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AETIOLOGY AND PATHOPHYSIOLOGY

Analysis of HLA-DQ genotypes and susceptibility in insulin dependent diabetes mellitus

Baish J.M., Weeks T., Giles R., Hoover M., Stastny P. and Capra J.D. Engl. J. Med. 1990; 322: 1836-41.

There is evidence that certain alleles at the HLA-DQ locus are correlated with susceptibility to insulin-dependent diabetes mellitus (IDDM) and in particular that DQ beta-chain alleles containing aspartic acid at position 57 are protective. The availability of a large group of patients with IDDM enabled us to assess the role of HLA-DQ alleles in susceptibility to the disease in order to confirm and extend recent observations derived from studies of smaller number of patients. Using allele-specific oligonucleotide probes and the polymerase chain reaction, we studied 266 unrelated patients with IDDM and 203 unrelated normal subjects for eight HLA-DQ bate-chain alleles.

Two major finding emerged from these studies. First, the presence of an HLA-DQw1.2 allele was protective. Only 6 of the 266 patients with IDDM (2.3 per cent) were positive for HLA-DQw1.2, as compared with 74 of the 203 normal subjects (36.4 per cent; $P < 0.001$). Thus, persons with the HLA-DQw1.2 allele, which is one of the polymorphic forms of the beta-chain of the HLA-DQ molecule rarely, had IDDM, no matter which other HLA-DQ beta-chain allele they inherited ('dominant protection'). Second the presence of the HLA-DQw8, allele increased the risk of IDDM. The relative risk of IDDM was 5.6 in persons homozygous for HLA-DQw8, and it was similar in persons with the HLA-DQw1.1/DWw8 or HLA-DQw2/DWw8 haplotype ('dominant susceptibility'). However, the relative risk of IDDM in persons who had the HLA-DQw1.2/DQw8 haplotype was 0.37, demonstrating that the protective effect of HLA-DQw1.2 predominated over the effect of HLA-DQw8.

We conclude that the presence of the HLA Class II antigen DQw1.2 is strongly protective against the development of IDDM, and that complete HLA. DQ typing is necessary for accurate assessment of susceptibility to IDDM.

A Prospective study of the development of diabetes in relatives of patients with insulin dependent diabetes

Riley W.J., Maclaren N.K., Krischer J., Spillar R. P. N Engl. J. Med. 1990; 323: 1167-72.

Background: The presence of cytoplasmic islet cell autoantibodies has been recognized as a risk factor for the development of diabetes mellitus in relatives of patients with insulin-dependent diabetes mellitus (IDDM) but the magnitude of the risk is unknown, as is the influence of other factors, such as age, sex, and race.

Methods: From 1979 through 1989, we studied 4015 initially nondiabetic relatives of 1590 probands with IDDM to determine the risk of IDDM according to the presence and titre of autoantibodies, as well as other factors.

Results: Of the 4015 nondiabetic relatives, 125 (3.1 per cent) has islet cell antibodies in their initial serum samples and 40 contracted IDDM. Islet cell antibodies were most frequent (4.3 per cent) in relatives who were under 20 years of age ($P = 0.001$) and in those (4.8 per cent) from families with more than one affected member (a multiplex pedigree) ($P = 0.003$). Independent risk factors for the development of diabetes in the relatives included age of less than 10 years at the time of initial study ($P = 0.02$) and a positive test for islet cell antibodies in the initial serum sample ($P = 0.0001$). Twenty seven of the relatives in whom diabetes developed (67.5 per cent) had positive tests for islet cell antibodies before the diagnosis of IDDM giving a relative risk of IDDM of 68 (95 per cent confidence interval, 34 to 134) for antibody-positive relatives. Islet cells antibody titres of 20 juvenile diabetes foundation units or higher were associated with an increasing risk of diabetes.

Conclusions: Nondiabetic relatives of probands with IDDM who are in the first two decades of life, are members of multiplex pedigrees, and have increased titres of islet cell antibodies are the most likely to contract IDDM themselves.

HLA-associated insulin autoantibody formation in newly diagnosed Type I diabetic patients

Zeigler A.G., Standl E., Albert E., and Mehnert H. Diabetes 1991; 40: 1146-49.

To assess a possible HLA association with anti-insulin autoantibodies (IAAs) in human insulin-dependent (type I) diabetes, 51 newly diagnosed type I diabetic patients (mean age 22 ± 8 yr) were typed for HLA-DR and HLA-DQ and studied for

IAAs before exogenous insulin therapy with a competitive radioimmunoassay (normal range ≤ 49 nU/ml). The level of IAAs in 16 patients exceeded our upper limit of normal, and 18 had high-titre islet cell antibodies (ICAs; ≥ 40 Juvenile Diabetes Foundation U). A striking association with HLA-DR4 (DQw3) in both the prevalence and the level of IAAs was found (IAA positivity in patients with DR4/4vs. DR4 heterozygous vs. non-DR4: 90 vs. 29%, corrected [c] P<0.01, vs. 5%, $P_c < 0.0001$; IAA positivity in patients with DR4 vs. non-DR4: 50 vs. 5%, $P_c < 0.005$; IAA level in patients with DR4/4 vs. DR4 heterozygous vs. non-DR4: 111 vs. 17 nU/ml, Pc < 0.01, vs. 20 nU/ml, $P_c < 0.0001$: IAA level in patients with DR4 vs. non-DR4: 45 vs. 20 nU/ml. $P_c < 0.01$). In contrast, none of the $DR3^+$ subjects has IAAs above normal range, except in conjunction with DR4 (DR3 vs. non-DR3: 12 vs. 42%, $P_c < 0.05$). However, there was no significant relationship between DR3 and IAAs after correcting for the number of DR4 alleles. No relationship was seen between age of onset, IAA levels, and HLA typing in our population, and no relationship was found between ICA positivity and HLA antigens. These data suggest that humoral autoimmunity to insulin may be genetically controlled in predominantly $DR4^+$ patients responding to insulin before exogenous insulin treatment.

Nonsense mutation in the glucokinase gene causes early-onset non-insulin-dependent diabetes mellitus

Vionnet N., Stoffel M., Takeda J., et al. Nature 1992; 356:721

Maturity-onset diabetes of the young (MODY) is a form of non-insulin-dependent (type 2) diabetes mellitus (NIDDM) which is characterized by an early age at onset and an autosomal dominant mode of inheritance. Except for these features, the clinical characteristics of patients with MODY are similar to those with the more common late-onset form(s) of NIDDM. Previously we observed tight linkage between DNA polymorphisms in the glucokinase gene on the short arm of chromosome 7 and NIDDM in a cohort of sixteen French families having MODY. Glucokinase is an enzyme that catalyses the formation of gluycose-6-phosphate from glucose and may be involved in the regulation of insulin secretion and integration of hepatic intermediary metabolism. Because the glucokinase gene was a candidate for the site of the genetic lesion in these families, we scanned this gene for mutations. Here we report the identification of a nonsense mutation in the gene encoding glucokinase and its linkage with early-onset diabetes in one family. To our knowledge, this result is the first evidence implicating mutation in a gene involved in glucose metabolism in the pathogenesis of NIDDM.

Linkage analysis of insulin-receptor gene in familial NIDDM

Elbein S.C., Sorensen L.K. and Taylor M. Diabetes 1992; 41: 648-56

Although non-insulin-dependent diabetes mellitus (NIDDM) is clearly inherited, the mode of inheritance and genetic aetiology remain unknown. Impaired insulin action is an important component of NIDDM, which may precede NIDDM onset, and appears to be inherited. Numerous defects of the insulin-receptor gene have been described in syndromes of extreme insulin resistance, and this gene is a strong candidate for genetic predisposition to NIDDM. To test this hypothesis, we examined 18 white pedigrees from Utah that had two or more siblings with NIDDM. For each pedigree, individuals not known to be affected were tested by standard oral glucose tolerance test, and diagnoses of NIDDM and impaired glucose tolerance were made by World Health Organization criteria. Each individual was typed for seven restriction-fragment-length polymorphism markers at the insulin-receptor locus, and marker phase was established by segregation. Linkage was examined with the LINKAGE programme under six models, including autosomal dominant and autosomal recessive, with individuals with impaired glucose tolerance counted either as affected or of unknown status and with or without sporadic cases of diabetes. Under each model, linkage was significantly rejected. Neither inspection of individual pedigree log of odds scores nor formal tests of heterogeneity suggested a subgroup in which linkage of NIDDM and insulin-receptor gene haplotypes among 108 affected sibling pairs drawn from the pedigrees did not deviate from that expected by chance alone. These data suggest that the insulin-receptor gene locus is unlikely to act as a major locus in the predisposition to NIDDM in most white pedigrees, although we cannot exclude a minor role of this locus under a highly polygenic model or a major role in rare pedigrees.

Major gene effect for insulin levels in familial NIDDM pedigrees

Schumacher M.C., Hasstedt S.J., Hunt S.C., Williams R.R. and Elbein S.C., Diabetes 1992; 41: 416-23

Insulin resistance and hyperinsulinaemia are familial traits that may precede and predict the

onset of non-insulin-dependent diabetes mellitus (NIDDM). In some populations, the distribution of fasting insulin levels and measures of in vivo insulin action suggest the effects of a single major gene. We previously noted hyperinsulinaemia among unaffected members of 16 large white pedigrees ascertained through two or more NIDDM siblings. To examine the hypothesis that insulin levels are determined by a single major genetic locus, we used segregation analysis to examine fasting insulin levels in 206 family members and 65 spouses who had normal glucose tolerance tests by World Health Organization criteria. Segregation analysis supported a major locus determining fasting insulin levels and segregating as an autosomal recessive allele with a frequency of 0.25. Thus, homozygotes represented 6.25% of the population, and homozygosity for the hyperinsulinaemia allele elevated the mean fasting insulin level from 70.3 to 211.1 pM (11.7-35.2 μU/ml). The analysis apportioned the variance in fasting insulin as 33.1% due to the major autosomal locus, 11.4% due to polygenic inheritance and 55.5% due to unmeasured effects. Homzygotes for the recessive allele had higher 1-h insulin levels than all others (911.7 vs. 427.2 pM [152.0 vs. 71.2 μU/ml]). We also found evidence for a major locus determining 1-h-stimulated insulin levels, with codominant inheritance as the most likely pattern in inheritance. The causal relationship between these findings and NIDDM has not been determined, and segregation of direct measures of insulin action remains to be demonstrated. However, we have found evidence for a major gene locus that may contribute to the observed familial aggregation of impaired insulin action in relatives of NIDDM individuals and the inherited predisposition to NIDDM.

The ratio of waist-to-hip circumference, plasma insulin level, and glucose intolerance as independent predictors of the HDL_2 cholesterol level in older adults

Ostlund R. E., Staten M., Kohrt W.M., Schultz J., Malley M.N. Engl. J. Med. 1990; 322: 229-34

Abstract high plasma levels of HDL_2, a subtraction of high-density lipoprotein (HDL) cholesterol, are associated with a reduced risk of coronary heart disease. To investigate the characteristics related to HDL_2 cholesterol levels, we measured lipoprotein levels and several metabolic and anthropometric variables in 146 healthy subjects (77 men and 69 women) in the seventh decade of life.

The level of HDL_2 cholesterol was inversely correlated with the ratio of the waist-to-hip circumference (r=-0.335 for men; r=-0.370 for women; P<0.01) and the plasma insulin level (r=-0.400 for men, r=-0.398 for women; P<0.001). In a multiple regression model including both sexes, 41 per cent of the variance in the HDL_2 level was explained by the combined effect of the waist-to hip ratio (P < 0.0001), the plasma insulin level (P=0.0003), and the degree of glucose tolerance indicated by the integrated area under the plasma glucose curve after an oral glucose-tolerance test (P=0.05). The body mass index, total percentage of body fat, maximal oxygen uptake, diet, and sex were not significant predicators of the HDL_2 level when added to this model, whereas the original variables remained significant predictors. The HDL_2 cholesterol level in subjects at the 25th percentile for waist-to-hip ratio was 153 per cent of that in subjects at the 75th percentile.

We conclude that HDL_2 levels are inversely correlated with truncal fat, plasma insulin levels, and the presence of glucose intolerance and are not independently associated with sex or total body fat.

Abdominal obesity and physical inactivity as risk factors for NIDDM and impaired glucose tolerance in Indian, creole, and chinese mauritians

Dowse G.K., Zimmet P.Z., Gareeboo H., et al. Diabetes Care 1991; 14: 271-82

Objective: We wanted to determine whether obesity, abdominal fat distribution, and physical inactivity act similarly and independently as risk factors for non-insulin-dependent diabetes mellitus (NIDDM) and impaired glucose tolerance (IGT) in Hindu and Muslim Asian Indians, African-origin Creoles, and Chinese Mauritians.

Research Design and Methods: We examined a population-based random cluster sample of 5080 adult subjects from the Indian Ocean Island of Mauritius. Glucose tolerance was assessed with 75-g oral glucose tolerance test and World Health Organization criteria.

Results: Univariate data and multiple logistic regression models indicated that age, family logistic regression models indicated that age, family history of diabetes, body mass index (BMI), waist-hip ratio (WHR), and physical inactivity conveyed similar risk for NIDDM (and (IGT) in each ethnic group. After adjusting for all other factors, Hindu ethnicity conferred additional risk for NIDDM (but not IGT) in men, but in women there were no clear ethnic differences. Although

BMI and WHR were independently significant risk factors, WHR conveyed relatively stronger risk for NIDDM than BMI in women, whereas the converse was true in men. For ethnic groups combined, the independent odds ratio for IGT associated with moderate and low physical activity scores (relative to high) were 1.56 and 1.71 ($P<0.05$), respectively, in men and 1.32 and 1.69 ($P<0.05$) in women. In subjects with asymptomatic NIDDM diagnosed during the survey, the independent odds ratios were 1.96 and 2.00 ($P<0.05$) in men and 1.73 and 2.70 ($P<0.05$) in women.

Conclusions: These data indicate that BMI, abdominally distributed fat, and physical inactivity are important independent risk factors for both IGT and NIDDM in diverse ethnic groups. Attributable risk fractions for Mauritius suggest that population-wide modification of levels of these risk factors could potentially result in substantially lower occurrence of NIDDM (and IGT). Such interventions should be attempted in high-risk populations.

Slow glucose removal rate and hyperinsulinaemia precede the development of type II diabetes in the offspring of diabetic parents

Warram J.H., Martin C.C., Krolewski A.S., Soeldner J.S., and Kahn C.R. Ann. of Int. Med. 1990; 133: 909-915

Objective: To determine whether insulin resistance or insulin deficiency is primary in the pathogenesis of type II diabetes.

Design: Cohort analytic study of persons with normal glucose tolerance but with a high risk for developing type II diabetes average follow-up time, 13 years).

Setting: Outpatients had an intravenous glucose tolerance test and were contacted periodically to ascertain diagnoses of diabetes.

Participants: One hundred and fifty-five normal offspring, ranging in age from 16 to 60 years, of two parents with type II diabetes and 186 normal control subjects in the same age range who had no family history of diabetes.

Measurements and main results: Two phenotypic characteristics distinguished the offspring of diabetic parents from control subjects. They had slower glucose removal rated (K_2) ($P<0.01$) and higher insulin levels (fasting and during the second phase of insulin response to intravencous glucose; ($P<0.0001$) than did control subjects, even after adjustment for differences in obesity. Sixteen percent of the offspring developed type II diabetes. Mean K_2 at baseline was 1.7%/min among off spring who subsequently developed diabetes, 2.2%/min among offspring who remained non-diabetic, and 2.3%/min among control subjects. Corresponding means for first-phase insulin were 498, 354 and 373 pM, respectively, whereas second-phase insulin means were 329, 117 and 87 pM, respectively. In multivariate analysis, low K_2 and high serum insulin levels independently increased the risk for developing diabetes among the offspring of diabetic parents.

Conclusions: One to two decades before type II diabetes is diagnosed, reduced glucose clearance is already present. This reduced clearance is accompanied by compensatory hyperinsulinaemia, not hypoinsulinaemia, suggesting that the primary defect be in peripheral tissue response to insulin and glucose, not in the pancreatic beta cell.

Under-expression of B cell high Km glucose transporters in non-insulin-dependent diabetes

Johnson J.H., Ogawa A., Chen l. et al Science. Vol. 250

The role of defective glucose transport in the pathogenesis of non-insulin-dependent diabetes (NIDDM) was examined in Zucker diabetic fatty rats, a model of NIDDM. As in human NIDDM, insulin secretion was unresponsive to 20mM glucose. Uptake of 3-0-methylglucose by islet cells was less than 19% of controls. The β cells were GLUT-2- positive, the response to glucose was absent and hyperglycaemia exceeded 11mM plasma glucose. We conclude that in NIDDM under-expression of GLUT-2 messenger RNA lowers high K_m glucose transport in β cells, and thereby impairs glucose-stimulated insulin secretion and prevent correction of hyperglycaemia.

Thromboxane biosynthesis and platelet function in type II diabetes mellitus

Dive G., Catalano I., Averna M. et al n. Engl. J. Med. 1990; 322: 1769-74

Abstract: It has been suggested that platelet hyperreactivity in patients with diabetes mellitus is associated with increased platelet production of thromboxane. We therefore compared the excretion of a thromboxane metabolite and platelet function in 50 patients with Type II diabetes mellitus who

had normal renal function and clinical evidence of macrovascular disease and in 32 healthy controls.

The mean (± SD) excretion rate urinary 11-dehydrothromboxane B_2 was significantly higher in the patients than in the controls (5.94 ± 3.68 vs. 1.50 ± 0.79 nmol per day; $P < 0.001$), irrespective of the type of macro-vascular complication. Tight metabolic control achieved with insulin therapy reduced the levels of 11-dehydro-thromboxane B_2 by approximately 50 per cent. The fractional conversion of exogenous thromboxane B_2 (infused at a rate of 4.5, 45.3, or 226.4 fmol per kilogram of body weight per second) to urinary 11-dehydrothromboxane B_2 was assessed in four patients, in whom it averaged 5.4 ± 0.1 per cent; this value did not differ from that measured in healthy subjects. Aspirin in low doses (50 mg per day for seven days) reduced urinary excretion of the metabolite by approximately 80 per cent in four patients. The fact that thromboxane biosynthesis recovered over the following 10 days was consistent with a platelet origin of the urinary metabolite.

We conclude that in Type II diabetes (1) increased 11-dehydro-thromboxane B_2 excretion reflects enhanced bio-synthesis of thromboxane A_2 by platelets rather than a shift in its metabolic disposition; (2) this is likely to reflect in vivo platelet activation; and (3) improved metabolic control as well as low-dose aspirin therapy may correct these abnormalities in platelet function to a variable extent.

Intracellular defects in glucose metabolism in obese patients with NIDDM

Kelley D.E., Mokan M. and Mandarino L.J. Diabetes 1992; 41: 698-706.

Skeletal muscle insulin resistance in obese patients with non-insulin-dependent diabetes mellitus (NIDDM) is characterised by decreased glucose uptake. Although reduced glycogen synthesis is thought to be the predominant cause for this deficit, studies supporting this notion often have been conducted at supraphysiological insulin concentrations in which glucose storage is the overwhelming pathway of glucose disposal. However, at lower, more physiological insulin concentrations, decreased muscle glucose oxidation could play a significant role. This study was undertaken to determine whether, under euglycaemic conditions, insulin resistance for leg muscle glucose uptake in NIDDM patients is due primarily to decreased glucose uptake in NIDDM patients is due primarily to decreased glucose storage or to oxidation. The leg balance technique and leg indirect calorimetry were used under steady-state euglycaemic conditions to estimate muscle glucose uptake, storage, and oxidation in eight moderate obese NIDDM patients and eight matched-control subjects. Leg muscle biopsies also were performed to determine whether alterations in muscle pyruvate dehydrogenase or glycogen synthesis activities could explain defects in glucose oxidation or storage. At insulin concentration of ~500 - 600pM, leg glucose uptake, oxidation, and storage in the NIDDM group (2.03 ± 0.42, 1.00 ± 0.13, 0.66 ± 0.36 μmol min^{-1} $100ml^{-1}$) were significantly lower ($p<0.05$) than rates in control subjects (5.14 ± 0.64, 1.92 ± 0.17, 2.80 ± 0.54). Pyruvate dehydrogenase and glycogen synthetase activities were also decreased, consistent with the in vivo metabolic defects. The average deficit in leg glucose uptake in NIDDM was 3.11 ± 0.42 μmol min^{-1} $100ml^{-1}$ Of this deficit, 66% (2.14 ± 0.36 μmol min^{-1} 100 ml^{-1}) was due to decreased leg glucose storage and 33% (0.92 ± 0.13 μmol min^{-1}) to decreased leg glucose oxidation. Our findings confirm that decreased muscle glucose storage during hyperinsulunaemia is the largest defect in glucose metabolism but also reveal a major defect in glucose oxidation. These studies reinforce the notion that muscle insulin resistance in obese NIDDM patients is characterized by panoply of intracellular defects in glucose metabolism and insulin action.

Impaired activation of glycogen synthetase in people at increased risk for developing NIDDM

Schalin-Jantti C., Harkonen M. and Groop L.C., Diabetes 1992; 41: 598-604.

To study whether impaired activation of muscle glycogen synthase represents an early defect in the pathogenesis of insulin resistance in non-insulin-dependent diabetes mellitus (NIDDM), we quantitated rates of nonoxidative glucose metabolism and measured activities of glycogen synthetase and physphorylase and concentrations of free glucose and glucose-6-phosphate in muscle biopsies, obtained before and after a euglycaemic insulin clamp, in 16 NIDDM patients, 18 first-degree relatives of NIDDM patients, and 16 non-diabetic control subjects. Insulin-stimulated glucose storage (20.1 ± 1.5 and 11.6 ± 1.7 vs. 27.9 ± 1.7 μmol kg^{-1} lean body mass [LBM] min^{-1}, $P<0.01$-0.001 [3.6 ± 0.3 and 2.1 ± 0.3 vs. 5.0 ± 0.3 mg kg^{-1} LBM min^{-1}] and 11.6 ± 1.3 vs. 18.3 ± 2.0 nmol min^{-1} protein, $P<0.01$), were impaired in relatives and diabetic subjects compared with control subjects. Glycogen synthase activity

correlated with the rate of glucose storage (r = 0.53, P<0.001). Glycogen phos phorylase fractional activity did not differ among the groups. Apart from increased intramuscular basl glucose concentrations in NIDDM patients, no consistent differences were observed in free glucose and glucose-6-phosphate concentrations between the groups. We conclude that impaired activation of muscle glycogen synthase by insulin is observed in-patients with a genetic risk of developing NIDDM and may represent and early defect in the pathogenesis of NIDDM.

Low plasma growth hormone binding protein in IDDM

Mercado M., Molitch M.E. and Baumann G. Diabetes 1992; 605-609

Poorly controlled insulin-dependent diabetes mellitus (IDDM) is associated with elevated basal plasma growth hormone (GH), disproportionally low insulin like growth factor I (IGF-I) levels, and impaired somatic growth. These derangements in the GH-IGF axis imply a state of GH resistance. The mechanism of GH resistance is unknown; it may involve a defect at the level of the GH receptor, unresponsiveness due to a postreceptor defect in GH action, or both. To investigate a potential receptor involvement, we measured plasma high-affinity GH-binding protein (GHBP), which represents a truncated GH receptor and may reflect GH receptor levels in tissues, in patients with IDDM, patients with non-insulin-dependent diabetes (NIDDM), and non-diabetic control subjects. Patients with IDDM had significantly lower plasma GHBP levels than either patients with NIDDM or non-diabetic control subjects (mean value 18.2 vs. 24.6 and 23.8% GH bound/ml plasma, respectively, P<0.001). This difference persisted when only lean patients (<115% ideal body wt) were included in the analysis. Basal plasma GH levels were significantly elevated in IDDM compared with either patients with NIDDM or nondiabetic control subjects (mean 6.9 vs. 2.1 and 2.0 µg/L, respectively, P<0.001), whereas IFG-I levels were not significantly different in IDDM and NIDDM. No correlations were found between levels of GHBP and HbA_1, duration were significantly correlated in NIDDM but not in IDDM. We conclude that IDDM is associated with low GHBP levels and that GH resistance found in this disorder may be mediated, at least in part, by a decrease in GH receptor levels. Insulinopenia may be the principal reason for GHBP/receptor deficiency.

Molecular defects in diabetes mellitus

Bell G., Diabetes 1991; 40: 413-22

The application of molecular biology to problems in diabetes mellitus has begun to reveal the underlying molecular defects contributing to the development of hyperglycaemia. Islet amyloid represents the most common pathological lesion occurring in the islets of NIDDM subjects. The use of both biochemistry and molecular biology has led to the identification of the major protein component of human islet amyloid and elucidation of the structure of its precursor. This protein, termed islet *amyloid polypeptide*, is related to two neuropeptides, calcitonin gene-related peptides 1 and 2, and, represents a new β -cell secretary product whose normal physiological function remains to be determined. The use of molecular biology has also led to a better understanding of the molecular defects contributing to insulin resistance. Characterization of the insulin-receptor gene. In patient with extreme forms of insulin resistance has resulted in the identification of mutations that impair its function and lead to tissue resistance to the action of insulin. Molecular biological approaches have also led to better understanding of the regulation of glucose transport. They have revealed that there is a family of structurally related proteins encoded by distinct genes and expressed in a tissue-specific manner that are responsible for the transport of glucose across the plasma membrane. Moreover, they have shown that specific depletion of the glucose-transporter isoform that mediates insulin-stimulated glucose transport is responsible for decreased transport activity in adipose tissue in insulin-resistant states.

Prospective analysis of the insulin-resistance syndrome (Syndrome x)

Haffner S.M., Valdez R. A., Hazuda H.P., Mitchell B. D., Morales P.A. and Stern M. P. Diabetes 1992; 41: 715-22

Many studies have shown that hyperinsulinaemia and/or insulin resistance are related to various metabolic and physiological disorders including hypertension, dyslipidaemia, and non-insulin-dependent diabetes mellitus. This syndrome has been termed syndrome X. An important limitation of previous studies has been that they all have been cross sectional and thus the presence of insulin resistance could be consequence of the underlying metabolic disorders rather than its cause. We examined the relationship fasting insulin concentration (as an indicator of insulin resistance) to the incidence of multiple metabolic abnormalities in the 8-yr follow-up of the cohort enrolled in the San Antonio Heart Study, a

population-based study of diabetes and cardiovascular disease in Medican Americans and non-Hispanic whites. In univariate analyses, fasting insulin was related to the incidence of the following conditions: hypertension, decreased high-density lipoprotein cholesterol concentration, increased triglyceride concentration, and non-insulin-dependent diabetes mellitus. Hyperinsulinaemis was not related to increased low-density lipoprotein or total cholesterol concentration. In multivariate analyses, after adjustment for obesity and body fat distribution, fasting insulin continued to be significantly related to the incidence of non-insulin-dependent diabetes mellitus. Baseline insulin concentrations were higher in subjects who subsequently developed multiple metabolic disorders. These results were not attributable t differences in baseline obesity and were similar in Mexican Americans and non-Hispanic whites.

These results support the existence of a metabolic syndrome and the relationship that syndrome to multiple metabolic disorders by showing that elevations of insulin disorders by showing that elevations of insulin concentration precede the development of numerous metabolic disorders.

G proteins and modulation of insulin secretion

Robertson P., Seaquist E.R. And Walseth T.F. Diabetes 1990; 40: 1-6

Guanine nucleotide-binding proteins (G proteins) are critically important mediators of many signaltransduction systems. Several important sites regulating stimulus-secretion coupling and release of insulin from pancreatic β -cells are modulated by G proteins. G_2 mediates increased in intracellular cAMP associated with hormone-induced stimulation of insulin secretion. G_1 mediates decreases in intracellular cAMP caused by inhibitors of insulin secretion, e.g., epinephrine, somatostatin, prostaglandin E_2, and galanin. G proteins also regulation channels, phospholipases, and distal sites in exocytosis. Cholera and pertussis toxins irreversibly ADP ribosylate G proteins and are important tools that can be used both to manipulate G-protein-dependent modulators of insulin secretion and detect and quantify G proteins by elecrtrophoretic techniques. The stage is set to pursue these initial observations in greater depth and ascertain whether G-protein research will provide important new insights into normal and abnormal regulation of insulin secretion.

TREATMENT: INSULIN THERAPY

Rationale for insulin management in gestational diabetes mellitus

Langer O., Berkus M., Brustman L., Anyaegbunan A., and Mazze R. Diabetes 1991; 40 (sippl. 2): 186-90

A prospective study was undertaken to test the hypothesis that insulin treatment in patients with gestational diabetes mellitus (GDM) with fasting plasma glucose (FPG) > 5.3 mM significantly reduces adverse perinatal outcome. Assigned to insulin or diet treatment based on FPG were 491 GDM women. Four factors believed to be associated with infants large for gestational age (LGA) were evaluated: FPG, overall glycaemic control, maternal weight, and treatment regimen. We found that when glycaemic control was optimized control, and incidence of 3.5% LGA was found. Patients in the mid-FPG group (5.3-5.8 mM) had a higher increased rate of LGA (28.6%) for diet-treated versus insulin-treated women (10.3%). In addition, an fourfold-increased risk for LGA was found in the diet-treated obese subjects in the mid-FPG group compared with insulin-treated obese women. Finally, treatment with insulin-treated obese women. Finally, treatment with insulin resulted in similar incidence of LGA within all FPG groups. We concluded that FPG > 50. mM can be the basis for initiation of Insulin treatment in GMD subjects with optimization of glycaemic control as the goal. This approach may contribute significantly to reduced neonatal risk and may foster a standardized method for rapid and effective assignment to treatment.

Encapsulation of insulin for oral administration preserves interaction of the hormone with its receptor in vitro

Roques M., Dange C., Michel C., Staedel C., Cremel G. and Hubert P. Diabetes 1992; 41: 451-56

It has been shown that insulin associated with nanocapsules of isobutylcyanoacrylate retains biological activity after oral administration to diabetic rats from 6 to 21 days. Because part of this action is unexplained, we focussed on the interaction of encapsulated insulin with the insulin receptor in vitro. We have shown that encapsulated insulin is able 1) to bind to insulin receptors both in rat liver plasma membranes and after solubilization from Chinese hamster ovary (CHO) cells transfected with the gene of human insulin receptor, 2) to accelerate ^{125}I-labelled insulin diassociation from its receptor, and 3) to ensure transduction of a signal leading to stimulation to b -subunit phosphorylation, with parameters similar to

those of native insulin. In addition, encapsulated ^{125}I-insilin was rapidly internalized in transfected CHO cells. Analysis of cell-associated radioactivity showed that encapsulated insulin remained largely intact (>80%) after 3 h, whereas native insulin was mostly degraded. These data indicate that encapsulated insulin fulfils all the earliest events at the receptor level leading to biological actions and suggests that encapsulation protects insulin against insulin degradation inside the cells.

Pioglitazone increases insulin sensitivity by activating insulin receptor kinase

Kobayashi M., iwanishi M., Egawa K. and Shigeta Y. Diabetes 1992; 41: 476-83

A new oral agent, 5-[4-(2-(5-ethyl 12-pyridyl) ethoxy] - benzoyl] - 2,4 - thiazolonedione (pioglitazone), has been developed for treatment of non-insulin-dependent diabetes mellitus (NIDDM). This agent increased insulin sensitivity in vivo in genetically obese Wistar fatty rats. Administration of the agent (3 mg/kg/day) for 10 days to the rats ameliorated hyperglycaemia and hyperinsulinaemia, indicating that it decreased insulin resistance. To clarify the mechanism of the drug to increases insulin sensitivity, we examined insulin binding and kinase activity of insulin receptors from muscles of both untreated and treated rats. Pioglitazone treatment did not change insulin binding in Wistar fatty rats but increased insulin-stimulated autophosphorylation of insulin receptors to 78% over the level in the control but not the basal state. Kinase activity toward exogenous substrate, poly Glu^{4} Tyr^{1}, was also increased to 87% over the level of untreated control lbese rats. In contrast, in lean rats, pioglitazone treatment did not increase outophosphorylation and kinase activity toward exogenous substrates. To further elucidate the mechanism, we incubated insulin receptors with the agent and measured kinase activity. Incubation of solubilized receptors with the agent did not increase kinase activity. However, the receptors from IM-9 cells, which were incubated with 10-8 M pioglitazone for 7 days, showed a 46% increase over the control in insulin-stimulated autophosphorulation and kinase activity. These results suggested that pioflitazone increased insulin sensitivity in part by activating kinases of the receptors through indirect effect on insulin receptors and that the drug may have useful benefits in insulin resistance of NIDDM.

DIET

Therapeutic potentials of acarbose as first-line drug in NIDDM insufficiently treated with diet alone

Hanefild H., Fischer S., Schulzc J. et al Diabetes Care 1991; 14: 732-37

Objective: Acarbose inhabits ∝-glucosidases of the small intestine and thus delays glucose release from complex carbohydrates. Therefore, its efficacy and acceptability as a first-line drug in non-insulin-dependent diabetes mellitus (NIDDM) insufficiently treated with diet alone was tested in a randomized double-blind placebo-controlled study.

Research Design and methods: Ninety-four NIDDM subjects, aged 43-70 yr. with average body mass index of 28 kg/m^2 and undergoing a pre-treatment period of at least 3 mo with diet alone, were treated with 100 mg acarbose three times daily or placebo for 24 wk. The patients were recruited after a 4 wk-screening period of dietary reinforcement. The inclusion limits for patients termed diet not satisfactory were fasting blood glucose (FBG) > 7.8 mM and /or postprandial blood glucose (BG) > 10 mM.

Results: FBG was lowered in the acarbose group from 9.8 to 8.4 mM and in the placebo group from 10.2 to 9.6 mM after 24 WK (P= 0.007 vs. placebo). The most impressive therapeutic effect was highly significant reduction of postprandial hyperglycemia for at least 5 h after the test meal (1-h postprandial BG with acarbose 10.4 mM snf placebo 13.5 mM at 24 wk, P < 0.001) accompanied by significant decrease in HbA, (acarbose 8.65%, placebo 9.32%, P=0.003). Whereas C-peptide and fasting random insulin was not significantly affected by acarbose, postprandial insulin increment was ~ 30% lower after 24 Wk compared with placebo. Furthermore, acarbose significantly reduced 1-h postprandial triglyceride levels. After an initial phase of > 4 WK (when 76.6% in the carbose group vs. 28% on placebo complained about flatulence, (p<0.001), the drug was well accepted. At the end of the study, only 32% showed mild to moderate gastrointestinal sensations.

Conclusions: Extrapolation shows that acarbose is an efficient and acceptable drug for the treatment of NIDDM with poor metabolic control by diet alone. It has beneficial effects on postprandial hyperinsulinaemia and postprandial hypertriglyceridaemi.

EXERCISE

Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus

Helmirch S. P., Ragland D. R., Leung R. W. and paffenbarger R. S. N. Engl. J. Med. 1991; 325: 147-52

Abstract Background: Physical activity is recommended by physicians to patients with non-insulin-dependent diabetes mellitus (NIDDM), because it increases sensitivity to insulin. Whether physical activity is effective in preventing this disease is not known.

Methods: We used questionnaires to examine patterns of physical activity and other personal characteristics in relation to the subsequent development of NIDDM in 5990 male alumni of the University of pennsylvania. The disease developed in a total of 202 men during 98,524 man-years of follow-up from 1962 to 1976.

Results: Leisure-time physical activity, expressed in kilocalories expended per week in walking, stair climbing, and sports, was inversely related to the development of NIDDM. The incidence rates declined as energy expenditure increased from less than 500 kcal to 3500 kcal. For each 500-kcal increment in energy expenditure, the age-adjusted risk of NIDDM was reduced by 6 per cent (relative risk, 0.94; 95 per cent confidence interval 0.90 to 0.98). This association remained the same when the data were adjusted for obesity, hypertension, and parental history of diabetes. The association was weaker when we considered weight gain between the time of college confidence interval, 0.90 to 1.00). The protective effect of physical activity was strongest in persons at highest risk for NIDDM, defined as those with a high body-mass index, a history hypertension, or a parental history of diabetes. These factors, in addition to weight gain since college, were also independent predictors of disease.

Conclusions: Increased physical activity is effective in preventing NIDDM, and the protective benefit is especially pronounced in persons at the highest risk for the disease.

TRANSPLANTATION AND IMMUNO-SUPPRESSION

Effects of pancreatic transplantation on diabetic neuropathy

Kennedy W. R., Navarro X., Goetx F. C. Sutherland D. E. R. and Najarian J. S.

* Abstract reestablishment of the euglycaemia state by successful transplantation of the pancreas might halt or reverse diabetic neuropathy. To test this possibility we evaluated neurologic function by clinical examination, nerve conduction studies and autonomic-function tests in-patients with insulin-dependent (Type I) diabetes mellitus before and after successful pancreatic transplantation. Sixty-one patients wee studied before and 12 months after transplantation, 27 again after 24 months, and 11 again after 42 months. A control group of patients with Type I diabetes treated with insulin underwent the same studies at similar intervals- 48 patients before and after 12 months had elapsed, 21 again after 24 months, and 12 months again after 42 months.

In the control group neuropathy tended to worsen during the follow-up period. The scores on the clinical examination indicated increased impairment after 12 months. Composite indexes of the degree of abnormality found on neurophsiologic testing of the function if peripheral motor, sensory and autonomic nerves indicated decreased autonomic function after 12 months. The examination score and the three index values worsened slightly but not significantly in the patients followed for 24 and 42 months. In contrast, in the patients who had received pancreatic transplants, the neuropathy tended to improve. There was significant improvement in the motor and sensory indexes 12 months after transplantation and in the sensory index 24 months after transplantation. The other measures improved slightly but not significantly at these times, as did all for measures in the patients studied 42 months after transplantation.

We conclude that the progression of diabetic polyneuropathy may be halted through the restoration of an euglycaemia state by successful pancreatic transplantation.

Promotion of pancreatic islet allograft survival by intrathymic transplantation of bone marrow

Posselt A. M. Odorico J. S., Barker C. F. and Naji A. Diabetes 1992; 41: 771-75

An important goal in the treatment of insulin-dependent diabetes by pancreatic islet transplantation is the development of strategies that allow permanent survival of islet allografts without continuous host immunosuppression. In this study, we demonstrate that inoculation of allogeneic bone marrow into the thymus of adult rats treated with a single dose of anti-lymphocytle serum induces an unresponsive state that permits survival of subsequent pancreatic islet allografts transplanted to an extrathymic site. This effect is donor specific, cannot be reproduced by systemic administration of

bone marrow, and is associated with persistence of chimeric cells in the thymus of the recipient. In addition, lymph node cells from long-term recipients of intrathymic bone marrow display markedly reduced proliferative responses to donor alloantigens in mixed lymphocyte culture. Interaction of maturing thymocytes with foreign alloantigens may produce the unresponsiveness. This model offers a potential approach for establishing donor-specific allograft acceptance in adult recipients.

Pancreas transplantation humans with diabetes mellitus

Robertson P. Diabetes 1991; 40: 1085-89

Pancreas transplantation, when successful, is a reproducibly effective method to normalize glycaemia without the use of exogenous insulin treatment in-patients with diabetes mellitus. Success rates for combined pancreas and kidney transplantation are 70%, and patient survival rates are ~ 90% 1 yr. postoperatively. Metabolic benefits of this procedure include normalization of levels of fasting plasma glucose and HbA_{1c}, Glucose-induced insulin secretion and intravenous glucose tolerance are normalized. Improvements are also observed in glucose recovery after insulin-induced hypoglycaemia and in glucagon secretion during hypoglycaemia. Pancreas transplantation is also associated with normalization of kidney structure and both motor and sensory nerve functions. However, no benefits have been observed with regard to pancreatic polypeptide secretion, kidney function, and retinal pathology of diabetes mellitus. Pancreas transplantation has reached a point in its history where the operative technique and its ancillary medical therapy have been optimized. Improvement in the rates of success, morbidity, and mortality will probably depend on improvement in immunosuppressive drugs and the physical condition of the recipients themselves. The time is at hand when we need to carefully consider whether it is ethical and advisable to make pancreas transplantation available for diabetes mellitus. Future studies of pancreas transplantation must incorporate more rigid experimental controls than have been used in the past to better assess the relative merits of this procedure.

MISCELLANEOUS

Glycaemic control and neuropsychologic function during hypoglycaemia in patients with insulin-dependent diabetes mellitus

Wisom B., Simonson D. C., Ann. of Int. Med. 1990; 112: 904-912

Subject Objective: To evaluate counterregulatory hormone secretion and neuropsychologic function during hypoglycaemia in two groups of patients with insulin-dependent diabetes mellitus: those with good and those with poor glycaemia control.

Design: Clinical research unit of a referral-based diabetes clinic.

Patients: Eight patients with well-controlled diabetes (glycosylated haemoglobin [$HgbA_1$], 8.0% ± 0.2), nine patients with poorly controlled diabetes ($HgbA_1$, 11.8% ± 0.4%), and ten healthy persons.

Interventions: The insulin clamp technique was used to produce a stepwise decline in plasma glucose from 5.0 to 2.2 mmol/L over 3 hours. Tests of attention, memory, visual-spatial skills, visual-motor skills, and global cognition; a symptom survey; and counterregulatory hormone measurements were done at glucose decrements of 0.6 mmol/L.

Measurements and main results: Patients with well-controlled diabetes did not differ statistically from those with poorly controlled diabetes regarding the median glucose threshold for dysfunction in visual-spatal skills, visual-motor skills, or global cognition. In contrast, glycaemic thresholds for an increase in adrenergic symptoms and release of epinephrine, norepinephrine, cortisol, and growth hormone were lower in-patients with well-controlled diabetes than in those with poorly controlled diabetes ($p<0.05$ to 0.005).

Conclusions: Despite alterations in the glucose levels at which adrenergic symptoms of hypoglycaemia occur and counterregulation begins, there is no statistically detectable change in the glucose threshold at which cognitive deterioration occurs in diabetic persons with strict glycaemia control. This dissociation of neuropsychologic function and counterregulatory hormone secretion suggests that diabetic patients with good glycaemia control are at increased risk for developing cognitive impairment before the onset of adrenergic symptoms during hypoglycaemia.

Newly identified pancreatic protein islet amyloid polypeptide
What is its relationship to diabetes?

Johnson K. B. O'Brien R. D. and Westermark P. Diabetes 1991; 40: 310-14

Islet amyloid polypeptide (IAPP) or amylin is a newly identified 37-amino acid COOH-terminal-amidated polypeptide that is the major protein

constituent of amyloid deposits in insulinomas and amyloid deposits in pancreatic islets on non-insulin-dependent (type II) diabetic humans and adult diabetic cats. IAPP is stored with insulin b -cell secretory vesicles and is consecrated with insulin in response to glucose and several secretagogues. IAPP has been demonstrated in normal pancreatic islets of many species, but IAPP-derived amyloid develops commonly in the islets of only a few species (e.g. humans and cats), especially in association with age-related diabetes. IAPP from the human and cat inherently contains a short amyloidogenic sequence that is not present in species that do not form islet amyloid. Studies in animals indicate that an aberration in the synthesis or processing of IAPP, leading to a local increase in concentration of IAPP in the islet, is also required to facilitate the conversion of IAPP to amyloid. The formation of islet amyloid may contribute to the development of type II diabetes by causing disruption of islet cells and by replacement of islets. It has also been proposed that an abnormality of IAPP inhibits glucose-stimulated insulin release by b -cells and that IAPP inhibits insulin-stimulated rates of glycogen synthesis and glucose uptake by skeletal muscle cells. These findings clearly have potentially great relevance to type II diabetes in that impaired insulin secretion and peripheral resistance to insulin are the clinical hallmarks of this form of diabetes. However, studies generally have not supported a role for IAPP as a physiologically relevant modular of insulin secretion, and it is yet to be demonstrated whether IAPP in physiological concentrations can induce the peripheral insulin resistance that is characteristic of type II diabetes. The potential role of this newly identified pancreatic polypeptide in the genesis of type II diabetes thus needs further investigation and confirmation in model systems utilizing physiological concentrations of IAPP. The significance of the strikingly greater responsiveness of IAPP secretion relative to insulin in severely hyperglycaemic states also is not clear. However, the observation may provide an important clue to the normal function of IAPP and points to an important area of future exploration.

COMPLICATIONS

Insulin, prostaglandin's, and the pathogenesis of hypertension

Axelrad D. Diabetes 1991; 40: 1223-27

Hypertension is associated with hyperinsulinaemia in the presence or absence of obesity or glucose intolerance. Physiological concentrations of insulin decrease the catecholamine-induced production of prostaglandin l_2 (PGI_2; prostacyclin) and PGE_2, two potent vasodilators, in adipose tissue, one of the largest organs in the body. This finding suggests that hyperinsulinaemia increases peripheral vascular resistance and blood pressure by inhibiting the stimulatory effect of adrenergic agonists (and perhaps other agonists) on the reduction of PGI_2 and PGE_2 in adipose tissue (and perhaps other tissues). This concept is supported by evidence that PGI_2 and PGE_2 modulate vascular relativity in states of health and disease. For example, during insulin deficiency, i.e. in diabetic ketoacidosis, PGI_2 and PGE_2 production by adipose tissue are increased, and peripheral vascular resistance and blood pressure are decreased. This hypothesis is also supported by evidence that blood flow through rat and human adipose tissue is decreased in obesity and that insulin decreases the blood flow through adipose tissue in nonobese rats. Thus, insulin may regulate PGI_2 and PGE_2, production by adipose tissue (and possibly other tissues) through a wide range of concentrations with important physiological and clinical consequences.

Link between hypertension and diabetes mellitus epidemiological study of Chinese adults in Taiwan

Tai T., Chuang L., Chen C., Lin B. J. Diabetes Care 1991; 14: 1013-20

Objective: To elucidate the relationship between hypertension and non-insulin-dependent diabetes.

Research Design and Methods: The study consisted a random sample of adults aged ³ 40 yr. from the Ta-An district of Taipei city and 5 of 12 villages of Taiwan province, which has established primary health-care centres since 1984. A total of 11,478 subjects were recruited into the survey with a response rate of 65.3 and 72%, respectively. Blood glucose and blood pressure levels were measured, and a structured questionnaire was given to each participant. Those identified as having diabetes received further blood tests for lipids and creatinine and were evaluated for vascular complications.

Results: The age and sex-adjusted prevalence of hypertension among diabetic subjects was twice that of non-diabetic subjects (30.6 vs. 16.4%, $P < 0.0005$). Hypertensive subjects had a higher prevalence of diabetes than normotensive subjects (10.2 vs. 4.9%, $P < 0.0005$). Among hypertensive subjects, the prevalence of diabetes was 12.7% for those taking antihypertensive drugs and 9.1% for those not taking any drug ($P < 0.05$). The prevalence of diabetes significantly increased as

mean arterial pressure rose, whether the subjects were stratified by various factors. Multiple regression analysis, including sex, age, body mass index, and other risk factors as independent variables, also showed a significant association between diabetes and hypertension.

Conclusions: The univariate and multivariate analyses revealed that there seemed to be a tight link between hypertension and non-insulin-dependent diabetes. Family history of diabetes, diabetes duration, diabetes regimen, control of blood glucose, and the presence of nephropathy, as attested by proteinuria, did not contribute to the risk of hypertension. Further studies are necessary to determine whether these two conditions are causally related.

Insulin and cardiovascular disease

Fontbonne A.M. Eschwege E. M. Diabetes Care 1991; 14: 461-9

The Paris prospective study is a long-term investigation of coronary heart disease (CHD) risk factors in a large population of working men. The baseline cohort included 7028 men, 6093 who had a 75-g oral glucose tolerance test with measurement of plasma insulin and glucose levels (0 and 2h) and 125 who were known non-insulin-treated diabetic patients. After a mean follow-up of 11 yr. 126 deaths ascribed to CHD were reported. Major independent predictors of CHD death were blood pressure, smoking, plasma cholesterol level, and fasting and 2-h postload plasma insulin level, impairment of glucose tolerance, including overt diabetes, did not rank as an independent predictor when other baseline variables cohort who presented with impaired glucose tolerance or diabetes (n = 943), 26 died from CHD during the follow-up. The strongest independent predictor of subsequent CHD death in this subsample with abnormal glucose tolerance was plasma triglyceride level. In view of the accumulating evidence that hyperinsulinaemia and hypertriglyceridaemia generally occur in the same type of subjects, in relation to insulin resistance and central obesity, the edidemiological findings of the Paris prospective study and of other investigations support the hypothesis that a constellation of mild metabolic abnormalities may play a deleterious role with regard to cardiovascular disease risk.

Trends in prevalence of diabetes mellitus in patients with myocardial infarction and effect of diabetes on survival
The minnesota heart survey

Sprafka J. M. Burke G. L., Folsom A. R. McGovern P. G., and Hahn L. P. Diabetes Care 1991; 14: 537-43

Objective: The purpose of this study was to document trends in the prevalence of diabetes among men and women hospitalized for myocardial infarction (MI) and to determine the effect of diabetes on in-hospital case fatality rates and long-term survival.

Research Design and Methods: The Minnesota heart survey is population-based surveillance system that has monitored trends in coronary heart disease morbidity since 1970. As part of this effort, a 50% random sample of acute MI discharge records in Minneapolis – St. Paul metropolitan area hospitals was abstracted in 1970, 1980, and 1985.

Results: The prevalence of diabetes among MI patients was compared over time, and the data indicated a significant increase between 1970 and 1985 in both men (8.2 vs. 16.8%, P. < 0.001) and women (16.0 vs. 25.8%, P = 0.01). Diabetic individuals had an odds ratio in-hospital death after an MI 1.5 times that of non-diabetic individuals (P < 0.01) after controlling for the effects of sex, age, and year of MI, Among discharged MI survivors, the risks of death was 40% higher (P < 0.01) in diabetic individuals than non-diabetic individuals after 6 yr. of follow-up. Compared with non-diabetic individuals, diabetic individuals appeared more likely to have cardiac (pump) failure with acute MI.

Conclusions: Our findings suggest that the risk of coronary heart disease morbidity over time. Therefore, clinicians need to take extra care in the management of MIs in diabetic individuals, and public health efforts to reduce diabetes prevalence are warranted.

Power spectral analysis of heart-rate variations improves assessment of diabetic cardiac autonomic neuropathy

Bellavere F., Balzani I. De Masi G. et al. Diabetes 1992; 41: 633-40

Power spectral analysis (PSA) of heart-rate variations has recently proved a useful tool in evaluating cardiovascular autonomic activity. If offers the possibility of examining both the functioning of parasympathetic and sympathetic pathways through breakdown into two frequency bands, and of their effects of heart-rate cyclic variability. We applied an autoregressive model for PSA to study overall autonomic tone in 20 male

age-matched control subjects and 53 insulin-dependent (type I) diabetic subjects, subdivided into three groups of 20, 15, and 18, each group presenting different degrees of autonomic involvement. We found that: 1) power spectrum density (PSD) values at highfrequency bands (parasympathetic dependent) were similar in diabetic subjects without cardiac autonomic neuropathy (CAN) and in control subjects, but differed significantly from diabetic subjects with mild CAN and severe CAN, both standing and lying; 2) PSD values at low frequency (mainly sympathetic dependent) were similar, or slightly different, in diabetic subjects without CAN and in control subjects, but differed significantly from diabetic subjects with mild and severe, CAN, both standing and lying; 3) as an expression of parasympathetic versus sympathetic coherence, correlations, both standing and lying existed between PSD values at low-and high-frequency bands in control and diabetic subjects without CAN, but not in diabetic subjects with CAN; and 4) different degrees of correlation characterized the PSD values of high and low frequencies versus traditional cardiovascular test values in the diabetic subjects. The best correlation was between PSD low-frequency values and the lying-to-standing manoeuvre. These data indicate that PSA 1) can discriminate between differing degrees of parasym-pathetic involvement, 2) can discriminate between different degrees of sympathetic involvement, and 3) offers a picture of overall autonomic activity that can be explored only partially by traditional cardiovascular autonomic tests and 4) can reveal parasympathetic versus sympathetic dyssynergia. These data suggest that cardiovascular autonomic tests may different aspects of autonomic pathways. Hence, PSA appears to be a powerful tool in the determination of autonomic tone in diabetic CAN.

NEPHROPATHY

Increase in glomerular filtration rate in-patients with insulin dependent diabetes and elevated erythrocyte sodium lithium conuntertransport

Carr S., Mbanya J. C., Thomas T., et al N Engl J. Med. 1990; 322: 500-5

Increased sodium lithium countertransport in erythrocytes is found in-patients with insulin-dependent diabetes mellitus (IDDM) and nephropathy. To determine whether such an increase precedes the onset of nephropathy and, if so, whether it is associated with changes in renal function, we measured erythrocyte sodium-lithium counter-transport in 52 patients with IDDM but not nephropathy or hypertension and in 32 control subjects.

Seventeen of the 52 patients with IDDM (33 percent) had sodium lithium countertransport activity that exceeded the maximal activity in the control subjects (0.39) mmol of lithium per hour per litre of cells). Eighteen of the 52 patients with IDDM were sodium lithium countertransport values had glomerular filtration rate (median), 159 ml per minute per 1.72 m^2 of body surface area; range, 134 to 197) that were significantly higher ($P < 0.01$) than those in the remaining 11 patients with IDDM and normal sodium-lithium countertransport (median, 126 ml per minute per 1.73 m^2; range, 110 to 176) or in the 10 control subjects (median, 128 ml per minute per 1.73m^2; range, 93 to 151) in the seven patients with elevated sodium lithium countertransport, the filtration fraction (median, 0.27, range, 0.22 to 0.37) was also greater ($P < 0.01$) than that in control subjects (median, 0.22; range, 0.18 to 0.28). There were no differences in renal function between the patients with IDDM and normal sodium lithium countertreansport and the control subjects.

We conclude that sodium lithium countertransport increased in-patients with IDDM before the onset of nephropathy and is associated with hyperfiltration. Thus, elevated sodium lithium countertransport activity may be an early marker of diabetic nephropathy.

Plasma prorenin activity and complications in children with insulin dependent diabetes mellitus

Wilson D. M., Leutscher J. A. N. Engl J. Med. 1990; 323: 1101-6

Background: Renin, secreted into the blood by the juxtaglomerular cells of the kidneys, is derived from a larger precursor prorenin. Plasma prorenin activity is increased in patients with insulin-dependent (Type I) diabetes mellitus who have microvascular complications of their diabetes. We undertook this study to determine prospectively whether rising prorenin activity can predict the development of complications in young patients with Type I diabetes.

Methods and Results: Plasma prorenin was measured in 35 children and adolescents with Type I diabetes. The mean (± SE) plasma prorenin activity among the 32 patients over the age of 10 years who had uncomplicated diabetes for 0.1 to 5 years was 8.43 ± 0.58 ng of angiotesin 1 per litre second as compared with 7.06 ± 0.32 in 37 control

subjects of the same age $P < 0.05$ in the 9 patients older than 10 who had retinopathy or overt albuminuria, the mean plasma prorenin activity was 13.09 ± 1.43 ng of angiotensin 1 per litre second ($P < 0.0001$).

In 34 patients 10 years old or older with uncomplicated diabetes, 3 to 13 measurements of plasma prorenin activity were taken during a follow-up period of 6 to 39 months. Urinary albumin was determined at each visit, and the patients had regular retinal examination. Only 1 of the 20 patients who had consistently normal plasma prorenin values had over albuminuria (ratio of urinary albumin to cratinine, > 0.017) or retinopathy, whereas one or both of these complications appeared in 8 of the 14 who had at least one high prorenin value. The plasma prorenin value was significantly higher in these eight patients at least 18 months before a complication was found.

Conclusions: Increased plasma prorenin activity identifies a group of young patients with diabetes who are at high risk for retinopathy or nephropathy.

Effect of strict glycaemic control on renal haemodynamic response to amino acids and renal enlargement in insulin dependent diabetes mellitus

Tuttle K. R., Bruton J. L., Peruser M. C., Lancaster J. L., Kopp D. T. and Defronzo R. A. N. Engl. J. Med. 1991; 324: 1626-32

Background: Many patients with insulin dependent diabetes mellitus have an increase in the glomerular filtration rate and renal enlargement early in the course of their disease. Both these changes may be risk factors for the later development of diabetic nephropathy. Their cause is not known, but they could be due to augmented renal responses to the increase in plasma amino acid concentrations that occurs when dietary protein intake is high, a factor known to increase gloemerular filtration and renal blood flow in normal subjects.

Methods: We measured the glomerular filtration rate and renal plasma flow after an overnight fast and during an infusion of amino acids in 12 patients with insulin-dependent diabetes mellitus and 9 normal subjects. The diabetic patients were studied when they were hyperglycaemic, when they were euglycaemic after an insulin infusion for 36 hours, and after intensive insulin therapy for 3 weeks. Kidney volume was measured by ultrasonography before and after the period of intensive insulin therapy.

Results: The glomerular filtration rate and renal plasma flow were normal after fasting when the patients were hyperglycaemic (mean (± SE) fasting plasma glucose level, 11.5 ± 0.7 mmol per liter). After the amino acid infusion, these values increased more in the patients (glomerular filteration rate, 2.65 ± 0.07 ml per second per 1.73 m^2 of body surface area, renal plasma flow, 13.30 ± 0.68 ml per second per 1.72 m^2, $P < 0.05$ for both) than in the normal subjects (2.25 ± 0.8 and 11.20 ± 0.65 ml per second per 1.73 m^2, respectively). The 36-hour infusion of insulin in the diabetic patients did not alter the glomerular filtration rate pr renal plasma flow either before or during the amino acid infusion. After three weeks of intensive insulin therapy (fasting plasma glucose level, 5.3 ± 0.2 mmol per liter), the glomerular filtration rate and renal plasma flow after amino acid infusion (2.33 ± 0.03 and 1130 ± 0.43 ml per second per 1.73 m^2 respectively) were similar to those in the normal subjects. The kidney volume in the normal subjects and the patients with diabetes were 219 ± 14 and 312 ± 14 ml per 1.73 m^2, respectively ($P < 0.01$), the volume decreased to 267 ± 22 ml per 1.73m^2 ($P < 0.001$) in the diabetic patients after weeks of intensive insulin therapy, which was not significantly different from the volume in the normal subjects ($P = 0.1$).

Conclusions: Conventionally treated diabetic patients who have augmented renal haemodynamic responses to increased plasma amino acid concentrations. The concomitant decrease in these haemodynamic responses and in kidney size with strict glycaemic control suggests that these phenomena are related and influenced by the metabolic state.

Low urinary chiro-inositol excretion in non-insulin-dependent diabetes mellitus

Kennington A. S., Hill C. R., Crarg J., et al N. Engl. J. Med. 1990; 323: 373-8

Background and Methods: Inositol is a major component of the intracellular mediators of insulin action. To investigate the possible role of altered inositol metabolism in non-insulin-dependent diabetes mellitus (NIDDM), we used gas chromatography and mass spectrometry to measure the myo-inositol and chiro-inositol content of urine specimens from normal subjects and patients with NIDDM. The study subjects were whites, blacks, and Pima Indians. The type of inositol and its concentration in insulin-mediator preparations from

muscle-biopsy specimens from normal subjects and diabetes patients were also determined.

Results: The urinary excretion of chiro-inositol was much lower in the patients with NIDDM (mean [± SE], 1.8 ± 26.9) m mol per day) than in the normal subjects (mean, 84.9 ± 26.9 m mol per day; $P < 0.01$). In contrast, the mean urinary myo-inositol excretion was higher in the diabetic patients than in the normal subjects (444 ± 135 vs. 176 ± 46 µmol per day; $P < 0.05$). There was no correlation between chiro-inositol excretion and the age, sex, or weight of the diabetic patients, nor was there any correlation between urinary chiro-inositol and myo-inositol excretion in either group. The results were similar in a primate model of NIDDM, and chiro-in-ositol excretion was decreased to a lesser extent in animals with pre-diabetic insulin resistance, chiro-inositol was undetectable in insulin-mediator preparations from muscle-biopsy samples obtained from patients with NIDDM. Similar preparations from normal subjects contained substantial amounts of chiro-inositol. Furthermore, the chiroinositol content of such preparations increased after the administration of insulin during euglycaemic-hyperinsulinaemic-clamp studies in normal subjects but not in patients with NIDDM.

Conclusions: NIDDM is associated with decreased chiro-inositol excretion and decreased chiro-inositol content in muscle. These abnormalities seem to effect the presence of insulin resistance in NIDDM.

Role of postglomerular microvessels in pathophysiology of diabetic nephropathy
Pinter G. G. and Atkins J. L. Diabetes 1991; 40: 791-5

Although glomerular damage plays a well-established and important role in the pathomechanism of diabetic nephropathy, it alone does not fully explain the progression of renal complications in long-term diabetes mellitus. We discuss experimental evidence showing involvement of the postglomerular microvessels (peritubular capillaries and venules) in diabetic microangiopathy. This involvement is manifest in increased permeability of these vessels to plasma proteins and in highly augmented lymphatic drainage of the extravasated proteins from the renal interstitium. We suggest that in the advanced phase of diabetic nephropathy, proteinuria (corresponding to excess leakage of proteins through the glomerular capillary wall) indicates the probability that postglomerular microvessels have also allowed leakage of plasma proteins. As long as lymphatic drainage is capable of removing the increased quantity of extravasated plasma proteins from the interstitium, renal function should not be deleteriously affected. However, if the excess amount of extravasated proteins exceeds the capacity of lymphatic drainage, increases in interstitial volume and pressure are unavoidable with detrimental consequences of glomerular filtration and tubular reabsorption. Under these conditions, a potential positive-feedback loop can be visualized that involves increased extravasation of plasma proteins leading to increased interstitial pressure that through dilation of the afferent and efferent arterioles results in a further increase in protein extravasation. These conditions combined with glomerular damage should lead to the eventual collapse of renal function.

Von Willebrand factor and development of diabetic nephropathy in IDDM

Coen D. A. Stehouwer, Erik S. G. et al Den Ottolander Diabetes 1991; 40: 971-6

We tested the hypothesis that dysfunction of vascular endothelium, indicated by an increase in plasma level of von Willebrand factor (vWF), is present in-patients with insulin-dependent diabetes mellitus (IDDM) who develop diabetic nephropathy (DN). DN was classified as absent (urinary albumin excretion [UAE] rate < 15 m g/min). We followed a cohort of 59 patients for a median of 3 yr. At base line, 52 patients had no DN, 6 had incipient DN, and 1 had clinical DN. At follow-up, 38 patients had no DN (group 1). Incipient DN had developed in 14 patients and worsened in 3 patients. Clinical DN had worsened in 1 patient. Together, these 18 patients comprised group 2. A decrease in UAE was observed in remaining three patients with incipient DN at baseline (group 3). In-group2, vWF-measured by immunoelectrophoresis and expressed as a percentage of normal-increased slightly (median 10%, range – 43 to 145, $P = 0.009$). In-group 2, vWF increased in all patients (median 80%, range – 14 to – 206, $P = 0.0002$ vs. baseline and group 1). In-group 2, vWF decreased (median – 19%, range – 44 to – 18). After correction for possible confounders, i.e., age, varying duration of follow-up, and initial level of vWF, the difference in vWF change between groups 1 and 2 remained significant ($P = 0.009$). Poor glycaemic control at baseline, estimated by glycosylated haemoglobin, was a significant predictor of increases in vWF in both group 1 and groups 1 and 2 combined. We conclude that dysfunction of vascular endothelium is present in patients who develop DN. Poor

glycaemic control may be related to endothelial dysfunction in patients with and without DN. Our data suggest that changes in vWF may serve as a useful marker of the state of the vascular endothelium in diabetes.

Atrial natriuretic peptide and response to changing plasma volume in diabetic nephropathy

Lieberman J. S., Parra L., Newton L., Scandling J. D. Nicholas L. and Myers B. D. Diabetes 1991; 40: 893-901

We evaluated the renal and hormonal responses to volume expansion induced by water immersion in subjects with diabetic nephropathy (n = 12) and in healthy control subjects (n = 9). Immersion induced similar average increments in sodium excretion (± 223) vs. 176 µmol/min) and comparable decrements in renovascular resistance (RVR; -15 vs. –16 U). However, whereas the control subjects responded uniformly, the response among diabetic subjects was highly variable, with a subset of patients exhibiting paradoxical antinatriuresis and vasoconstriction. Immersion was associated with marked elevation of atrial natriuretic peptide (ANP) in plasma of diabetic versus control subjects (61 ± 9 vs. 19 ± 2 pM, respectively; $P < 0.001$). Yet for each picomolar increment in plasma ANP during immersion, the corresponding increases in urinary excretion of cyclic guanosine monophosphate (26 vs. 279 pmol/min) and sodium (9 vs. 47 µmol/min) and the reciprocal lowering of RVR (0.7 vs. 19 C) were blunted in the diabetic versus control group. Volume contraction in the postimmersion period was associated with disproportionate antinatriuresis and renal vasoconstriction in the diabetic group, despite a persistent elevation of ANP (29 ± 2 vs. 16 ± 2 pM, $P < 0.01$). We propose that renal insensitivity to ANP in diabetic nephropathy could contribute to altered vasoreactivity and abnormal excretory responsiveness to changing plama volume. Blunted natriuresis in response to ANP release and enhanced sodium retention during volume contraction could account for the expanded extracellular fluid volume that has consistently been reported to accompany the development of diabetic nephropathy.

Advanced glycosylation end products in patients with diabetic nephropathy

Makita Z., Radoff S., Rayfield E. J., et al. N. Engl. J. Med. 1991; 325: 836-42

Background: Glucose reacts nonezymatically with proteins in vivo, chemically forming covalently attached glucose-addition products and cross-links between proteins. The excessive accumulation of rearranged late-glucose-addition products, or advanced glycosylation end products (AGEs), is believed to contribute to the chronic complications of diabetes mellitus.

Methods: To elucidate the relation of AGEs to diabetic complications, we used a radioreceptor assay to measure serum and tissue AGEs in diabetic (Types I and II) and nondiabetic patents with different levels of renal function. Serum AGEs were measured as a low-molecular-weight (< 10 kd) peptide fraction and a high-molecular-weight (> 10 kd) protein fraction.

Results: The mean (± SD) AGE content of sample of arterial-wall collagen from 9 diabetes patients was significantly higher than that of samples from 18 nondiabetic patients (14.5 ± 5.2 vs. 3.6 ± 1.5 AGE units per milligram, $P < 0.001$). Moreover, diabetic patients with end-stage renal disease had almost twice as much AGE in tissue as diabetic patients without renal disease (21.3 ± 2.8 vs. 11.5 ± 1.9) AGE levels in both serum fractions were elevated in the patients with diabetes and the levels o AGE peptide correlated directly with serum creatinine ($P < 0.001$) and inversely with creatinine clearance ($P < 0.005$), suggesting that levels of AGE peptide increased with the severity of diabetic nephropathy. In six patients with diabetes who required haemodialysis, the levels of AGE peptides were five times higher than in eight normal subjects (82.8 ± 9.4 vs. 15.6 ± 3.4 AGE units per millilitre, $P < 0.001$). In another group of diabetic patients, the mean serum creatinine level decreased by 75 per cent during a session of hemodialysis, whereas the level of AGE peptides decreased by only 24 per cent. Serum levels of AGE peptides were normal in two patients with normal serum creatinine levels after renal transplantation.

Conclusions: AGEs accumulate at a faster-than-normal rate in arteries and the circulation of patients with diabetes; the increase in circulating AGE peptide parallels the severity of renal functional impairment in diabetic nephropathy.

Glomerular structures in IDDM women with low glomerular filtration rate and normal urinary albumin excretion

Lane P.H., Steffes M.W. and Mauer S.M. Diabetes 1992; 41: 581-6

Eight women with insulin-dependent diabetes mellitus (IDDM) with low creatinine clearance rate (CCR) and normal urinary albumin excretion

(UAE) were compared with three other groups of diabetic women: 19 with normal creatinine clearance rate (CCR) and UAE, 7 with normal CCR and microalbuminuria, and 7 with low CCR and microalbuminuria. The four groups were similar in age, duration of diabetes, HbA_1, incidence of urinary tract infection, prevalence of bladder neuropathy, and urinary urea nitrogen excretion rate. The prevalence of hypertension was similar among the groups, although mean arterial pressure was higher in the low CCR and microalbuminuria group. Renal area index was lower in the low CCR and normal UAE groups than in the other groups of diabetic patients, but was not different from normal. Morphometric measures of mesangial expansion and estimates of arteriolar hyalinosis and global glomerulosclerosis were increased to a similar degree in the low CCR and normal UAE, normal CCR and microalbuminuria, and low CCR and microalbuminuria, groups compared with the group without abnormalities of renal function. Therefore, it is likely diabetic glomerulopathy is, at least in part, responsible for the loss of glomerular filtration rate seen in the low CCR and normal UAE patients. Thus, the definition of incipient nephropathy may have to expand beyond the concept of microalbuminuria if longitudinal study of such patients reveals anincreased risk of the subsequent development of overt nephropathy. Finally, screening for diabetic kidney disease among IDDM patients should include determination of glomerular filtration rate and measurement of UAE and blood pressure, especially among women.

Prospective study of microalbuminuria as predictor of mortality in NIDDM

Mattack M. B., Morrish N.J., Viberti G., Keen H., Fitzgerald A.P. and Jackson G. Diabetes 1992; 41: 736-41

Retrospective studies of patients with non-insulin-dependent diabetes mellitus (NIDDM) have suggested that microalbuminuria predicts early all-cause (mainly cardiovascular) mortality independently of arterial blood pressure. This finding have bot been confirmed in prospective studies and it is not known whether the predictive power of microalbuminuria is independent of other major cardiovascular risk factors. During 1985-1987, we examined a representative group of 141 non-proteinuric patients with NIDDM for the prevalence of coronary heart disease and several of its established and putative risk factors, including raised urinary albumin excretion (UAE) rate. Thirty-six patients had microalbuminuria (UAE 20-200 m g/min), and 105 had normal UAE (< 20ug/min). At follow-up, an average of 3.4 yr. later, 14 patients had died. There was a highly significant excess mortality (chiefly from cardiovascular disease) among those with microalbuminuria (28%) compared to those without microalbuminuria (4%, $P < 0.001$). In univariate survival analysis, significant predictors of all-cause mortality included microalbuminuria ($P < 0.001$), hypercholes- terolaemia ($P < 0.01$), hypertriglyceridaemia ($P < 0.05$), and pre-existing coronary heart disease ($P < 0.05$). The predictive power or microalbuminuria persisted after adjustment for the effects of other major risk factors ($P < 0.05$). We conclude that microalbuminuria is a significant risk marker for mortality in NIDDM, independent of the other risk factors examined. Its presence can be regarded as an index of increased cardiovascular vulnerability and a signal for vigorous efforts at correction of known risk factors.

NEUROPATHY

Effects of desipramine, amitriptyline and fluoxetine on pain in diabetic neuropathy

Max M. B., Lynch S. A., Muir J., Shoaf S. E., Smoller B. and Dubner R. N. Engl. J. Med. 1992; 326: 1250-6

Background: Amitriptyline reduces the pain caused by peripheral-nerve disease, but treatment is often limited by side effects related to the drug' s many pharmacologic actions. Selective agents might be sager and more effective.

Methods: We carried out two randomized, double-blind, crossover studies in patients with painful diabetic neuropathy, comparing amitriptyline with the relatively selective blocker of norepinephrine reuptake desipramine in 38 patients, and comparing the selective blocker of serotonin reuptake fluoxetine with placebo in 46 patients. Fifty-seven patients were randomly assigned to a study as well as to the order of treatment, permitting comparison among all three drugs and placebo as the first treatment. The patients rated the degree of pain present each day using verbal descriptors and they also assessed the extent of pain relief globally at the end of each treatment period.

Results: After individual dose titration, the mean daily doses of the drugs were as follows: amitriptyline, 105 mg; desipramine, 111 mg; and fluxetine, 40 mg. There was moderate or greater relief of pain in 28 of the 38 patients (74 per cent) who received amitriptyline, 23 of the 38 patients

(61 per cent) who received desipramine. 22 of the 46 patient (48 per cent) who received flyoxetine and 10 of the 46 patients (41 per cent) who received placebo. The differences in responses between amitriptyline and desipramine and between fluoxetine and placebo were not statistically significant, but both amitriptyline and desipramine were superior to placebo. Amitriptyline and desipramine were as effective in-patients who were not depressed as in depressed patients, but fluoxetine was effective only in depressed patients.

Conclusions: Desipramine relieves pain caused by diabetic neuropathy with efficacy similar to that of amitriplyline, offering an alternative for patients unable to tolerate the latter. Blockage of norepinephrine reuptake is likely to mediate the analgesic effect of these antidepressant drugs in diabetic neuropathy. Fluoxetine, which block serotonin uptake, is no more effective than placebo for the relief of pain.

Abnormal myoinositol influx in human leucocytes in diabetes but not specifically in diabetic neuropathy

Simmons D., Leong N.G. and Bomford J. Diabetes 1992; 41: 760-5

Abnormal myoinositol metabolism has been implicated as a contributor to the development of diabetic neuropathy. Furthermore, in vitro glucose inhibits animal and human myoinositol transporters. To investigate whether myoinositol transport is abnormal in diabetic subjects with and without neuropathy, we used a triple-isotope technique to measure [^{14}C] myoinositol uptake in leucocytes from 23 insulin-dependent diabetic subjects and 13 matched non-diabetic subjects. All subjects with diabetes underwent neurophysiological studies, and subjects without neuropathy were compared with those with various degrees of neuropathy. The relationship between glycaemia and flux was also studied. Diabetic subjects had similar intracellular and plasma myoinositol concentrations but had higher rates of uptake of myoinositol over the extracellular concentrations of myoionsitol studied. Although the derived K_m, V_{max}, and passive components were not significantly different, V_{max}:K_m ratio was significantly higher in diabetic subjects compared with non-diabetic subjects (0.25 [0.17-0.32] vs. 0.16 [0.13-0.19], respectively (P = 0.006). In diabetic subjects, the rate of myoinositol uptake correlated with HbA_{1c}, particular at 3μM extracellular myoinositol where active uptake was a high proportion of the total influx (P < 0.005). No difference in myoinositol uptake was found among diabetic subjects with various degrees of neuropathy. We conclude that although myoinositol transport is abnormal in diabetes, it is not specifically abnormal in diabetic neuropathy. Prolonged hyperglycaemia is associated with higher myoinositol flux.

RETINOPATHY

Risk of early-onset proliferative retinopathy in IDDM is closely related to cardiovascular autonomic neuropathy

Krolewski A. S. Barzilay J., Warram J. H. Martin B. C., Pfeifer M. and Rand L.I. Diabetes 1992; 41: 430-7

Determinants of proliferative diabetic retinopathy (PDR) that occur during the 2nd decade of insulin-dependent diabetes mellitus (IDDM) (early-onset PDR) were investigated in a nested case-control study. From an inception cohort of patients with juvenile-onset IDDM that now has 15-21 yr. diabetes duration, the patients with PDR cases, n=74 were selected for study along with a random sample of the patients in the cohort without PDR (control subjects, n = 88). The risk of PDR was associated with poor glycaemic control during the first 12 yr. of diabetes. Relative to patients in the first quartile of the index of hyperglycaemia, those in higher quartiles and nonattenders had a four to five fold risk of developing PDR. A striking relationship with cardiovascular autonomic neuropathy (CAN) was found. Relative to patients without CAN, patients with significant and mild CAN had odd ratios of 77.5 and 34.6, respectively. Patients with albumin excretion rates > 30 m g/min had moderately increased risk of PDR (ranging from 4-fold for microalbuminuria to 7-fold for proteinuria). In contrast, patients with impaired renal function had an extremely high risk of PDR. All 20 of these patients were cases; therefore the odds ratio was infinite. All three factors (poor glycaemic control, CAN, and various stages of nephropathy) were associated with PDR in multiple logistic regression analysis. However, in models including glycaemic control, the association between microalbuminuria or proteinuria and PDR was weakened. In conclusion, our findings are consistent with a hypothesis that the level of glycaemia is a primary determinant of early-onset PDR. Autonomic neuropathy, almost universal among cases, may be a strong risk factor for or a risk indicator of an aetiologic process underleying the development of PDR. Conditions associated with advanced diabetic nephropathy on the other

hand may accelerate the progression of non-proliferative retinopathy to PDR.

GENERAL AND MISCELLANEOUS

Intra-arterial urokinase infusion in diabetic patients with rapidly progressive ischaemic foot lesions

Vannini P., Ciavarella A., Mustacchio A. and Rossi C. Diabetes Care 1991; 14: 925-7

Objective: The effectiveness of local intra-arterial thrombolysis by urokinase was evaluated in eight non-insulin-dependent diabetic patients with angiographic evidence of infrapopliteal occlusive disease and rapidly progressive foot lesions.

Research Design and Methods: With an electric peristaltic pump, urokinase was infused for 96 h by a 5-6 F catheter introduced into the femoral artery and placed immediately above the occluded infrapopliteal arteries. After baseline, angiography was repeated at 24- to 48- h intervals and at conclusion of the treatment.

Results: Six patients showed immediate improvement of clinical symptoms. Angiography revealed the reestablishment of blood flow in collateral vessels of the leg and foot in the dorsal pedal artery in three patients and in the planter arch in two. Recanalization of the major arteries of the trifurcation was not achieved. After 12 month of follow-up, all limbs were salvaged, although four patients required vascular reconstruction to further improve foot perfusion and complete healing.

Conculsion: Intra-arterial urokinase, which opens collateral and smaller vessels of the leg and foot in patients with diabetes, may be effective in improving blood flow in lower extremities and in making the patient a better candidate for vascular surgery.

Inhibition of diabetes-associated complications by nucleophilic compounds

Kumari K., Umar S., Bansal V. and Sahib M. K. Diabetes 1991; 40: 1079-84

Mono and diaminoguanidine inhibited ambient glucose-induced glycosylated end product formation of albumin and collagen ^{125}I-labelled albumin covalent binding in vitro. diaminoguanidine was a stronger inhibitor than monoaminoguanidine. These compounds also inhibited rat eye lens aldose reductase activity in vitro non-competitively with respect to NADPH with K_1 = 30.6 mM for monoaminogunidine and K_1=12.5 mM for diaminoguanidine. When adiministered daily for 98 days at a dose of 25 mg/kg body wt i. p., both compounds lowered eye lens sorbitol and aldose reductase activity in normoglycaemic and alloxaninduced diabetes rats. Again, diaminoguanidine was a better inhibitor. Daily long- term administration of mono and diaminoguanidine (25mg/kg-body wt i. p.) inhibited and prevented experimental diabetes-induced lens opacity in rats, respectively. It appears that diaminogranidine has a better therapeutic potential in controlling diabetic complications.

DIABETES AND PREGNANCY

Biphasic effects of maternal metabolism on foetal growth

Metzger B. E. Diabetes 1991; 40 (suppl. 2) 99-106

More than a decade ago, Norbert Freinkel postulated that alteration in the maternal metabolic millieu at any time during gestation can influence intrauterine development and also may have long-term consequence for certain tissues such as adipocytes, myocytes, pancreatic β-cells, and neurons. This review illustrates that metabolic alteration early in gestation, such as those that occur in diabetes mellitus, may impair growth of the embryo and increase the risk of dysmorphogenesis. Such delayed growth of the embryo may in turn influence size at birth. In midgestation, metabolic perturbations may accelerate functional maturation of foetal pancreatic β-cells. Foetal β-cell development is very sensitive to alterations in the nutrient millieu and may be enhanced in gestational diabetes mellitus (GDM) with only minimal elevations of plasma glucose and minor alterations in other nutrient fuels, including insulinogenic amino acids. Data are reviewed that suggested that the ensuing foetal hyperinsulinaemia might promote the development of macrosomia even if metabolic control is satisfactory during late gestation. The overall potential influences of metabolic alterations on intrauterine growth are different in pregnancies complicated by diabetes mellitus throughout gestation (pregestational) and GDM. However, the implications in an individual pregnancy may be defined by the degree of metabolic control at the specific stages of gestation when growth of the embryo, development of fetal b -cell function, and growth insulin-sensitive tissues are most critically influenced by the metabolic millieu.

Functional maturation and proliferation of foetal pancreatic β-cells

Hellerstorme C. and Swenne I. Diabetes 1991; 40 (suppl. 2): 89-93

We review some key aspects of the maturation of stimulus-secretion coupling and the regulation of DNA replication in the foetal β-cell. During foetal life, the β-cell shows a poor insulin response to glucose, although it responds to several other non-nutrient stimuli. However, chronic exposure to glucose in excess of basal levels can induce maturation of the stimulus-secretion coupling. Studies of glucose metabolism and the transmembrane flow of K^+ and Ca^{2+} indicate that attenuated glucose-stimulated insulin release is due to an immature glucose metabolism resulting in impaired regulation of ATP-sensitive K^+ channels in the plasma membrane of the foetal β-cell. In late foetal life, glucose is also strong stimulus to β-cell replication, and metabolism of glucose is a prerequisite for this process. Glucose stimulates proliferation by recruiting β-cells from a resting state into a proliferative compartment composed of cells in an active cell cycle. The proliferative compartment comprises < 10% of the total islet cell population even at maximal stimulation. The proliferation of foetal β-cells is also regulated by several peptide growth factors such as growth factor I, and platelet-derived growth factor. The observation that glucose can both induce precocious maturation of the stimulus-secretion coupling and stimulate proliferation of the fetal β-cell explains the intrauterine hyperinsulinaemia and β-cell hyperplasia of the offspring of diabetic mother with relatively mild hyperglycaemia. However, severe hyperglycaemia, at least when induced in rats, seems to retard rather than stimulate b -cell growth.

Intermediary metabolism in pregnancy first theme of the Freinkel era

Herrara E., Lasuncion M. A., Palacin M., Zorano A. and Bonet B. Diabetes 1991: 40 (suppl 2) 83-8

During the first half of gestation in the rat, maternal net body weight increases rapidly, whereas in the second half of gestation, the mass of maternal structures declines, coincident with the rate of maternal fat accumulation. Enhanced maternal foot intake, extrahepatic tissue lipoprotein lipase (LPL) activity, and adipose tissue lipogenesis are responsible for the progressive accumulation of maternal fat. However, during late gestation, decreased fat synthesis in maternal adipose tissue, enhanced lipolytic activity, and decreased LPL activity deplete maternal fat depots. These changes, plus enhanced endogenous production of triglyceride-rich lipoproteins, are also responsible for maternal hypertriglyceridaemia, This condition benefits the offspring in two ways: 1) enhanced LPL activity in maternal liver when fasting increases triglyceride consumption for ketone body synthesis, giving the basis for accelerated starvation; and 2) induction of LPL activity in the mammary gland before parturition diverts maternal circulating triglycerides to milk synthesis in preparation for lactation. The magnitude of the maternal-foetal glucose transfer was higher than that of any of the other substrates studied, including alanine, and despite actions to spare glucose, this transfer causes maternal hypoglycaemia, which is especially intense in the fasting condition. This increases sympathoadrenal activity in the mother, which may contribute to her active gluconeogenesis. Glycerol was a more efficient glucose precursor than alanine and pyruvate, and whereas glycerol placental transfer is very small, it is proposed that the foetus benefits from the this product of adipose tissue lipolysis when it is previously converted into glucose. In thyroidectomized pregnant rats treated with thyroxine for different periods, restraining maternal accumulation of fat depots during the early part of gestation compromises the normal metabolic adaptations during late gestation, including the capacity for accelerated starvation, which negatively affects foetal development.

Impact of maternal fuels and nutritional state on foetal growth

Kalkhoff R. K. Diabetes 1991; vol. 40 (suppl. 2): 61-5

Several maternal plasma fuel abnormalities have been described in gestational diabetes mellitus (GDM), and all may contribute to the development of foetal macrosomia, generally because of the surfeit of calories they provide. Elevated maternal plasma glucose and amino acid concentrations represent key disturbances, because they are also well known foetal pancreatic b -cell secretagogues. Foetal hyperinsulinaemia contributes to macrosomia in a special way by selectively accelerating fuel utilization and storage in insulin-sensitive foetal tissues. Maternal obesity intensifies the insulin resistance already present in the late pregnancy and probably exaggerates the metabolic abnormalities attending GDM that impact on foetal growth and development. However, the means by which maternal obesity per se promotes the development of heavy babies in non-diabetic pregnancies remains poorly defined. Significant correlation's exist between new born birth weight and the levels of maternal plasma glucose, amino

acids, free fatty acids, and triglycerides in diabetic pregnancies. However, the relative influence of each disturbance on foetal birth weight remains controversial and requires more detailed investigation.

New National Academy of Sciences guidelines for nutrition during pregnancy.

King J.C. Diabetes 1991; 40 (suppl.2): 151

In June 1990,the Institute of Medicine of the National Academy of Sciences (NAS) released a report, *Nutrition during Pregnancy*, that recommends individualized assessment-based nutritional management for pregnant women. This is the first publication by the NAS on maternal nutrition since the Food and Nutrition Board' s landmark report Maternal Nutrition and the Course of Pregnancy published in 1970. The newer report is divided into two parts; the first part is on weight gain, and the second part deals with nutrient supplementation during pregnancy. Dr. Roy Pitkin, Chair of the department of obstetrics and gynaecology, School of Medicine, University of California, Los Angeles, chaired the committee on nutritional status during pregnancy and lactation, which authored the 1990 report.

Rather then setting a single weight-gain limit, the committee suggested a range of optimal weight gains, depending on the weight-for-height status of the mother at the beginning of pregnancy. Underweight women with a body mass index (BMI; defined as weight/height^2) of < 19.8 kg/m^2 should try to gain between 28 and 40 lb, normal-weight women with BMIs of 19.8-26.0 kg/m^2 should gain between 15 and 25 lb. Obese women (BMI > 29.0 kg/m^2) should gain at least 15 lb. Rate of gain is important. Women should ~ 1 lb/wk during the second and third trimesters; overweight women should work toward about half that rate. Gains of < 2 or > 6.5 lb/month for normal weight women should be evaluated. Among women studied in the United States, energy intake was a weak determinant of gestational weight gain. Nevertheless, energy supplementation of women who are undernourished should benefit gestational weight gain and therefore foetal growth.

Despite popular opinion that all pregnant women should routinely take vitamin and mineral supplements, the NAS committee concluded that food "is the normal vehicle for delivering nutrients, and nutrient supplementation [is] an intervention" that should be "based on evidence of benefit as well as lack of harmful effects." There is a danger that different nutrients will interact in adverse ways, and this is more likely with supplements than with foods. Supplements should not replace a wellbalanced diet.

Iron is the only nutrient for which routine supplementation of all pregnant women is recommended. A low-dose supplement of 30mg ferrous iron/day is suggested. This recommendation is based on the high prevalence of low iron stores among women of childbearing age in the U.S.

Intake of other nutrients in amounts less than the recommended daily allowance (RDA) is an insufficient basis for recommending supplementation. Because RDA provide "wide margin of safety, the needs of many pregnant women can be met with intakes below the RDA." The decision to provide special dietary intervention or nutrient supplementation should therefore be made after routine questioning of all pregnant women about their food intake and special problems that may affect their nutritional needs. For women found to have inadequate dietary intake or special problems, a multivitamin-mineral preparation containing iron, zinc, copper, calcium, vitamin B_6, folate, vitamin C, and vitamin D is recommended.

The NAS report did not address the nutritional concerns of women with insulin-dependent (type I) or gestational diabetes. Specific recommendations for the management of such patients await definition. However, based on the NAS guidelines, which focussed on healthy women, it is reasonable to recommend that diabetic women gain at least 15 lb. This is comparable to the amount of weight gain recommended for obese women.