ABSTRACT SERVICE

ETIOLOGY

Microsatellite polymorphisms at the glucokinase locus: a population association study in Caucasian type 2 diabetic subjects.

Hattersley AT, Saker PJ, Cook JT, Stratton IM, Patel P, Permutt MA, Turner RC, Wainscoat JS. Diabetic Medicine. 1993;10:694-8.

Glucokinase has a central role in glucose metabolism in pancreatic beta cells and hepatocytes and is an important candidate gene for Type 2 diabetes. Mutations of the glucokinase gene have been reported in Caucasian pedigrees with maturity-onset diabetes of the young and late onset Type 2 diabetes. In population studies of American blacks and Mauritian Creoles and association between alleles of a glucokinase polymorphism and Type 2 diabetes has been described. Two microsatellite polymorphisms (GCK 1 and GCK 2) flanking the glucokinase gene were investigated in Caucasian subjects. There was no significant linkage disequilibrium between the alleles of the two polymorphisms. The overall allelic frequencies for GCK 1 and the combined haplotyes did not significantly differ between 95 Type 2 diabetic and 76 mnormoglycaemic subjects. In an expanded cohort of 151 diabetic subjects the allelic frequencies at GCK 2 were also similar to controls. These results suggest that a singly mutation of the glucokinase gene is not a common cause of Type 2 diabetes in English Caucasians.

Localisation of a type 1 diabetes susceptibility locus to the variable tandem repeat region flanking and insulin gene.

Owerbach D, Gabbay KH. Diabetes. 1993;42: 1708-14.

A susceptibility gene for type 1 diabetes is present on chromosome 11p 15.5, but its location , identity, and mechanism of action are unknown. We have sequenced 14 kilobases of DNA flanking the human insulin gene and found new DNA polymorphisms and determined their frequencies in the general population site of transcription of the insulin gene, when present in the homozygous state, provides a relative risk for type 1 diabetes of 5.2 (P = 0.006). However, this DNA polymorphism as well as other diabetes – associated 3 markers are in linkage-disequilibrium with the actual susceptibility region, because these polymorphisms are found on haplotypes both positively and negatively associated with type 1 diabetes susceptibility. Nucleotide sequence analysis of the variable tandem repeat elements associated with these haplotypes to differ greatly in composition, i.e. , an ATAGGGGTGTGGGG repeat element is absent on a haplotype associated with type 1 diabetes susceptibility, but is found in 6-10 copies on two haplotypes negatively associated with the disease. These findings suggest that the type 1 diabetes susceptibility locus on chromosome 11p 15.5 is probably located in the 5' variable tandem repeat region rather that in 3' region of the insulin gene.

Decreased risk of type I diabetes in offspring of mother who acquire diabetes during adrenarchy

Bleich D, Polak M, Eisenbarth GS, Jackson RA. Diabetes. 1993;42:1433-9.

Fathers with type I diabetes transmit diabetes to their offspring 2-3 times more frequently than mothers with type I diabetes. This phenomenon has provoked both genetic and nongenetic hypotheses, but the mechanism remains obscure. We find that mothers who develop diabetes before age 8 transmit diabetes at the same rate as diabetic fathers, and that the sex difference in diabetes transmission is explained by a decreased transmission rate in mothers who acquired diabetes after age 8. We constructed a data base containing 2156 nondiabetic and diabetic offspring of parents with type I diabetes. Families we selected from our main data base, which contains demographic information and diabetes autoantiobody test results on > 8000 first-degree relatives of patients with type I diabetes and diabetic probands. Identification of offspring was made through diabetic parents who had participated in our autoantibody screening program at the Joslin Diabetes Center between 1983 and 1990. Questionnaires were sent to all other family members to determine the number of diabetic and nondiabetic offspring in each family. The 20-yr life-table risk of diabetes in offspring of diabetic fathers and mothers is 8.9 + /- 1.0 and 3.4 + /- 0.6%, respectively. For mothers acquiring diabetes before or after age 8, the risk of diabetes in offspring is 13.9 + /- 4.4 and 2.4 + /- 0.6% at 20yr of age, respectively. Further-more , we find that duration of diabetes in mothers before pregnancy has no effect on the risk of diabetes in their offspring.

Lack of immune responsiveness to bovine serum albumin in insulin-dependent diabetes.

Atkinson MA, Bowman MA, Kao KJ, Campbell L, Dush PJ, Shah SC, Simell O, Maclaren NK. New England Journal of medicine. 1993;329:1853-8.

BACKGROUND. Epidemiologic studies have implicated the ingestion of cow's milk in the pathogenesis of insulin-dependent diabetes mellitus(IDDM). Moreover, in a recent study, 100 percent of patients with new-onset IDDM had antibodies against 17-amino-acid BSA peptide (ABBOS). Cellular immune mechanisms are thought to be the principal mediators of pancreatic beta-cell destruction in IDDM. METHODS. We measured the responses of peripheral-blood mononuclear cells to BSA and ABBOS or serum IgG anti-BSA antibodies (by particle-concentration fluorescence immunoassay) in 71 patients with IDDM, 55 subjects at various degrees of risk for IDDM, 36 patients with other autommune disorders (chronic autommune thyroditis, rheumatoid arthritis, and systemic lupus erythematosus), and 48 normal subject. RESULTS. The responses of peripheral-blood monouclear cells to BSA or ABBOS were positive in 2 of 24 patients with new-onset IDDM, 1 of 25 first-degree relatives of patients with IDDM who were negative for islet-cell antibodies, 2 of 30 first-degree relatives of patients with IDDM who were positive for islet-cell antibodies, 1 of 28 patients with established IDD, and 1 of 29 normal subjects . Similarly, anti-BSA antibodies were not detected significantly more often in patients with new-onset IDDM (3 of 31, 10 percent) than in normal subjects (1of 37, 3 percent; P = 0.32). However, many patients with autommune disease and subjects at increased risk for IDDM had anti-BSA antibodies (frequency, 10 to 31 percent). CONCLUSIONS. Anti-BSA antibodies may reflect a general defect in the process of immunologic tolerance associated with a predisposition to autoimmunity rather that immunity specific to beta cells. The absence of cellular immunity to BSA and ABBOS in IDDM does not support a role for this antigen in the pathogenesis of the disorder.

PATHOPHYSIOLOGY

Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus. Prospective studies of Pima Indians.

Lillioja S, Mott DM, Spraul, Ferrao R, Foley JE, Ravussin E, Knowler WC, Bennett PH, Bogardus C. New England Journal of Medicine. 1993;329:1988-92.

BACKGROUND. The relative roles of obesity, insulin resistance, insulin secretory dysfunction, and excess hepatic glucose production in the development of non-insulin-dependent diabetes mellitus (NIDDM) are controversial. We conducted a prospective study to determine which of these factors predicted the development of the disease in a group of Pima Indians. METHODS. A body - composition assessment, oral and intravenous glucose-tolerance tests, and a hyperinsulineamic-englycemic clamp study were performed in 200 non-diabetic Pima Indians [87 women an d113 men; mean (+ / -SD) age, 26 + / -6 years]. The subjects were followed yearly thereafter for an average of 5.3 years. RESULTS. Diabetes developed in 38 subjects during follow-up. Obesity, insulin resistance(independent of obesity), and low acute plasma insulin response to intravenous glucose (with the degree of obesity and insulin resistance taken into account) were predictors of NIDDM. The six year cumulative incidence of NIDDM was 39 percent in persons with values below the median for both insulin action and acute insulin response 27 percent in those with values below the median for insulin action but above that for acute insulin response, 13 percent in those with values above the median for insulin action and below that for acute insulin response and 0 in those with values originally above the median for both characteristics CONCLUSIONS. Insulin resistance is a major for the development of NIDDM. A low acute insulin response to glucose is an additional but weaker risk factor.

Different sensitivity of glucose and amino acid metabolism to insulin in NIDDM.

Luzi L, Petrides AS, De Fronzo. RA. Diabetes. 1993;42:1868-77.

NIDDM subjects are characterized by impaired glucose tolerence and insulin resistance with respect to glucose metabolism. To examine whether the defect in glucose utilization extends to amino acid metabolism 6 NIDDM subjects (64 + /- 4 yr of age; ideal body weight of 107 + /- 3%) and 7 control subjects (58 + /- 4 yr of age; ideal body weight of 105 +/- , in combination with [1-14c] leucine and indirect calorimetry. All subjects participated in two studies. In study 1, agter 3 h of tracer equilibration , a 3-h insulin clamp (40 mU. M-2 X min-1) was performed to define the effect of insulin o n leucine kinetics and glucose metabolism. In study 2, subjects received a repeat 3-h insulin clamp, and a balanced amino acid solution was infused to increase the plasma amino acid concentrations approximately 2-fold to examine the effect of combined physiological hyperinsulinemia – hyperaminoacidemia on the rate of leucine and glucose disposal. Insulin-medicated total body glucose uptake was significantly reduced in NIDDM during both study 1 (5.6+ /- 0.4vs 6.9 + / - 0.6 mg. Kg-1 X min-1, P < 0.01) and study 2 (5.2 + /-0.4vs6.8 + / -0.6, P< 0.01). Basal plasma leucine (120 + / - 10 vs 123 + / - 11 microM) and alpha-ketoisocproic acid concentrations (28 + / - 3 vs. 25 + / - 2 microM) were similar in NIDDM and control subjects, respectively. In contrast the basal plasma glujcose concentration (8.9 + / - 0.8 vs.4.7+ / - 0.2 microM) and the HbA1c (8.5 + / - 0.2 vs. 5.7 + / - 0.2%) were significantly increased in NIDDM (P< 0.01). In the postabsorptive state, endogenous leucine flux, leucine oxidation, and nonoxidative leucine disposal were similar in NIDDM and control subject. When insulin was infused without amino acids (study 1), the decrement in plasma leucine (53 + /- vs. 48 +/-4 microM), endogenous leucine flux (13 +/- 2 vs. 11 + /- 1 mumol. M-2 X min-1), leucine oxidation (1.6 + /- 0.2 vs. 1.3 + /- 0.1 mumol. M-2 X min-1), and nonoxidative leucine disposal (10 +/- 0.1 vs. 8 + /-1 mumol. M-2 X min-1) was comoparable in both groups. During combined insulin and amino acid infusion (study 2) , plasma leucine concentration (185+ /- 20 vs. 190 + /- 15 microM) rose similarly in NIDDM and control subjects.

Insulinresistance in insulin-dependent diabetic patients with microalbumiinuria (see comments).

Yip J, Mattock MB, Morocutti A, Sethi M, Trevisan R, Viberti G. Lancet. 1993;342:883-7.

In insulin-dependent diabetes , microalbuminuria increases the risk of cardiovascular and renal disease. By means of euglycaemic hyperinsulinaemic clamp method, we measured total body glucose utilization rate and studied the interaction of this measure of insulin sensitivity with known risk factors for cardiovascular disease in 14 diabetic patients with microalbuminuria and 14 with normal albumin excretion (median albumin excretion rate [AER] 56.2 [range 39.2-80.6] vs 8.8 [7.4-10.7] micrograms per min). The two groups were of similar age, duration of diabetes, and body-mass index. Total-body glucose disposal rate was significantly lower in the patients with microalbuminuria than in those without (mean 7.86 [SD 1.40] vs 9.04 [0.90] mg/kg per min; p< 0.05). There were also significant differences between the groups in the daily insulin dose needed for equivalent glucose control (0.76 [0.20] vs 0.65 [0.10] U/kg, p < 0.05), mean systolic blood pressure over 24 h ambulatory monitoring (134[7] vs 127 [7] mm Hg; p < 0.05), and various plasma lipid concentrations, contributing to a more atherogenic profile in the microalbuminuric group. Total body glucose disposal rate was inversely correlated with body mass index and log10 AER. The insulin sensitivity of the microalbuminuric group remained impaired agree adjustment for blood pressure and body-mass index. Impaired insulin sensitivity is a feature of insulin-dependent diabetic patients with microalbuminuria, which adds, with other factors, to the increased risks of renal and cardiovascular disease in these patients.

Repair of pancreatic beta-cells. A relevant phenomenon in early IDDM?

Eizirik DL, Sandler S, Palmer JP. Diabetes. 1993;42:1383-91.

Most studies dealing with the pathogenesis of IDDM have emphasized the immune assault beta-cells. In this perspective , we review the data that suggest that the beta-cell destruction of IDDM depends on a balance between beta-cell damage and repair. The progressive beta-cell damage leading to IDDM seems to follow markedly different temporal courses in individual patients. Some individuals at high risk for developing IDDM, and presenting with impaired beta-cell function, appear to recover beta-cell function when followed prospectively. Moreover, after the clinical onset of IDDM, most patients experience a transitory period of improved insulin secretion. In vitro and in vivo experimental data suggest that beta-cells are indeed able to repair themselves after damage. Dispersed after a toxic assault. Furthermore, the abnormal insulin release and glucose oxidation of islets isolated from NOD mice during the prediabetic period is completely restored after 1 wk in tissue culture. Finally, treatment of NOD mice with monocional antibodies directed against infiltrating T-cells reverse the altered glucose metabolism of beta-cells. Note that beta-cell repair after exposure to different toxic agents can be enhanced both in vivo and in vitro. Potential enhancers of beta-cell repair are nicotinamide, glucose, protein-rich diets, and branched chain

amino acids. A basic question that remains to be answered is the nature of the repair mechanisms triggered by beta-cells.

Sulphatide and sulphatide antibodies in insulin-dependent diabetes mellitus.

Buschard K, Josefesen K, Horn T, Fredman P, Lancet. 1993;342:840.

Insulin-dependent diabetes mellitus (IDDM) is associated with neurological disorders. Sulph I, a monoclonal antibody to sulphatide (a neural epitope), stained secretory granules in alpha and beta cells of rat islets of Langerhans, but not exocrine tissue. Sera from 88% of 57 newly diagnosed IDDM patients was anti-sulphatide positive, and 76% were positive 6 months later. All 135 healthy controls were negative. Sulphatide antibody may be an IDDM marker.

Inhibition of lipolysis decreases lipid oxidation and gluconeogensis from lactate but not fastin ghyperglycemia or total hepatic glucose production in NIDDM.

Puhakainen I, Yki-Jarvinen H. Diabetes.1993;42:1694-9.

We determined whether overnight inhibition of lipolysis by a long-acting nicotinic acid derivative (acipimox) decreases gluconeogensis from lactate in NIDDM patients. For this purpose, 250 mg of acipimox or placebo was administered in a double-blind crossover study at 2400,0400, and 0800 to 8 NIDDM patients (54 +/- 4 yr of age, body mass index 29.5 mM). The next morning, total hepatic glucose production (glucose Ra) and gluconeogensis fromlactate were determined using primed, continuous infusions of [3-3H] glucose and [U-14C] acetate. Glucose and lipid oxidation rates were measured using indirect calorimetry. Mean overnight serum free fatty acid concentrations averaged 242 +/- 8 microM after acipimox and 721 +/- 30 microM after placebo (P< 0.001). Inhibition of lipolysis decreased lipid oxidation from 33 + /- 3 to 22 + /- 2 J. kg-1 Xmin-1(P < 0.001) and increased carbohydrate oxidation from 15 +/- 3 to 23 + /- 2 mumol. Kg-1 min-1 (P< 0.005). Gluconeogensis from lactate decreased by approximately 40% from 6.2 +/- 0.6 to 3.8 +/- 0.5 mumol. Kg-1 X min-1 (P <0.005); lactate oxidation increased from .6 +/- 0.8 to 7.9 +/- 1.1 mumol kg-1X min-1 (P<0.005), with no change in plasma lactate concentrations or total lactate Rd. Fasting plasma glucose concentrations were comparable at 2400 (10.0 +/- 1.1 vs. 10.6+/-1.3 and 11.3 + /- 1.3 mM, respectively) also, total glucose production rates remained unchanged (14.0 +/- 1.2 vs 14.9 +/- 1.3 mol. Kg-1 X min-1, respectively).

EPIDEMIOLOGY

Diabetes registers: a grassroots approach.

Howitt AJ, Cheales NA. BMJ 1993;307:1046-8.

OBJECTIVES—To compile a register of diabetic patients within the catchment area of a district general hospital ad evaluate the characteristics of the population using aggregated data from a general practice audit. DESIGN—Cross sectional study. Practices identified all known diabetics and completed a questionnaire from information in each patient's medical record. SETTING- Practices affiliated to a district audit group in south east England. MAIN OUTCOME MEASURE – Number of participating practices; prevalence of diabetes and its complications; and sex distribution of patients, age at diagnosis and similar data from other studies. RESULTS—41 out of 43 practices participated, and 2574 diabetic patients were identified (prevalence 1.18%). 52.4% of patients were male. The mean age was 61.6 years. 32% patients were treated with insulin, 51.5% with oral hypoglyucaemic agents, 16.5% with diet alone. The mean random blood glucose concentration was 10.4 mmol/l and glycosylated haemoglobin 10.1%. 8% had proteinuria, 7% a history of myocardial infarction, 5% a history of stroke, and 2% a diabetes related amputation. These proportions were not significantly different from those found in studies performed by different methods in Poole, Islington, Powys, Trowbridge, and Southall.

CONCLUSION – It is feasible to compile a register of diabetic patients in a district and evaluate their characteristics by using only general practice sources.

A review of the recent epidemiological data on the world-wide incidence of type 1 (insulin-dependent) diabetes mellitus. World Health Organization Diamond Project Group.

Karvonen M, Tuomilehto J, Libman I, LaPorte R. Diabetologia. 1993; 36:883-92.

Nearly 70 registries from more than 40 countries have collected and published incidence data of childhood Type 1 (insulin-dependent) diabetes mellitus up to the end of the 1980s. The majority of incidence data comes from regions of high incidence i.e. from Europe and North America. All these published data facilitate the descriptive comparison of incidence and variation of the occurrence of Type 1 diabetes roughly throughout the northern hemisphere. The aim of this paper is to review and compare the most recent epedemiology data on the incidence of Type 1 diabetes among children under the age of 15 years. A clear difference in incidence appeared between northern and southern hemisphere with no countries below the equator having an incidence greater than 15.0 per 100,000. In contrast above the equator the disease is common. Between continents the variation in incidence showed that the lowest incidence were found in Asia, followed by Oceania (Australia and New Zeland), South and North America, and the highest rates were in Europe. The incidence varied from 0.6 per 100,000 in Korea and Mexico to 35.3 per 100,000 in Finland showing prominent worldwide variation in incidence of Type 1 diabetes. The largest intracontinental variation incidence appeared in Europe, varying from the highest in Finland to the lowest (4.6 per 100,000) in northern Greece. ?The highest incidence in the world was in northern Europe, but within the continent scale there were some striking exceptions from the overall level of incidence.

Problems related to definitions and epidemiology of type 2 (non-insulin-dependent) diabetes mellitus: studies throughout the world.

Alberti KG. Diabetologia. 1993;36:978-84.

Many studies of Type 2 (non-insulin-dependent) diabetes mellitus assume that the condition is homogeneous and clearly defined. There are, however, several problems with these assumption. Thus, definition of Type 2 diabetes is one of exclusion of other types (insulin-dependent, malnutritions-related, gestational and other rate types) and inevitably contains a heterogeneous group of disorders the aetiology of which is largely unclearly, and separation from the insulin-dependent type can be problematic. Diagnosis is also imprecise in asymptomatic subjects due to the lack of accurate glucose tolerance. An alternative to the oral glucose tolerance test is urgently needed. Epidemilogical studies of Type 2 diabetes and it complications are also fraught with difficulties due to variability of the oral glucose tolerance test, potential problems in glucose measurement, heterogeneity, population selection and problems in international comparisons due to differing age structures and life expectancy. Great care is needed in all studies of Type 2 diabetes to ensure that the groups under study are properly selected, well-defined and fully described.

Incidence of insulin-dependent diabetes mellitus in young adults: experience of 1,587,630 US Navy enlisted personnel.

Gorham ED, Garland FC, Barrett-Connor E, Garland CF, Wingard DL, Pugh WM. American Journal of Epidemiology. 1993;138:984-7.

First hospitalizations (n = 1,293) for diabetes mellitus between 1974 and 1988 were used as a surrogate for insulin-dependent diabetes mellitus incidence among 17-34 year-old US Navy enlisted personnel followed for 6,077,856 person-years. In the 15-yer period, the overall incidence of insulin-dependent diabetes mellitus was 21.3 per 100,000 person-years. Incidence did not differ significantly by sex, but was higher for blacks than whites (28.4 vs 20.2 per 100,000 person-years, respectively; $p < 0.05$). Incidence increased with age threefold for white men and five fold for black men ($p < 0.005$) between the ages of 17-19 and 30-34 years.

Availability of type II diabetic families for detection of diabetes susceptibility genes.

Cook JT, Page RC, O'rahilly S, Levy J, Holmam R, Barrow B, Hattersley AT, Shaw AG, Wainscoat JS, Turner RC. Diabetes. 1993;42:1536-43.

Type II diabetes is a familial disorder, as evidenced by the increased prevalence in monozygotic cotwins and first-degree relatives of affected subjects; however, its genetic etiology is largely unknown. Well-characterized pedigrees are an essential resource for the study of susceptibility genes for type II diabetes . This study describes a 5-yr search for type II diabetic families in Oxfordshire, U.K. We interviewed 950 type II diabetic subjects concerning the availability of first-degree relatives; 127 Caucasian families ascertained through a proband with type II diabetes were studied, and 589 first-degree relatives were characterized. Three large pedigrees with maturity-onset diabetes of the young, and 8 multiplex multigenerational type II diabetic pedigrees were identified. We identified 12 sibpairs in which both siblings had type II diabetes; however, only 7 sib-pairs had both parent alive, and 2 of these had both parents affected. If one also considers one sib having diabetes and one sib have glucose intolerance as being an affected sib-pair, we identified 30sib-pairs of which 7 had both parents affected and probably had bilineal inheritance. We identified 76 complete nuclear families with both parents and offspring available for study, but only 6 were of optimal structure for link-age analysis. In conclusion, multiplex pedigrees and type II diabetic sib-pairs with living parents are uncommon, and their ascertainment requires a substantial investment of resources. Large-scale collaborative multicenter initiatives would be needed to collect a large resource of family material for the study of susceptibility genes for type II diabetes.

MONITORING CONTROL

Elevated long-term glycated haemoglobin precedes proliferative retinopathy and nephropathy in type 1 (insulin-dependent) diabetic patients.

Kullberg CE, Arniqvist HJ. Diabetologia. 1993;36: 961-5.

The importance of glycaemic control for the development of proliferative retinopathy and nephropathy was assessed by monitoring glycated haemoglobin for 5 years or more before the diagnosis of theses complications. The study comprised Type 1 (insulin-dependent) diabetic patients diagnosed at an age less than 31 years, and with diabetes duration 25 years or less. They were followed for an average of 7.9 years with 3.3 measurements per year. Of 172 patients screened for retinopathy 60 had no retinopathy, 104 had background retinopathy , and 8 had proliferative retinopathy. The mean HbAIc (95% confidence intervals) of the groups was 6.4% (6.2-6.7%), 7.3% (7.1-7.5%) and 8.9% (8.1-9.6%), respectively ($p < 0.0001$);the mean duration of diabetes was 12, 18, and 17 years. Of 186 patients 7 had nephropathy (albuminuria more than 200 mg/l). Mean HbA1c in patients without nephropathy was 7.0% (6.8-7.1%) and in patients with nephropathy 8.8% (7.8-9.9%, $p < 0.001$). Mean diabetes duration was 16 years in both groups . Multiple logistic regression including mean HbA1c , age at onset, duration, sex, and hypertension, was for both proliferative retinopathy and nephropathy significant only for mean HbA1c. In all cases , proliferative retinopathy and nephropathy were preceded by poor glycaemic control over several years, suggesting that these complications are caused by poor glycaemic control.

TREATMENT

Short-term effects of recombinant human insulin-like growth factor I on metabolic control of patients with type II diabetes mellitus.

Schalch DS, Turman NJ, Marchsisin VS, Hefferman M, Guler HP, Journal of Clinical Endocrinology & Metabolism. 1993; 77:1563-8.

Recombinant human insulin-like growth factor I (rhIGF-I) lowers blood glucose, serum insulin, C-peptide, and lipid levels in healthy and diabetic animals and humans. We hypothesized that rhIGF-I might control blood glucose levels and concomitaltly reduce pancreatic insulin secretion in patients with type II diabetes. If true, rhIGF-I might serve as a therapeutic agent that could mitigate some of the detrimental effects of hyperinsulinemia secondary to insulin resistance in these patients. In this study, we treated 12 patients with type II diabetes mellitus twice daily for 5 days with sc hrIGF-I in doses of 90, 120, or 160 micrograms/kg body weight. Metabolic parameters in the fasting and postprandial states were assessed during a 3-day follow-up period, respectively. Administration of rhIGF-I significantly reduced mean(+ /- SD) concentrations of fasting blood glucose (12.3 + /- 4.5 to 9.1 + /- 2.6 mmol/L), serum insulin (98 + /- 52 to 56 + /- 27 pmol/L), and /C-peptide (993 +/- 298 to 728 + /- 232 pmol/L). It also decreased postprandial (area under the curve) blood glucose ((32.5 + /-12.7 to 23.9 + /- 8.1 mmol/L.h), serum insulin (1102 + /- 707 to 467 + /- 332 pmol/L.h), and C-peptide (5958 + /- 2747 to 3442 + /- 1523 pmol/L.h). The administration of rhIGF-I was also associated with a small but significant reduction in serum triglycerides ((6.76 + /- 3.45 to 5.32 + /- 2.59 mmol/L) and total cholesterol (6.13 + /- 1.25 to 5.66 + /- 1.20 mmol/L), 24-h creatinine clearance increased significantly (85 + /- 30 to 133 + /- 51 mL/min), and microalbuminuria was unchanged. Although rhIGF-I was reasonably well tolerated, side effects included low-grade edema, mild and mainly asymptomatic orthostatic hypertension, and bilateral temporomandibular tenderness. We conclude that short-term treatment of type type II diabetic patients with rhIGF-I favorably affects metabolic control and enhances kidney function. An assessment of the risk/benefit ratio of rhIGF-I administration to this group of patients awaits extended experiments.

INSULIN

The effect of intensive insulin therapy on the insulin-regulatable glucose transporter (GLUT4) expression in skeletal muscle in type 1 diabetes.

Andersen PH, Vestergaard H, Lund S, Vedel P, Junker S, Kahn BB, Pedersen O. Diabetic Medicine. 1993; 10:699-706.

Studies in normal man and rodents have demonstrated that the expression of the dominant glucose transporter in skeletal muscle, GLUT4, is regulated by insulin at supraphysiological circulating levels. The present study was designed to determine whether intensified insulin replacement therapy for 24 h given to patients with Type 1 diabetes in poor metabolic control was associated with an adaptive regulation of GLUT4 mRNA and protein levels in vastus lateralis muscle. Nine Type 1 diabetic patients with a mean HbA1c of 10.3% were included in the protocol. After intensified treatment with soluble insulin for 24h the fasting plasma glucose concentration decreased from 20.8 + /- 2.3 (SD) to 8.7 + /- 2.3 mmol 1-1, whereas the fasting serum insulin level increased from 0.06 + /- 0.02 to 0.17 + /- 0.09 nmol 1-1. However, despite a 2.8-fold increase in serum insulin levels and more than a halving of the plasma glucose concentration for at least 15 h no significant alterations occurred in the amount of GLUT4 protein (0.138 + /- 0.056, poor control vs 0.113 + /- 0.026 arb. Units, improved control, p = 0.16) or GLUT4 mRNA (96432 + /- 44985, poor control vs 81395 + /- 25461 arb. Units, improved control, p = 0.54). These results suggest, that in spite of evidence that high insulin levels affect GLUT4 expression in muscle, changes in serum insulin within the physiological range do not play a major role in the short-term regulation of GLUT4 expression in Type 1 diabetic patients.

Insulin treatment, time-zones and air travel: a survey of current advice from British diabetic clinics.

Gill GV, Redmond S. Diabetic Medicine, 1993; 10: 764-7.

To investigate current advice given to insulin-treated diabetic patients undertaking international flights crossing time-zones, we have conducted a survey of UK physicians running diabetic clinics. Consultants were asked to give the general advice they would give to travelers on twice-daily short-and intermediate acting insulin in four different flight situations: westward London to New York (morning and evening departure) and eastward Manchester to Singapore (morning and evening departures). Response rate was poor (37%). Six percent of replies were unhelpful (e.g. 'ringthe BDA', 'carry on as usual'), and 14% liable to cause hypoglycaemia. Thirteen percent advocated change to a 'basal-bolus' system of insulin administration. The rest used variants of additional insulin for westward flights and reduced flights eastward. There was great variation in advice, and many regimens were excessively complicated. We recommend simple individualized advice, without attempts at over-zealous glycaemic control during travel. Locan arrival and departure times may fit in easily with insulin and means at standard times before and after flying, and little or no dosage alteration may be needed.

Intensive insulin therapy and weight gain in IDDM.

Carlson MG, Campbell PJ. Diabetes. 1993'42:1700-7.

Intensive insulin therapy is frequently complicated by excessive weight gain. The purpose of this study was to determine the cause and composition of this weight gain. Therefore, changes in body composition, energy expenditure, glycosuria, and substrate kinetics were evaluated in patients with IDDM who transferred from conventional insulin therapy to intensive insulin therapy. Six adult patients with IDDM were studied on conventional insulin therapy and after 2 mo of intensive insulin therapy while maintaining constant caloric intake and were compared with a group of 6 matched nondiabetic volunteers. Body composition was determined by underwater weighing. Energy expenditure was measured during 24-h stays in a whole-room calorimeter. Whole-body turnover rates of glucose, glycerol, palmitate, and leucine were determined by isotope dilution methods. Intensive insulin therapy lowered the mean daily blood glucose concentration and HbA1 (14.8 + /- 1.6 to 7.7 + /- 0.6 mM and 12.9 + /- 0.9 to 9.6 + /- 0.6%, both P < 0.01) and almost eliminated glycosuria (428 + /- 116 to 39 + /- 22 mmol/day, P < 0.05). Body weight increased 2.6 + /- 0.8 kg with intensive insulin therapy (P < 0.05) as a result of an increase in fat mass (2.4 + /- 0.8 kg, P < 0.05). Daily energy expenditure decreased 5% (118 = /- 32 kcal/day) with intensive insulin therapy (P < 0.05). The rates of glucose, glycerol, free fatty acid, and leucine turnover, triglyceride/free fatty acid cycling, and nonoxidative glucose and protein disposal were reduced in the diabetic volunteers during intensive insulin therapy.

Influence of combined C-peptide and insulin adminstration on renal function and metabolic control in diabetes type 1.

Hohansson BL, Kernell A, Shoberg s, Wahren J, Journal of Clinical Endocrinology & Metabolism. 1993; 77:976-81.

The possible influence of C-peptide on renal function and metabolic control in patents with type 1 diabetes was examined in a double blind, randomized study. Nine patients received insulin and equimolar amounts of biosynthetic human C-peptide for 1 month (group 1), and nine were given insulin only (group 2). C-peptide levels in plasma ranged from 0.3-2.6 nmol/L in group 1 during the study, whereas group 2 had undetectable levels. The urinary excretion of albumin in group 1 was 21 + /- 6 micrograms/min before the study and decreased by 40% and 55% after 2 and 4 weeks, respectively (P < 0.05) . No change was seen in group 2. The glomerular filtration rate fell by 6% after 2 and 4 weeks (P <0.05) in group1, whereas n change was observed in group 2. Fluorescein leakage across the blood-retinal barrier decreased by 30% in group 1 (P < 0.05) and was unaltered in group 2. Haemoglobin-A1c and fructosamine values decreased by 9-16% in group 1 (P <0.05), but not in group 2. The findings suggest that administration of C-peptide plus insulin, compared to insulin alone, to type 1 diabetic patients may reduce glomerular permeability and improve metabolic control.

DIET

Application of physicians' predictions of meal and exercise effects on blood glucose control to a computer simulation.

Hauser T, Campbell LV, Kraegen EW, Chishoim DJ. Diabetic Medicine. 1993;1-:744-50.

Our aim was to develop a computer simulator program that allows patients to practice insulin dose and dietary adjustment on a day of planned exercise, shows the resulting blood glucose response in an average diabetic patient. The degree of blood glucose change predicted by the program was determined from changes predicted by five local specialists in seven hypothetical scenarios involving exercise + /- dietary or insulin dose adjustments. The program was then tested against 18 outside specialists' responses in 7 different scenarios. The program simulates the 24 h glycaemic response after 45 min mild or moderate exercise starting 2 h after meals, as well as changes to this response induced by alterations in dietary carbohydrate and/or insulin dose. Coefficients of variation of specialists' blood glucose predictions were greater for exercise (35% local, 31% outside specialists) than dietary change (7% local, 10% outside specialists ; p = 0.002-0.04). The program's predicted change in blood glucose levels in the seven scenarios correlated well with the outside specialists' corresponding mean predictions (r = 0.97; p = 0.0001). We

conclude that specialists are less consistent in predicting glycaemic change with exercise than with dietary alteration. Nevertheless it is possible to represent their predictions in a computerized simulator for diabetic patient education.

Long-term effects of guar gum in subjects with non-insulin-dependent diabetes mellitus.

Groop PH, Aro A, Stenman S, Groop L. American Journal of Clinical Nutrition. 1993;58:513-8.

The effects of 15 g guar gum/d on glycemic control , lipids, and insulin secretion were studied in 15 (8 male, 7 female) diet-treated subjects with non-insulin-dependent diabetes mellitus for 48o wk. Mean age (+ /- SD) was 60 + /- 2 y (range 45-70 y), body mass index (in kg/m2) 28.6 + /- 0.9 (range 21.6 + /- 39.2) , and duration of diabetes 6 + /- 1 y (range 2-14 y). Guar gum was preceded and followed by 8-wk placebo periods. Guar gum improved long-term glycemic control, postprandial glucose tolerance and lipid concentrations. The C-peptide response to a test meal increased by time during guar gum treatment whereas the insulin response remained unchanged. This indicates that insulin secretion is enhanced by guar gum as reflected by increased C-peptide. A decreased molar ration of insulin to C-peptide suggests that guar gum has favourable long-term effects on glycemic control and lipid concentrations.

Protein and fat effects on glucose responses and insulin requirements in subjects with insulin-dependent diabetes mellitus.

Peters AL, Davidson MB. American Journal of Clinical Nutrition. 1993; 58:555-60.

The glucose responses (GR) and insulin requirements (Irs) were measured by a glucose-controlled insulin infusion system for 5 h after 12 patients with insulin-dependent diabetes mellitus consumed each of three meals : a 1890-kj standard meal, the standard meal with 840 kj added protein, and the standard meal with 840 kj added ft. The GR to the protein-added meal was greater (P=0.005) than to either the standard or fat-added meals, because of an increase in the late (last 150 min) GR. The late IR was greater for the protein-added mea(P < 0.005). The IR was not changed after the fat-added meal. Therefore, the addition of protein (but not fat) energy to a meal increases both the postprandial GR and late IR. This finding suggests that diabetic patients who inject premeal insulin may need to increase their insulin dose when protein is added to a meal.

PREGNANCY

Reproducibility of the oral glucose tolerance test in pregnant women.

Catalano PM, Avallone DA, Drago NM, Amini SB. American Journal of Obstertrics & Gynecology. 1993;169:874-81.

OBJECTIVE: The purpose of this study was to evaluate the reproducibility of the 3-hour oral glucose tolerance test during pregnancy and the potential factors associated with nonreproducible results. STUDY DESIGN: Thirty-eight women with a 1-hour glucose level > or 135 mg/dl had a 100 gm oral glucose tolerance test. During the test samples were obtained for glucose , insulin, cortisol, human placental lactogen, and no repinephrine levels. The oral glucose tolerance test was repeated 1 week later under similar metabolic conditions. RESULTS: The intrassay coefficient of variation in glucose from week 1 to week 2 was < 2%. There were no significant differences in the paired fasting 1-, 2- or 3-hour glucose concentration (p = 0.51 to 0.96) or the area under the glucose curve (p = 0.43) from week 1 to week 2 , although the mean absolute difference in glucose values ranged from 4 (fasting) to 18 (3 hours) mg/dl. Oral glucose tolerance test results were classified as either normal or abnormal from week 1 to week 2 ; 16o normal/normal, 13 abnormal/abnormal, seven abnormal/normal , and two normal/abnormal.
Norepinephrine (p = 0.03) and insulin (p = 0.05) were significantly greater in week 1 but not in week 2 in the abnormal/normal versus normal/normal and abnormal/abnormal groups. There were no significant differences in cortisol or human placental lactogen levels among groups at nay time CONCLUSION: The oral glucose tolerance test was not reproducible for diagnosis in 24% (nine of 38) of pregnant women. We speculate that maternal stress (increased no-repinephrin) may have been a factor for the abnormal results in week 1 in the abnormal/normal group.

Regulation of maternal IGF-1 by placental GH in normal and abnormal human pregnancies.

Caufriez A, Frankenne F, Hennen G, Copinschi G. American Journal of Physiology. 1993;265:E572-7.

Throughout gestation, maternal insulin-like growth factor I (IGF-I) increases progressively despite suppressed pituitary growth hormone (GH) secretion. We have previously shown that in normal pregnancy, a specific placental GH variant, rather than human placental lactogen (hPL), substitutes for pituitary GH in the regulation of maternal IGF-I. We studied the maternal IGF-I secretion in a cohort of 286 normal and abnormal pregnancies (617 blood sample). Regtardless of pathology and gestational age, IGF-I values correlated with corresponding placental GH but not with hPL values. Similar correlations were evidenced for each 2-wk gestational period between 32 and 39 wk . In pathological pregnancies, when only those hormonal results that are obtained before any treatment are considered and diabetes is excluded, IGF-I levels were closely related to corresponding placental GH, but not to hPL. In women with a fetoplacental unit disorder, low placental GH levels resulted in low IGF-I and in a secondary pituitary GH increase, whereas in patients without detectable impairment of the fetoplacental unit normal placental GH corresponded to normal pregnancy, placental GH, and not hPL, substitutes for pituitary GH to regulate the maternal IGH-I secretion.

CHILDHOOD DIABETES

Early Introduction of dairy products associated with increased risk of IDDM in Finnish children . The Childhood in Diabetes in Finland Study Group.

Virtanen SM, Rasanen L< Ylonen K, Aro a, Clayton D. Lang-holz B, Pitkaniemi J, Savilahti E, Lounamaa R, Tromilehto J. et al. Diabetes. 1993;42:11\786-90.

Associations between infant-feeding patterns and risk of IDDM were investigated in a nationwide Finnish case-control study of o690 IDDM children < 15 yr of age. Each child was matched by date of birth and sex to a randomly selected population-based control child. Univariate analysis revealed that the risk of IDDM was increased by approximately 1.5 in children for whom in those who were exclusively breast-feed for < 2 mo, and doubled in those who were introduced to diary products at < 2 mo of age. In further multivariate analyses of these factors, it was found the most important risk factor, and the observed univariate effects of duration of breast-feeding variables were explained by their correlation with this factor. This is the first observational study to show that early introduction of dairy products is independently associated with an increased risk of IDDM. Adjustment for mother's

education and age, child's birth order, or birth weight did not affect the results.

COMPLICATIONS

Is microalbuminuria part of the prediabetic state? The Mexico City Diabetes Study.

Haffner SM, Gonzales C, Valdez RA, Mykkanen L, Hazuda HP, Mitchell BD, Monterrosa A, Stern MP. Diabetologia. 1993';36: 1002-4.

Microabluminuria is associated with increase cardiovascular mortality in both diabetic and non-diabetic subjects. A number of studies have indicated that insulin resistance, increased blood pressure and dyslipidaemia precede the onset of clinical diabetes. We examined various correlates of microalbuminuria 1,298 non-diabetic subjects who participated in the Mexico City Diabetes Study, a population-based study of diabetes and cardiovascular risk factors. Both parental history of diabetes and impaired glucose tolerance were significantly associated with microalbuminuria. These results were not explained by differences in age or blood pressure between subjects with or without a parental history of diabetes or impaired glucose tolerance. In addition, subjects with microalbuminuria had increased 2-h insulin and triglyceride concentrations, a higher prevalence of hypertension, and decreased high density lipoprotein cholesterol concentrations relative to subject without microalbuminuria. These results that microalbuminuria may be a feature of the prediabetic state.

UK Prospective Diabetes Study (UKPDS).X. Urinary albumin excretion over 3 years in diet-treated type2, (non-insulin-dependent) diabetic patients, and association with hypertension, hyperglycaemia and hypertriglyceridaemia.

Anonymous. Diabeologia. 1993;36: 1021-9.

Urinary albumin excretion has been assessed in 585 newly presenting Type 2 (non-insulin-dependent) diabetic patients [aged 53(8) years, 67% male] at diagnosis with fasting plasma glucose 10.3 (3.2) mmol.l and over 3 years of dietary treatment. Urinary albumin at diagnosis, geometric mean (1 SD interval) corrected for dilution by regression on urine creatinine concentration of 10 mmol/l was 17 (5-58) mg/l compared with 8 (3-18) mg/l in an age-matched non-diabetic reference population. Values greater than 50 mg/l were found in 17% of diabetic patients compared with 4% in the reference group. After diet therapy for 3 months, fasting plasma glucose decreased to 6.9 mmol/l and urinary albumin to 12 (4-31) ,g/l ($p < 0.0001$). This suggests that increased urinary albumin excretion at diagnosis is in part functional possibly secondary to glomerular hyperfiltration caused by hyperglycaemia and raised blood pressure. Over the next 3 years, mean fasting plasma glucose was 7.2 mmol/l albumin excretion changed little, without significant increase either in patients with raised or normal albumin at diagnosis . Both at diagnosis and over 3 years urinary albumin excretion was independently associated with fasting plasma glucose and triglyceride levels and with systolic blood pressure, but the combination of these factors only explained 10% of the total variance. This suggests the presence urinary albumin. Urinary albumin was not associated with other variables included in syndrome X, such as HDL cholesterol, fasting plasma insulin, obesity or central adiposity.

Glomerulosclerosis in type 2 (non-insulin-dependent) diabetes mellitus: relationship to glycaemia in the University Group Diabetes Program (UGDP).

Carpenter AM, Goetz FC,, LeCompte PM, Williamson JR. Diabetologia. 1993;36:1057-63.

Kidney tissue of acceptable quality was available from autopsies of 55 patients who had been followed prospectively for 3 to 15 years as participants in the University Group Diabetes Program, a study of vascular disease in Type 2 (non-insulin-dependent) diabetic patients. Slides were prepared for light microscopic reading by uniform histologic techniques, and then were randomly intermixed and coded with tissues identically prepared from matched non-diabetic subjects(morphologic controls). After independent review by three morphologists, the results were tabulated and assigned to one of our four diagnostic groups: 1) typical diabetic nodular glomerulosclerosis; 2) mesangial changes suggestive of diabetes (diffuse lesion); 3) non-diabetic renal disease; 4) normal for age. Of the diabetic clerosis, and another 47% (26 to 55) showed suggestive changes; none of the morphologic control slides was read as showing nodular glomerulosclerosis, but some were judged to show suggestive mesangial (diffuse) changes. Although only 4 of the 17 diabetic patients with nodules had died of uraemia, many had hypertension, which may have contributed to their deaths from vascular disease. The patients with nodular glomerular changes also showed, on the average, the highest blood glucose levels during life. Type 2 diabetes in later life appears to be associated with a high risk for typical tissue changes of diabetic kidney damage, which may contribute significantly to morbidity and mortality and may be present before azotaemia and qualitative proteinuria have been recognized.

The course of kidney function in type 2 (non-insulin dependent) diabetic patients with diabetic nephropathy.

Gall MA, Nielsen FS, Smidt UM, Parvin HH. Diabetologia. 1993;36:1071-8.

We evaluated the impact of some putative progression promoters on kidney function in albyminuric Type 2(non-insulin –dependent) diabetic patients with biopsy-proven diabetic glomerulosclerosis. Twenty-six patients (1 female) with a mean age of 52 (standard error 2) years and a known mean duration of diabetes of 9 (1) years were followed-up prospectively for a mean of 5.2 (range 1.0-7.0) years. Twenty-one patients received antihypertensive treatment. During the observation period the glomerular filtration rate decreased from 83 (24-146) to 58 (2-145) ml. Min-1 X 1.37\\73m-2 [mean (range)] ($p < 0.001$). The mean rate of decline in glomerular filtration rate was 5.7 (-3.5 to 22.0) ml/min per year. Albuminuria increased from 1.2 (0.3-7.2) to 2.3 (0.4-8.0) g/24 h [geometric mean (range)] ($p < 0.001$). Arterial blood pressure remained unchanged: 162/93 (SE 4/3) and 161/89 (4/2) mm Hg. Univariate analysis showed the rate of decline in glomerular filtration rate to correlate with systolic blood pressure ($r=0.71$, $p < 0.001$), mean blood pressure ($r=0.56$, $p < 0.005$), albuminuria ($r=0.58$, $p < 0.005$) and the initial glomerular filtration rate ($r=-0.49$, $p < 0.02$). The rate of decline in glomerular filtration rate did not correlate significantly with dietary protein intake, total cholesterol, high-density lipoprotein cholesterol or HbA1c. Three patients died from uraemia and four patients died from cardiovascular disease. Two patients required renal replacement therapy at the end of the observation period. Our prospective observational study revealed that on-fifth of the patients developed end stage renal failure during the 5-year observation period.

Survival and predictors of death in dialysed diabetic patients.

Koch M, Thomas B, Tschope W, Titz E. Diabetologia. 1993;36:1113-7.

The objective of this study was to examine diabetic patients at the time of admission to maintenance haemodialysis and to follow them for 36 months in order to define predictors of cardiovascular and non-cardiovascular death. This prospective study comprised all consecutive diabetic patients admitted to 28 German dialysis centers between January 1985 and October 1987; 196 patients were examine, 67 Type 1 (insulin-dependent) diabetic (43 male, 75 female; median age 49 years, range 22-73) and 129 Type 2 (non-insulin-dependent) diabetic patients (54 male, 75 female, 64 years, range 37-82). Out come measures were death , i.e. myocardial infarction, sudden death, cardiac death of other causes stroke and non-cardiovascular death. Actuarial survival 36 months after the beginning of analysis was similar in Type 1 (40%) and Type 2 diabetic patients (43%) despite the age difference. Causes of death were myocardial infarction(18%) , sudden death (18%), other cardiac causes (18%); stroke (6%); septicaemia (17%) mostly originating from diabetic foot problems; and interruption of therapy. Survival raters the proportion dying from cardiac causes were similar in patients with diabetic nephropathy or with other primary chronic renal disease and coincidental diabetes. On analysis, de novo amaurosis or de novo amputation was not observed in any patient. The strongest predicator of myocardial infarction or sudden death was serum lipids on admission. Duration of hypertension, blood pressure at the time of admission to dialysis, left ventricular hypertrophy of end-diabetic giameter by echocardiography. Sokolow index and average predialysis blood pressure, smoking, interdialytic weight gain and type of dialysis were not predictive of cardiovascular death or death by all causes.

Pre-diabetic blood pressure predicts urinary albumin excretion after the onset of type 2 (non-insulin-dependent) diabetes mellitus in Pima Indians.

Nelson RG, Pettitt DJ, Baird hr, Charles MA, Liu QZ, Bennett PH, Knower WC. Diabetologia. 1993;36:998-1001.

Blood pressure was measured in 490 non-proteinuric Pima Indians from the Gila River Indian Community in Arizona at least 1 year before the diagnosis of Type 2 (non-insulin-dependent) diabetes mellitus. Urine albumin concentration was measured in the same subjects 0-24 years (mean 5 years) after diabetes was diagnosed. Prevalence rates of abnormal albumin excretion (albumin-to-creatinine ration> or = 100 mg/g) after the onset type 2 diabetes were 9%, 16% and 23% respectively, for the lowest to highest tertiles of pre-diabetic mean blood pressure. When controlled for age, sex, duration of diabetes and pre-diabetic 2-h post-load plasma glucose concentration, higher pre-diabetic mean blood pressure predicted abnormal urinary excretion of albumin after the onset of diabetes. This finding suggests that the higher blood pressure seen in diabetic nephropathy is not entirely a result of the renal disease, but may precede and contribute to it.

Microalbuminuria in a normotensive insulin-treated diabetic population.

Swislocki A, Noth R, Kaplan R, Dowdell L, Lamothe J, Claire D, Smith C, Fishman I, Onufer C. Hormone & Metabolic Research. 1993;25:532-5.

Twenty-five insulin-treated diabetics without overt proteinuria or hypertension, and taking no antihypertensive medications were screened at three clinical centers for the presence of microalbuminuria. In addition to the presence of albuminuria, patients were evaluated for duration and type of diabetes, retinopathy, blood pressure, and degree of diabetic control. In these patients, it was possible to examine the degree of microalbuminuria as a function of systolic and diastolic blood pressure, age and sex of the patient, site of recruitment, duration of diabetes, and glycemic control. On multivariate statistical analysis, systolic blood pressure was the only factor that contributed to microalbuminura. An additional 37 patients had urinary albumin excretion measured, although biochemical and clinical characteristics were incompletely determined. Blood pressures were documented to be normal in 23 of these individuals, while the other fourteen were normal by history. The range of urinary albumin excretion was comparable in the patients with complete databases and those without. Overall, 22.2% of the normotensive insulin-treated patients screened had microalbuminuria, 5.5% had gross albuminuria, while 72.2% had normal urinary albumin excretion. We agree with previous reports that microalbuminuria is relatively uncommon in the normotensive diabetic population, but further conclude that even in the context of "normal" blood pressure, systolic blood pressure should be carefully observed in diabetic patients. It is possible that these individuals should be considered for more aggressive monitoring programs, e.g. ambulatory blood pressure recording.

Effects of pancreas transplantation on glomerular structure in insulin-dependent diabetic patients with their own kidney.

Fioretto P, Mauer SM, Bilous RW, Goetz FC, Sutherland DE, Steffes MW. Lancet. 1993; 342:1193-6.

Pancreas transplantation prevents or retards development of early diabetic glomerular lesions in renal allografts transplanted to patients with insulin-dependent diabetes mellitus (IDDM), but its effect on established renal lesions in native kidneys of such patients is unknown. Renal biopsy samples were taken before and 5 years after pancreas transplantation from 13 non-uraemic IDDM patients and compared with baseline and 5-year biopsy samples from 10 persistently hyperglycaemic groups were similar in age, duration of diabetes, metabolic control, renal function, and blood pressure. Glomerular structures were measured by standard morphometric techniques. Haemoglobin A1 concentrations fell to within the normal range after pancreas transplantation but did not change in the comparison group. Glomerular basement membrance width did not significantly change in either group. Glomerular volume decreased and mesangial fractional volume increased in the pancreas transplant recipients but there was no significant change in total mesangial volume and mesangial fractional volume increased in the comparison patients, resulting in increased total mesangial volume. Diabetic glomerular lesions in patients with their own kidneys were not ameliorated by pancreas transplantation, despite 5 years of normoglycaemia. Pancreas transplantation can correct severe metabolic instability and thus improve quality of life, but it cannot yet be recommended for the treatment of established lesions of diabetic nephropathy.

Eicosanoids in the pathogenesis of the functional and structural alterations of the kidney in diabetes . [Review]

DeRubertis FR, Craven PA. American Journal of Kidney Diseases. 1993;22:727-35.

Diabetes mellitus alters the cellular production of eicosanoids in a number of tissues, including the kidney, and these agents have in turn been implicated in the pathogenesis of diabetic nephropathy. As delineated in the streptozotocin diabetic rat (SDR) model, a preferential enhancement of glomerular synthesis of the vasodilatory prostaglanins (PGs) PGE2 and

PGI2 with concurrent smaller increases in thromboxane (TX)A2 occurs within 1 week after induction of diabetes. This early alteration in glomerular synthesis of eicosandoids in the SDR has been linked to glucose-induced activation of the glomerular protein kinase C signaling system that enhances phospholipase A2 activity and, therefore, release of membrance-bound arachidonic acid for oxygenation. The preferential increase in glomerular production of vasodilatory PGs may contribute to the glomerular hyperfiltration that is characteristic of early diabetes. After more prolonged (months) diabetes in the SDR, glomerular generation and urinary excretion of thromboxane (TX) are preferentially enhanced. Studies with selective inhibitors of TX synthesis in the SDR have implicated this eicosanoid in the pathogenesis of both albuminiuria and glomerular structural changes (basement membreane thickening and mesanginal matrix expansion). Direct stimulation of matrix protein production has been demonstrated in cultured mesangial cells in response to both TX and high ambient concentrations of glucose. The actions of TX and glucose on mesangialcell matrix production appear to be interactive, with each signaled through distinct pathways of protein kinase C activation.

The quantitative relationship between treated blood pressure and progression of diabetic renal disease.

Dillon J.J. American Journal of Kidney Diseases. 1993;22:798-802.

Antihypertensive therapy reduces the rate at which glomerular filtration rate (GFR) decline (delta GFR) in diabetic nephropahty' however, the optimal blood pressure is unknown. The quantitative relationship between treated blood pressure and delta GFR was analyzed retrospectively in 59 patients with established diabetic nephropathy and treated hypertension using weighted univariate and weighted multicariate regression. The GFR was calculated using the Cockcroft and Gault formula . More rapid GFR loss correlated most strongly with higher diastolic blood pressures (r= 0.70; p < 0.0001); for each millimeter of mercury of diastolic blood pressure, the GFR decreased by 0.69 mL/min/yr. This relationship remained present if those individuals with diastolic pressures greater then 90 mm Hg were eliminated from the study(r=0.50; p < 0.001). The correlation for systolic blood pressure was weaker (r= 0.30; P < 0.05) and explained completely by covariance between systolic and diastolic blood pressures. The correlation for men blood pressure (r = 0.59; P < 0.0001) fell between the correlations for diastolic and systolic blood pressures. Proteinuria, serum albumin concentration also correlated with delta GFR. In multivariate analysis, neither these indices of disease severity nor the initial GFR explained the correlation between delta GFR an diastolic blood pressure. Age ,sex, race, type of diabetes, and percentage of glycosylated hemoglobin did not correlate with delta GFR.

Advanced glycosylation end products in continuous ambulatory peritoneal dialysis patients.

Korbet SM, Makita Z, Firnaek CA, Viassara H. American Journal of Kidney Diseases. 1993;22:588-91.

Low molecular weight advanced glycosylation end products (AGEs) were evaluated for by an enzyme-linked immunosorbent assay in 30 patients on continuous ambulatory peritoneal dialysis (29 patients) and continuous cyclic peritoneal dialysis (one patient). Thirteen patients were diabetic and 17 patients were nondiabetic. All patients underwent peritoneal equilibration tests and in addition to routine chemistries ,serum and dialysate were evaluated for AGEs . Serum creatinine levels were similar in the diabetic and nondiabetic patients, but serum AGE levels were significantly higher in the diabetic patients(16.2 + /- 5.3 v 8.2 + /-2.3 U/mL; P < 0.0001). Overall, the dialysate to plasma ration at 4 hours was 0.69 + /- 0.08 for creatinine and 0.18 +/- 0.06 for AGEs. The mass transfer areas coefficient for all patients was 12.4 /-3.12 mL/min for creatinine and 2.03 /-0.93 mL/min for AGEs. The peritoneal transport of AGEs as measured by dialysate to plasma ratios at 4 hours and by mass transfer area coefficients was significantly less (P <0.001) than that for creatinine. No significant difference in dialysate to plasma ratios or mass trabsfer area coefficient for creatinine or AGEs was noted between diabetic and nondiabetic patients . The peritoneal transport of AGEs is poor and leads to elevated serum levels, especially in patients with diabetes mellitus. The accumulation of AGEs may contribute to the increased cardiovascular mortality seen in patient with diabetes mellitus. The accumulation of AGEs may contribute to the increased cardiovascular mortality seen in patients with end stage renal disease. This is most marked in patients with diabetes mellitus.

Angiotensin-converting enzyme inhibition and renal protection. An assessment of implications for therapy. [Review]

Hollenberg NK, RaijL. Archives of Internal Medicine. 1993;153:2426-35.

The role of hypertension in the pathogenesis of renal damage is a subject of both historical interest and current investigation. Because of the difficulty associated with studying the patho-physiologic role of glomerular injury in systemic hypertension, experimental models have provided much of the data in this field. The mechanisms leading to glomerular injury are complex and not fully elucidated. Mesangial and endothelial cell injury are thought to be important pathophysiologic mechanisms in the renal injury associated with hypertension. One hypothesis suggests that glomerular hyopertension (i.e., a hemodynamic event) is the primary pathogenetic mechanism, but another supports the notion that glomerular hypertrophy (ie., abnormal growth-related events) contributes to injury. The intrarenal renin-angiotensin system may play an important pathogenetic role in end-stage renal disease. Angiotensin-converting enzyme (ACE) inhibition has been shown to arrest the progression of renal injury in animal models. Although the clinical database is incomplete, the findings of anecdotal reports and short-term studies suggest that ACE inhibition may preserve renal function in patients with scleroderma renal crisis, reduce proteinuria in patients with diabetic nephropathy, and normalize renal hemodynamics in patients with a variety of renal diseases. The beneficial effects of ACE inhibition may be due to both hemodynamic (eg, reduction in glomerular capillary and intraglomerular pressures) and nonhemodynamic (eg, potassium-spring and reduction in mesangial proliferation) mechanisms. The precise role of ACE inhibitors in the prevention of renal damage awaits the results of ongoing long-term, double-blind clinical studies. Nevertheless, ACE inhibition may be an appropriate therapeutic alternative in the hypertensive patient whose renal injury is progressing despite aggressive antihypertensive therapy.

The effect of angiotensin-converting –enzyme inhibition on diabetic nephropathy. The Collaborative Study Group.

Lewis E J, Hunssicker LG, Bain RP, Rhode RD. New England Journal of Medicine. 1993;329:1456-62.

BACKGROUND. Renal function declines progressively in patients who have diabetic nephropathy , and the decline may be slowed by antihypertensive drugs. The purpose of this study was to determine whether captopril has kidney-protecting properties independent of its effect on blood pressure in diabetic nephropathy. METHODS. We performed a randomized, controlled trial comparing captopril with placebo in patients with insulin-dependent diabetes mellitus in whom urinary protein excretion was > or = 500 mg per day and the serum creatinine concentration was < or = 2.5 mg per decliter (221 mumol per liter). Blood-pressure goals were defined to achieve control during a median follow-up of three years. The primary end point was a doubling of the base-line serum creatinine concentration. RESULTS. Two hundred seven patients received captoril, and 202 placebo. Serum creatinine concentrations doubled in 25 patients in the captopril group, as compared with 43 patients in the placebo group (P = 0.007). The associated reductions in risk of a doubling of the serum creatinine concentration were 48 percent in the captopril group as a whole, 76 percent in the subgroup with a baseline serum creatinine concentration of 2.0 mg per deciliter (177 mumol per liter/), 55 percent in the subgroup with a concentration of 1.5 mg per deciliter (133 mumol per liter/0, and 17 percent in the subgroup with a concentration of 1.0 mg per deciliter (88.4 mumol per liter). The mean (+ /- SD) rate of decline in cretinine clearance was 11 +/-21 percent per year in the captopril group and 17 + /- 20 percent per year in the placebo group (P = 0.03). Among the patients whose base-line serum creatinine concentrations was > or = 1.5 mg per decliter, creatinine clearance decline at a rate of 23 + /- 25 percent per year in the captopril group and at a rate of 37 + /- 25 percent per year in the placebo group (P= 0.01). Captopril treatment was associated with a 50 percent reduction in the risk of the combined end points of death, dialysis, and transplantation that was independent of the small disparity in blood pressure between the groups. CONCLUSIONS. Captopril protects against deterioration in renal function insulin-dependent diabetic nephropathy and is significantly more effectively more effective than blood-pressure control alone.

Diabetic neuropathy 3 years after successful pancreas and kidney transplantation.

Muller-Felber W, Landgraf R, Scheurer R, Wanger S, Reimers CD, Nusser J, Abendroth D, IIiner WD, Land W. Diabetes. 1993;42:1482-6.

Twenty-seven patients with successful transplantation and a control group of 14 patients with early rejection of the pancreas graft but functioning kidney graft were examined in a prospective study for 3 yr. Before transplantation, all patients had long-standing type I diabetes with advanced secondary complications, including end-stage diabetic nephropathy. After transplantation in the patients of both groups, kidney function was almost normal. Mean HbA1 levels were normal in the group with pancreas graft survival. In the control group, HbA1 levels were, on average, 1.5% higher compared with the group with pancreas survival (P = 0.00005). After 3 yr, the patients with functioning pancreas graft showed fewer symptoms (mean difference 1.0 in a symptom score ranging from 0 to 16, P = 0.004) compared with the control group. No statistically significant difference between both groups concerning clinical signs of polyneuropathy could be observed. In the pancreas and kidney transplantation group, peroneal and median nerve conduction velocities increased 7.2 m/s (P < 0.01) and 3.5 m/s (P < 0.05), respectively, where was no increase was registered in the control group. The change of median and sural sensory nerve conduction velocities, peroneal and median compound muscle action potentials, and sural and median sensory action potentials was insignificant. In conclusion, although the improvement of clinical symptoms and neurophysiological signs of polyneuropathy was modest in the pancreas and kidney transplantation group, our data suggest that successful pancreas transplantation is able not only to half the progression of diabetic polyneuropathy but also to improve it to some extent even at a far advanced stage.

Storage temperature and differing methods of sample preparation in the measurement of urinary albumin.

Collins AC, Sethi M, MacDonald FA, Brown D, Viberti GC. Diabetologia. 1993;36:993-7.

Microalbuminuria is a predictor of persistent proteinuria, renal failure and cardiovascular disease and therefore accurate determination of urinary albumin concentration is important. We examined the stability of albumin in urine under different conditions of storage, temperature and sample preparation. There was no significant difference in urinary albumin concentration between fresh urine and urine stored at either 4 degrees C or 20 degrees C for up to 7 days. Similarly in urine samples from diabetic patients there was no significant difference in albumin concentration at levels ranging from 1.3 to 1999.3 mg/1 between fresh urine at 4 degrees C and urine stored frozen for 1 week, 1 month or 6 months. Neither storage temperature (-20 degrees C or –40 degrees C) nor centrifugation of sample prior to assay made a significant difference to the albumin concentration. Multiple freezing and thawing of urine samples during 6 weeks of storage at –20 degrees C made to difference to albumin concentrations. Storage of urine sample in either polypropylene, polystyrene or borosilicate glass tubes did not result in a significant change in urinary albumin concentration after either 1 week or 1 month at –20 degrees C although, after 1 month of storage, urinary albumin concentrations tended to be lower by an average of approximately 7%. In tubes to which gelatine had been added this was reduced to 4%. We conclude that fresh urine can be kept at 4 degrees C or 20 degrees C for up to 7 days. Frozen urine samples can be stored for up to 6 months before assay without any loss of albumin concentration.

CARDIOVASCULAR

Effect of gemfibrozil on adipose tissue and muscle lipoprotein lipase.

Simsolo RB, Ong JM, Kern PA. Metabolism: Clinical & Experimental. 1993; 42:1486-91.

To better understand the mechanism of action of gemfibrozil on plasma triglycerides, lipoprotein lipase (LPL) concentration was measured in adipose tissue and muscle of 16 hypertriuglyceridemic patients were divided into three groups based on clinical criteria as follows: group 1, hypertriglyceridemia without secondary factors; group 2, hypertriglyceridemia with diabetes; and group 3, hypertriglyceridemia with renal insufficiency. LPL activity, impmunoreactive mass, synthetic rate, and mRNA levels were measured in the adipose tissue samples, and LPL activity and mass in the muscle samples. Serum triglyceride levels were decreased by 46% by gemfibrozi., and patients demonstrated no change in diet, weight, or glycohemoglobin during the 6 weeks of treatment. Despite the decrease of blood triglyceride levels, there was no significant change in any measure of LPL either in adipose tissue or muscle. Although several patients demonstrated increases in muscle LPL activity, these changes were inconsistent and not statistically significant. Because there was no significant change in LPL, we conclude that gemfibrozil in these patients decreased circulating triglyceride

levels predominantly by decreasing hepatic very-low-density lipoprotein (VLDL) secretion.

Risk factors for coronary heart disease among older men and women: a prospective study of community-dwelling eiderly.

Seeman T, Mendes de Leon C, Berkman L, Ostfeld A. American Journal of Epidemiology. 1993;138:1037-49.

Data from a community-based sample of 2,812 men and women aged 65 years and over, living in New Haven, Conecticut, were used to examine the associations between blood pressure, smoking, diabetes, anginal chest pain, and relative weight and 6-year incidence (1982-1988) of myocardial infraction and coronary heart disease mortality. Multivariate logistic regression analyses revealed that history of diabetes was associated with increased risk of incident myocardial infraction among women [odds ratio (OR) = 3.20; 95% confidence interval 1.46-7.01]. While higher relative weight was a significant risk factor among men (OR = 3.46, 95% confidence interval 1.34-8.95 for middle vs. lowest tertile and OR = 3.24; 95% confidence interval 1.10-9.53 for highest versus lowest tertile). For coronary heart disease mortality, age and were associated with increased risk among women, as was current smoking (OR = 3.96; 95% confidence interval 1.66-9.45). Among men, age, prevalent heart disease, and use of antihypertensive medication (OR = 1.84; 95% confidence interval 1.13-3.00) were risk factors for coronary heart disease mortality. These risk estimates and the relatively high prevalences of these risk factors suggest that attributable risks may be substantial. Observed sex differences as well as difference in patterns of risk factor associations for the two endpoints suggest that there may be different risk profiles for older men and women and for different coronary heart disease endpoints.

Predictors and long-term prognostic significance of recurrent infraction in the year after a first myocardial infarction. SPRINT Study Group.

Kornowaski R, Goldbourt U, Zion M, Mandelzweig L, Kaplinsky E, Levo Y, Behar S. American Journal of Cardiology. 1993; 72:883-8.

This study was undertaken to examine whether clinical factors predicts reinfraction within 1 year of a first acute myocardial infarction (AMI) and to quantify the subsequent influence of reinfarction on long-term mortality. Data from 3,695 patients with a first AMI included in the Secondary Prevention Reinfarction Isfarction incidence was 6.0% (220 of 3,695) and in-hospital mortality during reinfarction was 31%> Patients with reinfarction were older (63.0 vs 60.8 years) at entry. The independent clinical predictors for 1-year reinfarction were (adjusted relative odds): peripheral vascular disease (2.12), anterior location of the first AMI (1.62), angina before the first AMI (1.53), congestive heart failure on admission (1.34), diabetes (1.33), systemic hypertension (1.28), and age increme4nt (1.13). One-year reinfarction rate increased from 4.0% in patients with 0 or 1 risk factor to 23.3% in patients with 5 to 6 risk factors ($p < 0.0001$). Patients with reinfarction had significantly increased 1 and 5-year mortality compared with those who had no reinfacrction (11.8 vs 5.3% and 40.1 vs 20.3%, respectively, $p < 0.0001$). Recurrent AMI within 1 years was the most powerful predictor of long-term (mean 5.5 years) total mortality (adjusted relative risk = 4.76).

Multicenter trial of lonic versus nooionic contrast media for cardiac angiography. The lohexol Cooperative Study.

Hill JA, Winniford M, Cohen MB, Van Fossen DB, Murphy MJ, Halpern EF, Ludbrook PA, Wexler L, Rudnick Mr, Goldfarb S, American Journal of Cardiology. 1993; 72: 770.

Contrast agents used for cardiac angiography are different in regard to ionicity, osmolality and physiologic effects. The nonionic contrast media have been shown to have less toxic effects and a better safely profile than do higher osmolar agents. To better assess this risk, clinically stable patients undergoing cardiac angiography were stratified according to the presence of diabetes mellitus, and then randomized to receive either iohexol (Omnipaque 350) or sodium meglumine diatrizoate (Renografin 76). All adverse events that occurred during and immediately after angiography were tabulated. A multivariate model was used to identify patients at increased risk for adverse outcome. The 1.390 patients were randomized to iohexol (n = 696) or diatrizoate (n = 694). Significants differences were found in the number of patients with contrast media-related adverse (iohexol vs diatrizoate: 10.2 vs 31.6%: $p < 0.001$) and cardiac adverse (7.2 vs 24.5%: $p < 0.001$) events. Severe reactions and the need for treatment were more frequent with diatrizoate than with iohexol, but there was no difference in the incidence of death. The presence of New York Heart Association classification 3 or 4 and serum creatinine > or = 1.5 mg/dl predicted a higher incidence of adverse events as a result of contrast media alone. Use of iohexol is associated with a lower incidence of all types of adverse events during cardiac angiography than is diatrizoate.

Alteration of lipoprotein (a) concentration with glycemic control in non-insulin-dependent diabetic subjects without diabetic complications.

Nakata H, Horita K, Eto M. Metabolism: Clinical & experimental. 1993;42:1323-6.

Recently, a high plasma level of lipoprotein (a) [LP(a)] has been considered an independent risk factor for atherosclerosis and its sequelae, particularly myocardial infarction. Patients with non-insulin-dependent diabetes mellitus (NIDDM) have an increased mortality rate from cardiovascular and cerebrovascular disease. Therefore, plasma concentrations of Lp(a) were determined and the relationship between fasting plasma Lp(a) level and diabetic control was investigated in NIDDM patients without any diabetic complications. Fasting plasma Lp(a) levels were measured using enzyme-linked immunosorbent assay kits [Terumo Medical Corp, Elkton, MD, Lp(a)] in 61 NIDDM subjects [30 men aged 56 + /- 2.0 years, 31 women aged 53 + /- 2.1 years (mean + /- SEM)] who were without any diabetic macroangiopathy and microangiopathy such as retinopathy, nephropathy, and neuropathy and in 56 healthy age and sex-matched controls. Plasma Lp(a) levels were significantly higher in the diabetic group than in the control group [23.5 + /- 2.5 v 11.7 + /- 1.4 mg/dL (mean + /- SEM), $P < .001$]. There was no significant correlation between log-transformed plasma Lp(a) levels and other factors such as age, sex, body mass index (BMI), blood pressure, duration of diabetes, fasting plasma glucose (FPG) levels, glycosylated hemoglobin (HbA1C) level, and plasma lipid levels except for low-density lipoprotein cholesterol (LDL-C) levels in diabetic patients. A significant positive correlation was noted in diabetic patients between the changes of log Lp(a) and HbA1C levels after a 3-month follow-up period ($P < .05$).

Diabetes and heart disease: a new strategy for managing lipid disorders.

Garber AJ. Geriatrics. 1993; 48:34-6, 39-41.

Dyslipidemias represent an underdiagnosed and undertreated clinical problem in the management of diabetic patients. Glycemic control by itself is not sufficient ot correct elevated triglycerides and low HDL levels, which greatly increase the risk of cardiovascular disease. Careful monitoring and aggressive intervention can dramatically reduce the risk that these dyspidiemias pose in diabetic and prediabetic patients. Weight loss by obese patients, low-fat diets, and gradually increased aerobic exercise should be tried for 6 months. If lipid levels are still outside the acceptable range, consider adding lipid-lowering drug therapy. Age should be no barrier to intervention, as coronary risk factors continue to contribute to the incidence of events into advanced age. [Reference: 22].

Living with diabetes: relationship to gender, duration and complications. A survey in northern Sweden.

Gafvels C, Lithner F, Borjeson B. Diabetic Medicine. 1993: 10:768-73.

A questionnaire was sent to 561 insulin-treated diabetic patients aged 20-50 years living in the province of Vasterbotten in Northern Sweden to assess their experience of living with diabetes. The response rate was 87% (n = 488). Difference in the experience of living with diabetes related to gender, age, duration of diabetes, and chronic diabetic complications were reported. Men seemed to underestimate problems related to diabetes more than women. They worried less about long-term complications and hypoglycaemia, but were more troubled by the limitation of personal freedom caused by their diabetes. In spite of their worries, women more often than men found positive aspects in having diabetes. Younger patients also had a more positive attitude towards their disease, even though they more often thought that diabetes had negatively affected their relationships with friends. Patients with a shorter diabetes duration were more concerned about the management of their diabetes than were patients with a long duration. The fear of chronic complications increased with diabetes duration. Chronic complications most affected patients' views of diabetes, their self-perception, and social life. Patients with childhood onset of diabetes knew less about the implications of the disease, and this reduced the intensity of their psychological response to the diagnosis. In conclusion, social and medical factors affected how diabetic patients perceived their disease. These findings suggest that the outcome of diabetes health care might improve if it was more individually adapted to each patient's personal experience of the disease and the psychological needs related to it.