Overnight IV insulin was adjusted to achieve prolonged euglycaemia (5.4 ± 0.3 mmol/L) or hyperglycaemia (8.6 ± 0.3 mmol/L) before exercise. This allowed for comparisons between HF and EG1 (constant infusion) and between C and EG2 (to approximate physiological hyperinsulinaemia by doubling the infusion rates at exhaustion for 56 ± 7 min during recovery). Subjects exercised to 89-98% of their individual maximum oxygen consumption for 12.8 ± 0.3 min. Glycaemia increased to maximum values at 6 min of recovery (9.8 ± 0.5 in HG, 6.9 ± 0.4 in EG1, 7.3 ± 0.3 in EG2 and 6.9 ± 0.4 mmol/L in C). Whereas in EG2 and C, glucose returned to resting values in 50-80 min, it remained elevated at 120 min recovery in HG and EG1. During exercise, [3-3H]-glucose-determined glucose production increased markedly and exceeded disappearance in all groups, but less so in the HG subjects than in the other groups. An early recovery decline in glucose production did not differ among groups, but MCR (rate of glucose disappearance/glycaemia) were markedly lower in HG and EG1, in whom plasma free insulin remained unchanged from 15 min of recovery onward (MCR, 1.6-1.9 vs. 2.3-2.8 ml/kg.min in C). Doubling the insulin infusion rate in EG2 restored the MCR response to that of C subjects. In summary, constant insulin infusion is insufficient to prevent prolonged post exercise hyperglycaemia in IDDM subjects, even when provided at a rate suficient to maintain normal resting glycaemia and glucose turnover. The finding that increasing the rate of insulin infusion restored plasma glucose to normal in IDDM subjects suggests that the post-exercise increase in insulin levels observed in normal subjects is essential to return plasma glucose to resting levels. Therefore, special strategies, differing from those for less strenuous exercise, ares required for the management of insulin therapy in IDDM during and after intense exercise.

Loss of the normal relationships between growth hormone, growth hormone-binding protein and insulin-like growth factor-I in adolescents with insulin-dependent diabetes mellitus.

Clayton KL, Holly JM, Carlsson LM, Jones J, Cheetham TD, Taylor AM, Dunger DB. Clinical Endocrinology 1994; 41 : 517-24.

Objective : It has been proposed that the dissociation between growth hormone secretion and insulin-like growth factor-I (IGF-I) concentrations in insulin-dependent diabetes mellitus arises because of partial resistance at the GH receptor. In order to explore this hypothesis further we have examined the relations between IGF-I, GH-binding protein (GHBP) and GH secretion in normal subjects and patients with diabetes during puberty.

Design and subjects : Blood samples for the estimation of IGF-I and GHBP levels were obtained from 104 patients with diabetes and 89 puberty matched controls. Thirty-four of the controls and secretory profile with measurements of GH every 15-20 minutes between 2000 and 800 h.

Results : In multivariate analysis using sex, puberty stage and presence or absence of diabetes as dependent variables, diabetes was associated with ;increased GH levels ($F = 23.04$, $P < 0.001$), reduced IGF-I (($F = 10.89$, $P < 0.001$) and reduced GHBP levels ($F = 31.36$, $P < 0.001$). A negative relation between GH and GHBP levels ($r = -0.44$, $P < 0.001$) was found in normal subjects but this was absent in those with diabetes. Both GHBP and IGF-I levels in the diabetic subjects were correlated with total insulin dose ($r = 0.04$, $P < 0.001$and $r = 0.46$, $P < 0.001$, respectively). Yet there was no direct correlation between GHBP and IGF-I concentrations. The variation in IGF –I levels was also related to glycosylated haemoglobin levels in the diabetics ($r = -0.27$, $P = 0.01$). In a stepwise multiple regression analysis, insulin dose contributed 23%, HbA_1 4.4% and C-Peptide levels 3.7% to the variation in IGF-I levels.

Conclusion : In adolescents with insulin-dependent diabetes mellitus, the elevated GH concentrations are associated with low circulating IGF-I and GHBP are both related to insulin dose, there is no direct correlation between these variables. This may indicate that GHBP reflects GH receptor numbers but not necessarily post receptor events and the weak positive correlation between GH and IGF-I indicates that increased growth hormone secretion may compensate for reduced receptor numbers.

Clinical review 63 : Diabetes and pancreatic cancer : clues to the early diagnosis of pancreatic malignancy.

Noy A.., Bilezikian JP. Journal of Clinical Endocrinology and Metabolism 1994; 79 : 1223-31.

Purpose : To review the relationship between pancreatic cancer and diabetes, particularly as this pertains to the early detection of pancreatic cancer.

Data sources : Studies published from 1985 to 1992 identified by computerized literature searches of Index Medicus and Medline and hand searches of referenced articles.

Study selection : Selected epidemiology studies were those exploring the relationship between diabetes and pancreatic cancer.

Data extraction : Data concerning the risk of developing pancreatic cancer given a history of diabetes was evaluated with particular attention given to the duration of diabetes before a diagnosis of pancreatic cancer. The characteristics of diabetes presenting within the 2 yrs before the diagnosis of pancreatic cancer were also investigated.

Results of data synthesis : Whereas diabetes is a risk factor for the development of pancreatic cancer, the diagnosis of a pancreatic tumor in some cases is preceded by a brief history of diabetes, which appears to be caused by the malignancy itself. This diabetes may be a typical with regard to a lack of family history of diabetes,

absence of obesity and a rapid progression to insulin dependence.

Conclusion : Recongnition of atypical diabetes as an early manifestation of pancreatic cancer could lead to earlier diagnosis of tumors at a stage when they are still amenable to resection and cure.

TREATMENT : GENERAL ASPECTS

Effect of pancreas transplantation on lipoprotein lipase, postprandial lipaemia and HDL-Cholestrol.

Foger B, Konigsrainer A, Palos G, Brandstatter E, Ritsch A, Konig P, Miesenbock G, Lechleitner M, Margreiter R, Patsch JR. Transplantation 1994; 58 : 899-904.

Pancreas transplantation with systemic venous drainage of the graft causes elevated plasma levels of insulin, known to be a potent regulator of plasma lipoprotein metabolism. We studied 11 post Type 1 diabetic pancreas-kidney trasplant recipients, 9 Type 1 diabetic kidney transplant recipients displaying peripheral hyperinsulinaemia due to subcutaneous insulin treatment, 11 non-diabetic kidney transplant recipients as controls for the effects of immunosuppressive medication and 11 healthy control subjects, all matched for age, sex and body mass index. We determined fasting lipids, lipoproteins and lipolytic enzymes, as well as postprandial lipid metabolism after a standardized oral fat load. High density lipoprotein (HDL) cholesterol averaged 1.98 (0.40) mmol/L in pancreas-kidney transplant patients, clearly higher than that of kidney transplant recipients (1.52 (0.36) mmol/L, $P < 0.05$) or of controls (1.50 (0.38) mmol/L, $P < 0.05$). In pancreas-kidney transplant patients post-prandial lipaemia was lowest and lipoprotein lipase activity was highest (average 32% and 154% respectively, of the mean of the controls) compared with non-diabetic kidney transplant recipients ($P < 0.005$, $P < 0.05$) and healthy controls ($P < 0.001$, $P < 0.01$). In Type 1 diabetic kidney transplant recipients the levels of HDL-cholestrol (1.88 (0.63) mmol/L), post-prandial lipaemia and lipoprotein lipase activity were intermediate between pancreas-kidney transplant patients and healthy controls. The distinctly elevated HDL-cholesterol in pancreas-kidney transplant patients can be readily explained by the low post-prandial triglyceride levels resulting from a high activity of lipoprotein lipase. The very favourable lipid profile in post-diabetic pancreas-kidney trasplant recipients could be expected to counteract the severe atherosclerotic risk of long-standing diabetes.

INSULIN THERAPY : GENERAL ASPECTS

Interval between insulin injection and breakfast in diabetes.

Sackey AH, Jefferson IG. Archives of Disease in Childhood 1994; 71 : 248-50.

The relationship between the insulin-breakfast interval, post-prandial increase in blood glucose and glycaemic control was studied in 58 children with diabetes. Patients recorded insulin-breakfast intervals in a home diary over a seven day period and during a 24-hour period at the weekend provided eight serial capillary dried blood spots for glucose analysis. The highest mean blood glucose value occurred two hours after breakfast and showed a significant correlation with fructosamine concentrations. Weekend insulin-breakfast intervals ranged from 2-30 minutes, with70% reporting intervals of less than 15 minutes. There was a significant correlation between the weekend insulin-breakfast interval and the after breakfast increase in blood glucose with a mean increment of 0.4 mmol/L in the 30-minute group of 7.2mmol/L in the 2-minute group. Over the whole study period children with mean insulin-breakfast intervals of 2 to 12 minutes had a mean fructosamine concentration of 376 mμmol/L compared with 341 mμmol/L in those with intervals of 15-35 minutes. The study has shown that the interval between insulin injection and breakfast significantly influences the morning postprandial rise in blood glucose and consequently short term glycaemic control. It is therefore important that patients are encouraged to leave an interval of about 30 minutes between insulin injection and breakfast.

INSULIN THERAPY : DELIVERY AND PHARMACOKINETICS

The effects of subcutaneous insulin-like growth factor-I infusion in insulin-dependent diabetes mellitus.

Bach MA, Chin E, Bondy CA. Journal of Clinical Endocrinology and Metabolism 1994; 79 : 1040-5.

Insulin-dependent diabetes can be associated with low insulin-like growth factor-I (IGF-I) levels despite normal or even high GH secretion. The basis of the diabetic abnormalities in GH-IGF dynamics that contribute to insulin resistance and impaired fuel metabolism are not well understood. To further investigate these matters, this study evaluated baseline IGF system parameters and responses to recombinant human IGF-I in four diabetic adolescents and six pubertal stage-matched controls. Spontaneous overnight and arginine-stimulated GH secretion, insulin, IGF-I, IGF-II, IGF-binding protein-1 (IGFBP-1) and IGFBP-3 levels were measured before, during and after daily 10-hour sc infusions of saline or IGF-I (20 μgrams/kg/h). Baseline overnight GH secretion and IGFBP-1 and 3 levels were not significantly different in the two groups, but IGF-I levels were significantly lower and IGF-II levels were higher in diabetic subjects. IGF-I infusion produced a 3-fold increase in serum IGF-I levels and a reciprocal profound reduction in IGF-II levels in both groups. IGFBP-1 levels increased dramatically in diabetics and modestly in normal subjects in response to IGF-I infusion, but IGFBP-3 levels were not significantly altered. Spontaneous overnight and arginine-stimulated GH secretion were suppressed by about 50% in both groups after IGF-I infusion. Insulin requirements were substantially reduced in diabetics receiving IGF-I and insulin secretion was suppressed in normal subjects, with no evidence of a change in insulin half-life. Blood glucose remained stable in both groups throughout saline and IGF-I infusions and no hypoglycaemia or other adverse effects occurred during IGF-I infusions. Further studies are necessary to determine whether the addition of IGF-I to insulin replacement therapy may stably reduce the insulin requirement, maintain normal GH levels and perhaps achieve better metabolic and anabolic balance in the treatment of insulin-dependent diabetes.

Pharmacokinetics, pharmacodynamics and glucose counterregulation following subcutaneous injection of the monomeric insulin analogue [Lys (B28), Pro(B29)] in IDDM.

Torlone E, Fanelli C, Rambotti AM, Kassi G, Modarelli F, Di Vincenzo A, Epifano L, Ciofetta M, Pampanelli S, Brunetti F, et al. Diabetologia 1994; 37 : 713-20.

The aim of these studies was to compare the pharmacokinetics, pharmacodynamics, counter-regulatory hormone and symptom responses, as well as cognitive function during hypoglycaemia induced by s.c. injection of 0.15 IU/kg of regular human insulin (HI) and the monomeric insulin analogue [Lys (B28), Pro (B29)] (MI) in insulin-dependent-diabetic (IDDM) subjects. In these studies glucose was infused whenever needed to prevent decreases in plasma glucose below 3 mmol/L. After MI, plasma insulin increased earlier to a peak (60 vs 90 min) which was greater than after HI (294 ± 24 vs 255 ± 24 pmol/L) plasma glucose decreased earlier to a 3 mmol/L plateau (60 vs 120 min) ($P < 0.05$). The amount of glucose infused to prevent plasma glucose falling below 3 mmol/L was approximately three times greater after MI than HI (293 ± 26 vs 90 ± 25 mμmol.kg-1 60-375 min-1, $P < 0.05$). After MI, hepatic glucose production was more suppressed (0.7 ± 1 vs 5.9 ± 0.54 $m\mu mol.kg^{-1}. min^{-1}$) and glucose utilization was less

suppressed than after HI (11.6 ± 0.65 vs 9.1 ± 0.11 mμmol. $Kg^{-1}.min^{-1}$) ($p < 0.05$). Similarly, plasma NEFA, glycerol and betal-OH-butyrate were more suppressed after MI than HI ($P < 0.05$), whereas plasma lactate increased only after MI , but not after HI. Responses of counterregulatory hormones, symptoms and deterioration in cognitive counterregulatory hormones, symptoms and deterioration in cognitive function during plasma glucose plateau of 3 mmol/L were superimposable after MI and HI (P = NS).

ORAL HYPOGLYCAEMIIC AGENTS

Bed- time dosing of glyburide and the treatment of Type 2 diabetes mellitus.

Hennessey JV, Bustamante MA. Teter ML, Markert RJ, McDonald SD. American Journal of the Medical Sciences 1994; 308 :234-8.

Suppression of nocturnal hepatic glucose production is key in the treatment of non-insulin-dependent diabetes mellitus (NIDDM). In this article, the authors compare the effectiveness of dosing glyburide at bedtime versus in the morning on glycaemic control in patients with NIDDM under suboptimal control. In a placebo-controlled, double – blind crossover trial, 32 patients with NIDDM with suboptimal control on chronic glyburide treatment fulfilling entry criteria were randomized to receive one of two regimens: (1) glyburide at bed-time and placebo in morning or (2) placebo at bed-time and glyburide in the morning. After 6 months of a regimen, patients crossed over to the other treatment and completed an additional 6-month period. After base-line assessment, fasting blood sugar, history, physical examination and compliance assessments were performed monthly. HbA_1C was measured bimonthly and Sustacal tolerance tests were performed at the end of each 6-month treatment period. During the initial 6-month comparison, fasting blood sugar concentration decreased 5% in bed-time ingesters and rose 10% in the morning patients. These changes were not statistically significant. HbA_1C decreased significantly in the morning group but remained unchanged in the bed-time group. At the end of 12 months, night-time dosing resulted in better home glucose monitoring values, fasting blood sugar results and Sustacle tolerance profiles, but the differences were not statistically significant. No hypoglycaemia was observed in the monitored data collected. Bed-time dosing of glyburide resulted in measurable improvement in fasting blood sugar and carbohydrate tolerance curves, but not to a degree justifying general recommendation of the technique in patients with NIDDM with secondary failure to oral agents.

Improvement in glucose tolerance and insulin resistance in obese subjects treated with troglitazone.

Nolan JJ, Ludvik B, Beerdsen P, Joyce M, Olefsky J. New England Journal of Medicine 1994; 331: 1188-93.

Background: Troglitazone decreases insulin resistance and hyperglycaemia in patients with non-insulin-dependent diabetes mellitus (NIDDM), but its effects on subjects without diabetes are not known.

Methods: We performed oral and intravenous glucose tolerance tests, studies with the oral and intravenous glucose tolerance tests, studies with euglycaemic hyperinsulinaemic clamp, meal tolerance tests and 24-hour blood pressure measurements at base line and after the administration of troglitazone, 200 mg orally twice daily or placebo for 12 weeks in 18 non-diabetic obese subjects, 9 of whom had impaired glucose tolerance.

Results: The mean (± SD) rates of glucose disposal increased from 4.7 ± 1.7 to 6.0 ± 1.7 mg per kilogram of body weight per minute (P = 0.004) and from 9.0 ± 1.8 to 9.9 ± 1.3 mg per kilogram per minute(P = 0.02) during insulin infusions of 40 and 300 mU per square meter of body surface area per minute respectively in the troglitazone group. The insulin-sensitivity index, calculated from the results of intravenous glucose tolerance tests, increased from 0.7 ± 0.6 x 10 (-4) to 1.6 ± 0.9 x 10(-4) in subjects given troglitazone and their glycaemic response to oral glucose and to mixed meals decreased. The mean fasting plasma insulin concentration decreased by 48 percent (P = 0.002) and the plasma insulin response to oral glucose and mixed meals decreased by 40 and 41 percent respectively. The changes were similar in the subjects with normal glucose tolerance and those with impaired glucose tolerance. Systolic and diastolic blood pressure decreased by 5 ± 2 mm Hg (P = 0.05) and 4 ± 2 mm Hg (P = 0.04) respectively, after treatment with troglitazone. There were virtually no changes in the placebo group.

Conclusion : Troglitazone decreased insulin resistance and improves glucose tolerance in obese subjects with either impaired or normal glucose tolerance. The ability of troglitazone to reduce insulin resistance could be useful in preventing NIDDM.

Long-term efficacy and safety of acarbose in the treatment of obese subjects with non-insulin-dependent diabetes mellitus.

Coniff RF, Shapiro JA, Seaton TB. Archives of Internal Medicine 1994; 154 : 2442-8.

Background: Acarbose delays the release of glucose from complex carbohydrates and disaccharides by inhibiting intestinal alpha-glucosidases, attenuating post-prandial increments in blood glucose and insulin. This multicentre double-blind study compared the efficacy and safety of acarbose with placebo in the treatment of obese subjects with non-insulin-dependent diabetes mellitus (NIDDM) managed by diet.

Methods: Two hundred twelve obese subjects with NIDDM who had not received any diabetic medication for at least 12 weeks were randomized to receive acarbose or placebo. The subjects were stratified by fasting glucose level above or below 11.1 mmol/L (200 mg/dl). Based on the subject's therapeutic response and tolerance, the acarbose dosage was titrated from 50 to 300 mg three times per day. This 36-week study consisted of a 6-week pre-treatment period, a 24-week double-blind treatment period and a 6-week post-treatment period.

Result: Ninety-one subjects given acarbose and 98 subjects who received placebo were evaluable for efficacy. During a standard meal tolerance test at the double-blind and point, the differences between treatment groups in mean change from baseline were as follows: 0.9 mmol/L (16 mg/dl) for fasting plasma glucose level, approximately 2.8 mmol/L (50 mg/dl) for post-prandial plasma glucose level and 0.59% ($P < 0.0001$) for haemoglobin A_1C concentration (for all three measurements, values decreased in the acarbose group and increased in the placebo group).

Conclusion: Acarbose improved both fasting and postprandial hyperglycaemia and improved overall glycaemic control as measured by the haemoglobin A_1 C level. These findings suggest a beneficial role for acarbose in combination with diet in the treatment of obese subjects with NDDM.

DIET AND NUTRITION

Alternative snack system for children and teenagers with diabetes mellitus.

Loghmani E, Rickard KA. Journal of the American Dietetic Association 1994; 94 : 1145-8.

An alternative snack system facilities diabetes management and provides a teaching tool for age-appropriate nutrition education of children and teenagers with diabetes mellitus. The system consists of four snack sizes: Mini-7 to 10 g available glucose, Little-15 to 20 g, Big-30 to 35 g and Super Big-50 to 55 g. Within each category, several snack patterns are equivalent to each other in terms of available glucose and energy. By using this system, a child or teenager can eat snacks that contain different food groups and still adhere to the overall meal plan. When additional carbohydrate is needed for exercise or the prevention of night-time hypolycaemia, a snack from the next largest category will increase available glucose by approximately 15 g and energy intake by approximately by 100 kcal. Generally, for every hour of extra physical activity, a little snack is added. When blood glucose concentrations before a night-time snack are 4.4 to 6.7 mmol/L, a little snack is added to the usual bedtime snack and when levels are less than 4.4 mmol/L, a big snack is added. Further, adjustments are made for children younger than 5 years old. The alternative snack system is a valuable nutrition education tool for the management of diabetes in children and teenagers.

PREGNANCY

Amniotic Fluid volume reflects recent glycaemic status in gestational diabetes mellitus.

Bar, Hava I, Scarpelli SA, Barnhard Y, Divon MY. American Journal of Obstetrics and Gynaecology 1994; 171: 952-5.

Objective: Our purpose was to determine the association between amniotic fluid volume and recent glucose status in gestational diabetes.

Study Design: Serial amniotic fluid index values, mean blood glucose levels and percent hyperglycaemia (≥ 120 mg/dl) 1 day and 1 week before the ultrasonographic examinations were prospectively collected in 399 gestational diabetics. Patients demonstrating at least one amniotic fluid index measurement within the normal range (i.e. 5 cm < amniotic fluid index ≤ 20 cm) and at least one elevated measurement (i.e. amniotic fluid index > 20 cm) formed the study group. With each patient serving as her own control, glucose index values preceding normal and elevated amniotic fluid index values were compared.

Results: Significantly higher mean blood glucose values 1 day (114.7 mg/dl vs 102.8 mg/dl, P < 0.01) and 1 week before (111.0 mg/dl vs 102.0 mg/dl, P < 0.05) were calculated for examinations resulting in elevated amniotic fluid index values compared with normal amniotic fluid index values, respectively. Similarly, significantly higher percents of hyperglycaemia 1 day (32 % vs 16.5 % P < 0.05) but not 1 week (30.8% vs 21.7% P > 0.05) before the elevated amniotic fluid index were documented.

Conclusion: Amniotic fluid volume reflects recent glycaemic status in gestational diabetes mellitus.

Gestational diabetes: postpartum glucose tolerance testing.

Dacus JV, Meyer NL, Muram D, Stilson R, Phipps P, Sibai BM. American Journal of Obstetrics and Gynaecology 1994; 171 : 927-31.

Objective: Our purpose was to determine the incidence of and evaluate risk factors for postpartum glucose intolerance among predominantly back gestational diabetic women.

Study Design: One hundred forty-five gestational diabetics underwent a standard 2-hour glucose tolerance test in the early puerperium according to the criteria of the National Diabetes Data Group.

Results: Fourteen patients (10%) were diabetic and eight (5%) showed impaired glucose tolerance. Maternal age, race or obesity did not predict abnormal postpartum glucose tolerance testing. The requirement of insulin for glucose control during gestation and gestational age at diagnosis were significantly associated with abnormal postpartum glucose tolerance (P < 0.0001 and P = 0.012 respectively). Multivariate analysis showed that only a requirement for insulin for glucose control was significant (P < 0.001).

Conclusion: Pregnancies complicated by gestational diabetes are at increased risk of glucose intolerance during the early postpartum period. Abnormal glucose tolerance occurs predominantly among those patients requiring insulin therapy during gestation or those diagnosed before 24 weeks gestation.

Gestational diabetes: does the presence of risk factors influence perinatal outcome?

Weeks JW, Major CA, de Veciana M, Morgan MA. American Journal of Obstetrics and Gynaecology 1994; 171 : 1003-7.

Objective: Our purpose was to determine whether gestational diabetics with risk factors for gestational diabetes have worse glucose tolerance and poorer birth outcomes than those without risk factors.

Study Design: We conducted a nonconcurrent cohort study of gestational diabetics identified by universal screening and delivered from Jan. 1 1990 to Dec. 31 1992. Multiple gestations and patients with chronic medical conditions were excluded. The following risk factors for gestational diabetes mellitus were abstracted: obesity (> 80 kg), family history of diabetes, previous gestational diabetes mellitus and previous macrosomic, stillborn or anomalous fetus. Patients with one or more risk factors were compared with those without risk factors. A group of low risk non-diabetic patients served as controls. The incidence of A2 diabetes mellitus, caesarean section, neonatal macrosomia and shoulder dystocia were the outcome variables of interest.

Results: Selective screening would have failed to detect 43 % of gestational diabetics. Twenty eight percent of the missed gestational diabetics would have required insulin (class A2). When compared with controls, patients with gestational diabetes mellitus were at increased risk for macrosomia (26 % vs 11%, P < 0.01), caesarean section (37 % vs 15 %, P < 0.01) and shoulder dystocia (9% vs 2%, P< 0.05). Patients with and without risk factors did not differ in mean maternal age, gestational age at delivery, birth weight, incidence of requiring insulin, macrosomia or caesarean delivery. The similarities between those with or without risk factors remained after stratification by maternal age (≥ 30 years).

Conclusion: Gestational diabetics are at increased risk for adverse birth outcomes compared with low risk controls. Class A2 diabetes mellitus and foetal macrosomia with its attendant risks are equally prevalent among patients with and without risk factors for gestational diabetes mellitus. Because > 40% of cases will be missed with selective screening, universal screening should be favoured for detection of gestational diabetes mellitus.

Random plasma glucose and the glucose challenge test in pregnancy.

Mathai M, Thomas TJ, Kuruvila S, Jairaj P. National Medical Journal of India 1994; 7: 160-2..

Background: The oral glucose tolerance test for detecting women with gestational diabetes is too complicated and prolonged for

routine use. Similar and less time consuming screening tests have been proposed including random plasma glucose estimation and the glucose challenge test (blood glucose estimation one hour after a 50 g glucose load). However, in practice, correct timing of the blood sample, which is of critical importance in the interpretation of the results of these tests, is difficult to ensure. This study was designed to evaluate these two screening tests in identifying women with abnormal glucose tolerance in pregnancy.

Methods: One hundred and eleven consecutive pregnant women at risk for gestational diabetes and 121 consecutive pregnant women with no risk factors had random plasma glucose estimation followed by the 50 g glucose challenge test at 26 to 30 weeks of gestation. A 100 g 3-hour oral glucose tolerance test was done within two weeks of the screening tests. The sensitivity and specificity of screening tests in predicting abnormal tolerance were calculated.

Results: Seven (6.3%) women in the high risk group and four (3.3%) in low risk group had gestational diabetes, while 11 (9.7%) and 8 (6.6%) had impaired glucose tolerance. Random plasma glucose level of 90 mg/dl or greater had a sensitivity of 63% and specificity of 66% in predicting abnormal glucose tolerance, while a threshold level of 115 mg/dl for the glucose challenge test yielded a sensitivity of 63 % and a specificity of 55%.

Conclusion: Neither random plasma glucose estimation nor the glucose challenge test is a useful screening procedure for abnormal glucose tolerance in pregnancy.

Prevalence and predictive value of islet cell antibodies and insulin autoantibodies in women with gestational diabetes.

Damm P, Kuhl C, Buschard K, Jakobsen BK, Svejgaard A, Sodoyez-Goffaux F, Shattock M, Bottazzo GF, Molsted-Pedersen L. Diabetic Medicine 1994; 11: 558-63.

The objective of the present study was to investigate the predictive value of islet cell antibodies (ICA) and insulin autoantibodies (IAA) for development of diabetes in women with previous gestational diabetes (GDM). Two hundred and forty-one previous diet treated GDM patients and 57 women without previous GDM were examined 2-11 years after the index pregnancy. In sub-groups, plasma from the diagnostic OGTT during index pregnancy was analysed for ICA and IAA. Among the previous GDM patients, 3.7% had developed Type 1 diabetes and 13.7% Type 2 diabetes. Four (2.9%) of the 139 GDM patients tested for ICA were ICA-positive and three of these had Type 1 diabetes at follow-up as well as three ICA-negative patients. The sensitivity, specificity and predictive value of ICA-positivity for later development of diabetes were 50%, 99% and 75% respectively. None of the women were IAA-positive during pregnancy. In conclusion, the majority of the patients with GDM did not show evidence of ongoing autoimmune destruction of the beta cells during the index pregnancy. However, ICA-positive GDM patients had a high risk of developing Type 1 diabetes later in life.

COMPLICATIONS, GENERAL ASPECTS

Whole body composition and regional bone mass in women with insulin-dependent diabetes mellitus.

Compston JE, Smith EM, Matthews C. Schofield P. Clinical Endocrinology 1994; 41: 289-93.

Objective: Reduced bone mass has been reported in adult patients with insulin-dependent diabetes mellitus but there are few data on bone density in the axial skeleton or on whole body composition in this group. The aim of this study was to determine whether whole body and regional bone mass are normal in middle-aged women with insulin-dependent diabetes mellitus.

Design: Total and regional bone mass were measured in 24 post menopausal women aged 43-69 years (mean 56.3) with insulin-dependent diabetes, recruited during routine clinic attendance. Results were compared with those obtained from 24 age and weight matched community-based post-menopausal women.

Measurements: Whole body bone mineral content and bone mass in the lumbar spine and femoral neck were measured by dual energy X-ray absorptiometry on a Lunar DPX.

Results: Whole body bone mineral content was significantly lower in the diabetic women than in community based controls ($P = 0.002$). There was no significant difference between the two groups in whole body bone density or lumbar spine bone density. Mean bone density in the femur was lower in the patient group at all sites assessed (femoral trochanter $P = 0.003$, femoral neck, $P = 0.057$). Values for all regional bone density measurements in the diabetic women were within the Lunar reference range (mean ± 2 SD) and at all sites the mean value was close to 100% of the sex and age matched reference value. There was no correlation between duration or control of diabetes and bone mass at any site.

Conclusion: Insulin-dependent diabetes mellitus in middle aged women is associated with small reductions in total body bone mineral content and in femoral bone density; the clinical significance of these findings in terms of subsequent fracture risk remains to be established. No evidence was found in this study for a reduction in whole body or lumbar spine bone density.

Dramatic increase in incidence of insulin-dependent diabetes mellitus in Western Australia.

Kelly HA, Russia MT, Jones TW, Byrne GC. Medical Journal of Australia 1994;161 : 426 – 9.

Objectives: To document and suggest possible reasons for a dramatic increase in the incidence of insulin dependent diabetes mellitus (IDDM) in Western Australia in 1992.

Patients: Children aged 0-14 years with IDDM diagnosed in Western Australia from 1985 to 1992 inclusive.

Design: A population-based register in Western Australia, using name-identified data from two separate ascertainment sources, provided numerator data. Denominator data were estimated from census figures collected in 1986 and 1991 by the Australian Bureau of statistics. The completeness of case ascertainment was estimated by the capture recapture method.

Results: Case ascertainment for 1985-1992 was estimated as 99.6% complete. Between 1985 and 1991 the incidence of IDDM in the 0-14 year age group varied between 11.8 and 15.5 per 100,000 person-years without a significant increase. In 1992 however, based on previous seven years, 52 cases would have been expected but 84 cases were observed and incidence of 22.2 per 100,000 person-years. The increase in incidence occurred across all age groups and in both sexes. Place of residence at diagnosis, the prevalence of islet cell antibody positivity at diagnosis and the proportion of new cases with a first degree relative with IDDM were no different in 1992 than in preceding years.

Conclusion: This is the first report of a significant increase in the incidence of IDDM in Australia. It appears to be a period, rather than a cohort effect and provides further evidence for environmental antigens as the disease triggers.

CARDIOVASCULAR COMPLICATIONS

Effect of autonomic nervous system dysfunction on the circadian pattern of myocardial ischaemia in diabetes mellitus.

Zarich S, Waxman S,Freeman RT, Mittleman M, Hegarty P, Nesto RW. Journal of the American College of Cardiology 1994; 24: 956-62.

Objectives: The of this study was to determine the prevalence and characteristics of ambulatory myocardial ischaemia in patients with diabetes mellitus and to delineate the relation between the presence and severity of autonomic nervous system dysfunction and the incidence and time of onset of myocardial ischaemia.

Background: Conflicting data exist with regard to the circadian pattern of myocardial infarction and other cardiovascular events, such as ambulatory ischaemia, in diabetes.

Methods: We performed ambulatory electrocardiographic monitoring in 60 patients with diabetes and coronary artery disease. Autonomic nervous system testing was performed in a subgroup of 25 patients with myocardial ischaemia after discontinuation of all anti-anginal medications.

Results: Thirty-eight of 60 patients had evidence of ambulatory ischameia; 91% of all ischaemia episodes were asymptomatic. The 25 patients with ambulatory ischaemia who underwent autonomic nervous system testing had a peak incidence of ischaemia between 6 am and noon (46 of 133 ischaemia episodes, $P < 0.007$), compared with the other three 6-h periods. Fifteen of the 25 patients had no or mild autonomic nervous system dysfunction and demonstrated a similar peak incidence of ischaemia between 6 am and noon ($P = 0.0009$). However, the 10 patients with moderate to severe autonomic nervous system dysfunction did not experience a morning peak of ischaemia and the number of episodes were distributed evenly throughout the day ($P = 0.4$).

Conclusion: Silent ischaemia is highly prevalent among patients with diabetes and coronary artery disease. Time of onset of ischaemia in diabetic patients follows a circadian distribution, with a peak incidence in the morning hours. However, patients with significant autonomic nervous system dysfunction did not demonstrate such a peak, suggesting that alterations in sympathovagal balance may have an effect on the circadian pattern of cardiovascular events.

Haemostatic abnormalities persist despite glycaemic improvement by insulin theraphy in lean Type 2 diabetic patients.

Knobl P. Schrnthaner G, Schnack C, Pietschmann P. Proidl S, Prager R, Vukovich T. Thrombosis and Haemostasis 1994; 71: 692-7.

Diabetes mellitus is associated with disturbances of the haemostatic system, which might contribute to the development of diabetic vascular disease. We investigated the effect of metabolic improvement by insulin therapy on the haemostatic system in 61 patients with Type 2 diabetes mellitus and secondary sulfonylurea failure compared with 45 healthy control subjects matched for age, sex and BMI. Median age was 65, median diabetes duration 10 years. Median HbA_1C (10%) and fructosamine (4.0 mM) levels were elevated before induction of therapy and decreased significantly within 6 months of insulin treatment to 7.5% and 3.0 mM respectively ($p<0.0001$). Compared with control subjects, median plasma levels of fibrinogen (317 vs 286 mg/dl), coagulation factor VII activity (1.1 vs 0.89 U/I), von Willebrand factor (1.6 vs 1.3 U/I), D-dimer (105 vs 86 µg/I), protein C: Ag (1.24 vs 0.95 U/I), total protein S: Ag (1.5 vs 0.91 U/I) and antithrombin III activity (1.17 vs 1.08 U/I) were significantly elevated . Levels of free protein S were not different from control values. No significant decline of coagulation parameters could be recorded during insulin therapy. Patients with diabetic vasculopathy had higher levels of D-dimer than those without (133 vs 76 µg/I before, 109 vs 88 µg/I during therapy), whereas the other haemostatic parameters were not different. Our data indicate a significant activation of the coagulation system in diabetic patients with secondary failure to sulfonylurea drugs, with signs of a prethrombotic state and endothelial cell disturbance.

Platelet activation in diabetic patients with asymptomatic atherosclerosis

Kawamori R, Imano E, Watarai T, Nishizawa H, Matsushima H, Kodama M, Yamasaki Y, Kamada T. Diabetes Research and Clinical Practice 1994; 24: 89-95.

We studied 27 non-insulin-dependent diabetics without apparent atherosclerosis (AS) to investigate whether abnormal platelet function is related to asymptomatic atherosclerosis in diabetes mellitus. The degree of AS was quantitatively evaluated by determining the intimal plus medial thickness (IMT) of the carotid artery wall with ultrasound high resolution B-mode imaging. Based on our previous finding that the upper threshold of the IMT was 1.1 mm in healthy subjects, the patients were divided into the AS-positive group with the IMT > 1.1 mm (n= 17) and the AS-negative group with the IMT < 1.1 mm (n= 10). Among five variables measured as the factors concerned with thrombogenesis, only plasma levels of beta-thromboglobulin (beta-TG) and platelet factor 4 (PF4) were significantly higher in the AS–positive group than in the AS-negative group. Chronic administration of pentoxifylline (300 mg/day) significantly reduced the abnormally high plasma levels of beta-TG and PF4 in 7 patients of the AS-positive group to normal levels, without lowering the normal plasma beta-TG and PF4 levels in the remaining 10 patients. Pentoxifylline treatment did not affect the plasma levels of the 3 other variables, von Willebrand factor, 6-keto prostaglandin F1 alpha and the thromboxane B2. This study suggests that the progress of atherosclerosis in diabetes mellitus is associated with in vivo platelet activation and platelet activation does not occur in diabetics without carotid atheosclerosis. Pentoxifylline may impede the vicious cycle in which atherosclerosis is accelerated by platelet activation.

Hyperinsulinism in patients with coronary artery disease.

Job FP, Wolfertz J, Meyer R, Hubinger A, Gries FA, Kuhn H, Coronary Artery Disease 1994; 5: 487-92.

Aim: To assess the clinical impact of hyperinsulinism and major coronary risk factors in patients with angiographically documented or excluded coronary artery disease (CAD), a clinical study was carried out in 268 men admitted for left heart catheterization.

Methods: Fasting immunoreactive insulin (IRI) levels were correlated to all major cardiovascular risk factors and to the presence and degree of CAD.

Results: IRI levels were correlated significantly with the degree of CAD (one vessel disease: mean IRI 9.4 µU/ml ± 0.43 SEM; two vessel disease: mean IRI 10.4 µU/ml ± 0.71 SEM; three vessel disease: mean IRI 11.88 µU/ml ± 0.98 SEM) and inversely to the high –density lipoprotein level ($P<0.05$). In patients with arterial hypertension, IRI levels were elevated, without a significant difference between those with and those without CAD, whereas the IRI levels of non-hypertensive men with CAD (n= 81; mean IRI 9.85 µU/ml ± 0.51 SEM) differed significantly ($P < 0.05$) from those of non-hypertensive men without CAD (n=59; mean IRI 7.76

μU/ml ± 0.43 SEM). IRI levels were significantly higher (P < 0.05) in obese patients (n= 65; mean IRI 11.68 μU/ml ± 0.70 SEM versus n + 203 ; mean IRI 9.32 μU/ml ± 0.34 SEM), in patients with elevated triglycerides (n = 58 mean IRI 11.59 μU/ml ± 0.81 SEM various n = 210; mean IRI 9.42 μU/ml ± 0.33 SEM) and in patients with lowered HDL cholesterol (n = 178; mean IRI 11.06 μU/ml ± 0.63 SEM versus n = 90; mean IRI 9.29 μU/ml ± 0.34 SEM). Diabetic patients on angiotensin converting enzyme converting enzyme inhibitor therapy (n = 11; mean IRI 7.91 μU/ml ± 0.91SEM) had significantly (P < 0.05) lower IRI levels than those not treated with ace inhibitors (n= 25; mean IRI 12.96 μU/ml ± 1.47 SEN). IRI levels exceeding 8 μU/ml were associated with a 1.98 fold risk for CAD compared with IRI levels below 8 μU/ml. Stepwise logistic regression showed that insulin was an independent determinant of CAD.

Conclusion: Knowledge of the fasting insulin level is an important contribution to the identification of patients with, or at risk of CAD.

Evidence of higher insulin resistance in NIDDM patients with ischaemic heart disease.

Inchiostro S. Bertoli G, Zanette G, Donadon V. Diabetologia 1994; 37 : 597-603 .

Prospective studies have shown a relationship between hyperinsulinaemia, and indirect index of insulin resistance and IHD in men with normal glucose tolerance. In NIDDM, this association is less clear possibly due to the poor significance of insulin and C-peptide concentrations as an index of insulin resistance. Therefore, only a direct measurement of insulin sensitivity could clarify the possible relationship between insulin resistance and IHD in NIDDM. We have evaluated insulin sensitivity by means of an ITT and some risk factors for IHD in 72 men with NIDDM, 36 with and 36 without IHD, attending our out-patient Diabetic Clinic. The two groups were of similar age, duration of diabetes, glycaemic control and body composition. Subjects with IHD were more insulin resistant (K(ITT) index 2.45 ± 0.18 vs 3.12 ± 0.13% per min, in patients with and without IHD respectively, P < 0.004), had higher total (P = 0.011) and LDL serum cholesterol levels (P = 0.010) and greater prevalence of hypertension (P = 0.001) compared to subjects without IHD. Using step wise logistic regression analysis, insulin resistance (odds ratio 2.57, 95% CI 1.87-3.28, P + 0.008), hypertension (odds ratio 8.17, 95% CI 6.86-9.48, P = 0.002), total serum cholesterol levels (odds ratio 1.02, 95% CI 1.005-1.035, P = 0.015) and BMI (0.79, 95% CI 0.67-0.97, P = 0.049) were independently associated with IHD. After adjustment for age and duration of diabetes, only insulin sensitivity was directly related to the age of onset of IHD independently from other clinical and metabolic parameters (P< 0.015).

Association of elevated lipoprotein(a) levels and coronary heart disease in NIDDM patients. Relationship with apolipoprotein (a) phenotypes.

Ruiz J, Thillet J, Huby T, James RW, Erlich D, Flandre P, Froguel P, Chapman J, Passa P. Diabetologia 1994; 37 : 585-91.

Non-insulin-dependent diabetes mellitus (NIDDM) is a strong and independent risk factor for coronary heart disease. We assessed the potential relationship between plasma Lp(a) levels, apo(a) phenotypes and coronary heart disease in a population of NIDDM patients. Seventy-one patients with coronary heart disease, who previously have had transmural myocardial infarction or significant stenosis on coronary angiography or positive myocardial thallium scintigraphy or in combination, were compared with 67 patients without coronary heart disease who tested negatively upon either coronary angiography, myocardial thallium scintigraphy or a maximal exercise test. The prevalence of plasma Lp(a) levels elevated above the threshold for increased cardiovascular risk (> 0.30 g/L) was significantly higher (P = 0.005) in patients with coronary heart disease (33.8%) compared to the control group (13.4%). The relative risk (odds ratio) of coronary heart disease among patients with high Lp(a) concentrations was 3.1 (95% confidence interval, 1.31-7.34; P = 0.01). The overall frequency distribution of apo(a) phenotypes differed significantly between the two groups (P = 0.043). However, the frequency of apo(a) isoforms of low apparent molecular mass (≤ 700 kDa) was of borderline significance (P = 0.067) between patients with or without coronary heart diseae (29.6% and 16.4% respectively). In this Caucasian population of NIDDM patients, elevated Lp(a) levels were associated with coronary heart disease, an association which was partially accounted for by the higher frequency of apo(a) isoforms of small size. In multivariate analyses, elevated levels of Lp(a) were independently associated with coronary heart disease (odds ratio 3.48, P = 0.0233).

EYE COMPLICATIONS

Laser flare intensity in diabetics: correlation with retinopathy and aqueous protein concentration.

Ino-ue M. Azumi A. Shirabe H. Tuskahara Y. Yamamoto M. British Journal of Ophthalmology 1994; 78 :694-7.

The laser flare intensity in diabetics, measured with the scattering of a light beam, was evaluated and compared with actual aqueous protein concentration obtained during surgery. Measurement of the laser flare intensity in 120 diabetics and 108 normal subjects was performed with the laser flare cell meter (FC1000 Kowa, Tokyo). Aqueous protein concentration in 26 diabetics and six controls who underwent intraocular surgery was measured by the method of Bradford. No significant difference in the laser flare intensity was found between normal subjects and diabetics without retinopathy. A significant increase in the laser flare intensity was observed after six decades in diabetics with background retinopathy and all with proliferative retinopathy. The laser flare intensity correlated with the duration of diabetes mellitus. There was a significant linear relation between the laser flare intensity and actual aqueous protein concentration. The linear regression formula was X = Y1.39 x 1.02 (X = protein concentration, mg/dl; Y = flare intensity, photon counts/ms). The precise value of the laser flare intensity provides a new indicator to evaluate the diabetic change in the function of the ocular barrier.

Outcome of cataract operations performed to permit diagnosis, to determine eligibility for laser therapy or to perform laser therapy of retinal disorders.

Edwards MG, Schachat AP, Bressler SB, Bressler NM. American Journal of Ophthalmology 1994; 118: 440-4.

Cataract operations may be recommended when retinal disease is suspected but cannot be adequate by diagnosed or treated because of lens opacity. We evaluated the outcome of cataract operations performed under those circumstances. We reviewed the records of 119 patients who were examined at the Wilmer Retinal Vascular Center and within three months underwent a cataract operation. We identified 17 patients (20 eyes) who underwent a cataract operation at the recommendation of a retinal specialist to permit diagnosis, to determine eligibility for laser therapy or to perform laser therapy. After the cataract operation, eight (40%) of the 20 eyes were found to have a retinal disease for which laser therapy was recommended and six (30%) of the 20 eyes underwent laser therapy that, before the cataract operation, had been impossible. These results indicate that a cataract operation may be useful when lenticular opacity prevents diagnosis or treatment in a patient with a suspected retinal disorder.

Relationship of hyperglycaemia to the long-term incidence and progression of diabetic retinopathy.

Klein R, Klein BE, Moss SE, Cruickshanks KJ. Archives of Internal Medicine 1994; 154: 2169-78.

Background: The object was to examine the relationship of hyperglycaemia, as measured by glycosylated haemoglobin level, to the incidence and progression of diabetic retinopathy over a 10-year period.

Methods: Patients who were younger (n = 682) and older (n = 834) than 30 years at onset of diabetes participated in baseline (1980-1982) and follow-up (1984-1986 and 1990-1992) examinations of a population based cohort study. Glycosylated haemoglobin levels were measured by microcolumn. Retinopathy was determined from stereoscopic fundus photographs.

Results: Persons with glycosylated haemoglobin levels in the highest quartile at baseline were more likely to have progression of retinopathy than persons with levels in the lowest quartile (younger onset group: relatively risk [RR] 2.9; 95% confidence interval [CI], 2.3 to 3.5; older onset group taking insulin: RR 2.1; 95% CI, 1.6 to 2.8; and older onset group not taking insulin: RR 4.3; 95% CI, 3.0 to 6.2) and were more likely to develop proliferative diabetic retinopathy (younger-onset group: RR 7.1; 95% CI, 4.6 to11.1; older onset group taking insulin: RR 3.1; 95% CI, 1.5 to 6.1; and older onset group not taking insulin: RR 13.8; 95% CI, 4.8 to 39.5). These relations were significant (P < .005) in all groups examined, even after controlling for other risk variables.

Conclusion: These data are compatible with the hypothesis that long term control of hyperglycaemia, as measured by glycosylated haemoglobin levels, is a significant risk factor for the long term progression of diabetic retinopathy and that lower levels of glycosylated haemoglobin, even later in the course of diabetes, may modify the risk imposed by higher levels earlier in the course of disease in people with both younger and older onset diabetes.

The relation between retinopathy and albumin excretion rate in insulin-dependent diabetes mellitus. From the Funen County Epidemiology of Type 1 diabetes Complications Survey.

Johansen J, Sjolie AK, Elbol P, Eshoj O. Acta Ophthalmologica 1994; 72: 347-51.

In a population based patient material of 138 insulin-dependent diabetics aged 25-34 years and with a diabetes onset before 30 years of age, the relation between retinopathy and albumin excretion rate was studied. The prevalence rate of any retinopathy was 59% (81) and of proliferative retinopathy 17% (23). After 10 years' duration of diabetes, the prevalence of any retinopathy increased steeply and reached a maximum of about 90% after more than 20 years. Very few patients had proliferative retinopathy during the first 20 years, followed by gradual increase in prevalence up to 40-50% after 25 years. Twenty-one percent (29) of the study population was found to have an increased urinary albumin excretion rate. These patients were found to have a statistically significant increase in frequency of retinopathy ($p < 0.01$) and in particular of proliferative retinopathy with increasing levels of urinary albumin excretion. Our results suggest a need for more frequent screening for diabetic retinopathy in diabetic patients with than without increased albumin excretion rate.

GENITO URINARY AND RENAL COMPLICIATIONS

Study of sexual function of male diabetics.

Yamaguchi Y, Kumamoto Y. Nippon Hinyokika Gakkai Zasshi Japanese Journal of Urology 1994; 85: 1327-35.

We studied the actual general state of sexual dysfunction in 201 male diabetics (age range: 22-76 years) who were commuting outpatients, using the Sapporo Medical University's Sexual Function Questionnaire. The control group consisted of 6,426 healthy male subjects. The principal parameters taken into account by the questionnaire were the libido and ability to achieve/maintain an erection, with consideration given to the factor of the subject's age. The results were as follows

1. The diabetic patients who were experiencing neuropathy showed a decrease in the ability to achieve/maintain an erection at an earlier age than the patients without neuropathy. In addition, the number of patients with a decreased ability to achieve/maintain an erection was found to bee 30 (45%) of 67 cases with neuropathy compared with 24 (18%) of 134 cases without neuropathy. The severity of that decreased ability was also greater in the cases with neuropathy.

2. In comparison with the healthy male control subjects, the diabetics showed decreases in libodo and the ability to achieve/maintain an erection which were not very severe at younger ages, but became striking after the age of about 60 years. Thus, the degree of dysfunction accelerated with increasing age. After the age of 60 years, the erection score was found to decrease in 31.7% of the patients without neuropathy and in 61.1% of the patients with neuropathy.

3. Weighted regression analysis showed that the most important factor involved in the ability to achieve/maintain an erection was the subject's age (contribution rate: 27.2%), followed by neuropathy (7.4%). These two factors represented the explanatory factor of erectile dysfunction in approximately 1/3 of the diabetics.

Kidney size in infants of tightly controlled insulin-dependent diabetic mothers.

Bos AF, Aalders AL, Van Doormaal JJ, Martijn A, Okken A. Journal of Clinical Ultrasound 1994; 22 : 443-6.

The aim of this study was to evaluate the influence of insulin-dependent diabetes mellitus in pregnant women on the kidney size of their infants. We measured kidney length in the first week of life using ultrasonography in 20 infants of tightly controlled insulin-dependent diabetic mothers and 20 healthy newborn controls, matched for birth weight. In the infants of diabetic mothers, the left kidney length ranged from 3.6 cm to 6.0 cm (4.2 cm ± 0.5 cm, mean ± SD). The right kidney length ranged from 3.3 cm to 4.9 cm (4.0 cm ± 0.4 cm). In the control infants the left kidney length was 3.3 cm to 5.4 cm (4.3 cm ± 0.6cm) and the right kidney length was 3.4 cm to 5.3 cm (4.2 cm ± 0.5 cm). There was no statistically significant difference in right or left kidney length between the two groups. We conclude that in this group of tightly controlled diabetic mothers, the diabetic state does not influence kidney size in their infants.

Effects of steroid withdrawal on long term renal allograft recipients with post transplantation diabetes mellitus.

Fabrega AJ, Cohan J, Meslar P, Pollak R. Surgery 1994; 116 : 792-7.

Background: Post transplantation diabetes mellitus (PTDM), a common complication of current immunosuppressive regimens, has been attributed to the diabetogenic effects of prednisone and cyclosporine. We report our experience with steroid withdrawal (SW) in renal allograft recipients with PTDM.

Methods: SW was attempted on 12 selected renal allograft recipients with PTDM and its effects on various clinical parameters were recorded before and more than 3 months after SW.

Results: Patients and graft survival was 100% and all patients had a stable serum creatinine level survival was 100% and all patients had a stable serum creatinine level and remained steroid free 15.4 ± 5 months after SW. Ten patients had a significant improvement in their diabetic management. Glycosylated haemoglobin decreased from 13.6% ± 2.3% to 9.2 % ± 2.9% (p = 0.0002); body weight decreased from 92 ± 21 kg to 86 ± 21 kg (p = 0.0134) and management of hypertension improved in eight of nine (89%) recipients with hypertension. The total cholesterol level decreased form 253 ± 57 mg/dl to 208 ± 40 mg/dl (p = 0.0041), but the high-density lipoprotein cholesterol also decreased from 46 ± 8.9 mg/dl to 39.7 ± 10.9 mg/dl (p = 0.073), so that the total cholesterol/high – density lipoprotein ratio was not significantly affected (p = 0.775).

Conclusion: SW in selected, stable, long-term renal allograft recipients with PTDM has a favourable effect on glucose homoeostasis, body weight and management of hypertension; its effect on lipid metabolism and subsequent cardiovascular risk factors warrant further study.

Ambulatory blood pressure in the transition from normo to microalbuminuria. A longitudinal study in IDDM patients.

Poulsen PL, Hansen KW, Mogensen CE. Diabetes 1994; 43: 1248-53.

To describe the development of blood pressure (BP) in relation to urinary albumin excretion (UAE) more exactly, 44 initially normoalbuminuric Type 1 diabetic patients and 21 healthy individuals were included in a 3.1 year follow-up study by using ambulatory BP (AMBP) monitoring. Six patients developed microalbuminuria according to accepted criteria (progressors; UAE at follow-up was > 20 µgrams/min). Initial UAE was higher in this group (9.0 ÷ by 1.4 µgrams/min) compared with both the nonprogressors (5.2 ÷ by 1.6 µg/min) and the control subjects (3.9 ÷ by 1.6 µg/min), P < 0.01. The values were almost identical for initial 24-hour AMBP between the progressors and the two other groups. The transition to microalbuminuria (31.7 ÷ by 1.8 µg/min) was associated with an increase in 24-hour systolic AMBP of 11.5 ± 8.3 mmHg, which was significantly higher than the increase in the nonprogressors (3.1 ± 7.7 mmHg) and the control subjects (2.2 ± 6.1 mmHg, P = 0.02). Significant correlations were detected between development in UAE and development in systolic and diastolic 24-hour AMBP (r = 0.39, r = 0.41, P < 0.01). In addition, an increase in UAE, even including increases within the normoalbuminuric range, was always associated with an increase in 24-hour AMBP (P < 0.01). Ordinary clinical measurements did not reveal any of these differences or correlations. In conclusion, a close association between increases in UAE and 24-hour AMBP emerges in this study. Initial BP was not increased in the progressors.

Long term treatment with either enalapril or nitrendipine stabilizes albuminuria and increases glomerular filteration rate in non-insulin-dependent diabetic patients.

Ruggenenti P, Mosconi L, Bianchi L, Cortesi L, Campana M, Pagani G, Mecca G, Remuzzi G. American Journal of Kidney Diseases 1994; 24: 753-61.

The effect of short (98 days) and long term (1 year) treatment with nitrendipine (10 to 40 mg/d) and enalapril (5 to 20 mg/d) on kidney function was studied prospectively in a parallel group design in 16 microalbuminuric non-insulin-dependent diabetic patients with mild hypertension and biopsy proven diabetic glomerulopathy. At the end of the short term treatment period diastolic blood pressure significantly decreased from 95.4 ± 2.5 mm Hg to 83.5 ± 3.5 mm Hg (P < 0.001) in the nitrendipine group and from 96.7 ± 2.5 to 86.7 ± 5.6 mm Hg (P < 0.001) in the enalapril group. Both overnight urinary albumin excretion rate and albumin fractional clearance tended to increase in the nitrendipine group and to decrease in the enalapril group, whereas the glomerular filtration rate and the renal plasma flow were similar to baseline in both study groups. At the end of the long-term treatment period diastolic blood pressure significantly decreased from 95.4 ± 2.5 mm Hg to 86.0 ± 6 mm Hg (P < 0.005) in the nitrendipine group and from 96.7 ± 2.1 to 9.8 ± 4.3 mm Hg (P < 0.05)in the enalapril group. Overnight urinary albumin excretion and albumin fractional clearance were similar to baseline in both study groups. The glomerular filtration rate significantly increased from 70.2 ± 14.2 to 96.8 ± 20.4 (P < 0.05) in the nitrendipine group and from 58.9 ± 10.7 to 78.5 ± 11.0 (P < 0.05) in the enalapril group. The renal plasma flow also significantly increased from 456.6 ± 165.3 to 597.2 ± 178.9 (P < 0.01) in the nitrendipine group.

Captopril and atenolol are equally effective in retarding progression of diabetic nephropathy. Results of a 2-year prospective, randomized study.

Elving LD, Wetzels JF, van Leir HJ, de Nobel E, Berden JH. Diabetologia 1994; 37: 604-9.

The progression of diabetic nephropathy can be positively influenced by maintain a low blood pressure level. This has been shown in studies with conventional antihypertensive treatment as well as ace inhibitors. Whether the latter group of drugs is more effective remains to be proven and was the aim of our study. In a prospective randomized study we compared the effects of ace inhibition and beta-blockade on retarding progression of renal function in IDDM patients with an early stage of overt diabetic nephropathy. Twenty-nine patients were studied for 2 years, 15 were randomized for treatment with captopril and 14 for atenolol. Every 6 weeks blood pressure and urinary albumin and total protein excretion were measured. GFR was measured every 6 months as 51Cr-EDTA clearance. Baseline values for blood pressure, renal function and albuminuria were identical in the two groups. The effect of both drugs on blood pressure was not significantly different. In the captopril treated patients MAP before and after 2 years was 110 ± 3 (SEM) and 100 ± 2 mm Hg, respectively and in the atenolol treated patients 105 ± 2 vs 101 ± 2 mm Hg . Both drugs reduced albuminuria and total proteinuria to the same extent. With captopril albuminuria decreased from 1549 (989-2399) to 851 (537-1380) mg/24 h and proteinuria from 2.5 (1.6-3.8) to 1.2 (0.8-1.8) g/24 h. With atenolol albuminuria decreased from 933 (603-1445) to 676 (437-1047) mg/24 h and proteinuria from 1.5 (1.0-2.4) to 0.9(0.6-1.5) g/24 h.

Monitoring kidney function in diabetic nephropathy.

Rossing P, Astrup AS, Smidt UM, Parving HH. Diabeteologia . 37: 1994 ; 708-12.

Progression in diabetic nephropathy is usually determined by repeated measurements of glomerular filtration rate and expressed as rate of decline in glomerular filtration rate. Our aim was to evaluate the agreement between rate of decline in glomerular filtration rate estimated from the Cockroft – Gault formula: (140-age)*K* body weight* (1/S-creatinine) and measured by the plasma clearance of 51 Cr-EDTA. All insulin –dependent diabetic patients with diabetic nephropathy followed-up for at least 5 years with at least 5 simultaneous measurements of glomerular filtration rate, s-creatinine and weight were included in the study. Forty-three

patients, (32 male/11 female), age 31 (18-61) years were enrolled. Observation period: 6.6 (5.1-9.9) years and number of investigations per patient 6 (5-16) (median (range)). Baseline glomerular filtration rate (ml/min) was 97 (30) measured and 107(37) estimated (mean (SD)) ($p < 0.001$) and the 95 % limits of agreement were –42.0 to 20.8 ml/min. Measured and estimated glomerular filtration rate correlated significantly ($r = 0.91$, $p < 0.00001$). Rate of decline in kidney function $ml.min^{-1}. year^{-1}$ was 4.7 (3.3) measured and 4.8 (3.5) estimated (mean (SD)), (NS), but the 95% limits of agreement showed a wide range –3.9 to 3.5 $ml.min_{-1}. year_{-1}$. A significant correlation between rate of decline in measured and estimated glomerular filtration rate was present ($r = 0.84$, $p < 0.00001$). In conclusion, glomerular filtration rate is overestimated by the Cockroft-Gault formula. The mean rates of decline in glomerular filtration rate are comparable, but the limits of agreement are wide, which make the Cockroft-Gault method unacceptable for clinical purposes, i.e. monitoring progression in kidney function in the individual patient.

NEUROLOGICAL COMPLICATIONS

1231-MIBG myocardial scintigraphy in diabetic patients: association with autonomic neuropathy.

Nagamachi S, Hoshi H, Ohnishi T, Jinnouchi S, Futami S, Watanabe K, Nakatsuru K, Toshimori T, Matsukura S. Kaku Igaku-Japanese Journal of Nuclear Medicine 1994; 31: 1059-69.

1231-metaiodobenzylguanidine (MIBG) myocardial scintigraphy was performed in 20 diabetic patients (NIDDM) and 8 control subjects to investigate the association between clinical autonomic nerve dysfunction and myocardial accumulation of MIBG. We used coefficient variance of R-R interval (CVR-R) as an index of the autonomic neuropathy and categorized diabetes into two groups (CVR-R $\geq$ 2.0: non-autonomic neuropathy. CVR-R < 2.0: autonomic neuropathy). In planar imaging studies, heart to mediastinum MIBG uptake ratio (H/M) was calculated on both early and delayed images. The washout ratio of 1231-MIBG in the heart (%WR) was also obtained using myocardial tracer activity on both the images. Mean value of these indices in diabetic group did not reveal any significant difference with the value in the control group. On the SPECT images, low uptake was observed in the posterior-inferior wall with normal uptake of 201TI in diabetic patients with non-autonomic neuropathy. These areas extended in patients with autonomic neuropathy. The mean value of count ratio of posterior-inferior to anterior wall (posterior-inferior/anterior ratio: PI/A) in the diabetic autonomic neuropathy group was significantly higher than in the control group on the both early and delayed images. And the mean value of regional % WR in the posterior –inferior wall calculated by both the MIBG SPECT images was significantly higher in the non-autonomic neuropathy group than in the control group. In the diabetic patients, retention mechanism of 123I-MIBG was considered to be involved at an early stage without autonomic nerve dysfunction clinically. As autonomic neuropathy progressed severely, uptake mechanism was also supposed to be involved. Therefore, 123I –MIBG myocardial scintigraphy was useful for early detection of cardiac sympathetic nervous dysfunction in diabetic patients.

Brain metabolism after recurrent insulin induced hypoglycaemic episodes: a PET study.

Chabriat H, Sachon C, *Levasseur M, Grimaldi A, Pappata S, Rougemont D, Masure MC, De Recondo A, Samson Y. Journal of Neurology, Neurosurgery and Psychiatry 1994; 57: 1360-5.*

Neuropsychological testing was carried out and the rate of oxygen metabolism in the brain was measured by PET in 15 highly selected patients with Type 1 diabetes. The aim was to investigate the impact on the brain of hypoglycaemic comas resulting from insulin treatment. No significant difference was found between nine patients with a history of more than 10 hypoglycaemic comas and six others who denied any history of such events. These data suggest that intensified insulin treatment, although increasing the frequency of hypoglycaemic coma, may not always be harmful for the brain. This may be explained by the limited duration of hypoglycaemic coma induced by conventional insulin treatment.

Clinical and neurophysiological study in diabetic children and adolescents.

Moglia A, Lorini R, D'Annunzio G, Lanzi G, Berardinelli A, Zandrini C. Functional Neurology 1994; 9 : 75-82.

We investigated 82 unselected insulin-dependent diabetes mellitus children and adolescents by clinical and electrophysiological evaluation to assess the frequency of diabetic neuropathy and to relate the results to age and height of patients, duration of illness and degree of metabolic control. Clinical abnormalities were found in about 1/3 of patients: these signs of diabetic neuropathy were related to the age and the duration of diabetes but not to the degree of metabolic control. Neurophysiological study showed alterations, especially of sensory nerve conduction. These results were seen to be related to height and age of patients and duration of illness but not the degree of metabolic control, probably due to the young age of the patients. Our study confirms that diabetic neuropathy is a heterogeneous disorder that may be caused by the interaction of host susceptibility and vascular, metabolic and perhaps environmental components also in diabetic children.

Association between "diabetic thick skin syndrome " and neurological disorders in diabetes mellitus.

Forst T, Kann P, Pfutzner A, Lobmann R, Schafer H, Beyer J. Acta Diabetologica 1994; 31 : 73-7.

Skin thickness on the extremities of patients with diabetes mellitus has been described controversially. Using high resolution ultrasonography, we were able to show a significant increase in skin thickness at the forearm ($P < 0.05$), thigh ($P < 0.001$) and lower limb ($P < 0.05$) of diabetic patients, most prominent at the thigh. No difference in skin thickness was found at the dorsum of the foot. In addition, skin thickness was not related to the duration of diabetes, age or HbA_1. A close association was found between diabetic neuropathy and increasing skin thickness. Diabetic patients with neurological disorders had a significant increase in skin thickness versus diabetic patients without neuropathy. The present findings suggest that diabetic neuropathy and abnormalities of connective tissue have a common aetiological link in their development or that both are time dependent processes. Whether changes in capillary blood flow, increase of nonenzymatic glycosylation, polyol accumulation or other metabolic disorders are responsible for these findings remains still to be established.

PSYCHOSOCIAL ASPECTS/EDUCATION/MOTIVATION

Attitudes and knowledge regarding contraception and pregnancy counseling in insulin dependent diabetes.

Gibb D, Hockey S, Brown LJ, Lunt H. New Zealand Medical Journal 1994; 107: 484-6.

Aims: To assess knowledge and attitudes of women with insulin-dependent diabetes to contraception, pre-pregnancy planning and genetic risk.

Method: Women with insulin-dependent diabetes, aged 18 to 40, were identified from a population based register of insulin users in

North Canterbury. Participating subjects underwent a structured face to face interview, assessing current contraceptive practices and their knowledge and attitudes to the areas outlined above.

R*esults:* One hundred and twenty four women, representing 86% of eligible women, agreed to participate. Eighty five subjects were using some form of contraception. The most popular choices were the combined oral contraceptive pill (35%), the progesterone only pill (12%), condoms (24%), vasectomy (12%) and tubal ligation (12%). All subjects recognized the importance of good blood glucose control during pregnancy. Thirty nine percent of subjects using contraception avoided the combined oral contraceptive pill because of concerns about metabolic and vascular side effects. Only 52% of subjects knew the correct figure for genetic risk of passing insulin-dependent diabetes on to an offspring.

Conclusion: Patient education regarding the need for pre-pregnancy planning in women with insulin dependent diabetes appeared adequate and the percentage of subjects using contraception was higher than that described in overseas diabetic populations. Over a third of subjects were however concerned about the risks of contraceptive options in insulin-dependent diabetes, particularly with regard to the use of the combined oral contraceptive pill. This finding suggests that discussion about the advantages and disadvantages of contraceptive choices should be an integral part of patient education for women with insulin-dependent diabetes mellitus of child-bearing age. Knowledge about genetic risk was inadequate in half the subjects interviewed and this area of patient education could also be improved.

Patient and physician analytic goals for self –monitoring blood glucose instruments.

Weiss SL, Cembrowski GS, Mazze RS. American Journal of clinical Pathology 1994; 102: 611-5.

The study's objective was to determine the maximum analytical error that is allowed in portable whole blood glucose meters. Interviews were conducted to derive personal reference values and significant deviations from these values for the limit of hypoglycaemia, the limit of hyperglycaemia and the upper and lower limits of acceptable blood glucose for physicians and patients with diabetes at the Park Nicollet Medical Center, Minneapolis, Minnesota. Fifty patients with diabetes (30 Type 1 and 20 Type 2), and 43 physicians (14 endocrinologists, 14 family practitioners, and 15 general internists) were enrolled in the study. The results showed no significant differences between Type 1 and Type 2 diabetic patient responses. Nor were there significant differences among family practitioner, internist and endocrinologist responses for any of the parameters (the limit of hypoglycaemia, the limit of hyperglycaemia, the upper and lower limits of acceptable blood glucose for the patient and corresponding allowable coefficients of variation at each of these glucose levels). There were significant differences when patients were compared to physicians. Physicians require the highest degree of precision at the limit of hyperglycaemia (8.4 ± 0.28 mmol/l [150.8 ± 5.1 mg/dl]), with a maximum allowable coefficient of variation (CV) of 7 %, a CV significantly lower than that of the patients (CV =10 %). Patients require the highest precision for glucose concentration around the lower acceptable limit (4.7 ± 0.13 mmol/l [B4.1 ± 2.5 mg/dl]), with an allowable CV of 8%, a CV significantly lower than that of the physicians (CV = 14%). The authors conclude that the accuracy required by patients and physicians at normal and higher glucose concentrations is achievable by currently available meters. Manufacturers should ascertain that glucose measurements are optimally accurate at glucose levels of 4.7 mmol/L (84.1 mg/dl) and have CVs no higher than 7%.

Do doctors address the concerns of patients with diabetes?

Benett IJ. Diabetic Medicine 1994; 11: 586-9.

Diabetes has an impact on people at both a biomedical and a holistic level. Furthermore there is a legitimate and substantial 'medical agenda' which doctors must address. But does this mean that they fail to deal with the concerns of their patients? A questionnaire study of diabetic patients attending the Manchester Diabetes Centre found that not all the patients' concerns were addressed in 25.5% of consultations. Two hundred and twenty (98%) patients were recruited from 225 approached. Not surprisingly, those who expressed three or more concerns were significantly less likely to have all their concerns addressed compared with those who had only one or two concerns (P = 0.001). The probability of having an individual concern addressed was 0.82. It was also found that Black-Caribbeans were significantly less likely to have their concerns addressed than Whites especially if they were over 60 years old (P = 0.03). This study concludes that doctors should be particularly aware of the needs of patients who express many concerns and especially if they are Black-Carribbeans. Further research should develop strategies for improving the ability of doctors to identify and address the concerns of their patients.

A method to measure quality of diabetes treatment: results from an outpatient clinic.

Sando dSH, Hagen C, Beck-Nielsen H. International Journal for Quality in Health Care 1994; 6: 47-54.

It is essential for patients, hospital staff and hospital administrators to know the quality of hospital care. We have developed a system to evaluate the quality in an outpatient clinic. The aims of this study are: to develop a system for quality monitoring of outpatient diabetes care, to evaluate the effectiveness of this system and to develop procedures for feedback to the patients and the staff. In this paper we report on the results related to the first two aims. The metabolic control of diabetes mellitus is evaluated by measurement of serum HbA_1C, serum triglyceride, serum total cholesterol, body weight and blood pressure and the result is used in the calculation of a metabolic score. Diabetic nephropathy and retinopathy are evaluated once a year according to international classifications. The data were collected from 1 January to 31 December 1991. We were able to collect data on HbA_1C in 94% of the diabetic patients, but we obtained data in only 46-75% of the patients for all other parameters. Concerning glycaemic regulation, 52.3% of the insulin-dependent diabetes mellitus patients and 41.5% of the non-insulin-dependent diabetes mellitus patients had poor regulation. The results for the parameters included in the metabolic score were more satisfactory. There was a significant correlation between the number of days the patients were in hospital and the HbA_1C value. In conclusion, the system enables us to determine the degree of metabolic regulation and regular evaluation of diabetic late complications. Through the measurement of outcome parameters, we have discovered failure in process quality in our hospital department.