Abstract Service*

AETIOLOGY

Search for a third susceptibility gene for maturity-onset diabetes of the young. Studied with eleven candidate genes.

Vaxillaire M, Vionnet N. Vigouroux C, Sun F, Espinosa R 3rd, Lebeau MM, Stoffel M, Lehto M, Beckmann JS, Detheux M, et al. Diabetes 1994; 43: 389-95.

Maturity - onset diabetes of the young (MODY) is a model for genetic studies of non-insulin-dependent diabetes mellitus. We have identified 15 MODY families in which diabetes is not the result of mutations in the glucokinase gene. This cohort of families will be useful for identifying other diabetes-susceptibility genes. Nine other candidate genes potentially implicated in insulin secretion or insulin action have been tested for linkage with MODY in these families, including glucokinase regulatory protein, hexokinase II, insulin receptor substrate 1, fatty acid binding protein 2, glucagon-like peptide-1 receptor, apolipoprotein C-II, glycogen synthase, adenosine deaminase (a marker for the MODY gene on chromosome 20) and phosphoenolpyruvate carboxykinase. None of these loci showed evidence for linkage with MODY, implying that mutations in these genes do not make a major genetic contribution to the development of MODY. In addition to these linkage analyses, one or two affected subjects from each family were screened for the presence of the A to G mutation nucleotide 3,243 of the mitochondrial tRNA [Leu (UUR)] gene. This mutation was not found in any of these subjects. Finally, we report the localization of the gene encoding the regulatory protein of glucokinase to chromosome 2, band p22.3 and the identification of a restriction fragment length polymorphism at this locus.

Ethnic difference in human leukocyte antigen markers of susceptibility to IDDM.

Cruickshanks KJ, Jobim LF, Lawler-Heavner J, Neville TG, Gay EC, Chase HP, Klingensmith G, Todd JA, Hamman RF. Diabetes Care. 1994; 17:132-7.

Objective: To determine whether genetic differences explain the lower risk of developing insulin-dependent diabetes mellitus (IDDM) for Hispanic versus non-Hispanic white children in Colorado.

Research Design and Methods: Hispanic (n=62) and non-Hispanic white (n=82) subjects with IDDM identified from the Colorado IDDM Registry and healthy, non-diabetic control subjects were recruited. Human leukocyte antigen (HLA) serologic typing and sequence specific oligonucleotide typing of DQA1 and DQB1 alleles were performed.

Results: HLA and allele associations with IDDM were similar in both ethnic groups. HLA-DR3 and HLA-DR4 were more common in IDDM subjects in both ethnic groups. Subjects with DQB1 alleles encoding aspartic acid (Asp) in position 57 were less likely to have IDDM, irrespective of ethnic background. HLA-DR3 was less common among Hispanic subjects than non-Hispanic white control subjects (4.4vs. 17.5%, Hispanics vs. non-Hispanic whites, p=0.04).

Conclusions: These data suggests that the lower prevalence of HLA-DR3 in the Hispanic population, a pattern consistent with the presence of Amerindian admixture, may explain the lower rate of IDDM in the Hispanic population.

A subtype of diabetes mellitus associated with a mutation of mitochondrial RNA.

Kadowaki T, Kadowaki H, Mori Y, Tobe K, Sakuta R, Suzuki Y, Tanabe, Sakura H, Awata T, Goto Y et al., New England Journal of Medicine. 1994; 330: 962-8.

Background: Several families have been described in which a mutation of mitochondrial DNA, the substitution of guanine for adenine (A⇒G), at position 3243 of leucine transfer RNA, is associated with diabetes mellitus and deafness. The prevalence, clinical features and pathophysiology of diabetes with this mutation are largely undefined.

Methods: We studied 55 patients with insulin-dependent diabetes mellitus (IDDM) and a family history of diabetes (group 1), 85 patients with IDDM and no family history of diabetes (group 2), 100 patients with non-insulin-dependent diabetes mellitus (NIDDM) and a family history of diabetes (group 3), and 5 patients with diabetes and deafness (group 4) for the mutation. We also studied the prevalence and characteristics of diabetes in 39 patients with a syndrome consisting of mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes that were known to have the mutation and 127 of their relatives (group 5).

Results: We identified 16 unrelated patients with diabetes associated with the A⇒G mutation: 3 patients from group 1 (6 percent), 2 patients from group 3 (2 percent), 3 patients form group 4 (60 percent), and 8 patients from group 5 (21 percent). We also identified 16 additional subjects who had diabetes and the mutation among 42 relatives of the patients with diabetes and the mutation in-groups 1, 2, 3 and 4 and 20 affected subjects among the 127 relatives of the patient's in-group 5. Diabetes cosegregated with the mutation in a fashion consistent with maternal transmission, was frequently (in 61 percent of cases) associated with sensory hearing loss and was generally accompanied by impaired insulin secretion.

Conclusions: Diabetes mellitus associated with the A⇒G mutation at position 3243 of mitochondrial leucine transfer RNA represents a subtype of diabetes found in both patients with IDDM and patients with NIDDM in Japan.

Linkage analysis of acute insulin secretion with GLUT2 and glucokinase in Pima Indians and the identification of a missense mutation in GLUT2.

Janssen RC, Bogardus C, Takeda J, Knowler WC, Thompson DB. Diabetes. 1994; 43: 558-63.

The acute insulin response (AIR), a measure of Pancreatic beta-cell function, aggregates in families and is a predictor for the development of non-insulin-dependent diabetes mellitus (NIDDM) in insulin resistant Pima Indians. To assess the genetic components of AIR and NIDDM, polymorphic dinucleotide repeat regions in two candidate genes, the liver/islet glucose transporter gene (GLUT2) and the glucokinase gene, were evaluated. Sib-pair linkage analyses were performed to determine if linkage exists between these marker loci and measurements of AIR and NIDDM. No linkage was found between glucokinase and either AIR or NIDDM. Robust sib-pair linkage analyses suggest linkage between GLUT2 and acute insulin response (P = 0.04), but no linkage was observed with NIDDM. The coding region of the GLUT2 gene was screened for mutations using polymerase chain reaction-single-strand conformation polymorphism analysis. A single base change was identified in exon 3 in approximately 5% of the study population, and it constitutes the first reported mutation in the human GLUT2 gene. This base change resulted in an amino acid substitution (Thr110⇒IIe110) in the second membrane-spanning region the GLUT2 protein. No significant association was noted between AIR and the presence of absence of the Mutation. Thus, this mutation in GLUT2 is unlikely the cause of a low AIR in Pima Indians.

Effect of adjuvant therapy on development of diabetes in mouse and man.

Shehadeh N, Calcinaro F, Bradley BJ, Bruchlim I, Vardi P, Lafferty KJ. Lancet. 1994; 343: 706-7.

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Freund's complete adjuvant (CFA) and BCG Vaccine modulate the development of type 1 diabetes in animal models. In non-obese diabetic mice, CFA and BCG significantly reduced the proportion developing diabetes compared with controls. Histological examination showed that autoimmune disease still developed but had been diverted to become nondestructive. In a preliminary trial in 17 newly diagnosed, type 1 diabetic patients, intracutaneous administration of 0.1 mL of BCG 1 mg/ml led to clinical remission in 11 (65%)-- by week 4 in 6. Remission has been sustained in 3 for 6-10 months. No side effects were reported. A double-blind trial of BCG is warranted.

Diabetes and fructose metabolism.

Gerrits PM, Tsalikian E. American Journal of Clinical Nutrition. 1993; 58: 786S.

The clinical aspects of fructose supplementation in the diets of individuals with diabetes should focus on the balance between beneficial effects and possible side effects. Fructose supplementation in diabetes mellitus was advocated before insulin was discovered. Fructose elicits a lower glucose and insulin response in healthy individuals and in individuals with diabetes. The use of fructose as a sweetener in the diets of diabetics has been debated repeatedly. Short-term studies have now shown that substitution of fructose for sucrose in the diets of individuals with diabetes improves glycaemic control and does not appear to have substantial side effects. In balanced diets, reasonable amounts of fructose supplementation do not affect lipoprotein metabolism or result in gastrointestinal symptoms. Long-terms studies are still needed to ascertain that long-term fructose supplementation has a sustained beneficial effect in diabetes and is devoid of deleterious side effects.

Impaired vasodilator response to atrial natriuretic factor in IDDM.

Smits P, Hersbach FM, Jansen TL, Thien T, Lutterman JA. Diabetes. 1993; 42: 1454-61.

Diabetes mellitus has been associated with both elevated plasma concentrations of the natriuretic and vasorelaxant hormone atrial natriuretic factor and with a reduced natriuretic response to this hormone. We now hypothesize that the vasodilator response to atrial natriuretic factor is attenuated in IDDM. Forearm vasodilator responses to the infusion of six increasing dosages of atrial natriuretic factor into the brachial artery were registered by venous occlusion strain into the brachial artery were registered by venous occlusion strain gauge plethysmography in 10 patients with uncomplicated IDDM and in 10 age-sex-, and weight- matched control subjects. Baseline levels of blood pressure forearm blood flow and plasma concentrations of atrial natriuretic factor were not different between control subjects and patients with diabetes. In control subjects, atrial natriuretic factor induced a percentage fall in the forearm vascular resistance of -29 +/- 5% at the lowest to -72 +/- 4% at the highest infusion rate. In patients with diabetes this fall was significantly attenuated, measuring -2+/-7and -45+/-4%, respectively, (P < 00.001 vs. control subjects). During infusion of atrial natriuretic factor into the brachial artery, the calculated regional production of cGMP (second messenger of atrial natriuretic factor) increased from 1.2 +/- 1.1 to 22.8+/-4.8 pmol. min-1 x 100 ml-1 in the control subjects, whereas hardly any change occurred in the patients with diabetes (from -2.1 +/- 1.2 to 2.9 +/- 4.7 pmol. min-1 x 100 ml-1). Furthermore, both control and diabetic subjects demonstrated an equal forearm vasodilator response to increasing infusion rates of the control vasodilator sodium nitroprusside. We conclude that uncomplicated IDDM is associated with a specific reduction in the vascular responsiveness to atrial natriuretic factor.

Association of HLA-DQB1 *0201 with stiff-man syndrome.

Pugliese A, Solimena M, Awdeh ZL, Alper CA, Bugawan T, Erlich HA, De Camilli P, Eisenbarth GS. Journal of Clinical Endocrinology and Metabolism: 1993; 77: 1550-3.

Stiff-man syndrome (SMS) is a rare disorder of the central nervous system of probable autoimmune origin. Patients with SMS often have other autoimmune diseases, in particular type I (insulin-dependent) diabetes mellitus (IDDM). Approximately 60% of patients with SMS have high titers of autoantibodies against the enzyme glutamic acid decarboxylase. Similar to SMS, the majority of patients with IDDM have autoantibodies against glutamic acid decarboxylase at or before diabetes onset, although usually at a lower titer and with a different reaction pattern than patients with SMS. To investigate the immunogenetic basis of SMS, we HLA-typed 18 patients with the disease. Seventy-two percent carried the DQB1*0201 allele (13 of 18, P = 0.02 vs. 18 of 48 controls), indicating that SMS is associated with this allele. DQB1*0201 is also a susceptibility allele for IDDM and other auto immune diseases. Patients with SMS carried the IDDM protective DQB1*0602 allele and other sequence-related DQB1*06 alleles with the same frequency observed in controls. In contrast, these alleles are rarely found in IDDM. Five of 8 (62.5%) SMS patients lacking a DQB1*06 allele were diabetic in contrast to only 2 of 10 (20%) with a DQB1*06 allele (P = 0.08), suggesting that the presence of DQB1*0602 or other DQB1*06 alleles may be associated with a reduced prevalence of diabetes among patients with SMS.

Insulin resistance in related to albuminuria in patients with type II (non-insulin-dependent) diabetes mellitus.

Niskanen L, Laakso M. Metabolism: Clinical and Experimental. 1993; 42: 1541-5.

To determine whether albuminuria is associated with insulin resistance in patients with type II (non-insulin-dependent) diabetes mellitus, we performed hyperinsulinaemic (40 mU/m2/min) euglycaemic clamp studies in patients with a urinary albumin excretion (UAE) rate greater than 30 mg/24 h and in patients with a UAE less than 30 mg/24 h. The UAE- positive group (n = 22) did not differ significantly from the UAE-negative group (n = 18) with respect to age, sex, treatment of diabetes, body mass index, fasting or postload blood glucose or plasma insulin levels, blood pressure, or known duration of diabetes. The mean glucose disposal rate (GDR) was significantly lower in the UAE-positive group than in the UAE-negative group (3.44 +/- 0.29 v 4.75 +/- 0.52 mg/kg/min, P < 0.05). When patients with hypertension were excluded, GDR was still markedly lower in the UAE-positive group than in the UAE-negative group (3.89 +/- 0.54 v 6.68 +/- 0.71 mg/kg/min, P = 0.01). The difference between groups persisted even after adjustment for body mass index, sex, and hypertension (ANCOVA; P < 0.05). These results indicate that the presence of microalbuminuria is associated with impaired insulin action in patients with type II diabetes mellitus.

PATHOPHYSIOLOGY

Insulin sensitivity in non-diabetic relatives of patients with non-insulin-dependent diabetes from two ethnic groups.

Gelding SV, Niththyananthan R, Chan SP, Skinner E, Robinson S, Gray IP, Mather H, Johnston DG, Clinical Endocrinology. 1994; 40: 55-62.

Objective: Non-insulin-dependent diabetes is a heterogeneous disorder, the basis of which may differ in different ethnic groups. In order to investigate early metabolic abnormalities occurring during the development of the condition we assessed insulin secretion and insulin action in subjects predisposed to the later development of non-insulin-depended diabetes from two different ethnic groups.

Design: Subjects were studied on two separate occasions by an oral glucose tolerance test and a short insulin tolerance test.

Patients: Twenty-four glucose-tolerant first-degree relatives of patients with non-insulin- dependent diabetes (12 of European and 12 of Asian origin) were compared with 24 ethnically matched control subjects with no family history of diabetes.

Measurements: Insulin, pro-insulin, glucose and intermediary metabolites were measured during a 75-g oral glucose tolerance test. Insulin sensitivity was assessed using a 15-minute insulin tolerance test (0.05 units/kg).

Results: Asian relatives compared to Asian controls had significantly higher fasting levels of immunoreactive insulin (83+/-17 vs. 40+/-6 pmol/l $p < 0.05$), which were not due to increased pro-insulin. Blood glycerol concentrations were elevated (83 +/-9 vs. 51 +/-4 mumol/l $p< 0.005$), but fasting glucose and non-esterified fatty acid (NEFA) concentrations were similar. Relatives of European origin did not differ from their European controls in any of these measurements. The glucose response to oral glucose was similar in relatives and controls, irrespective of ethnic group. The insulin responses were non-significantly greater in relatives from both ethnic groups. Proinsulin levels were not significantly different. Asian relatives had higher circulating glycerol and NEFA levels after oral glucose than Asian controls, but these differences were not observed in the European group. Insulin sensitivity was reduced in the Asian relatives compared to their controls (183 +/- 7 vs. 139 +/- 12 mumol /l/ min, $p<0.01$) but there was no difference in insulin sensitivity between the European relatives and European controls (167+/-11 vs. 160+/- 11mumol/l/min).

Conclusions: First-degree relatives of non-insulin-dependent diabetic patients of Asian, but not of European, origin are insulin insensitive in terms of both glucose metabolism and lipolysis, and have true hyperinsulinaemia. This suggests that insulin insensitivity may be an early abnormality in the development of non-insulin-dependent diabetes in the Asian population.

Islet amyloid polypeptide in patients with pancreatic cancer and diabetes.

Permert J, Larsson J, Westermark GT, Herrington MK, Christmanson L, Pour PM, Westermark, P, Adrian TE. New England Journal of Medicine. 1994: 330: 313-8.

Background: The diabetes mellitus that occurs in patients with pancreatic cancer is characterized by marked insulin resistance that declines after tumour resection. Islet amyloid polypeptide (IAPP), a hormonal factor secreted from the pancreatic beta cells, reduces insulin sensitivity in vivo and glycogen synthesis in vitro. In this study, we examined the relation between IAPP and diabetes in-patients with pancreatic cancer.

Methods: We measured IAPP in plasma from 30 patients with pancreatic cancer, 46 patients with other cancers, 23 patients with diabetes and 25 normal subjects. IAPP immunoureactivity and IAPP messenger RNA were studied in pancreatic cancers, pancreatic tissue adjacent to cancers, and normal pancreatic tissue.

Results: Plasma IAPP concentrations were elevated in the patients with pancreatic cancer as compared with the normal subjects (mean [+/-SD], 22.3 +/- 13.6 vs. 8.0 +/- 5.0 pmol per liter; $p < 0.001$), normal in the patients with other cancers, and normal or low in the patients with diabetes. Among the patients, with pancreatic cancer, the concentrations were 25.0 +/- 8.7 pmol per liter in the 7 patients with diabetes who required insulin 31.4 +/- 12.6 pmol per liter in the 11 patients with diabetes who did not require insulin, and 12.2 +/- 2.4 pmol per liter in the 9 patients with normal glucose tolerance (3 patients had impaired glucose tolerance; their mean plasma IAPP concentration was 11.7 +/- 5.5 pmol per liter). Plasma IAPP concentrations decreased after surgery in the seven patients with patients with pancreatic cancer who were studied before and after subtotal pancreatectomy (28.9 +/- 16.4 vs. 5.6 +/- 3.4 pmol per liter, $p=0.01$). Pancreatic cancers contained IAPP but the concentrations were lower than in normal pancreatic tissue (17 +/- 16 vs. 183 +/- 129 pmol per gram, $P < 0.001$). In samples from the patients with both pancreatic cancer and diabetes, immunostaining for IAPP was reduced in islets of pancreatic tissue surrounding the tumour; in situ hybridization studies suggested that transcription occurred normally in these islets.

Conclusions: Plasma IAPP concentrations are elevated in patients with pancreatic cancer who have diabetes. Since IAPP may cause insulin resistance, its overproduction may contribute to the diabetes that occurs in these patients.

Assessment of insulin action in NIDDM in the presence of dynamic changes in insulin and glucose concentration.

Katz H, Homan M, Jensen M, Caumo A, Cobelli C, Rizza R. Diabetes. 1994; 43: 289-96.

Both glucose and insulin are important regulators of glucose uptake and hepatic glucose release. Because insulin concentrations rarely if ever increase under daily living conditions, unless glucose concentrations also increase, we sought to determine whether hepatic and extrahepatic responses to changes in insulin and glucose concentration are impaired in patients with non-insulin-dependent diabetes mellitus (NIDDM). To address this question, glucose metabolism was measured in diabetic and non-diabetic subjects. A computer-driven infusion system was used to produce a non-diabetic postprandial insulin profile in both groups while sufficient exogenous glucose was infused to mimic non-diabetic-postprandial glucose concentrations. Although NIDDM was associated with greater ($p<0.05$) hepatic glucose release both before and during the prandial insulin infusion, suppression did not differ in the diabetic and non-diabetic subjects (-1.06 +/- 0.20 vs. -0.86 +/- 0.15 mmol/kg every 4 h). In contrast, stimulation of both glucose disappearance (0.77 +/- 0.27 vs. 1.68 +/- 0.27 mmol/kg every 4 h) and forearm glucose uptake (187 +/- 81 vs. 550 +/- 149 mumol/dl every 4 h) was lower ($p < 0.05$) in diabetic than in non-diabetic subjects. Thus, despite increased basal rates of glucose production, obese individuals with NIDDM had decreased stimulation of glucose disappearance but normal suppression of hepatic glucose release in response to non-diabetic prandial glucose and insulin concentrations. These data indicate that the increase in glucose that occurs with carbohydrate ingestion is likely to compensate for hepatic but not extrahepatic insulin resistance.

Role of human skeletal muscle insulin receptor kinase in the in vivo insulin resistance of non-insulin-dependent diabetes mellitus and obesity.

Nolan JJ, Freidenberg G, Henry R, Reichart D, Olefsky JM. Journal of Clinical Endocrinology and Metabolism.1994; 78: 471-7.

To assess the role of insulin receptor (IR) tyrosine kinase in human insulin resistance, we examined the kinase activity of IR of skeletal muscle biopsies from eight leans and five obese non-diabetics and six obese subjects with non-insulin-dependent diabetes mellitus (NIDDM). Biopsies were taken during euglycaemic clamps at insulin infusion rates of 0, 40, and 120, and 1200 mU/m2.min. IRs were immobilized on insulin agarose beads, and autophosphorylation and histone 2B phosphorylation were measured. Phosphatase and protease inhibitors preserved in the vivo phosphorvlation state of the IRs. Glucose disposal rates (GDR) were reduced according to insulin dose by 23-30% in the obese ($p < 0.05$) and 43-64% in the NIDDM subjects ($p < 0.0005$). IR autophosphorylation was increased up to 9-fold in controls and was reduced ($p= 0.04$) in NIDDM compared to obese subjects. Histone-2B kinase was increased up to 6-fold in controls and was reduced by 50% in NIDDM. Kinase values by both methods were similar in lean and obese controls. In vivo stimulation of kinase was well correlated to the increase in GDR, as was the decrement in kinase in NIDDM to the decrement in GDR. These results suggest that defects in muscle IR kinase are significant in the in vivo insulin resistance of NIDDM, but not that of obesity.

Role of hepatic glucose production and glucose uptake in the pathogenesis of fasting hyperglycemia in type 2 diabetes: normalization of glucose kinetics by short-term fasting.

Fery F. Journal of Clinical Endocrinology and Metabolism. 1994; 78: 536-42.

The relative impact of hepatic glucose production (HGP) and peripheral glucose uptake (GU) on plasma glucose concentration was assessed in 54 noninsulin-dependent diabetes mellitus (NIDDM) and 50 control subjects submitted to a variable period of fasting (14-108h) with special focus on the normal and low hyperglycemic range. Within each population we found a highly significant ($p < 0.001$) positive correlation between plasma glucose concentration and HGP in the whole range of glycemia, but the slope of the regression line was steeper ($p < 0.001$) in the diabetic than in the control group. The two curves intersected at a glucose level of 4.0 mmol/L. Therefore, for a given HGP rate above the intersection point, diabetic patients had a higher plasma glucose concentration than nondiabetic individuals, owing to an approximately 15% reduction ($p < 0.025$) in the metabolic clearance rate, despite the fact that the plasma insulin level was 2-fold higher ($p<0.05$) in the diabetic patients. When diabetic and nondiabetic subjects were compared at a similar low glucose level of 4.0 mmol/L brought about by short-term fasting; all parameters of glucose kinetics were identical in both groups. We thus conclude that 1) HGP is the major determinant of plasma glucose concentration in control as well as in diabetic subjects whatever the nutrition state; 2) the slight hyperglycemia prevailing in mild NIDDM results from the combination of an impaired insulin-induced inhibition of HGP and stimulation of GU because both parameters are inappropriately normal in the face of elevated plasma glucose and insulin levels; and 3) the normalization of GU and HGP after short-term fasting suggests that pathways of noninsulin-mediated GU operate in normal way in NIDDM.

Insulin production following intravenous glucose, arginine, and valine, different pattern in patients with impaired glucose tolerance and non-insulin-dependent diabetes mellitus.

Fasching P, Ratheiser K, Nowotny P, Uurzemann S, Parzer S, Waldhausi W. Metabolism: Clinical and Experimental. 1994; 43: 385-9.

To better understand abnormal insulin production (IP) in states of carbohydrate intolerance, insulin release was quantified following equimolar (2.4 mmol/kg) infusions of glucose, arginine, and valine in healthy subjects ([HS] age, 45 +/- 3 years, body mass index [BMI, kg/m2], 26.3 +/- 2.4; means +/- SEM), obese subjects with impaired glucose tolerance ([IGT] age, 43 +/- 5 years; BMI, 35.4 +/- 2.4), and non-obese patients with chronic non-insulin-dependent diabetes mellitus ([NIDDM] age, 55 +/- 3 years; BMI, 26.4 +/- 1.4; duration of disease, 13 +/- 3 years). There were eight subjects per group. Incremental IP (metabolic clearance rate of C-peptide [MCRCP] x total incremental area under the curve of plasma C-peptide [AUCCP], pmol/kg) following substrate infusion was as follows: glucose: HS, 227 +/- 14; IGT, 1,050 +/- 184 ($p < .001$ v HS); NIDDM, 114 +/- 27 ($p < .001$ v HS); arginine: HS, 139 +/- 23; IGT, 488 +/- 106 ($p < .01$ v HS); NIDDM, 206 +/- 47; and valine; HS, 21 +/- 7; IGT, 32 +/- 10; NIDDM, 54 +/- 12 ($p < .01$ v HS). The fractional clearance rate ([FCR] k, %/min) was impaired in IGT and NIDDM for glucose (HS, 3.9 +/- 0.4; IGT, 2.3 +/- 0.3 [$p < .01$] v HS); NIDDM, 1.4 +/- 0.1 [$p < .001$ v HS]), arginine (2.4 +/- 0.1; 1.9 +/- 0.2 [$p < .01$ v HS]; 1.9 +/- 0.2[$p< .01$ v HS]); and valine (0.95 +/- 0.06; 0.65 +/- 0.09 [$p < 0.5$ v HS]; 0.74 +/-0.1 [$p < .05$ v HS]).

EPIDEMIOLOGY

Predictors of mortality from idiopathic dilated cardiomyopathy in 356, 222 men screened for the Multiple Risk Factor Intervention Trial.

Coughlin SS, Neaton JD, Sengupta A, Kuller LH. American Journal of Epidemiology. 1994; 139: 166-72.

Possible predictors of mortality from idiopathic dilated cardiomyopathy were studied in 356, 222 men who were screened as part of the Multiple Risk Factor Intervention Trial. The vital status of each member of this cohort was ascertained through 1986. Death certificates were obtained from state health departments and coded by a trained nosologist. Individuals with a history of myocardial infraction were excluded. A total of 206 deaths due to idiopathic dilated cardiomyopathy occurred in the cohort of 356,222 men after an average of 12 years of follow-up. The age-specific rates of mortality from idiopathic dilated cardiomyopathy increased from 0.10 per 10,000 person-years among men aged 35-39 years to 1.16 per 10,000 person-years among men aged 55-57 years. The proportional hazards model was used to obtain adjusted estimates of relative risks. Statistically significant, independent associations were observed with cigarettes smoked per day ($p < 0.001$), diastolic blood pressure ($p < 0.001$, and diabetes mellitus (relative risk (RR) = 2.97, $p < 0.001$). Black race was also associated with an increased risk of death from idiopathic dilated cardiomyopathy (RR = 1.59 and $p = 0.045$ without adjustment for income; RR = 1.58 and $p = 0.058$ with adjustment for income). No association was found with serum cholesterol or income. The information about possible risk factors obtained in this study may contribute to future preventive programs for idiopathic dilated cardiomyopathy.

South African Indians show a high prevalence of NIDDM and bimodality in plasma glucose distribution patterns.

Omar MA, Seedat MA. Dyer RB, Motala AA, Knight LT, Becker PJ. Diabetes Care: 1994, 17: 70-3.

Objective: To determine the prevalence of diabetes mellitus and impaired glucose tolerance (IGT) and to test for bimodality in the plasma glucose distribution in South African Indians.

Research Design and Methods: Subjects were selected by systematic cluster sampling in various areas of Durban. They underwent a modified glucose tolerance test whereby fasting and 2-h postglucose (75 g) plasma glucose levels were measured. The program MIX was used to test for bimodality in the plasma glucose distribution.

Results: We tested 2,479 subjects (1,441 women and 1,038 men). Based on the revised World Health Organization criteria, the crude prevalence of diabetes mellitus was 9.8%, and the crude prevalence of IGT was 5.8%, the age and sex-adjusted prevalence was 13.0 and 6.9% respectively. IGT was significantly more common in men (7.6%) than in women (4.4%). Obesity was a feature of both diabetes mellitus and IGT, particularly in women. Both fasting and 2-h plasma glucose values did not conform to a single normal distribution pattern in any age-group, whereas unequivocal evidence of bimodality was seen in the 55-to 74-year age-group of both sexes for fasting and 2-h glucose and also in the 2-h levels of men in the 25- to 34-year age-group.

Conclusions: This study has highlighted a high prevalence of non-insulin dependent diabetes mellitus in South African Indians and bimodality in the plasma glucose distribution.

Incidence of renal failure in NIDDM. The Oklahoma Indian diabetes study.

Lee ET, Lee VS, Lu M, Lee JS, Russell D, Yeh J. Diabetes. 1994; 43: 572-9

The incidence of and risk factors for renal failure were determined in 912 Oklahoma Indians with non-insulin-dependent diabetes mellitus in a follow-up study conducted between 1987 and 1990. The incidence rate was 15.7/1.000 person-years after an average follow-up time of 10.2 years. Among those who had no qualitatively positive proteinuria at baseline, the incidence of renal failure was 10.3/1,000 person-years compared with 19.3- and 56.2/1,000 person-years, respectively, in those with slight and heavy proteinuria at baseline. Fasting plasma glucose (FPG) > or = 11.1 mM (200 mg/dl) increased the risk of renal failure to 2.9- fold (95% confidence interval [CI] = 1.9-4.6) higher than a level < 7.8 mM (140mg/dl), and twofold (95% [CI = 1.4-3.1) higher than a level between 7.8 (140 mg/dl) and 11.1 mM (200mg/dl.) The hypertensive patient had twice the incidence of renal failure than the

normotensive subject (rate ratio = 2.1, 95% CI =1.4-3.0). Patients with a lower blood pressure under antihyprtensive medication had a lower incidence of renal failure than those whose hypertension remained uncontrolled with or without use of medication. Significant independent risks factors for renal failure, identified from Cox's proportional hazards model, were duration of diabetes, FPG, age hypertension, and insulin use ($p < 0.05$). In-patients without proteinuria at baseline, FPG and hypertension were significant predictors of renal failure as identified by multivariate analyses, whereas in patients who had proteinuria at baseline, insulin use was significant. Thus, hyperglycemic and hypertension control are suggested strongly for diabetic Oklahoma Indians as potential strategies to prevent the development of rental failure.

The Gulf War and diabetes mellitus.
Rubinstein A, Koffler M, Villa Y, Graff E. Diabetic Medicine. 1993; 10:774-6.

The Gulf war was a traumatic and stressful event for the inhabitants of Tel-Aviv and vicinity. The entire population changed its way-of-life. In order to evaluate the influence of the war stress on glucose control, we reviewed the charts of all diabetic patients attending the outpatient clinics at the Tel-Aviv Medical Centre, whose weight and glycated haemoglobin was determined between 15.1.91 and 2.5.91 (the war period), with comparative measurements within 4 ½ months both before and after these dates. Sixty-six patients with non-insulin dependent diabetes mellitus (NIDDM) and 16 with insulin-dependent diabetes mellitus (IDDM) were examined. During the war, their glycated haemoglobin increased by 10.1 to 10.9% and from 9.6 to 10.2% respectively. Weight increased from 76.1 to 77.5 kg in the NIDDM and from 63.2 to 64.7 kg in the IDDM patients. Both measurements returned to baseline after the war. No correlation was found between the changes in glycated haemoglobin and weight.

Determinants of incident non-insulin-dependent diabetes mellitus among blacks and whites in a national sample. The NHANES I Epidemiologic Follow-up Study.
Lipton RB, Liao Y, Cao G, Cooper RS, McGee D. American Journal of Epidemiology 1993; 138: 826-39.

The excess incidence of non-insulin-dependent diabetes mellitus noted among African Americans in the past two decades may be attributable to variations in the distribution of specific risk factors, or the impact of these risk factors may differ by ethnicity or sex. Over the 16 years (1971-1987) of the first National Health and Nutrition Examination Survey (NHANESI) Epidemiologic Follow-up Study, 880 incident cases of diabetes mellitus developed among, 11,097 white and black participants who were between the ages of 25 and 70 years at baseline. There were substantial differences among the four race/sex group with respect to age at baseline, as well as marked differences in the distribution of several major risk factors for diabetes, including obesity, subscapular and triceps skinfold thickness, blood pressure, income, activity, and educational level. The age adjusted incidence of diabetes over the course of the study was 15.0% among black women, while it was 10.9% among black men. White women and men experienced similar, more moderate risks of 7.0% and 6.9% respectively. The 100% excess risk among black women and the 50% excess among black men can in large measure explain the recent marked increase in diabetes rates in the black community. Furthermore, at nearly every level of obesity, blacks had a higher risk of diabetes than whites, suggesting that other factors contributed to risk. A significant interaction between race and body mass index [weight (kg)/height $(m)^2$] was likewise demonstrated in multivariate analysis. Baseline age, race, body mass index and ratio of subscapular skinfold to triceps skinfold were significantly related to incident diabetes, both overall and in separate models for men and women; in the entire cohort and in women alone, blood pressure, activity level, and education also contributed to risk. Other interactions were tested but were not found to be important. Despite sampling difficulties and inconsistencies in the data, the NHANES I Epidemiologic Follow-up Study provides evidence that the association of anthropometric and sociodemographic variables with diabetes may vary among subgroups which have different mean levels and distributions of these risk factors.

CLINICAL

The size of the pancreas in diabetes mellitus.
Alzaid A, Aideyan O, Nawaz S. Diabetic Medicine. 1993; 10: 759-63.

To determine whether there was an association between the size of the pancreas and the type of diabetes, ultrasonography of the pancreas was performed on 57 diabetic patients 14 with Type 1 (insulin-dependent) diabetes, 10 insulin-treated and 33 tablet-treated patients with Type 2 (non-insulin-dependent) diabetes, and 19 non-diabetic subjects. The pancreas of patients with Type 1 diabetes was markedly smaller ($p < 0.0001$) than the pancreas in non-diabetic subjects. The pancreas of patients with Type 2 diabetes was more moderate in size larger ($p < 0.001$) than that of Type 1 diabetic patients but smaller. ($p < 0.5$) than the pancreas of the control group. Pancreatic size of patients with Type 2 diabetes was also related to basal insulin secretion with insulin-deficient patients (low or undetectable C- peptide) having smaller ($P < 0.05$) pancreases than those with normal insulin secretion. There was no difference in the size of the pancreas in the different treatment groups of Type 2 diabetic patients. Pancreatic size did not correlate with age, body mass index or the duration of diabetes. We conclude that the pancreas is a smaller organ in patients with diabetes mellitus and that the decrement in size is maximal in insulin-dependent/insulin-deficient subjects. Ultrasonography, therefore, can potentially serve to discriminate between he different types of diabetes.

Dermatoglyphics in type 1 diabetes mellitus.
Ziegler AG, Mathies R, Ziegelmayer G, Baumgartl HJ, Rodewald A. Diabetic Medicine. 1993; 10: 720-4.

Although fingerprints and handprints are widely used in criminology, it is only recently that this approach has been applied to the filed of medical and genetic diagnoses. In order to investigate dermatoglyphics in Type 1 diabetes mellitus, quantitative characteristics of fingers and palms (ridge count and main line indices) as well as qualitative parameters such as digital and interdigital patterns, the position of the palmar axial triradii and main line courses were analysed in 88 male and 108 female Type 1 diabetic patients and compared with data from 100 male and 99 female normal controls. Type 1 diabetic patients show a lower third finger ridge count ($p < 0.05$) and a-b ridge count ($p < 0.001$) and higher transversality of the main lines as indicated by the main line index value ($p < 0.001$) or the ending of the main line A in a specific sector 5, 5", and 5" ($p < 0.001$) compared with controls. In addition, diabetic patients show higher frequency of palmar axial t' and t" triradii ($p < 0.001$) and a lower frequency of 'true' patterns in the fourth interdigital and thenar area ($p < 0.001$) than controls. By multivariate analysis of quantitative and qualitative variables a predictive value of 78.6% and 77.3% respectively, for male, and 81.4% and 82.2% respectively, for female Type 1 diabetic patients was found. In conclusion, dermatoglyphics seem to be an interesting tool for genetic studies related to Type1 diabetes.

IMMUNOLOGY

Detection of GAD65 antibodies in diabetes and other autoimmune diseases using simple radioligand assay.
Petersen JS, Hejnaes KR, Moody, A, Karlsen AE, Marshall MO, Hoier Madsen M, Boel E, Michelsen BK, Dyrberg T. Diabetes. 1994; 43: 459-67.

Autoantibodies to glutamic acid decarboxylase (GAD) are frequent at or before the onset of insulin-dependent diabetes mellitus (IDDM). We have developed a simple, reproducible, and quantitative immunoprecipitation radioligand assay using as antigen

in vitro transcribed and translated [35S] methionine-labeled human islet GAD65. By using this assay, 77% (77 of 100) of serum samples from recent-onset IDDM patients were positive for GAD65 antibodies compared with 4% (4 of 100) of serum samples from healthy control subjects. In competition analysis with unlabeled purified recombinant human islet GAD65, binding to tracer was inhibited in 74% (74 of 100) of the GAD65-positive IDDM serum samples compared with 2% of the control samples. The levels of GAD antibodies expressed as an index value relative to a standard serum, analyzed with or without competition, were almost identical (r = 0.991). The intra- and interassay variations of a positive control serum sample were 2.9 and 7.6%, respectively (n = 4). The frequency of GAD antibodies was significantly higher with IDDM onset before the age of 30 (80%, 59 of 74) than after the age of 30 (48%, 10 of 21) (P < 0.01). The prevalence of islet cell antibodies showed a similar pattern relative to age at onset. Because simultaneous occurrences of multiple autoimmune phenomena are common, we analyzed sera from patients with other autoimmune diseases. The frequency of GAD antibodies in sera positive for DNA autoantibodies (8% [2 of 25] and 4% [1 of 25 in competition analysis) or rheuma factor autoanitibodies [12% (4 of 35) and 3% (1 of 35) in competition analysis] was not different from that that in control samples. In contrast, in sera positive for ribonucleoprotein antibodies the frequency of GAD antibodies was significantly increased (73% [51 of 70] and 10% [7 of 70] in competition analysis [P < 0.025]). In conclusion, even large numbers of serum samples can now be tested for GAD65 antibodies in a relatively short time, allowing screening of individuals without a family history of IDDM for the presence of this marker.

Associations of anti-GAD antibodies with islet cell antibodies and insulin autoantibodies in first-degree relatives of type I diabetic patients.
Roll U, Christie MR, Standl E, Ziegler AG. Diabetes. 1994; 43: 154-60.

Sera from 114 first-degree relatives of insulin-dependent-diabetes mellitus (type I diabetes) patients and 81 healthy individuals living in Germany were analyzed for antibodies to rat brain glutamic acid decarboxylase (GAD-ab) using an immunopracipitation assay. The determination of GAD –ab in the 81 islet cell antibody (ICA) and insulin autoantibody (IAA) negative healthy individuals established a normal range (mean +/- 2 SD); 2 healthy individuals (2.5%) possessed GAD-ab levels above this range but became negative on follow-up. None of 86 ICA-/IAA-first-degree relatives had GAD-ab; whereas, 42.9% of 28 ICA+ and/or IAA+ relatives were positives were positive for GAD-ab. Presence of GAD-ab was negatively correlated with IAA (P = 0.02) and positively with ICA (P = 0.0006). Follow-up samples were obtained from 25 of 28 ICA+ and/or IAA+ relatives with a mean (+/-SD) follow-up period of 20.6 +/- 12.1 months. In these 25 relatives, GAD-ab were positive in 70% ICA+/IAA-, 0% ICA-/IAA+, and 57.1% ICA+/IAA+ relatives in the first sample and in 57.1% ICA+/IAA-, 0% ICA-/IAA+, and 70% ICA+/IAA+ relatives in the last sample. GAD-ab, once detected, persisted in 9 of 11 GAD-ab+ relatives. Of the relatives, 2converted to GAD-positivity, concomitant with the appearance of ICA, and 2 others lost GAD-ab during follow-up. Of the 28 ICA+ and/or IAA+ relatives, 6 progressed to overt type I diabetes on follow-up, and GAD-ab was detectable in 4 of these relatives.

Cow's milk exposure and type I diabetes mellitus. A critical overview of the clinical literature.
Gerstein HC. Diabetes Care. 1994; 17: 13-9.

Objective: To critically review and summarize the clinical evidence relating a short duration of breast-feeding or early cow's milk exposure to insulin-dependent (type I) diabetes.

Research Design and Methods: All relevant citations retrieved through comprehensive searching of the medical literature were critically reviewed and analyzed. Those case-control studies that minimized the possibility of bias were meta-analyzed to determine overall odds ratios (ORs) and 95% confidence intervals (Cls).

Results: Ecological and time-series studies consistently showed a relationship between type I diabetes and either cow's milk exposure or diminished breast-feeding. In the case-control studies, patients with type I diabetes were more likely to have been breast-fed for < 3 months (overall OR 1.43; 95% CI 1.15- 1.77) and to have been exposed to cow's milk before 4 months (overall OR 1.63; 95% CI 1.22-2.17). Slightly lower ORs were obtained when all of the case-control studies were meta-analyzed in a sensitivity analysis.

Conclusions: Early cow's milk exposure may be an important determinant of subsequent types I diabetes and may increase the risk approximately 1.5 times.

Peptide therapy for diabetes in NOD mice.
Elias D. Cohen IR. Lancet. 1994; 343:704-6.

NOD mice spontaneously develop autoimmune diabetes that mimics insulin-dependent diabetes mellitus (IDDM) in man. A peptide of the 60 kDa heat shock protein (hsp60), designated p277, can serve as a target for diabetogenic T-cell clones, and diabetes was prevented by using the p277 peptide to turn off anti-p277 immunity early in life. We report that the p277 peptide, administered once, can arrest the autoimmune process even after it is far advanced. Successful therapy was associated with down-regulation of the autoimmune process and regression of islet inflammation. Thus the immune system is responsive to manipulation by a specific signal even in the face of a virulent, full-blown autoimmune process.

TREATMENT

Effects of a small quantity of omega-3 fatty acids on cardiovascular risk factors in NIDDM. A randomized, prospective, double blind controlled study.
Axelrod L, Camuso J, Williams E, Kleinman K, Briones E, Schoenfeld D. Diabetes Care. 1994; 17: 37-44.

Objective: To study the effects of a low dose of omege-3 fatty acids on platelet function and other cardiovascular risk factors in patients with non-insulin-dependent diabetes mellitus (NIDDM).

Research Design and Methods: We performed a randomized, prospective, double-blind, controlled study of a low dose of omege-3 fatty acids (2.5 g/day) in 20 ambulatory subjects with NIDDM. Subjects ingested five 1-g fish oil capsules each containing 0.5-g omega-3 fatty acids of five 1-g safflower oil capsules per day for 6 weeks followed by a 6-week washout period.

Results: Nine subjects completed the study in each group. Both groups exhibited moderate control of glucose levels; modest elevations in baseline total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride (TG) levels; and normal blood pressure values. In the fish oil group, plasma omega-3 fatty acid levels increased significantly. Fish oil significantly reduced the slope of the dose-response curves for collagen-induced platelet aggregation to one-third the value observed with safflower oil. No difference was observed in collagen- induced production of the thromboxane A2 (TXA2, measured as the stable derivative TXB2), or in adenosine-5'-diphosphate- (ADP) induced platelet aggregation or TXA2 generation. Patients with high initial collagen-induced platelet TXA2 production showed a significantly larger drop after fish oil than safflower oil. Fish oil significantly reduced TG levels by 44 mg/dl and decreased upright systolic blood pressure (sBP) by 8 mmHg compared with safflower oil. Fish oil caused a significant but small increase in HbA1c (0.56%) and total cholesterol (20 mg/dl) but had no effect on fasting glucose, high-density lipoprotein cholesterol, or LDL-cholesterol levels.

Conclusions: Small doses of fish oil inhibit platelet aggregation and TXA2 production, reduce upright sBP and TG levels, and have only a small effect on glucose and cholesterol levels in patients with moderately controlled NIDDM. Small quantities of omega-3 fatty

acids or dietary fish are safe and potentially beneficial in NIDDM patients.

Long-term randomized placebo-controlled double blind therapeutic comparison of glipizide and glyburide. Glycaemic control and insulin secretion during 15 months.

Birkeland KI, Furuseth K, Melander A, Mowinckel P, Vaaler S. Diabetes Care. 1994; 17(1): 45-9

Objective: To examine the long-term (15 months) effects on glycaemic control and insulin secretion of glipizide and glyburide treatment in-patients with non-insulin-dependent diabetes mellitus (NIDDM).

Research Design and Methods: Prospective, randomized, double-blind, placebo-controlled study on 46 NIDDM patients comparing fasting levels and test-meal responses of glucose and insulin during 15 months of follow-up.

Results: A comparable reduction in HbA_{1c} levels by both agents versus placebo was observed throughout the study period, but after a marked initial reduction in both sulfonylurea groups, all three groups showed gradually increasing HbA_{1c} levels. However, both glipizide and glyburide achieved and maintained lowered postprandial glucose levels and increased fasting and postprandial insulin levels compared with placebo.

Conclusions: Both glipizide and glyburide may achieve and maintain glycaemic reduction and stimulation of insulin secretion during long-term treatment. However, these agents do not prevent the gradual increase in overall glycaemia that develops over time in NIDDM patients.

Mortality and treatment side-effects during long-term intensified conventional insulin treatment in the Stockholm Diabetes Intervention Study.

Reichard P, Pihl M. Diabetes. 1994; 43:313-7.

Altogether, 102 patients were randomized to intensified conventional treatment (ICT) (n=48) or standard treatment (ST) (n=54). After 7.5 years, 89 patients remained, and it was shown that microangiopathy was retarded by the lower blood glucose concentrations seen in the patients in the ICT group. HbA_{1c} was reduced from (means +/- SE 9.5 +/- 0.2% to 7.1 +/- 0.1% in the ICT group and from 9.4 +/- 0.2% to 8.5 +/- 0.1% in the ST group ($P < 0.001$). Of the patients, 4 in the ICT group and 3 in the ST group died. Mortality was predicted by albuminuria, the amplitude of the sural nerve action potential, and the test of arm blood flow during contraction of the contralateral hand (sympathetic nerve function) at baseline ($P < 0.05$). Weight increased by 4.4 +/- 1.1 kg in the ICT group and 1.8 +/- 0.7 kg in the ST group ($P = 0.05$). Atherosclerosis, measured with digital pulse plethysmography, was approximately the same in the groups at baseline and after five years. In each group, 3 patients had myocardial infractions, and 2 from each group had ketoacidosis once. There was a mean of 1.1 episodes per patient and per year of serious hypoglycemia in the ICT group and 0.4 episodes per patient and per year in the ST group. No adverse incidents or accidents were observed in either group, and there were no differences between the groups with regard to cognitive function measured with a battery of tests.

Pronounced blood glucose-lowering effect of the antilipolytic drug acipimox in non-insulin- dependent diabetes mellitus patients during a 3-day intensified treatment period.

Worm D, Henriksen JE, Vaag A, Thye-Ronn P, Melander A, Beck-Nielsen H. Journal of Clinical Endocrinology and Metabolism. 1994; 78:717.21.

Acute administration of the antilipolytic nicotinic acid analog acipimox to patients with non-insulin-dependent diabetes mellitus (NIDDM) is associated with increased peripheral and hepatic insulin sensitivity. However, long term acipimox treatment (250 mg, 3 times/24 h) of NIDDM patients does not improve blood glucose control, possibly due to rebound lipolysis. The current study assessed the influence of intensified acipimox administration (125 mg, 12 times/24 h) on diurnal plasma profiles of glucose, insulin, nonesterified FFA (NEFA), and triglycerides during a 3-day period. Eight NIDDM patients [mean age, 58.9 year (range, 46-68); mean body mass index, 31.4 kg/m2 (range, 24.9- 39.6)] were included in a randomized, double blind, placebo controlled, cross-over study. Blood samples were collected every second hour during the study. The acipimox and placebo treatments were separated by a 2-week washout period. Acipimox treatment was associated with reduced diurnal mean plasma concentrations of NEFA [0.26 +/- 0.03 (+/- SEM) vs. 0.63 +/- 0.06 mmol/L; $P < 0.001$], triglycerides (1.74 +/- 0.21 vs. 2.10 +/- 0.18 mmol/L; $P < 0.03$), glucose (12.7 +/- 1.0 vs. 15.8 +/- 1.2 mmol/L; $P < 0.002$), and insulin (157 +/- 21 vs. 207 +/- pmol/L; $P < 0.05$). However, despite the overall reduction in mean NEFA, during acipimox treatment NEFA increased from days 1-3 (0.18 +/- 0.03 vs. 0.34 +/- 0.04 mmol/L; $P < 0.001$), whereas plasma glucose (13.4 +/- 1.2 vs. 12.3 +/- 0.9 mmol/L; $P < 0.03$) and plasma insulin (168 +/- 23 vs. 148 +/- 17 pmol/L; $P < 0.04$) decreased steadily from days 1-3 during active treatment. In conclusion, inhibition of lipolysis using the intensified acipimox treatment regiment was associated with a pronounced blood glucose and plasma insulin lowering effect. However, minor rebound effects of lipolysis occurred in some patients despite the presence of allegedly effective acipimox levels. This suggests that caution should be employed concerning long term use of acipimox as a hypoglycemic agent in NIDDM patients.

Changes in insulin-like growth factor (IGF)-binding proteins after IGF-I injections in non-insulin-dependent diabetics.

Young SC. Clemmons DR. Journal of Clinical Endocrinology and Metabolism. 1994; 78:609-14.

Insulin-like growth factor-I (IGF-I) exerts insulin-like effects on fuel metabolism and suppresses insulin secretion in normal subjects. Unlike insulin, circulating IGF-I is bound to high affinity binding proteins (IGFBPs), which modulate IGF action. We have previously shown that IGF-I administration increases IGFBP-1 and -2 and reduces IGFBP-3 in normal subjects. To determine whether similar effects could be demonstrated in an insulin- resistant state, we administered recombinant human IGF-I for 4 days by sc injection to six obese type II diabetics and determined the effects on fasting concentrations of glucose, C- peptide, IGF-I, and IGFBPs. The changes that occurred in glucose C-peptide and IGFBP levels during oral glucose tolerance testing were also quantified. There was no significant decrease in the mean fasting serum glucose or C-peptide level despite a 7-fold increase in mean fasting IGF-I concentrations ($P < 0.01$). As expected, during oral glucose tolerance testing, the area under the curve of C-peptide was suppressed after an injection of IGF-I ($P < 0.05$), but the area under the glucose curve did not change significantly. Mean fasting daily IGFBP-1 and -2 rose 2-fold ($P < 0.05$) and 1.9-fold ($P < 0.05$), respectively, whereas IGFBP-3 fell by 16% ($P < 0.01$) after 4 days of injections. IGFBP-1 was suppressed by 32% after oral glucose alone, whereas an injection of IGF-I plus oral glucose were associated with a more marked fall of 53% (despite suppression of C-peptide). In contrast, mean IGFBP-2 concentrations rose by 40% ($P < 0.05$) after IGF-I and oral glucose, but there was no change in response to oral glucose alone. These changes in IGFBP-1, -2 and -3 could alter the distribution of IGF-I among the various IGFBPs in the circulation. They may also prove to be a marker of metabolic responsiveness to IGF-I. In a substrate-sufficient state, e.g. after oral glucose, IGFBP-1 and -2 show opposite acute responses to IGF-I, and IGF-I has an apparent acute insulin-like effect on IGFBP-1 concentrations that differs from its longer-term effect.

Effects of the carbohydrase inhibitor miglitol in sulfonylureatreated NIDDM patients.

Johnston PS, Coniff RF, Hoogwerf BJ, Santiago JV, Pi-Sunyer FX, Krol A. Diabetes Care. 1994; 17: 20-9.

Objective: To examine the affects of the carbohydrase inhibitor miglitol (BAY m 1099) on the metabolic profiles of non-insulin-dependent diabetes mellitus (NIDDM) patients suboptimally controlled on maximal daily doses of sulfonylurea (SFU) agents.

Research Design and Methods: Multicenter, double blind, randomized, placebo-controlled 14-week clinical trial with six-week, singleblind placebo lead-in and run-out periods. NIDDM volunteers (192) with fasting plasma glucose (FPG) 140-250 mg/dl and haemoglobin A_{1c} (HbA_{1c}) 6.5-12.0% after at least 4 weeks of treatment with SFU at maximal dose were stratified by baseline HbA_{1c} (above and below 9.0%) and then randomly assigned within strata to placebo (n = 63), 50 mg miglitol 3 times a day (n = 61), or 100 mg miglitol 3 times a day (n = 68). Efficacy was assessed by HbA_{1c}, FPG, insulin, and lipid concentrations, and by plasma glucose and serum insulin responses to a standard meal.

Results: In the 50 and 100 mg miglitol treatment groups the mean changes from baseline in HbA_{1c} (with placebo values subtracted) were 0.82 and 0.74%, respectively, and were highly significant ($P = 0.0001$ in each case). Mean peak plasma glucose levels after a standard test meal were comparably lowered by 57 mg/dl with the 50mg miglitol dose, and by 64 mg/dl with the 100 mg miglitol dose compared with placebo ($P = 0.0001$ for each), with associated reductions in integrated serum insulin response ($P < 0.05$). No significant drug-associated changes in FPG, insulin, or cholesterol levels were noted, but fasting triglyceride levels were lowered significantly with the 50mg miglitol dose. Miglitol's side effects were limited to flatulence, loose stools, and abdominal discomfort, which were dose-re-lated, rapidly resolved on drug discontinuation, and led to withdrawal from the study of 5 and 15% of patients taking 50 and 100 mg miglitol, respectively.

Conclusions: Miglitol may be indicated as effective adjuvant therapy in NIDDM patients with suboptimal metabolic control despite conventional treatment with diet and maximal daily doses of SFU. The dose of 50 mg miglitol 3 times a day may be preferable to 100 mg miglitol 3 times a day because of comparable efficacy and substantially reduced side effects.

Linear loss of insulin secretory capacity during the last six months preceding IDDM. No effect of antioedematous therapy with ketotifen.

Bohmer KP, Kolb H, Kuglin B, Zielasek J, Hubinger A, Lampeter EF, Weber B, Kolb-Bachofen V, Jastram HU, Bertrams J. Diabetes Care. 1994; 17: 138-41.

Objective: To investigate the effect of an antioedematous therapy with the histamine antagonist ketotifen on beta-cell function in late prediabetes.

Research Design and Methods: In a randomized double-blind placebo-controlled study, ketotifen was administered for 3 months to 9 islet cell antibody positive (ICA+) prediabetic patients with a firstphase insulin response (FPIR) below the 2.5^{th} percentile to preserve residual betal-cell function. Patients were followed by intravenous glucose tolerance tests (IVGTTs) every 4-6 weeks for determination of FPIR, HbA_1, ICAs, and insulin autoantibodies. In 5 patients, the immune activation state was followed by determination of serum levels of tumour necrosis factor-alpha (TNF-alpha), beta 2-microglobulin, and C-reactive protein (CRP).

Results: Seven of nine patients developed diabetes within one year of follow-up. Irrespective of treatment with ketotifen, a slow and linear decline ($P < 0.05$) of 1 + 3-min insulin values was observed in sequential IVGTTs in those 7 patients who developed insulin-dependent diabetes mellitus (IDDM) during follow-up. The 2 other patients showed wide fluctuations of the insulin response with a threefold increase of initial insulin levels. HbA_1 did not correlate with FPIR. Fasting blood glucose increased significantly during the study ($P < 0.05$). Individual levels of serum TNF-alpha, CRP, and beta 2-microglobulin did not change during the study.

Conclusions: The study could not demonstrate preservation of beta-cell function by ketotifen in the late stage before manifestation of clinical diabetes. Manifestation is preceded in the last 6 months by a steady loss of the FPIR without rapid deterioration immediately before diagnosis and without signs of increased immune activity.

Insulin receptor down-regulation and impaired antillipolytic action of insulin in diabetic patients after pancreas/kidney transplantation.

Boden G, Chen X, Ruiz J, Heifets M, Morris M, Badosa F. Journal of Clinical Endocrinology and Metabolism. 1994; 78: 657-63.

Patients with insulin-dependent diabetes who receive pancreas/kidney transplants lose their need for insulin injections, but they become hyperinsulinaemic and insulin resistant, and sometimes develop non-insulin-dependent diabetes mellitus. The reason for the insulin resistance is not well understood. Specifically, it is not known whether they become resistant to the action of insulin on lipid metabolism. Euglycaemic-hyperinsulinaemic clamps were performed in six pancreas/kidney (P/K) recipients, six kidney (K) recipients (to control for immunosuppressive therapy), and eight healthy controls. Measured were leg blood flow (by plethysmography), rates of lipolysis (with [2H5] glycerol), fatty acid oxidation (by indirect calorimetry), fatty acid reesterification (with [2H5] glycerol and [1-13C] palmitate), monocyte membrane insulin binding (with [125I] Tyr-A14 insulin), and insulin receptor mass (by RIA). Fasting plasma insulin concentrations were 2 times higher in P/K and K recipients (108 pmol/L) than in controls (54 pmol/L). Insulin receptor mass in solubilized monocyte membranes from P/K and K recipients was reduced by 61% and 63%, respectively, whereas insulin binding was reduced by 73% and 70%, respectively. P/K and K recipients were resistant to the inhibitory action of insulin on lipolysis (P/K vs. controls, $P < 0.01$; K vs. controls, $P < 0.02$) and on fatty acid reesterification (P/K vs. controls, $P < 0.02$; K vs. controls, $P < 0.03$). P/K recipients appeared to be more resistant than K recipients, but the differences between the two groups were not statistically significant. We conclude that P/K recipients were hyperinsulinaemic, had down-regulated the number of their monocyte insulin receptors, and were resistant to the antilipolytic action of insulin.

Long-term follow-up evaluation of blood glucose awareness training.

Cox DJ, Gonder-Frederick L, Julian DM, Clarke W. Diabetes Care. 1994; 17: 1-5.

Objective: Blood glucose awareness (BGAT) has been found effective in teaching individuals with insulin-requiring diabetes to improve their ability to better recognize blood glucose (BG) fluctuations. This study investigated whether subjects who underwent BGAT a mean of 4.9 years previously were superior to past control subjects in terms of their ability to recognize BG fluctuations, and whether past BGAT subjects had fewer automobile crashes and lost work days and better glycosylated haemoglobin than control subjects. Additionally, the beneficial effects of providing booster training to past BGAT subjects also was evaluated.

Research Design and Method: This study followed up 28 past BGAT subjects. Half of these subjects (n =14) received a simple boostertraining program. Twelve previous control subjects also were evaluated. Booster subjects were given a BGAT diary to complete for 2 weeks before evaluation. Evaluation for all subjects included completion of retrospective questionnaire on work and driving history, blood drawing for a glycosylated haemoglobin analysis, and having subjects estimate and measure their BG levels 50-80 times during a 3 to 4-week period during their daily routine.

Results: At long-term follow-up, BGAT subjects had significantly fewer automobile crashes than control subjects. BGAT subjects receiving booster training were significantly more accurate at estimating their BG levels and were more aware of hypoglycaemia.

Post hoc analyses indicated that the ability to accurately estimate BG fluctuations correlated positively with follow-up glycosylated haemoglobin and the number of hypoglycemic symptoms participants demonstrated. Both BGAT and control subjects demonstrated significantly improved glycosylated haemoglobin relative to baseline measures.

Conclusions: These data suggest that BGAT have long-term benefits, which can be enhanced with booster training. Specifically, BGAT and simple booster training may result in reduction of severe hypoglycemic episodes and automobile crashes in the long term.

Exercise for older patients: why it's worth your effort.
Rooney EM. Geriatrics. 1993; 48:68, 7-4, 77.

Two-thirds of all adults age 65 or older are either irregularly active or completely sedentary. With this inactivity comes an increased risk of chronic diseases, including coronary heart disease, hypertension, diabetes, osteoporosis, and depression. Adequate aerobic exercise – even when started as late as age 60 – is associated with a 1- to 2- year increase in life expectancy, as well as increased functional independence. Even chairbound patients can benefit from a program of simple exercises. To help prevent injuries, your exercise prescription should include stretching exercises and exercises to strengthen the muscle surrounding weak joints.

COMPLICATIONS

Effect of adjuvant therapy on development of diabetes in mouse and man.
Shehadeh N, Calcinaro F. Lancet. 1994; 343: 706-7.

Freund's complete adjuvant (CFA) and BCG vaccine modulate the development of type 1 diabetes in animal models. In non-obese diabetic mice, CFA and BCG significantly reduced the proportion developing diabetes compared with controls. Histological examination showed that autoimmune disease still developed but had been diverted to become nondestructive. In a preliminary trial in 17 newly diagnosed, type 1 diabetic patients, intracutaneous administration of 0.1 ml of BCG 1 mg/ml led to clinical remission in 11 (65%)- by week 4 in 6. Remission has been sustained in 3 for 6-10 months. No side effects were reported. A double-blind trial of BCG is warranted.

PAI-1 and factor VII activity are higher in IDDM patients with microalbuminuria.
Gruden G, Cavallo-Perin P, Bazzan M, Stella S, Vuolo A, Pagano G. Diabetes. 1994; 43:426-9.

Microalbuminuria is associated with an increased risk of cardiovascular disease (CVD) in insulin-dependent diabetes mellitus (IDDM) patients, but the pathophysiological basis of this association is not clear. To see whether or not haemostatic dysfunctions might contribute to explain this association, we measured tissue plasminogen activator (t-PA), plasminogen activator inhibitor-1 (PAI-1), factor VII activity plasma fibrinogen, and plasma enodothelin-1 (ET-1) in 13 microalbuminuric (albumin excretion rate [AER], 20-200 micrograms/min) and in 13 comparable normoalbuminuric (< 20 micrograms/min) IDDM patients. t-PA and ET-1 were similar in the two groups, whereas PAI-1 activity (5.65 +/- 1.92 vs. 0.85 +/- 0.58 IU/ml, P < 0.05), factor VII (87.85 +/- 4.94 vs. 76.54 +/- 2.31%, P < 0.05), and plasma fibrinogen (3.38+/-0.21 vs. 2.65+/-0.13 g/l, P <0.05) were significantly higher in microalbuminuric than in normoalbuminuric patients. Plasma fibrinogen was related to AER (r2 = 0.23, P < 0.05), whereas triglycerides and factor VII were related to PAI-1 (r2 = 0.39, P < 0.001and r2 = 0.10, P < 0.05). These results suggest that microalbuminuria is associated with a hypercoagulative and hypofibrinolytic state. Haemostatic dysfunctions might be a pathogenetic link between microalbuminuria and CVD.

Relationship between retinal and glomerular lesions in IDDM patients.
Chavers BM, Mauer SM, Ramsay RC, Steffes MW. Diabetes. 1994; 43:441-6.

Current knowledge regarding the concordance and discordance of the eye and kidney complications of diabetes is based on observations by ophthalmoscopy of retinal structural changes, which may be present at early stages of the disorder, and renal functional changes, which only become apparent at the later stages of the disease. For this reason we investigated the relationship between retinal structural lesions and quantitative measures of glomerular structure in-patients with insulin-dependent-diabetes mellitus (IDDM). Renal biopsies were evaluated using morphometric techniques, and retinopathy classification was determined by retinal fundus photography in 86 patients with IDDM: age 30.4 +/- 7.3 years and duration of IDDM 18.9 +/- 6.3 years (mean +/- SD). Retinopathy score correlated with glomerular basement membrane width (r = 0.39, P = 0.0002), mesangial volume fraction (VvMes/Glom) (r = 0.35, P = 0.0009), surface density of the peripheral capillary wall (SyPGBM/Glom) (r = 0.34, P = 0.0013), and index of arteriolar hyalinosis (r = 0.36, P = 0.0008). Abnormalities in VvMes/Glom and SvPGBM/Glom were more pronounced in-patients with both retinopathy and hypertension. Four of the 15 patients (27%) with either normal urinary albumin excretion (UAE) or low-level microalbuminuria had advanced retinopathy but normal VvMes/Glom. In conclusion, the presence of advanced retinal disease with or without hypertension in-patients with IDDM indicates a greater likelihood of advanced nephropathy as evidenced by increased VvMes/Glom and decreased SvPGBM/Glom. However, marked discordance between retinopathy and nephropathy occurs, as illustrated by patients with normal UAE or low-level microalbuminuria, normal glomerular structural measures, and advanced retinopathy.

Impaired insulin-induced glucose uptake by extrahepatic tissue is hallmark of NIDDM patients who have or will develop hypertension and microalbuminuria.
Nosadini R, Solini A, Velussi M, Muollo B, Frigato F, Sambataro M, Cipollina MR, De Riva F, Brocco E, Crepaldi G. Diabetes. 1994; 43:491-9

Insulin resistance may be a mechanism linking non-insulin-dependent diabetes mellitus (NIDDM) to hypertension and cardiovascular mortality. Microaluminuria also is an independent risk factor of cardiovascular mortality and of hypertension. Little information is available in the literature on the relationship between microalbuminuria and insulin action. This study investigated the relationships between blood pressure (BP) levels, microallbuminuria, and insulin resistance in NIDDM patients. Seventy-five NIDDM patients attending the outpatient clinic of the Department of Internal Medicine of the University Hospital in Padua, Italy participated in the cross-sectional part of our study. These subjects were divided into four groups on the basis of BP levels and albumin excretion rate (AER): 28 normotensive normoalbuminuric (NIDDM1), 19 hypertensive normoalbuminuric (NIDDM2), 15 normotensive microalbuminuric (NIDDM3), and 13 hypertensive microalbuminuric patients (NIDDM4). We defined microalbuminuria as an AER > 20 micrograms/min. Patients with BP levels > 145/90 mmHg were considered hypertensive. A group of 20 normal subjects served as control subjects. The results from the cross-sectional study indicate that the mean of insulin-induced whole-body glucose utilization, primarily an index of extrahepatic insulin action, was lower at all insulin infusion steps in the group of hypertensive and/or microalbuminuric patients than in the group of normotensive normoalbuminuric patients and control subjects. Hepatic glucose output, an index of insulin action in the liver, was on average less efficiently inhibited in all of the patients than in the control subjects, regardless of the BP levels or the AER.

Cytokines in vitreous humor: Interleukin-6 is elevated in proliferative vitreoretinopathy.

Kauffmann DJ, Van Meurs JC, Mertens DA, Peperkamp E, Master C, Gerritsen ME. Investigative Ophthalmology Visual Science. 1994; 35:900-6.

Purpose: To measure the levels of interleukins (IL) 1 beta, 6, and 8, and tumor necrosis factor-alpha (TNF alpha) in the vitreous of patients with proliferative vitreoretinopathy (PVR), proliferative diabetic retinopathy (PDR), vitreous hemorrhage, and macular pucker.

Methods: Vitreous samples were collected, undiluted, from patients with PVR, PDR of varying severity, and miscellaneous lesions (vitreous hemorrhage from trauma, macular degeneration, vein occlusion, and non-PVR patients with giant tear, retinal detachment, and macular pucker). Immunoreactive levels of the cytokines, IL-1 beta, IL-6, IL-8, and TNF alpha were determined by enzyme-linked immunoadsorbent assays, and samples were analyzed for protein and hyaluronic acid content using standard assays.

Results: The levels of TNF alpha were below detection limits of the assay (< 3 pg/ml). In 45 of the 47 samples tested, IL-1 beta levels also were below detection limits of the assay (< 3 pg/ml). IL-6 levels ranged from < 30 to 5487 pg/ml, with the highest values observed in the PVR patients. IL-8 levels ranged from < 20 to 1900 pg/ml, and were consistently high in the miscellaneous group. Some of the PVR patients with C2 and C3 level severity also exhibited IL-8 levels exceeding 100 pg/ml. In a second study, IL-6 content of vitreous from miscellaneous and PVR patients was compared. In this study, significantly elevated levels of IL-6 were observed in the PVR patients (91.5 +/- 18 pg/ml) compared to the miscellaneous group (10.3 +/- 3.7 pg/ml).

Conclusions: Elevated levels of IL-6 in the vitreous occur in PVR, implicating a role for this cytokine in the pathogenesis of this ocular disorder.

Counterregulatory hormone responses to hypoglycemia in the elderly patient with diabetes.

Meneilly GS, Cheung E, Tuokko H. Diabetes. 1994; 43:403-10.

In patients with non-insulin-dependent diabetes mellitus (NIDDM), the risk of severe or fatal hypoglycemia associated with the use of oral agents or insulin increases exponentially with age. We conducted this study with the hypothesis that this increased susceptibility to hypoglycaemia is caused by alterations in release of counterregulatry hormones and psychomotor performance during hypoglycaemia. Ten healthy nonobese elderly subjects (74 +/- 1 year of age; body mass index, 24.5 +/- 0.6 kg/m2) and 10 nonobese elderly NIDDM subjects (72 +/- 1 years of age; body mass index, 25.6 +/- 0.9 kg/m2) underwent two hyperinsulinaemic glucose clamp studies (insulin infusion, 60 mU.m-2 x min-1). In the control study, glucose was maintained at 5 mM for 5 h; in the hypoglycaemic study, glucose was kept at 5 mM for 1 h and then lowered in a stepwise fashion to 4.4, 3.8, 3.3, and 2.8 mM in each subsequent hour. At regular intervals in each study, neuropsychological tests were performed, counterregulatory hormones were measured, and hypoglycemic symptom questionnaire was administered. At a glucose level of 2.8 mM, NIDDM patients had reduced incremental glucagon (normal subjects, 114 +/- 18 ng/l; NIDDM subjects, 63 +/- 9 ng/l; P < 0.05) and growth hormone responses (normal subjects, 13.8 +/- 1.0 micrograms/l; NIDDM subjects, 7.0 +/- 2.0 micrograms/l; P < 0.01) and increased epinephrine (normal subjects, 925 +/- 198 pM; NIDDM subjects, 4175 +/- 824 pM; P < 0.001) and cortisol responses (normal subjects, 291 +/- 49 nM; NIDDM subjects, 524 +/- 92 mM; P < 0.05). Symptom scores were similar in both groups at all levels of glycaemia.

Epinephrine secretion, hypoglycemia unawareness, and diabetic autonomic neuropathy.

Hoeldtke RD, Boden G. Annals of Internal Medicine. 1994; 120:512-7.

The failure of some type 1 diabetic patients to secrete epinephrine and glucagon in response to hypoglycaemia has been documented by many investigators, and most studies have confirmed that an inability to secrete these counterregulatory hormones places patients at risk for developing clinical hypoglycaemia. Inadequate acute glucose counterregulation can result from multiple mechanisms. Failure of central glucoreceptors to recognize hypoglycaemia and to activate counterregulation may be the most common. Decreased central recognition of hypoglycaemia results from either strict antecedent glucose control or from a recent hypoglycaemic event. Controversy about the relation between autonomic neuropathy and counterregulatory hormone secretion has arisen because divergent criteria have been used in the published studies for the diagnosis of autonomic neuropathy. Advanced adrenergic neuropathy as evidenced by orthostatic hypotension, generally leads to decreased epinephrine secretion after hypoglycaemia. Subclinical neuropathy, however, as diagnosed from measurement of heart rate variability, may diminish the awareness of hypoglycaemia but does not affect counterregulatory hormone secretion in some patients with type I diabetes, however, may represent a selective autonomic neuropathy; the disease has limited the patient's ability to secrete epinephrine and pancreatic polypeptide in response to hypoglycaemia even though it has spared the autonomic neurons responsible for cardiovascular reflexes. Finally recent provocative reports indicate that decreased responsiveness to adrenergic stimuli may cause hypoglycaemia unawareness in some patients. Further documentation of this mechanism us required, and its relative importance with respect to other mechanisms needs to be established. These questions are increasingly important clinically because the Diabetes control and complications Trial has confirmed that the prevalence of severe hypoglycaemia remains a major obstacle to attempts to prevent diabetic complications with intensive insulin therapy. Until glucose counterregulation is more fully understood and methods for preventing hypoglycaemia unawareness or a history of hypoglycaemia related accidents should probably not be treated with intensive insulin therapy.

Use of runs test to assess cardiovascular autonomic function in diabetic subjects.

Chau NP, Mestivier D, Chanudet X, Bauduceau B, Gautier D, Larroque P. Diabetes care. 1994; 17: 146-8.

Objective: We suggest a simple, noninvasive method to assess the autonomic function in diabetic subjects. The method requires only a monitoring of heart rate (HR) with subjects in the sitting position.

Research Design and methods: Sixty diabetic subjects, 44 men and 16 women, between 20-80 years of age, were recruited, chronologically, for this study. Subjects treated for high blood pressure were not included. Their autonomic function was assessed by the total score of five classical cardiovascular function tests. In the same subjects and in 44 healthy subjects, blood pressure and HR were determined from beat to beat by the Finapres system with subjects in the sitting position. We examined the randomness of the HR changes by calculating the zeta statistic of the runs test on 1,000 successive HR readings (the zeta value is low if the HR changes are random). When the HR changes are random, we consider that the autonomic control of HR is impaired.

Results: The zeta values of HR changes were significantly lower in diabetic subjects compared with normal subjects (2.98+/- 0.97 vs. 3.54 +/- 0.97, p< 0.004). In diabetic subjects, the zeta value was closely correlated to the total score of disautonomy (r = -0.66, p < 0.0001, after correction for age effect) and to the office systolic blood pressure (r= -0.43, p <0.001).

Conclusions: The zeta value of HR changes might be a market of the autonomic function in diabetic subjects.

The squatting test. A useful tool to assess both parasympathetic and sympathetic involvement of the cardiovascular autonomic neuropathy in diabetes.

Marfella R, Giugliano D, di Maro G, Acampora R, Giunta R, D' Onofrio F. Diabetes: 1994, 43: 607-12.

The heart rate responses observed after both squatting and standing are thought to be of reflex nature and may be useful to assess the functional integrity of parasympathetic and sympathetic nerves in diabetes. In the standard manoeuver, each subject stood still for 3 min, then squatted down for 1 min, and at last stood up during an inspiratory phase. In 10 healthy subjects (25-31 years of age), lengthening of the R-R interval during squatting was abolished by atropine, whereas propranolol markedly attenuated shortening of the R-R interval at standing from squatting. Squatting test (SqT) ratios (SqT vagal [SqTV] = ratio between the R-R interval mean before squatting and the longest R-R interval after squatting; SqT sympathetic [SqTs] = ratio between the basal R-R interval and the shortest R-R interval at standing) were calculated in 558 healthy subjects and 346 diabetic patients (insulin- dependent diabetes mellitus/non-insulin- dependent diabetes mellitus: 103/ 243). Normal ranges (95 and 99% confidence intervals [Cls]) for subjects 20-74 years of age showed a statistically significant negative correlation with age. SqTV was outside the 99% CI in 145 (42%) diabetic patients and in 7 (1.3%) of the control subjects. The corresponding figures for SqTs were 40 and 0.8%, respectively. Age and duration of diabetes had a negative influence on SqT ratios. SqT ratios were compared with other reflex tests currently used for diagnosis of autonomic neuropathy: deep breathing (DB), lying-to-standing (LS), Valsalva manoeuver, and blood pressure change after standing (orthostatic hypotension [OH]).

The predictive value of microalbuminuria in IDDM. A five-year follow-up study.

Almdal T, Norgaard K, Feld-Rasmussen B, Deckert T. Diabetes care. 1994; 17: 120-5.

Objective: To investigate the predictive value of microalbuminuria and the annual increase of albumin excretion as risk factors for diabetic nephropathy.

Research Design and Methods: A 5-year follow-up of patients with microalbuminuria (urinary albumin excretion [UAE] = 30-299 mg/24 h) and matched patients with normoalbuminuria (UAE < 30mg/24h). The initial classification was based on one single 24-h urine collection. The annual Increase in UAE was calculated by linear regression analysis of log-transformed UAE on time. This study was conducted at the outpatient clinic of the steno Diabetic Center. The study subjects included 118 insulin-dependent diabetes mellitus (IDDM) patients between 18 and 50 years of age with mocroalbuminuria and 112 matched control patients with normal UAE with an age at diabetes onset of < 31 years. The main outcome measures were UAE, annual change in UAE rate (percentage per year), and the prevalence of retinopathy.

Results: After 5 years, 39 (33%, 24-42 CI [95% confidence interval]) patients with mocroalbuminuria had normoalbuminuria, 57 (48%, 38-57 CI) still had micro-albuminuria, and 22 (19%, 12-27 CI) had developed diabetic nephropathy. Among the 112 patients with normoalbuminuria in 1985, 9 (8%, 4-15 CI) had developed microalbuminuria, and 2 (2%, 0-6 CI) had developed diabetic nephropathy. Of the 79 patients with persistent albuminuria, only 36 (46%, 34-57 CI) were progressor with a rate of progression of > 5% years. Progressors had significantly higher HbA_{1c}, higher mean blood pressure, and a higher incidence of proliferative retinopathy compared with nonprogressors. Multiple regression analysis only identified mean HbA_{1c} as an independent predictor of the rate of progression. Smoking was significantly more prevalent in patients with persistent albuminuria.

Conclusions: Microalbuminuria is a predictor of progression to diabetic nephropathy; however, not as strong as suggested previously. Calculation of the annual increase in UAE seems to be a more specific method of identifying patients who will develop diabetic nephropathy.

Smoking is associated with progression of diabetic nephropathy.

Sawicki PT, Didjurgeit U, Muhlhauser I, Bender R, Heinemann L, Berger M. Diabetes Care. 1994; 17: 126-31.

Objective: To investigate the association between cigarette smoking and the progression of diabetic nephropathy.

Research Design and Methods: A prospective follow-up study over one year was conducted in a sequential sample of 34 smokers, 35 nonsmokers, and 24 ex-smokers with type I diabetes, hypertension, and diabetic nephropathy. Progression of renal disease was defined according to the stage of nephropathy as an increase in proteinuria or serum creatinine or a decrease in the glomerular filtration rate.

Results: Progression of nephropathy was less common in nonsmokers (11%) than in smokers (53%) and patients who had quit smoking (33%), $p < 0.001$. In a stepwise logistic regression analysis, cigarette backs years, 24-h sodium excretion, and GHB were independent predictive factors for the progression of diabetic nephropathy. Because blood pressure (BP) was well controlled in these patients and most values were within a normotensive range, neither standing, nor supine BP values were associated with progression of nephropathy.

Conclusions: Cigarette smoking representes an important factor associated with progression of nephropathy in treated hypertensive type I diabetic patients.

Mlcroalbuminuria precedes the development of NIDDM.

Mykkanen L, Haffner SM, Kuusisto J, Pyorala K, Laakso M. Diabetes. 1994; 43: 552-7.

Several studies have indicated that insulin resistance elevated blood pressure (BP) and dyslipidemia precede the onset of non-insulin-dependent diabetes mellitus (NIDDM). Little data, however, exist on the presence of renal disease in prediabetic subjects. We measured albumin excretion in a cross-sectional population study in subject's 65-74 years of age living in eastern. Finland in relation to the risk of developing diabetes 3.5 years later. The prevalence of microalbuminuria (urinary albumin-to-urinary creatinine ratio > or =2 mg/mmol) was 1.3-, 1.8-, and 2.0-fold higher among subjects with impaired glucose tolerance (n= 242), newly diagnosed NIDDM subjects (n=92), and previously diagnosed NIDDM subjects (n = 136), respectively, compared with subjects with normal glucose tolerance (n = 826). Nondiabetic subjects with microalbuminuria had multiple abnormalities in cardiovascular risk factors including elevated BP, high triglyceride concentration, and a low high-density lipoprotein cholesterol concentration, a cluster of risk factors typical for pre-diabetic individuals. The relationship between microalbuminuria and the incidence of NIDDM over the 3.5-year follow-up was studied in 891 subjects who were free of diabetes at baseline. Converters to diabetes (n = 69) had a higher prevalence of hypertension (68.1 vs. 54.4%, $p < 0.05$) and a higher prevalence of microalbuminuria (43.5 vs. 30.4%, $p < 0.05$) than nonconverters (n=822). In logistic regression analysis, microalbuminuria predicted the development of NIDDM independently of BP level.

Comparison of the course to end-stage renal disease of type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetic nephropathy.

Pugh JA, Medina R, Ramirez M. Diabetologia. 1993; 36:1094-8.

Is the course leading to diabetic end-stage renal disease similar for Type 1 (insulin-dependent) and Type 2 (non-insulin-dependent) diabetes mellitus? We identified all diabetic end-stage renal disease patients starting renal replacement therapy from 1989 to 1991 in two urban countries in Texas. Three ethnic/racial groups were enrolled: Mexican Americans, non-Hispanic Whites, African Americans. Patients were interviewed and their medical records, both inpatient and out-patient, were abstracted for relevant diagnostic and therapeutic information. We attempted to obtain records as far back as the onset of diabetes or hypertension and from

all physicians who had cared for the patient. An historical algorithm was used to determine diabetic type. Of the patients enrolled, 91 were Type 1 and 438 were Type 2 diabetic patients. Type 1 diabetic patients had higher mean glucose levels in the first 10 years of diabetes (16.3 vs. 11.4 mmol/l) but lower systolic blood pressures (148 vs. 157 mmHg). The duration of diabetes prior to end-stage renal disease was longer for Type 1 than Type 2 patients (22 vs. 17 years). Type 1 diabetic patients were more likely to have other microvascular complications (retinopathy, neuropathy, gastroparesis), less likely to have coronary disease (myocardial infarction and congestive heart failure), and had similar rates of stroke and vascular surgery procedures (carotid endarterectomy, coronary artery bypass surgery, aortofemoral bypass). Type 1 and Type 2 diabetic patients were just as likely to have a first degree relative with hypertension (60.5 vs. 65.5%).

Effect of metabolic factors and blood pressure on kidney function in proteinuric type 2 (non-insulin-dependent) diabetic patients.

Hasslacher C, Bostedt-Kiesel A, Kempe HP, Wahl P. Diabetologia. 1993; 36: 1051-6.

Decline of kidney function with time and its influencing factors were investigated in the present longitudinal study in Type 2 (non-insulin-dependent) diabetic patients with clinical diabetic nephropathy. Compared to a control group of Type 2 diabetic patients without proteinuria, the proteinuric patients showed a higher prevalence of hypertension, higher systolic blood pressure values and serum triglyceride levels.

The annual loss of glomerular kidney function was much higher in the proteinuric patients (5.3 ml.min-1 x 1.73 m2) than in the control subjects (0.9 ml.min-1 x 1.73 m2). Correlation analyses revealed a close correlation between the annual decrease of kidney function and the factors, systolic and diastolic blood pressure, triglyceride and postprandial blood glucose level as well as body mass index. Regression analyses showed for the first time that in addition to the systolic blood pressure and metabolic control, the triglyceride level is also an independent factor influencing the progression of nephropathy. Higher values of these parameters were associated with a more rapid deterioration of kidney function.

Thrombogenic factors are related to urinary albumin excretion rate in type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetic patients.

Knobl P, Schemthaner G, Schnack C, Pietschmann P, Griesmacher A, Prager R, Muller M. Diabetologia. 1993; 36: 1045-50.

Parameters of haemostasis, endothelial cell markers and lipid peroxide levels were studied in 64 Type 1 (insulin-dependent) and 94 type 2 (non-insulin-dependent) diabetic patients according to their urinary albumin excretion rate in comparison with age matched control subjects. We determined plasma levels of fibrinogen (Clauss method), coagulation factor VII: activity (clotting assay), factor VII antigen, protein C and S antigen, von Willebrand factor antigen, D-dimer concentration (ELISA), and lipid peroxide levels (thioarbituric acid) in relation to urinary albumin excretion rate (RIA). Significant positive correlations were found between urinary albumin excretion rate and plasma fibrinogen ($p < 0.005$, $p < 0.02$), factor VII activity ($p < 0.0002$, $p < 0.002$), factor VII antigen ($p < 0.0001$, $p < 0.001$), protein C ($p < 0.003$, $p < 0.05$), and lipid peroxides ($p < 0.02$, $p < 0.004$) in Type 1 as well as in Type 2 diabetes. Von Willebrand factor ($p < 0.001$) and protein S ($p < 0.0005$) correlated with albuminuria only in patients with Type 1 diabetes. Although most of the haemostatic abnormalities are already found in normoalbuminuric patients the significant positive correlations to urinary albumin excretion indicate that endothelial cell damage and coagulation disorders deteriorate with the progression of diabetic nephropathy.

Microalbuminuria in a random cohort of recently diagnosed type 2 (non-insulin-dependent) diabetic patients living in the greater Munich area.

Standl E, Stiegler H. Diabetologia. 1993; 36: 1017-20.

Still under debate is the prevalence of microalbuminuria in patients with recently diagnosed Type 2 (non-insulin-dependent) diabetes mellitus and its relation to existing macro-vascular disease and the major vascular risk markers. Hence, from a representative sample of 1512 patients with Type 2 diabetes of varied duration (recruited from 22 non-specialized medical practices of the Greater Munich Area) 68 (28 males, 42 females) of 71 eligible subjects with a known duration of diabetes of up to 17 weeks and not less than 4 weeks were examined in the present study. Median age was 61 (39 to 75 years), prevalence of ischaemic heart disease (case history plus ECG, Minnesota code, Whitehall criteria) 41.2% and that of peripheral vascular and carotid artery disease (both assessed by ultrasound-Doppler) were 35.3 and 4.4%, respectively. Diabetes was well controlled (HbA1c: 6.9%, 5.6-8.3; fasting blood glucose: 7.7 mmol/1, 5.4-10.4; median +/- interquartile range IQ), the cardiovascular risk profile was most prominent in terms of triglycerides (3.1 mmol/l, 2.1-4.6, median +/- IQ range) and systolic blood pressure (164 mm Hg, 140-186, median +/- IQ range). 13.2% showed signs of urinary tract infection. Of the remainder, 19.0% exhibited microalbuminuria (RIA > 30-200 mg/l), and 5.2% macroalbuminuria (> 200mg/l). significant correlations ($p < 0.05$) were found between urinary albumin concentration and beta 2-microglobulin in serum, systolic blood pressure, serum triglycerides, serum HDL-cholesterol (inversely), HbA1c, and peripheral vascular disease.

Advanced glycosylation end products in continuous ambulatory peritoneal dialysis patients.

Korbet SM, Makita Z, Firanek CA, Vlassara 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 cyclic 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 ratio at 4 hours was 0.69 +/- 0.08 for creatinine and 0.18 +/- 0.06 for AGEs. The mass transfer area 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 transfer 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 patients 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.