AETIOLOGY

Reevaluation of autoantibodies to islet cell membrane in IDDM

Vives M., Somoza N., Soldevija G., et al. Diabetes 1992; 41: 1624-31.

Since their demonstration in 1975, ICSAs have been proposed as serological markers and pathogenic elements in IDDM. ICSAs are detected in the sera of most newly diagnosed IDDM patients by indirect IFL that uses viable preparations of rat islet or insulinoma cells as substrate, but they also can be detected by using human insulinoma or foetal islet cells. We have tried to demonstrate ICSAs in the sera of 31 newly diagnosed diabetic patients, including 6 positive samples on human foetal islet cells, which used their natural target for the first time: normal human islet cells. In spite of using different types of preparation of these cell (i.e. freshly dispersed cell suspensions, monolayer cultures, or dispersed islets after culture), ICSAs could not be detected by IFL under the UV microscope, nor by flow cytometry. In contrast, 9 to 29 of the sera gave a positive staining on the RIN rat insulinoma cells. In an attempt to establish whether the putative ICSA autoantigen is present in the surface of human islet cells in the diabetic pancreas, the insulitis microenvironment was emulated by exposing the islets to three types of stress: 1) cytokines (IFN-γ and TNF-α); 2) heat shock; and 3) hyperglycaemia. However, diabetic sera failed again to recognize membrane antigens on the islet cells after either of these treatments. Neither were islet cells from a newly diagnosed diabetic patient stained by its autologous serum (ICA titre > 80 JDF U). These results suggest that ICSA autogantigen is not expressed in the membrane of human islet cells and therefore raises doubts about their proposed pathogenic role.

PATHOPHYSIOLOGY

Quantitative and qualitative lipoprotein abnormalities in diabetes mellitus

Taskinen M. R. Diabetes 1992; 41 (suppl.2) 12-17.

In people with diabetes, the concentration of an individual lipoprotein or apolipoprotein can be highly variable and is totally different in the two major forms of the disease. Alterations in the concentrartion of major lipids and lipoproteins are well characterized in both IDDM and NIDDM. In general, the lipoprotein pattern is antiatherogenic in individuals with IDDM who are treated and have optimal glycaemic control. In contrast, NIDDM is associated with athorogenic changes of serum lipids and lipoproteins regardless of the mode of treatment. In people with both types of diabetes, the distribution of apoE phenotype seems to be similar to that in nondiabetic populations. IDDM patients with microalbuminuria show atherogenic changes of lipoproteins and have elevated levels of Lp(a), which is a risk factor of coronary artery disease. Whether glycaemic control influences the concentration of Lp(a) is still an open question. An important issue is that the concentration of a lipoprotein can be normal without excluding compositional abnormalities that are potentially atherogenic. Such alterations are present in people with both IDDM and NIDDM. Consequently, it has been questioned whether the target values to start treatment should be lower in diabetic than in non-diabetic populations.

Platelet abnormalities in diabetes mellitus

Winocour P.D. Diabetes 1992; 41 (suppl.2.): 26-31.

Although platelets can contribute to atherosclerosis and its thromboembolic complications in the nondiabetic population, the role of platelets in enhanced vascular disease in the diabetic populations remains unclear. Most studies indicate that platelet function in vitro is enhanced in platelets from people and animals with diabetes, and the mechanisms are being identified. There remains some controversy about whether platelet changes occur before, and therefore could contribute to, vascular complications or whether they are secondary to vascular disease. It is possible that only intervention trials to determine if inhibiting platelet function limits the progression of vascular disease in diabetic patients will definitively answer this question. The earlier premise that enhanced activity of the archidonate pathway is responsible for the hypersensitivity of platelets from diabetic humans needs to be modified to recognize that additional mechanisms are involved in platelet activation and are modified in people with diabetes and also that altered activity of the arachidonate pathway may reflect changes in
earlier pathways involved in platelet activation. Clearly, alterations in these nonarachidonate pathways need to be taken into account when considering the appropriate antiplatelet agents to use in intervention trials. Information about whether hypersensitivity of platelets from people with

diabetes persists in vivo and, if so, how this influences platelet-vassel wall interactions and thrombotic tendencies needs to be pursued more intensely in suitable animal models so that the theories developed from studies in vitro can be tested in the more complex environment in vivo. These are important areas for research in the future.

Changes in blood coagulation, platelet function, and plasminogen-plasmin system in diabetes

Kwaan H.C. Diabetes 1992; 41 (suppl.2) : 32-5.

The increased risk of thromboembolism in people with diabetes mellitus is in part due to changes in the haemostatic mechanism including abnormal platelet function leading to platelet activation, increase in several coagulation factors, decrease in natural anticoagulants, and impaired fibrinolytic activity. Both microangiopathy and atherosclerosis in people with diabetes will enhance the thrombotic potential of these abnormal haemostatic changes. The recent recognition of a role of the components of the plasminogen-plasmin system in many biologic functions at the cellular level has led to studies showing that the angiopathic complications of diabetes may also be caused by impaired plasminogen activator function.

Receptor-mediated interactions of advanced glycosylation end products with cellular components within diabetic tissues

Vlassara H. Diabetes 1992; 41 (suppl.2) : 52-6.

AGEs are nonenzymatically glycosylated adducts of proteins that accumulated in vascular tissues within ageing and at an accelerated rate in people with diabetes; AGEs are closely linked to tissue damage due to their high reactivity in protein cross-linking. A macrophage-monocyte receptor system for AGE moieties is shown to mediate the uptake of AGE-modified proteins by a process that also induces cachectin-TNF , IL-1, IGF-l, and PDFG secretion. Thus, in addition to removing senescent glucose-modified proteins and cells, AGE-mediated release of growth-promoting factors may represent a mechanism by which macrophages signal mesenchymal cells the need for replacement of senescent proteins. The age of the macrophage correlates inversely with the binding and removal capacity of the AGE receptor, possibly preventing the clearance of cross-linked proteins and the compoundings aging-related tissue damage. In addition to monocyte and macrophages, other cells express similar receptors for AGE-proteins, including nedothelial cells, fibroblasts, and mesangial cells. Endothelial cell AGE-receptors mediate transcytosis of AGEs to the subendothelium, induce increased permeability, and enhance endothelium-dependent procoagulant activity. Renal mesangial AGE receptors mediate PDGF-dependent extracellular matrix protein production. Fibroblast AGE receptors may influence cellular proliferation by EGF and EGF-receptor regulation. These findings, in connection with the known abundance of AGEs in aged and diabetic tissues, indicate that AGE-ligand-receptor interactions are crucial for the development of age and diabetes-related vascular tissue and renal pathology.

Lipoprotein oxidation and lipoprotein-induced cell injury in diabetes

Chisoim G.M. , Irwin K.C. and Penn M.S. Diabetes 1992; 41: (suppl.2) : 61-6.

There is ample evidence that oxidized lipoproteins exist in vivo, not only in atherosclertic lesions, but also associated with some experimental models of diabetes. Whether the lipoprotein oxidation is an epiphenomenona of other atherogenic or diabetogenic agents or processes or whether it is casually related to lesion formation in atherosclerosis or other forms of tissue damage in people with diabetes is unresolved. Intense Interest in testing these ideas derives from in vitro observations of the ways in which oxidized lipoproteins interact with cells that are unlike the interactions with native lipoproteins. Many of these altered interactions suggest known features of atherosclerotic lesions, and recent data show that antioxidant treatment reduces the progression of vascular lesions. There are reasons to believe that hyperglycaemia may worsen lipid and lipoprotein oxidation. If this observation is the case in vivo, and if it is ultimately proved that lipoprotein oxidation facilitates lesion development, these events may help explain the accelerated atherosclerosis suffered by diabetic patients. The multiple pathways for which there is evidence that hyperglycaemia may contribute to oxidative events - for example, by enhancing free radical production in stimulated inflammatory cells or by forming glycation products that can propagate free radical events- suggest avenues for further research and may ultimately indicate points for intervention in the various manifestations of the disease.

Antibodies to GAD and tryptic fragment s of islet 64k antigen as distinct markers for development of IDDM

Christie M.R. , Tun R.Y.M. , Lo S.S.S. , et al. Diabetes 1992;41: 782-7.

Insulin-dependent diabetes mellitus (IDDM) is associated with antibodies to a 64,000-M_r islet cell protein, at least part of which is identified as glutamic acid decarboxylaso (GAD). These antibodies are detected as two distinct antibody specificates to 50,000-M_r tryptic fragments of the autoantigen (50k and 37K antibodies , respectively). We determined the frequencies of antibodies to intact GAD, tryptic fragments of islet 64,000 Mr antigen, islet cell antibodies (ICAs), and insulin autoantibodies (IAAs) in sera from 58 nondiabetic identical twins of patients with IDDM, of whom 12 subsequently developed diabetes. ICA, antibodies to intact GAD, and those to tryptic fragments were detected at similar frequencies in prediabetic twins (67-75%), but only 25% had IAA. Of 46 twins who remain nondiabetic, GAD antibodies, 50K antibodies, and ICA were detected in 6 (13%), 7 (15%), and 5 (11%), respectively, whereas only 1 (2%) possessed 37K antibodies and 2 (4%) had IAA. Eight of 9 twins with 37K antibodies and all 6 twins with ICA > 20 Juvenile Diabetes Foundations U have developed diabetes. Antibodies to GAD are sensitive markers for diabetes development but may also be present in genetically susceptible individuals who are unlikely to develop disease. Antibodies to 37,000/40,000-M_r fragments of the 64000-M_r antigen or high-titre ICA were the best markers for diabetes development in these twins.

Human islet glucokinase gene

Koranyi L.I. Tanizawa Y., welling C.M., Rabin D.V. and Permutt M.A. Diabetes 1992; 41: 807-11.

Pancreatic islet glucokinase (ATP:$_D$ –hexose-6—phosphotransferase) cDNAs were isolated from a human islet CDNA library in λ-gt11. One clone (*hlGLK2)*, 2723 bp plus additional poly(A) residues, appeared to be full length because its size was consistent with a single 2.9-kb glucokinase mRNA on Northern-blot analysis of islet RNA. This cDNA contained an open reading frame of 1395 bp from an ATG condon at position 459, encoding a predicated protein of 465 amino acids (52,000 M_r). Comparison of the nucleotide sequences of the human islet human glucokinase cDNA with that of the recently isolated human liver glucokinase cDNA revealed that the two cDNA differed completely on their 5' –ends, followed by an identical 2204-bp overlap extending to the 3' –ends. The 5' –ends of islet and liver glucokinase cDNAs predicted proteins that differ by 15 NH_2 –terminal residues. The overall sequence identity (70%) between the first exons of the human islet and rat islet cDNAs suggested that the islet promoter regions, like the liver promoter regions, have been conserved through evolution. Thus, NH_2 terminal differences for human liver and islet enzymes might be explained by use of alternate promoters between the two tissues, analogous to the NH_2 –terminal differences of the rat liver and rat islet enzymes. If so, this relationship predicts important tissue-specific regulatory functions of these regions. Variations in the glucokinase gene are likely to occur in humans. Isolation of a human islet glucokinase cDNA has provided the sequence necessary to determine whether these variants are important determinants in the genetic predisposition for diabetes mellitus.

A key to understanding the pathogenesis of diabetes (indirect effects of insulin)

Vranic M. Diabetes 1992;41: 118.

This article is divided into two parts. A retrospective overview summarizes some of the work that provided the framework and tools of the more recent studies. The five novel areas of research are related to the indirect effects of insulin. Regulation of plasma glucose is of central importance in health and diabetes. Understanding this precise regulation requires sensitive isotope dilution methods that can measure the rates at which glucose is produced by the liver and used by the tissues on a minute-to –minute basis. Validation studies indicated that the non-steady-state tracer methods yields reasonable results when the specific activity of plasma glucose does not change abruptly. During hyperinsulinaemic glucose clamps, the decrease in specific activity of glucose can be prevented by the MSTI. During exercise, the decrease of specific activity can be only in part ameliorated by step-tracer infusion. Depancreatized dogs are used extensively as a model of selective insulin deficiency , because dog stomach secrets physiological amounts of glucagon. This strategy can avoid injections of somatostatin, which can have other affects in addition to the suppression of insulin and glucagons. In human diabetes, in addition to an increase of glucose cycling in the liver. In animal models of diabetes, mild NIDDM , and in glucose intolerance, the percentage of increments of glucose cycling are much larger than those of glucose production. We hypothesize, therefore, that measurements of glucose cycling can be used as an early marker of glucose intolerecne Application of different tracer strategies and use of the depancreatized dog as a model of diabetes, we investigated the importance of the indirect effects of insulin in the pathogenesis of the indirect effects of insulin in the pathogenesis of diabetes. 1) Because, in the treatment of NIDDM , insulin is administered by the peripheral routes we compared the relative importance of hepatic and

peripheral effects of insulin in regulating the rate of glucose production. Experiments were performed in depancreatized dogs that were initially maintained at moderate hypergluycaemia (10mM) with subbasal portal insulin infusion. During the experimental period, insulin was infused either peripherally or portally at 0.9 mU kg^{-1} min^{-1}. In addition, peripheral infusions were also given at 0.45 mU. Kg^{-1} min^{-1}. We concluded that when suprabasal insulin levels are provided to moderately hyperglycaemic depancreatized dog, the suppression of glucose production is more dependent on peripheral than portal insulin concentrations. This indirect effect of insulin may be mediated by limitation of the flow of precursors and energy sub-strates for gluconeogensis and/or by suppressive effect of insulin on glucagons secretion. These results suggest that the absence of a portal-peripheral gradient in insulin-treated diabetic subjects may not be important for postprandial suppression of glucose production. 2) The glucagons-insulin ratio is an important regulator of glucose production by the liver during moderate exercise, whereas during intense exercise the catecholamines play a prominent role. Regulation of glucose uptake during exercise is very complex. In vivo, insulin can play an indirect role by inhibiting the FFA-glucose cycle and by maintaining nor-moglyaemia; both of these factors influence glucose uptake by the muscle . 3) Streptozocin-induced diabetes in rats decreases the number of cytochalasin B binding and by assessment of GLUT4 transporters. Normalization of glycaemia in the diabetic rats by a 2-day phlorizin treatment, which does not affect the insulinconcentration, normalizes glucose transporter number in the plasma membrane., We concluded that hyperglycaemia, per se, plays an important role in regulating glucose transporter number in the muscle.

Syndrome of insulin resistance

Flier J. S. Diabetes 1992;41: 1207-19.

The syndrome of insulin resistance are a group of clinically diverse disorders, and our understanding of their molecular pathogenesis has advanced in parallel with our understanding of the structure of the insulin receptor and the mechanism of insulin action. The most straightforward progress has related to defining the role of both anti-receptor antibodies and mutations in the insulin receptor gene in causing these disorders. Despite this progress, the cause of severe target cell resistance in patients without defects in the receptor locus remains unknown and we are limited in our ability to relate specific molecular defects in insulin signalling to in vivo phenotypes, such as those relating to growth and development and function of adipose tissue and muscle. Answers to these questions may ultimately be explained by the existence of multiple species of insulin receptors expressed in different tissues, brought about by alternative splicing and receptor hybrids, and by divergent pathways of insulin signaling with different consequences for specific tissues. The possibility that the insulin receptor and GLUT4 may be candidate genes for inherited insulin resistance in NIDDM has been addressed with the aid of genetic screening techniques such as SSCP. Currently , the loci have not been implicated in studies in most patients. Transgenic methodologies will be powerful tools for pursuits of unanswered questions in the field of insulin resistance in coming years.

Impact of insulin deficiency ion glucose fluxes and muscle glucose metabolism during exercise

Waserman D. H., Mohr T., Kelly P., Lacy D. B. and Bracy D. Diabetes 1992;41: 1229-38.

Exercise in the insulin-deficient diabetic state is characterized by a further increase in elevated circulating glucose and NEFA levels and by excessive counterregulatory hormone levels. The aim of this study was to distinguish the direct glucoregulatory effects of insulinopenia during exercise from the indirect effects that result from the metabolic and hormonal environment that accompanies insulin deficiency. For this purpose, dogs underwent 90 min of treadmill exercise during SRIF infusion with (SRIF + INS, n = 8) or without (SRIF – INS, n = 6) intraportal insulin replacement. Glucagon was not replaced, thus allowing assessment of the direct effect of insulinopenia at the liver independent effect for insulinopenia at the liver independent of the potentiation of glucagons action. Glucose was infused to maintain euglycaemia. Hepatic glucose production (R_a) ; glucose utilization (R_d) ; and LGIcU, LGIcE, and LGIcO were assessed with tracers ($[^3H]$ glucose, $[^{14}C]$ glucose) and arteriovenous differences. With exercise , insulin fell from 66 ± 6 to 42 ± 6 pM in the SRIF + INS group , and was undetectable in SRIF – INS group. Plasma glucose was 6.33 ± 0.38 and 6.26 ± 0.30 mM at rest in the SRIF ± INS and SRIF – INS groups, respectively, and was unchanged with exercise. R_a, rose from 7.5 ± 2.3 to 16.5 ± 2.2μ mol., kg^{-1} ., min^{-1} and 9.1 ± 2.0 to 31.4 ± 3.9μ mol. Kg^{-1}., min^{-1} with exercise in the SRIF + INS and SRIF – INS groups, whereas R_d rose from 19.5 ± 2.0 to 46.8 ± 3.9 μmol kg^{-1} min^{-1} and 15.1 ± 1.8 to 29.9 ± 3.3 mmol kg^{-1} min^{-1}. LGIcU rose from 36 ± 9 to 112 ± 25 μmol/min and 15 ± 4 to 59 ± 13 μmol/min and LGIcO rose from 5 ± 2 to 61 ±12 μmol/min and 5 ± 2 to 32 ± 9 μmol/min with

exercise in the SRIF + INS and SRIF – INS groups, respectively. Arterial levels and limb balances of NEFAs and glycerol were similar in the two groups. In summary, during exercise: 1) marked insulinopenia attenuates the increase in muscle glucose uptake and oxidation by ~ 50%, independent of changes in circulating metabolic substrate levels; 2) substantial increase in muscle glucose uptake and oxidation are, however, still present even in the absence of detectable insulin levels; and 3) insulinopenia facilitates the increase in R_a independent of the potentiation of basal glucagons action. In conclusion, marked insulinopenia contributes directly to the exacerbation of glucoregulation during exercise in the diabetic state by limiting the rises in glucose uptake and metabolism and by enhancing hepatic glucose production.

Further defects in counterregulatory responses induced by recurrent hypogluycaemia in IDDM

Davis M.R. , Mellman M. and Shamoon H. Diabetes 1992; 41: 1335-40.

We evaluated the effect of previous experimental hypoglycaemia on counterregulatory responses to hypoglycaemia in 13 IDDM patients. These patients had defects in counterregulatory responses to hypoglycaemia compared with 7 nondiabetic control subjects. Plasma EPI and glucagon responses to hypoglycaemia in IDDM patients were ~60% of levels in nondiabetic subjects ($P < 0.02$ and $P < 0.001$, respectively). Hepatic glucose output ([3-^{3}H] glucose) was reduced by ~60% of normal ($P < 0.005$) , and the glucose infusion rate required to maintain plasma glucose was correspondingly greater in people with IDDM ($P < 0.001$). With a modified glucose clamp (plasma insulin ~330 pM), the diabetic subjects underwent two sequential 120 –min periods of hypoglyucaemia (~3.0mM) with an intervening 60-min euglycaemic recovery period. In the IDDM patients, there were 30-50% decreases in plasma GH ($P <0.005$) and cortisol ($P <0.001$) responses during the second hypoglycaemic period compared with the first. In addition glucose output, already defective compared with that in nondiabetic subjects, was further reduced by 33% ($P = 0.03$) during the second period of experimental hypoglycaemia. There was no effect of repeated hypoglycaemia on the responses of plasma glucagons , EPI, or NE , though plasma EPI was correlated directly with glucose output ($P <0.001$) and inversely with glucose uptake ($P < 0.05$). There was no correlation between the rise in glucose output during hypoglycaemia and antecedent glycaemic control as measured by HbA_1. We conclude that in IDDM patients with preexisting defects in counterregulatory responses to hypoglycaemia, recurrent, mild hypoglycaemia is associated with additional reductions in pituitary-adrenocortical hormonal secretion and further impairment of hepatic glucose production.

Pathogenic factors responsible for glucose intolerance in patients with NIDDM

Taniguchi A., Nakai Y., Fukushima M., et al. Diabetes 1992; 41: 1540-6.

To define the pathogenic factors responsible for glucose intolerance in IDDM, we estimated insulin secretory capacity, S_1, and S_G in 11 healthy, nondiabetic subjects and 8 NIDDM patients who had no S_1 impairment. All subjects studied were nonobese and normotensive. Each underwent a 75g OGTT and a modified FSIGT : glucose was administered (300 mg/kg body weight), and insulin was infused (20 mU/kg over 5 min) from 20 to 25 min after the administration of glucose. S_1 and S_G were estimated by Bergman's minimal-model method. The insulin response to oral glucose was significantly lower in NIDDM patients than in normal control subjects. First-phase insulin secretion expressed as the integrated area of plasma insulin above the basal level during the first 20 in was much smaller in NIDDM subjects (214 ± 112pM. Min) than in control subjects (4643 ± 885 pM. Min, $P < 0.001$). S_I was not statistically different in normal control subjects (1.27 ± 0.18 X 10^{-4} min^{-1}. pM^{-1}). Versus diabetic patients (1.62 ± 0.33 X 10^{-4} min^{-1} $pM^{-1)}$. However, S_G was significantly lower in diabetic subjects (1.11 ± 0.17 C 10^{-2} min^{-1}) than in control subjects (2.35 ± 0.26 X 10^{-2} min^{-1}, $P< 0.01$). These results suggest that impaired insulin secretion and decreased S_G are the factors responsible for glucose intolerance of Japanese NIDDM for normal insulin sensitivity. Because S_I and S_G are the factors responsible for glucose intolerance of NIDDM patients with insulin resistance , it is conceivable that decreased S_G is common in NIDDM patients regardless of their S_I index.

Intermittent hypoglycaemia impairs glucose counterregulation

Widom B. and Simonson D. C. Diabetes 1992; 41: 1597-1602.

IDDM patients who maintain strict glycaemic control have impaired counterregulatory hormone and symptomatic responses to hypoglycaemia. To test the hypothesis that intermittent exposure to hypoglycaemia plays anaetiological role in these defective responses, we produced 4 consecutive

daily episodes of hypoglycaemia in 10 healthy, non-diabetic volunteers by using the insulin clamp technique. Fasting (5.3 ± 0.1 vs. 5.4 ± 0.1 mM) and nadir (2.3 ± 0.1 vs. 2.4 ± 0.1 mM) glucose levels achieved during insulin infusion did not differ on study days 1 and 4, in contrast, the glucose levels required to stimulate an increase in EPI (2.8 vs. 3.1 mM), glucagon (2.8 vs. 3.2 mM), cortisol (2.4 vs, 2.9 mM) , GH (2.6 vs. 3.0 mM), and autonomic hypoglycaemic symptoms (2.2 vs. 2.5 mM) were all significantly lower on study day 4 versus study day 1 ($P < 0.005$-0.05). Basal levels of EPI and cortisol, but not glucagon, GH, or NE also were reduced on the final study day. We conclude that intermittent hypoglycaemia can result in arttenuation of the hormonal and symptomatic responses to insulin-induced hypoglycaemia and may contribute to the defective counterregulatory responses in patients with well-controlled IDDM.

Lack of feedback inhibition of insulin secretion in denervated human pancreas

Luzi L., Battezzati A., Persegjom G.,, et al Diabetes 1992; 41: 1632-9.

In this study, pancreas transplantation is used as a clinical model of pancreas denervation in humans. To assess the role of innervation on the feedback autoinhibition of insulin secretion, we studied four groups of subjects – group 1: 16 patients with combined pancresas and kidney transplantation (plasma glucose=5.1 mM, HbA1c = 6.4%, creatinine = 86 mM); group 2: 8 patients with chronic uveitis on the same immunosuppressive therapy as transplanted patients (12 mg/day prednisone, 5 mg. Kg^{-1} day^{-1} CsA); group 3:4 uraemic, nondiabetic patients in chronic haemodialysis; group 4:7 normal, nondiabetic control subjects. The following means were used to study the groups: 1) a two-step hyperinsulinaemic euglycaemic clamp (insulin infusion rate = 1 mU an d5 mU. Kg^{-1} min^{-1}); and 2) a 0.3 $mU.kg^{-1}$ min^{-1} hypoglycaemic clamp (steady-state plasma glucose 3.1 mM). Basal plasma-free IRI (84 ± 6, 42 ± 12, 72 ± 12, and 30 ± 6 pM in groups 1,2,3, and 4 respectively), basal C peptide (0.79 ± 0.05, 0.66 ± 0.05, 3.04 ± 0.20, and 0.59 ± 0.06 nM in groups 1,2,3 and 4 respectively), and glucagon (105 ± 13, 69 ± 4, 171 ± 10, and 71 ± 5 pg/ml in groups 1 and 3 with respect to groups 2 and 4 ($P < 0.01$). During euglycaemic hyperinsulinaemia, plasma C-peptide decreased by 45,20 and 44% in groups 2,3 and 4 respectively, but showed no significant change from the basal in patients with transplanted pancreases. During insulin-induced hypoglycaemia, C-peptide concentration was suppressed by 80 and 85% in groups 2 and 4 , respectively, but only by 57 and 40% in groups 1 and 3, respectively; glucagons response was blunted in patients with transplanted pancreaes in all groups. In conclusion, these results support the hypothesis that feedback inhibition of insulin secretion is mediated by neural control in humans. The partial restoration of inhibition of insulin secretion during hypoglycaemia presumably is attributable to catecholamine release, or to exposure of the b –cell to low glucose concentration.

Biosynthetic human proinsulin

Galloway J. A., Hooper S.A. Spradlin C.T. et al. Diabetes care 1992;15: 666-92.

Objective – To describe the rationale for the preclinical and clinical developmental course of human proinsulin (HPI), the second product after human insulin for the treatment of diabetes mellitus to be manufactured by DNA technology.

Research design and Methods – The relevant and available published and unpublished preclinical and clinical information generated on pork proinsulin and human proinsulin has been integrated to demonstrate how certain clinically attractive features of pork proinsulin (a soluble intermediate-acting and possibly hepatospecific insulin agonist) led to the development of HPI.

Results – Clinical pharmacology studies demonstrated that HPI was definitely, although marginally, hepatospecific. More striking was the finding that the intrasubject/patient coefficient of variation of response to HPI was significantly less than that observed with NPH insulin. However, the fact that unique efficacy in controlled multicentre studies was not demonstrated suggested that these pharmacological features were not translated into clinical benefit., In one multicentre new patient study there were six myocardial infarctions, including two deaths, in patients treated for ≥ 1 yr with HPI and none in the control group.

Conclusion – To obtain an independent review of the risks and benefits of HPI, in February 1988, Lilly convened a consultant group that examined all relevant information on HPI available . These experts shared our concerns about the safety of HPI in light of the failure to demonstrate unique efficacy. Accordingly, clinical trials with HPI were suspended in February 1988. Experience with HPI demonstrates the challenge associated with the development of new drugs in general and insulin agonists in particular.

Effect of glycaemic control on growth velocity in children with IDDM

Wise J.E., Kolb E.L. and Sauder S.E. Diabetes care 1992;15:826-30.

Objective- To determine the effect of glycaemic control on growth velocity in children with insulin-dependent diabetes mellitus.

Research Design and Methods – One hundred twenty-tow children with insulin dependent diabetes mellitus were studied over a 5-yr period. Every 4 mo, glycaemic control was assessed by measuring total glycosylated haemoglobin (GHb), pubertal status was determined by physical examination, and height was measured with a stadiometer. Height measurements were normalized for age and sex by converting them to Z scores (the number of SD above or below the mean for age and sex). Alterations in growth velocity were determined by the change in Z scores (ΔZ) between visits (i.e ,no change in Z score = normal growth velocity; decrease in Z score= growth deceleration; and increase in Z score = growth acceleration).

Results – A linear relationship was seen between GHb levels and the change in Z scores (r = ~0.117, P = 0.001). GHb values < 8% were associated with growth acceleration ($\Delta Z = +0.10 \pm 0.03$) , and the greatest growth deceleration occurred when GHb was > 16% ($\Delta Z = -0.07 \pm 0.03$). The level of GHb \at which growth suppression occurred (mean Δ Z became negative) was dependent on pubertal status: Tanner stage 1 $\geq$ 10% , Tanner stages 2 and 3 $\geq$ 8% ,Tanner stages 4 and 5 $\geq$ 16%.

Conclusions- Linear growth velocity in children with insulin-dependent diabetes mellitus is heavily related to metabolic control. Children who are prepubertal or in the early stages of puberty are the most vulnerable to growth suppression. Once puberty is well established, growth suppression does not occure until marked hyperglycaemia (GHb > 16%) exists.

Intracellular free magnesium deficiency plays a key role in increased platelet reactivity in Type II diabetes mellitus

Nadler J.L., Malayan S., Luong H., Show S., Natarajan R.D and Rude RiK. Diabetes Care: 1992; 15: 835-41.

Objective – Mg deficiency may be an important factor leading cardiovascular disease. Diabetic subjects show an increase in platelet reactivity that can enhance the risks of vascular disease. In addition, diabetic patients have been reported to be at risk of developing extracellular Mg deficiency. However, the intracellular free Mg concentration and its role in the enhanced platelet reactivity in diabetes is not known.

Research Design and Methods – We evaluated the intracellular erythrocyte (RBC) Mg^{2+} concentration in 20 non-insulin-dependent (type II) diabetics. In addition, the effects of intravenous 3-h drip or 8 wk of oral Mg supplementation on intracellular RBS. Mg^{2+} levels and platelet reactivity was studied. To more clearly evaluate the direct role of Mg in these effects, we induced isolated Mg deficiency in 16 nondiabetic control subjects with an Mg-free liquid diet for 3 wk.

Results – The intracellular RBC Mg^{2+} concentration of diabetic patients was significantly reduced compared with values in nondiabetic control subjects (166 ± 7 vs. 204 ±7 μM., P < 0.01). Serum Mg levels were also reduced in the diabetic patients compared with the control subjects (1.59 ± 0.04 vs. 1.9 ± 0.1 mEq/L, P < 0.05). Oral Mg supplementation for 8 wk (400 mg/day) restored RBC Mg^{2+} concentration to normal without significantly changing serum Mg concentration. Both intravenous and oral Mg supplementation markedly reduced platelet reactivity in response to the thromboxane A2 analogue, U46619. The Mg-free diet resulted in a significant reduction in RBC Mg^{2+} concentration and markedly enhanced the sensitivity of platelet aggregation to U46619 and ADP.

Conclusions - These results suggest that type II diabetic patients have intracellular Mg^{2} deficiency and that Mg deficiency may be a key factor in leading to enhanced platelet reactivity in type II diabetes. Therefore, Mg supplementation may provide a new therapeutic approach to reducing vascular disease in patients with diabetes.

Dyslipidaemias among normaoglycaemic members of familial NIDDM pedigrees

Schumacher M.C. Maxell T.M., Wu L.L., Hunt S.C., Williams R.R. and Elebein S.C. Diabetes Care 1992; 15 : 1285-9.

Objective – To examine the hypothesis that hyperinsulinaemia among relatives of NIDDM probands will increase the prevalence of DLPs, we measured insulin levels and examined the frequency of DLPs among NIDDM pedigree members.

Research Design and Methods - We performed 2-h 75-g OGTTs and measured lipid and insulin levels of 287 family members and 86 spouses from 16

large Utah pedigrees ascertained for 2 siblings with NIDDM.

Results - One-hour insulin levels were higher among 206 family members with NGT than among 65 NGT spouses (483.3 vs 361.7 pM, P = 0.05). Among the NGT family member, 32% had cholesterol levels at or above the age and sex specific 90th percentile level defined by the LRC studies, 33% had HDL levels $\leq$ 10th percentile, and 20% had triglyceride levels $\leq$ 90th percentile. DLP (any of the three abnormalities) was found among 58% of NGT family members, which was significantly higher that the expected 27% (P < 0.00001) and the prevalence among spouses of 45% (P < 0.05). By NCEP criteria for hyperlipidaemia, 40% of the family members met criteria for diet and/or pharmacological therapy.

Conclusions – Normoglycaemic members of NIDDM pedigrees have a high prevalence of DLPs which approaches the prevalence in patients with NIDDM. Our data suggest that members of NIDDM pedigrees should be screened carefully for lipid abnormalities.

Effect of high carbohydrate intake on hyperglycaemia, islet function ,and plasma lipoproteins in NIDDM.

Garg A., Grundy S.M. and Koffler M. Diabetes Care 1992; 15: 1572-80.

Objective – To study effects of high carbohydrate intake of hoyperglycaemia, islet functions and plasma lipoproteins in patients with NIDDM.

Research Design and Methods - An attempt was made to induce hyperglycaemia in 10 men with NIDDM by feeding them an isocaloric high carbohydrate diet (65% of energy as simple carbohydrate [31% as glucose] and 20% as fat) for 28 days in a metabolic ward. Response to the high-carbohydrate diet was compared with that of feeding a diet rich in monounsaturated fat (45% of energy as fat [31% as monounsaturated fat] and 38% as carbohydrates) for 28 days in a cross-over manner. Islet functions were assessed by evaluating plasma glucose, insulin, C-peptide and glucagons responses to standard meal tolerance tests on days 0,14, 21 an d28 of each dietary period.

Results - The high-carbohydrate diet caused significant but modest accentuation of hyoperglycaema, particularly in patients with moderately severe diabetes mellitus, whereas no change was observed with the high-monounsaturated fatty-acid diet. Accentuation of hyperglycaemia was accompanied by an increase in plasma glucagon levels, but no significant change in insulin and C-peptide responses. In 1 patient, feeding the high carbohydrate diet for 68 days produced marked hyoperglycaemia and caused definite suppression of insulin and C-peptide responses along with an increase in glucagons levels compared with the high monosaturated fat diet, the high-carbohydrate diet also raised plasma triglyceride and VLDL cholesterol concentrations.

Conclusions – High-carbohydrate diets may cause accentuation of hyperglycaemia and a rise in plasma glucagons levels in NIDDM patients. High Carbohydrate diets also adversely affect lipoproteins and therefore may not be desirable in all NIDDM patients.

CLINICAL FEATURES

Measurements of health status in diabetic patients

Hammond G.S. and Aoki T.T. , Diabetes Care 1992; 15: 469-77.

Objectives – To develop an instrument to measure health status in adult insulin-dependent (type 1) and non-insulin-dependent (type ll) diabetic patients.

Research Design and Methods- Correlative study to examine psychometric properties of the questionnaire. Test-retest reliability, item-scale correlations, principal-components analysis, correlations with global clinical ratings and correlations with clinical data extracted from medical records were examined at the diabetes clinics at the University of California, Davis, Medical Center. Patients were volunteer clinic patients able to complete the questionnaire. One hundred thirty patients completed a first administration of the questionnaire, and 52 completed a second administration.

Results – Test-retest reliability was satisfactory item-scale correlations showed that 40 of 44 questionnaire items were highly correlated with subscale and total scale scores. Principal-components analysis identified one major factor measured by the questionnaire. Cronbach's α , a measure of the scales' internal consistency, was of satisfactory magnitude. Global ratings of clinical status by patients and clinicians were highly correlated with scale scores. Correlations of scale scores with clinical data were generally of low magnitude but, where significant, were consistently in the direction hypothesized if the scale truly measures health status or disease impact.

Conclusions- The diabetes impact management scales (DIMS) is an easily administered questionnaire with internal consistency and test-retest reliability. Preliminary correlative analyses support the validity of the instrument as a measure of health status in adult type II and type II diabetic patients. Further work will be necessary to firmly establish the validity of the DIMS and its usefulness in clinical outcomes research.

Impact of associated conditions on glycaemic control of NIDDM patients.

Ferrannini E., Stern M.P. , Galvan A.Q., Mitchell B.D. and Haffner S.M. Diabetes Care 1992; 15: 5089-514.

Objective- To assess the impact of associated conditions (obesity , dyslipidaemia and hypertension) on the glycaemic control of non-insulin-dependent diabetes mellitus (NIDDM) patients under home-life conditions..

Research Design and Methods – We analyzed the metabolic data of 271 NIDDM patients 89% Mexican American) screened in a population-based survey (the San Antonio Heart study).

Results – Obesity was present in 77% of the patients, hypertension in 23% , hypertriglyceridaemia (serum triglycerides > 2.9 mM) in 23% ,and hypercholesterolaemia (serum total cholesterol > 6.5 mM) in 14% . Forty per cent of the patients had two or more comorbid conditions. With the use of a multiple linear regression model which was adjusted for age, sex, ethnicity, distribution of body fat (waist-hip ratio), plasma-insulin , and treatment of both diabetes and hypertension), we found that the presence of higher serum triglyceride concentrations was associated with significantly higher plasma glucose levels both in the fasting state (1.4 mM, $P < 0.001$) and 2h after an oral glucose load (1.2 nM, $P = 0.003$). The presence of obesity, hypertension , or high serum cholesterol levels was not associated with significant changes in glycaemic control. When the entire group was stratified by diabetes treatment (untreated n = 89, diet n= 75, oral agents n = 82, insulin n = 25) and after adjusting for age ,sex, ethnicity ,and waist-hip ration, only fasting and 2-h plasma glucose and insulin concentrations were significantly different across treatment groups, with diet and oral agents being associated with higher fasting ($P < 0.001$) and post glucose ($P < 0.005$) plasma glucose levels and lower plasma insulin concentrations ($P < 0.005$) compared with newly diagnosed patients. Neither serum lipids nor blood pressure differed across treatment.

Conclusion – IN NIDDM patients under home-life conditions, higher serum triglycerides are associated with higher fasting and postglucose hyoperglycaemia regardless of antidiabetic treatment. The presence of obesity, hypertension, or high serum cholesterol levels is not associated with significant changes in glycaemic control.

TREATMENT

INSULIN THERAPY

Clinical trial of programmable implantable insulin pump for Type l diabetes

Selam J.L., Micoss P., Dunn F.L. and Nathan D.M. Diabetes Care 1992;15: 877-85.

Objective- The first step in the evolution of an artificial pancrease is the development of a reliable implantable pump for insulin delivery. Despite recent advances, significant issues remain, including small size of studies and frequent irreversible catheter obstructions. We report safety, feasibility, and efficacy results from 56 patients, representing 73 patient-yr of pump experience , entered into a multicentre trial with a new implantable programmable pump.

Research Design and Methods – All patients had insulin-dependent (type-l) diabetes, were 38 ± 8 yr old, and were not prone to severe hypoglycemia. The pump (Infusaid 1000) has a pulsatile mechanism powered by freton-vapour pressure. Its rate is regulated by battery-powered values, operated via a hand-held programmer. The pump is refilled transcutaneously with 25 ml U100 insulin (Hoechst 21 PH) on a monthly basis and has a second spectrum (side port) proximal to the catheter, which allows flushing the catheter or lavaging the pump unit. The pumps were implanted after 3 mo intensive subcutaneous insulin therapy and catheters were positioned either in peritoneum (i.p., n = 38) or the superior vena cava (i.v., n = 18).

Results – All implanted pumps have functioned safely with no instance of overdelivery or stoppage. The most frequent complications were flow slow downs, presumably due to insulin precipitation within the pump, which occurred in 86% of pumps and were resolved in all but one case by lavaging the pump in situ with alkaline solution. Flow slow downs due to catheter obstruction occurred in 52% of the intravenous catheters but only 21% of the intraperitoneal catheters ($P < 0.05$) and were resolved in all but two cases by diluent flushing through the sideport. Incidence of severe

hypoglyycaemia decreased from 0.47 before implant to 0.05 episodes/patients-yr after pump implantation ($P < 0.001$). Mean HbA_1c fell from 7.4 ± 1.2% after intensive subcutaneous therapy to 7.1 ± 1.0% 12 mo after implantation. Only 2 patients withdrew from study after recurrent catheter problems, and quality-of-life questionnaires showed improvement in satisfaction with diabetes-specific quality of life when on implantable pump therapy.

Conclusions – Insulin therapy with implantable pumps is effective and safe for periods upto 1.7 yr with a decreased risk of severe hypoglycaemia than with intensive subcutaneous insulin therapy.

Effect of insulin therapy on blood pressure in NIDDM patients with secondary failure

Randeree H.A. Omar M.A.K., Motala A.A. and Seedat M.A. Diabetes Care 1992;15: 1258-63.

Objective – To assess the effect of insulin therapy on blood pressure in NIDDM patients with secondary failure.

Research Design and Methods – The influence of insulin treatment on blood pressure was assessed retrospectively in a group of 80 NIDDM patients with secondary failure to diet and maximum doses of oral hypoglycaemic agents. Weight, blood glucose, and blood pressure were recorded over a 3-mo period before and after the initiation of insulin therapy.

Results – There was a significant rise in systolic (131.8 ± 1.7 to 148 ± 1.9 mmHg. $P < 0.05$) and diastolic (80.9 ± 0.9 to 89.2 ± 1.0 mmHg, $P < 0.02$) blood pressures with insulin treatment, Insulin treatment was associated with a significant decrease in blood glucose (18.36 ± 0.28 to 10.4 ± 0.34 mM, $P < 0.01$) and an increase in weight (72.1 ± 1.6 to 78 ± 1.7 kg, $P = 0.01$). A control group of 80 NIDDM patients matched for age, weight, BMI, and duration of diabetes demonstrated no significant change in blood pressure over a matched period of follow-up.
Conclusions – This study has shown that insulin therapy is associated with significant elevation of both systolic and diastolic blood pressure.

ORAL HYPOGLYCAEMIC AGENTS

Successful treatment of sever refractory sulfonylurea-induced hypoglycaemia with octreaotide

Krentz A.J., Boyle P.J., Justice K. M., Wright A. D. and Schade D.S. Diabetes Care 1992; 15: 184-6.

Objective - To test the clinical use of ocreotide in the treatment of sulfonylurea-induced hypoglycaemia.

Research Design and Methods – A case is reported of sulfonylurea-induced hypoglycaemic coma in a nondiabetic subject, which was complicated by relapse of hypoglycaemia after resuscitation with intreavenous dextrose. Subcutaneous octreotide, 50 µg12 hourly, suppressed stimulated endogenous insulin secretion, thereby preventing a further recurrence of hypoglycaemia.

Results- No adverse of treatment were observed.

Conclusions – These results suggest a significant role for octreotide as an adjunct to intravenous dextrose in the management of severe and refractory cases of sulfonylurea-induced hypoglycaemia.

EXERCISE

Effect of thermal biofeedback-assisted relaxation training on blood circulation in the lower extremities of a population with diabetes

Rice B.I. and Schindler J.V. Diabetes Care 1992; 15: 853-8.

Objective- Investigate the effect of relaxation training /thermal biofeedback on blood circulation in the lower extremities of diabetic subjects.

Research Design and Methods- Diabetic subjects (n = 40)aged 17-73 yr were volunteers recruited through the University of Wisconsin-La Crosses, the local ADA Chapter, and a medical clinic. A within-subjects experimental design was used. During phase 1 , all subjects used a self-selected relaxation method and recorded toe temperatures daily. During phase 2, subjects were taught a biofeedback-assisted relaxation technique designed to elicit sensations of warmth in the lower extremities and increase circulation and temperature. Subjects relaxed at home with the use of designed relaxation tape. They measured and recorded toe temperatures. Each phase lasted 4 wk.

Results- Toe temperature and blood volume pulse (BVP) data were gathered at the beginning and end of phases 1 and 2 . Paired *t* tests compared the means of temperature per cent change scores between 1 and 2. Mean temperature change score were 8.73% (phase 1) and 31.38% (phase 2) ($t = -8.00$, $df = 39$, $P < 0.001$). Mean BVP change scores were 2.33% (phase 1) and 22.47% (phase 2) ($t = -9.24$, $df = 35$, $P < 0.001$). Based on eta square, 71% of the BVP increase in phase 2 was attributed to the

relaxation technique. A multiple regression analysis indicated that none of the other examined variables affected by diabetes were significant predictors of BVP increase.

Conclusions- Data indicate that diabetic patients show significant increases in peripheral blood circulation with this technique . This noninvasive method could serve as an adjunct treatment for limited blood flow in some complications of diabetes.

Glucose turnover in type l diabetic subjects during exercise

Benn J.L., Brown P.M., Beckwith L.J. Farebrother M. and Sonksen P.H. Diabetes Care 1992; 15: 1721-6.

Objective- To assess the effect of selective β_1-blockade (atenolol and betaxolol) and nonselective β-blockade (propranolol) on glucose turnover in subjects with insulin-dependent (type 1) diabetes mellitus during moderate exercise.

Results – Plasma glucose, initially 9.2 ± 0.5 mmol/L (mean ± SE) when insulin infused and 14.0 ± 0.8 when insulin was withdrawn, fell on exercise by 3.4 ± 1.1 mmol/L ($P < 0.05$) saline, 4.0 ± 0.8 mmol/L ($P < 0.01$) with betaxolo, 308 ± 0.7 mmo/L ($P < 0.01$) with atenolol , 5.0 ± 0.6 mmol/L ($P < 0.005$) with propranolol, and 1.7 ± 1.0 mmol/L (NS) when insulin was withdrawn . Propranolol, but not the other β-blockers, caused a significantly greater fall in glucose on exercise than during the control study. Glucose appearance (R_a) was similar basally and rose to an almost identical level in all five groups during exercise. Glucose disappearance rate (R_d) rose similarly during exercise, except after propranolol when the rise was significantly greater than with saline ($P < 0.01$). Failure of glucose to change significantly during exercise when insulin had been withdrawn was associated with the smallest rise in R_d and the highest nonesterified fatty acid concentrations. Propranolol and betaxolol, but not atenolol, reduced nonesterified fatty acids.

Conclusion- We conclude that the greater fall in glucose on exercise after β-blocking drugs is probably largely a direct effect of β2-blockage on muscle, increasing the exercise-induced rise in R_d glucose . This offers support to the use of β1-specified drugs, where β-blockade is necessary in type l diabetes.

TRANSPLANTATION AND IMMUNOSUPPRESSION

Somatic gene therapy for diabetes with an immunological safety system for complete removal of transplanted cells.

Kawakami T., Yamaoka T., Hirochika R., Yamashita k., Itakura M. and Nakauchi H. Diabetes 1992; 41: 956-61.

To develop somatic gene therapy for diabetes, we studied an animal model with proinsulin-producing fibroblasts with an immunological safety system. Cultured mouse fibroblasts of the Ltk^- cell line were transfected first with the efficient human proinsulin expression vector pBMG-Neo-Ins. Initially, 2 x 10^6 cells with proinsulin-production rate of 91 ng $24h^{-1}$ 10^6 $cells^{-1}$ were transplated i.p. into streptozocin-induced diabetic C3H mice. The blood glucose concentrations improved between the first and the 28^{th} day, but the animals died of hypoglycaemia between the 29^{th} and 46^{th} days. The proinsulin-producing Ltk^- cells were further transfected with a second plasmid, pHEBo-CD8.2 encoding BALB/c mouse T-cell differentiation antigen. The CD8.2 allotype is different from CD8.1 allotype by only one amino acid substitution and should be only slightly antigenic to the recipient C3H mice. Somatic genetherapy with these doubly transfected cells followed by the consecutive administration of a monoclonal antibody to CD8.2 resulted in an initial decrease of blood glucose concentrations followed by the permanent recurrence of hoyperglycaemia, thus proving the complete removal of the transplanted cells. Cultured fibroblasts were thus proven capable of supplying sufficient proinsuolin to lower the blood glucose concentrations in diabetic animals. The immunological safety system with a combination of artificial expression of cell surface antigen and the administration of the specific monoclonal antibody was an effective safety system of somatic gene therapy.

Does nitric oxide mediate autoimmune destruction of β -cells?

Corbett J.A. and Mcdaniel M. Diabetes 1992; 41: 897-903.

Cytokines have been implicated as immunological effector molecules that induce dysfunction and destruction of pancreatic β-cell . The mechanisms of cytokine action on the β-cell are unknown ; how ever, nitric oxide, resulting from cytokine-induced expression of nitric oxide synthase, has been implicated as the cellular effector molecule mediating β-cell dysfunction. Nitric oxide is a free radical that targets intracellular iron-containing enzymes, which results in the loss of their function.

The cytokine IL-1β induces the formation of nitric oxide in islolated rat islets and the insulinomia cell line, Rin-m5F. NMMA and NAME, both inhibitors of nitric oxide synthase, completely protect islets from the deleterious effects of IL-1 β. These inhibitors are competitive in nature and inhibit both the cytokine-inducible and constitutive isoforms of nitric oxide synthase with nearly identical kinetics. This may preclude their use as therpeutic agents because of increase in blood pressure which result from the inhibition of constitutive nitric oxide synthase activity. Aminoguanidine, and inhibitor of nonenzymatic glycosylation of cellular and extracellular constituents associated with diabetic complications, recently has been reported to inhibit nitric oxide synthase. Aminoguandidine is ~40-fold more effective in inhibiting the inducible isoform of nitric oxide synthase, suggesting that aminoguanidine or analogues may serve as potential therapeutic agents to block diseases associated with nitric oxide production by the inducible isoform of nitric oxide synthase. In vivo administration of TNF IL-1 has been shown to induce antidiabetogenic effects in the NOD mouse. This antidiabetogenic effect of cytokines appears to conflict with evidence suggesting that cytokines mediate β-cell dysfunction. The role of nitric oxide in both cytokine-mediated β-cell dysfunction, and the antidiabetogenic effects of cytokines, as well as the potential therapeutic use of aminoguanidine, are evaluated in this study.

Islet transplantation with immunoisolation

Lanza R.P. , Sullivan S.J. and chick W.L. Diabetes 1992;41: 1503-10.

Immunoisolation is a potentially important approach to transplanting islets without need for immunosuppressive drugs. Immunoisolation systems have been conceived in which the transplanted tissue is separated from the immune system of the host by an artificial barrier. These systems offer a solution to the problem of human islet procurement by permitting use of islets isolated from animal pancreases. The devices used are referred to as biohybribe artificial organs because they combine synthetic, selectively permeable membranes that block immune rejection with living transplants. Three major types of biohybrid pancreas devices have been studied. These include devices anastomosed to the vascular system as AV shunts, diffusion chambers, and microcapsules. Results in diabetic rodents and dogs indicate that biohybrid pancreas devices significantly improve glucose homeostasis and can function for more than a year. Recent progress made with this approach is discussed , and some of the remaining problems that must be resolved to bring this technology to clinical reality are addressed.

CD8 T cells are not required for islet destruction induced by a $CD4^+$ islet-specific T-cell clone

Bradley B.J. Haskins K., La Rosa F.g. and Lafferty K.J. diabetes 1992;41: 1603-8.

A panel of $CD4^+$ T-cell clones has been isolated from the spleen and lymph nodes of diabetic NOD mice. These clones have been shown to be islet-specific both in vivo and in vitro. One of the clones, BDC-6.9, initiates extensive damage to islet tissue when placed adjacent to and NOD islet graft that has been used to reverse diabetes in (CBA x NOD) F1 recipients or when injected intraperitoneally into such animals. In this study, we show that BDC-6.9 T cells can initiate islet destruction in absence of detectable CD8 T cells either in the periphery or in the lesion that develops after the transfer of the cloned islet-reactive T cells.

COMPLICATIONS

CARDIOVASCULAR

Immune mechanisms of aterosclerosis in diabetes mellitus.

Lopes-Virella M.F. and Virella G. Diabetes 1992; 41: (suppl 2) : 86-91.

It was recently proposed that the increased levels of modified lipoproteins in diabetic patients may be responsible for the accelerated development of macrovascular complications associated with the disease. Modified lipoproteins are believed to induce the transformation of macrophages into foam cells and, in some cases, to induce endothelial cell damage. In addition, modified lipoproteins trigger and immune response leading the formation of antibodies and then to the formation of LDL-containing immune complexes. In this review, we summarize the evidence linking LDL glycation and oxidation with intracellular accumulation of cholesterol esters and foam-cell formation, and we discuss their potential for inducing an autoimmune response and the formation of lipoprotein-containing immune complexes. The formation of LDL-Ics seems particularly significant, because these ICs are avidly taken up by macrophages through their Fc receptors and induce not only massive intracellular accumulation of CE but also paradoxical increase in LDL-receptor expression. Our experimental data suggest that the uptake of LDL-IC is facilitated by RBC adsorption, in agreement with the role of RBC in the adsorption of

circulating IC and their delivery to phagocytic cells. In addition, macrophages are activated when ingesting LDL-IC and release IL-1β and TNF- α , which can contribute to the initiation and progression of an atheromatous lesion by several mechanisms. Although it is difficult of envisage how LDL-IC could initiate an endothelial lesion, it is easy to speculate about their role as cofactors in the initiation and progression of the atherosclerotic process.

Lipoprotein-immune complexes and diabetic vascular complications

Gisinger C. and Lopes-Virella M.F. Diabetes 1992; 41: (suppl. 2) : 92-6.

In earlier studies, we showed that incubation of HMM with LDL IC led to cellular CE accumulation and to the transformation of macrophages into foam cells. This study demonstrates that the stimulation of macrophages with RBC-LDL-IC also increases the uptake of native LDL, most likely because of an increased LDL receptor number, as shown by Scatchard plot analysis (x-axis intercept 1257 vs. 352 ng LDL/mg protein in control cells) To determine whether the increase in LDL-receptor activity was secondary to a decrease in the macrophage free (nonassociated) cholesterol content, we measured the T-UC and the UC associated with intracellular intact LDL and demonstrated that 50% of the T-UC is associated with intact LDL. UC not associated with LDL (free cholesterol) was lower in LDL-IC-stimulated cells than in control cells. These results suggest that UC associated with non-degraded intracellular LDL is nonregulatory, a conclusion that was also supported by finding increased sterol synthesis (192.8 ± 22.9 pmol/mg protein vs. 94.8 ± 11.8) in RBC-LDL-IC-stimulated macrophages. In conclusion, the uptake of RBC-LDL-IC by macrophages led to increased intracellular accumulation of CE and UC, to a decrease in the cell regulatory pool of free cholesterol, and to an increase in LDL-receptor activity.

Lipid-lowering therapy and macrovascular disease in diabetes mellitus.

Garg A. Diabetes 1992 ; 41: (suppl 2) : 111-`5.

Patients with diabetes mellitus are at increased risk of morbidity and mortality from macrovascular disease manifesting coronary heart disease, cerebrovascular accidents and peripheral vascular disease. Increased frequency of dyslipidaemia, hyperglycaemia, obesity, hypertension, and associated nephropathy may contribute to accelerated atherogenesis in diabetic patients. Therefore, besides intensive control of hyperglycaemia, management of dyslipidaemia, hypertension, and obesity should also be emphasized in diabetic patients. Those who smoke should be strongly encouraged to quit smoking. Besides attempts to achieve normal levels of plasma lipoproteins , consideration also should be given normalization of compositional abnormalities of various lipoproteins in patients with diabetes mellitus. The therapeutic goals for cholesterol reduction should be lower in diabetic patients than nondiabetic subjects. The first step is to achieve good metabolic control of diabetes mellitus by diet, exercise and weight reduction and, if needed, with sulfonylureas or insulin therapy. Because most of the patients with insulin-dependent diabetes mellitus achieve normal levels of plasma lipoproteins with intensive insulin therapy, lipid-lowering medications are rarely needed. In patients, with non-insulin-dependent diabetes mellitus, however, dyslipidaemia often persists despite good glycaemic control. Lipid-lowering medications should be considered in such patients. Because nicotinic acid can cause marked deterioration in glycaemic control, and bile acid-binding resins may accentuate hypertriglyceridaemia, these agents are less desirable for use by diabetic patients. Inhibitors of hydroxymethylglutaryl coenzyme. A reductase may be preferred in patients with elevated LDL cholesterol and mild hoyper-triglyceridaemia. For diabetic patients with marked hypertriglyceridaemia, however, fibric acid derivatives should be the drug of choice.

Association of 24-h cardiac parasympathetic activity and degree of nephropathy in IDDM patients

Molgaard M., Christensen P.D. Sorensen K.E. , Christensen C.K. and mogensen C.E. Diabetes 1992; 41: 812-7.

In insulin-dependent diabetic patients, nephropathy is a predictor of mortality and coronary heart disease. Impaired cardiac vagal function is an important factor in the pathophysiology of sudden cardiac death in coronary heart disease. Autonomic neuropathy in particular involves, vagal function. Besides tests and 24-h measurements of cardiac parasympathetic activity were compared in 37 insulin-dependent diabetic patients, and the relationship between 24-h vagal activity and degree of nephropathy was investigated. Nephropathy was classified according to urinary albumin excretion as normoalbuminuria, incipient, and overt nephropathy. Mean age (~ 30 yr) was not different among groups . The 24-h measurements of

parasympathetic activity appeared more sensitive than besides tests, as 33% of patients without cardiac autonomic neuropathy in beside tests had 24-h vagal activity values below the 95% confidence limits of 14 healthy control subjects. Patients with incipient or overt nephropathy had significantly lower mean values for vagal activity during both wake and sleep time than healthy control subjects. Increasing degree of nephropathy was associated significantly with increasing attenuation of 24-h vagal activity ($P < 0.001$). The covariation of degree of neuropathy and nephropathy may suggest common pathogenetic mechanisms. The reduced 24-h vagal activity , even in the early stages of nephropathy, could be an important risk factor for cardiac death in insulin-dependent diabetic patients.

Coronary heart disease incidence in NIDDM patients in the Helsinki heart study

Koskinen P., Manttari M., Manninen V. Huttunen J.K., Heinonen O.P. Diabetes Care 1992; 15: 820 - 5.

Objective- To determine coronary heart disease (CHD) incidence among dyslipidaemic subjects with non-insulin-dependent diabetes mellitus (NIDDM) and to assess the effect of lipid-modifying treatment on serum and lipoprotine lipids and the CHD incidence in these patients.

Research Design and Methods – Of the 4081 men participating in the Helsinki Heart Study, a coronary primary prevention trial with gemfibrozil in middle-aged men with high non-high-density lipoprotein (HDL) cholesterol (> 5.2 mM; 20 mg/dl). 135 had NIDDM ate entry. The incidence of definite myocardial infarction and cardiac death and changes in serum and lipoprotein lipids were determined during the 5-yr trial in the NIDDM patients and compared with those observed in nondiabetic trial participants.

Results- Compared with nondiabetic subjects, NIDDM patients had lower HDL cholesterol ($P < 0.001$), higher triglyceride concentration ($P < 0.0001$) ,and greater body mass index ($P < 0.001$), there were more hypertensive patients ($P < 0.001$) among them. The incidence of myocardial infarction and cardiac death was significantly higher among diabetic than nondiabetic participants (7.4 vs 3.3%, respectively , $P < 0.02$) CHD incidence in the gemfibrozil-treated diabetic men ($n = 59$) was 3.4% compared with 10.5% in the placebo group (NS). In multivariate analysis, diabetes ($P < 0.05$), age ($P < 0.0001$), smoking ($P < 0.0001$), low HDL cholesterol ($P < 0.05$), and high low-density lipoprotein cholesterol ($P < 0.005$) were independently related to CHD incidence. Gemfibrozil-induced serum and lipoprotein lipid changes in diabetic patients were similar to those observed in nondiabetic subjects.

Conclusions – Compared with similarly dyslipidaemic nondiabetic subjects, patients with NIDDM are at markedly increased risk of CHD. This elevated risk can be somewhat reduced by gemfibrozil.

Prevalence of cardiovascular autonomic dysfunction assessed by spectral analysis and standard tests of heart-rate variation in newly diagnosed IDDM patients.

Ziegler D., Dannehl K., Volksw D., Muhlen H., Spiller M. and Gries F.A. Diabetes Care 1992; 15: 905-17.

Objective – To determine the prevalence of cardiovascular autonomic nerve dysfunction in patients with newly diagnosed insulin-dependent diabetes mellitus (IDDM) compared with healthy nondiabetic subjects.

Research Design and Methods – A battery of cardiovascular reflex tests was performed in 130 newly diagnosed IDDM patients aged 12-40 yr at mean blood glucose levels of 7.2 mM after insulin had been administered for 3-39 days. Age-dependent lower limits of normal of these tests were defined at the 2.3 percentile in 120 nondiabetic subjects. Tests of heart-rate variation (HRV) included the coefficient of variation (C.V.) and the low-frequency (LF), midfreqeuncy (MF) ,a and high-frequency (HF) bands of spectral analysis at rest, HRV during deep breathing (C.V. expiratory-inspiratory ratio, and mean circular resultant), Valsalva ratio, and maxi-mum/minimum 30 : 15 ratio. In addition , spectral analysis on standing, the change in systolic blood pressure to standing, and diastolic blood pressure response to sustained handgrip were determined in 50 patients.

Results - A significantly higher percentage of abnormal test responses in the diabetic group compared with the control group was noted for power spectrum in the LF band (7.3 vs. 0.8%, $P < 0.05$) and MF band (10.6 vs 0%, $P < 0.001$) at rest and HF band on standing (10.0 vs 0.9% , $P< 0.005$), maximum/minimum 30:15 ratio (25.4 vs. 5.0% , $P < 0.001$) and Valsalva ratio (17.5 vs. 4.2% , $P < 0.001$). There were no significant differences between both groups in regard to the remaining parameters. Ten (7.7%) diabetic patients but none of the nondiabetic subjects had cardiovascular autonomic neuropathy defined by the strict criterion of abnormal results in more than three of six tests (

P < 0.001). In addition 12 (9.2%) patients but only 2 (1.7%) control subjects had abnormal results in two of six tests (P < 0.01)

Conclusions – Cardiovascular autonomic nerve dysfunction is relatively common in newly diagnosed IDDM patients after correction of the initial metabolic imbalance. A combination of tests based on spectral and conventional analysis of HRV appears suitable for detection of early abnormalities in autonomic function in diabetics.

Randomized prospective double-blind trial in healing chronic diabetic foot ulcers

Steed D.L., Goslen J.B., Holloway G.,A., Malone J.M. Bunt T.J. and Webster M.W. Diabetes Care 1992 ; 15: 1598-1504.

Objective - To assess the efficacy of topically applied CT-102 APST for treating diabetic neurotrophic foot ulcers.

Research Design and Methods - Thirteen patients entered a randomized, double-blind trail of topically applied CT-102 APST vs. placebo (normal saline) guaze dressings for the treatment of nonhealing diabetic neurotrophic foot ulcers. CT-102 APST (Curative Technologies, Setauket,NY) was prepared from homologous platelets and contained multiple growth factors including PDGF, PDAF, EGF, PF-4, TGF-β , aFGF, and bFGF. Inclusion criteria for subjects included diabetes, ulcer of > 8 wk duration , periwound transcutaneous oxygen tension >30 mmHg platelet count > 100,000/mm^3, and no wound infection. Wounds were exercised before entry and were > 700 mm^3 in volume, < 100 cm^2 in area, and involved subcutaneous tissue.

Results - In the CT-102 group, 5 of 7 ulcers were healed (100% epithelialized) by 15 wk, but only 1 of 6 ulcers was healed by 20 wk with placebo (P < 0.05). average per cent reduction in ulcer area at 20 wk was 94% for CT-102 vs. 73% for placebo. Daily reduction in ulcer volume was 73.8% ± 42.4% ,mm^3 / day (mean ± SE) for CT-102 vs. 1.8 ± 0.4 mm^3 /day for placebo (P < 0.05) .

Conclusions- CT-102 significantly accelerated wound closure in diabetic leg ulcers when administered as part of a comprehensive programme for the healing of chronic ulcers.

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

Quattrin T., Albini C.H. Reiter E.O., Mills B.J. and Macgillivray M.H. Diabetes Care 1992; 15: 490-4.

Objective- To compare the urinary output of insulinlike growth factor 1 (IGF-l) and growth hormone (GH) in prepubertal and pubertal children with insulin-dependent diabetes mellitus (IDDM) versus nondiabetic subjects and to analyze the relationship between the urinary excretion of these peptides and degree of metabolic control.

Research Design and Methods - Group l included 30 IDDM patients who had diabetes for 4.9 ± 0.7 yr and had normal renal function (mean age 11.6 ± 0.9 yr); group 2 consisted of 31 control subjects (mean age 9.2 ± 0.6 yr). Sensitive radioimmunoassays were used to measure IGF-l and GH in urine aliquots from 12-h timed overnight collections that had been dialyzed, concentrated 50-fold , and lyophilized.

Results - Significantly lower IGF-l and GH outputs per kilogram body weight per 12h were observed in IDDM subjects compared with control subjects. When data were expressed per kilogram of body weight, no difference was observed between the urinary output of IGI-l and GH between prepubertal subjects within group 1 or group 2 . The prepubertal children had significantly lower HbA_1 than the pubertal population; however, no correlation was found between urinary output of IGF-I or GH and HbA_1 A positive correlation was observed between urinary IGF-I and GH (r = 0.85 p < .001).

Conclusions- Patients with long-standing IDDM excrete significantly lower urinary levels of IGF-I and GH compared with normal subjects. Serial measurements of these peptides from onset of IDDM are needed to define whether the changes observed are present at diagnosis or are secondary to duration of disease.

NEPHROPATHY

Microalbuminuria in type I diabetic patients Prevalence and clinical characteristics.

Microalbuminuria collaborative study group. Diabetes Care 1992; 15: 4956-501.

Objective- To estimate the prevalence of microalbuminuria, overnight urinary albumin excretion rate (AFR) ≥ 30 and ≤ 250 µg/min ,in a large sequential sample of nonhypertensive insulin-dependent (type l) diabetic patients attending hospital diabetic clinics, to identify micro-and normoalbuminuric patients in this sample for subsequent intervention and natural history follow-up studies, and to compare the clinical characteristics of the micro- and normoalbuminuric patients identified.

Research Design and Methods – screening was conducted in two phases. In phase l, eligible patients were asked to provide an early morning urine specimen for measurement of albumin-creatinine ratio. In phase 2, all patients with an albumin concn ≥ 15 mg/L and/or an albumin-creatinine ratio ≥ 3.5 mg/ mmol and a random sample of those with an albumin concn < 15 mg/L and albumin-creatinine ratio < 3.5 mg/mmol were asked to collect a timed overnight urine specimen for determination of AER.

Results – Among 1988 patients (16-60 yr old, diabetes onset < 40 yr, and duration of diabetes < 35 yr) who were screened, the prevalence of microalbuminuria was ~ 3.7% (95% confidence interval (CI) 2.7-7.6%). Duration of diabetes was significantly longer in micro-than normoalbuminuric patients (20 vs. 15 yr. respectively $P < 0.001$), and in no patient with microalbuminuria was the duration of diabetes < 5 yr. Systolic and diastolic blood pressures, higher in micro-than normoalbuminuric patients (132 vs. 122 mmHg, $P < 0.01$; 77 vs. 72 mmHg. $P < 0.01$), were strongly associated with AER.

Conclusion - Microalbuminuria in type l diabetes, which appears to represent an earlier phase in the development of clinical nephropathy, is associated with elevated blood pressure and a longer duration of diabetes.

Accurate estimation of glomerular filtration rate in diabetic nephropathy form age, body weight, and serum cretinine

Sampson M.,J. and Drury P.L. Diabetes care 1992; 15: 609=12.

Objective - To assess, in diabetic nephropathy, the accuracy of a method that estimates glomerular function with age, body weight, and serum creatinine as parameter.

Research Design and Methods – Glomerular filtration rate (GFR) was measured 57 times in 20 subjects with insulin-dependent diabetes mellitus and nephropathy with a single injection of ^{51} Cr-EDTA. At the same time, the estimated creatitnine clearance (ml/min) was calculated with the cockroft-Gault formula.

(140 – age [yr] x body wt [kg] x K/serum creatinine [mol/L])
k = 1.23 for men, 1.05 for women

These values were ten correlated for body surface area (1.73 m^2).

Results - For GFR measurements < 100 ml, min^{-1} $1.73m^{-2}$ (n = 41) , there was strong positive correlation with the estimated creatininie clearance corrected for body surface area ($r = 0.94$ $P < 0.0001$). The slope of this regression line did not differ significantly form identify or the y-intercept from zero. On average , the Cockroft-Gault formula (corrected for body surface area) underestimated the GFR by only 3.1 ml. Min $^{-1}$ 1.73^{-2} (9.7 SD).

Conclusions - This formula , corrected for body surface area, gives accurate estimates of GFR when GFR < 100 ml min^{-1} 1.73^{-2}. This formula could be used with an acceptable degree of confidence when repeated isotope assessments of renal function in diabetic nephropathy are impracticable.

Lipoprotein(a) in diabetic patients with and without chronic renal failure

Guillausseau P.J/, Peynet J., Chanson P. et al. Diabetes care 1992; 15: 976-9.

Objective - To examine the distribution of Lp(a) plasma levels in patients with IDDM and NIDDM, and in nondiabetic and IDDM, patients with chronic renal failure.

Research Design and Methods- Cross sectional study of Lp(a) plasma levels in a population of diabetic patients with stable metabolic control , with simultaneous determination of plasma lipids, fasting plasma glucose, and HbA_1 . Thirty six patients with IDDM , 90 with NIDDM, and 41 with chronic renal failure (20 IDDM , 21 nondiabetic) were compared with 78 control subjects.

Results-Lp(a) plasma levels were significantly higher in IDDM and NIDDM patients, as well as in nondiabetic and IDDM patients with chronic renal failure compared with control subjects. No correlation was observed between Lp(a) and lipid plasma levels, fasting plasma glucose, and HbA_1.

Conclusions- Lp(a) my contribute to the increased prevalence of atherosclerotic disease in diabetic patients and patients with chronic renal failure, especially in IDDM patients whose lipoprotein pattern was not different from that of the control group.

NEUROPATHY

Treatment of diabetic neuropathy with γ-linolenic acid

Keen H., Payan J., Allawi J .et al , Diabetes care 1992; 15: 8-15.

Objective – To compare the effects of placebo and GLA on the course of mild diabetic neuropathy over 1 yr.

Research Design and Methods – We entered 111 patients with mild diabetic neuropathy form seven centers into a randomized , double-blind , placebo – controlled parallel study of GLA at dose of 480 mg/day, MNCV, SNAP, CMAP, hot and cold thresholds , sensation, tendon reflexes, and muscle strength were assessed by standard tests in upper and lower limbs.

Results- For all 16 parameters, the change over 1 yr in response to GLA was more favourable than the change with placebo, and for 13 parameters, the difference was statistically significant. Sex age, and type of diabetes did not influence the result, but treatment was more effective in relatively well-controlled than in poorly-controlled diabetic patients.

Conclusions – GLA had beneficial effect on the course of diabetic neuropathy.

Glycaemic control and peripheral nerve conduction in children and young adults after 5-6 months of IDDM

Allen C., Duck S.C. Sufit R.L., Swick H.M. and Alessio D.J. Diabetes Care 1992; 15: 502-7.

Objective – A cohort of people (n = 86) was examined in the first few months after insulin-dependent diabetes mellitus (IDDM) diagnosis to evaluate the effect of hyperglycaemia on nerve conduction velocities and latencies.

Research Design and Methods- Unselected cases with IDDM, who were 6-29 yr of age, were identified at diagnosis from a large, geographically defined area of southern Visconsin. Peripheral nerve conduction was measured on sample from this cohort.

Results- Peroneal nerve conduction velocity was significantly inversely related to glycosylated haemoglobin (P <0.05, age and height adjusted). All other nerve conduction velocities and latencies (median motor, median sensory and sural) showed the same tendency , but the associations were not statistically significant. Twenty-four-hour urine C-peptide and duration of diabetes (3-11 mo) were not consistently related to nerve conduction parameters after controlling for age and height.

Conclusions- These findings suggest that as early as 5-6 mo after diabetes diagnosis and at a time frequently characterized by partial remission of IDDM hyperlgycaemia has a role in the acute slowing of nerve conduction velocity. Other factors such as residual endogenous insulin production do not appear to influence these early changes.

Pittsburgh epidemiology of diabetes complications study

Maser R.E., Becker D.J. Drash A.L. et al . Diabetic Care 1992; 15: 525-7.

Objective – This project evaluated the utility of quantitative sensory techniques in predicting the development of neuropathy for subjects participating in a prospective study.

Research Design and Methods - Distal symmetric polyneuropathy was evaluated in 77 insulin dependent diabetes mellitus individuals via quantitative sensory testing, nerve conduction studies, and clinical examination.

Results – Although the specificity and positive predictive value were low for the quantitative sensory techniques as predictors of neuropathy diagnosed on clinical exam ~ 2yr later, the sensitivity for vibratory thresholds was high (100%). Variability over the 2-yr interval was shown on follow-up testing for each of the objective assessment modalities and it was not explained by differences for potential risk factors measured at baseline.

Conclusion- Despite a cross-sectional relationship between the assessment modalities and clinically overt neuropathy at baseline, these follow-up data suggest that potential for the objective modalities as predictors of clinically diagnosed neuropathy may be limited.

Microalbuminuria associated with diabetic neuropathy

Bell D.S.H. Ketchum C.H., Robinson C.A., Wagenknecht L.E. and Williams B.T. Diabetes Care 1992; 15: 528-31.

Objective – To test the hypothesis that microalbuminuria may show an independent statistical association with diabetic neuropathy.

Research Design and Methods- An observational study of a prospectively identified cohort was conducted at the University Medical Centre. The cohort consisted of 78 consecutive diabetic patients who fulfilled the criteria of having diabetes for > 10 yr, a normal serum creatinine, urine negative for macroalbuminuria by a commonly used dipstick

method, a blood glucose < 13.8 mM (< 250 mg/dl), and HbA1 < 11% (normal range 5.5 – 8.5%). Medical record review established the presence of chronic complications of diabetes. Urine albumin level was measured by radioimmunoassay. Albumin concn ≥ 15mg/L was used as a cutoff value of microalbuminuria.

Results- Twenty-five of 78 patients (32%) showed microalbuminuria. Of these , 51% had neuropathy, 39% had retinopathy, 35% arterial hypertension, 17% peripheral vascular disease, and 15% ischaemic heart disease . After adjusting for age, sex, and type and duration of diabetes, diabetic neuropathy and hypertension showed a significant association with microalbuminuria. After adjusting for other diabetic complications, diabetic neuropathy showed a significant association with microalbuminuria.

Conclusions- Microalbuminuria is independently associated with diabetic neuropathy . This association lends support to the theory of vascular aetiology for diabetic distal symmetrical neuropathy.

Mexiletine in the tretment of diabetic neuropathy

Stracke H., Meyer U.E. Schumacher H.E. and Federien K. Diabetes Care 1992;15: 1550-5.

Objective – To prove the efficacy of mexiletine in painful diabetic neuropathy.

Research Design and Methods- Treatment was provided in three dosages. For pain measurements, a VAS and McGilll's verbal rating scale were chosen. Ninety-five patients were included in the study.
Results- A global assessment of the VAS among patients showed no differences between mexiletine treatment and placebo. The total evaluation (PRIT) of the McGill scale fell just below the level of significance. More specific exploratory evaluations of subclasses of the McGill scale representing different degrees of pain, gave remarkable differences between mexiletine and placebo in sensory and miscellaneous items. In special subgroups, which were formed according to types and courses of complaints complied at the beginning of this evaluation, the substantial advantages of the mexiletine treatment were shown in both the VAS and the McGill scale.

Conclusions - Evidence strongly indicates that, in particular, those patients with stabbing or burning pain, heat sensations ,or formication will benefit most by mexiletine therapy. Concerning the dosage, a medium regimen of 450 mg/day seems to be appropriate. With an increase in the antiarryhthmic dosage level, the efficacy does not rise proportionally. Mexiletine proved to be a safe therapy with negligible, side effects at the medium close range, even less than placebo; and reamarkably, no cardiovascular side effects were noted. Further studies should avoid global assessments and pay more attention to the variety of complaints and quality of life.

RETINOPATHY

Genetic marker association with proliferative retinopathy in persons diagnosed with diabetes before 30 yr of age

Cruickshank K.J., Moss C.M.V.S.E., Roth M.P., et al Diabetes 1992; 41: 879-85.

It has been suggested that HLA-DR4 is a marker of genetic predisposition to proliferative retinopathy. To investigate this relationship and potential associations between other polymorphic genes and proliferative retinopathy, a sample (n = 428) of participants in the population–based Visconsin Epidemiologic Study of Diabetic Retinopathy was selected for typing for HLA-A, -B,-C, and –DR and a panel of other polymorphic genes. The presence of proliferative retinopahty was determined from grading of stereoscopic colour fundus photographs taken at 2 examinations, 4 yr apart. In logistic regression models with repeated measures, persons with HLA-DR4 who were negative for DR3 were five times more likely to have proliferative retinopathy than those negative for both antigens after adjusting for other potential risk factors (Odds ratio = 5.43, 95% Confidence interval (CI) = 1.04, 28.30). HLA-C2, AK-2, and MNSs-S also were associated positively with proliferative retinopathy and HLA-DRB was associated inversely with this complication of diabetes in each case before adjusting for the number of comparisons. These data suggest that the genetically determined immunopathic mechanisms leading to diabetes, and in linkage disequilibrium with DR4, may independently contribute to the development of proliferative retinopathy.

DIABETES AND PREGNANCY

Longitudinal study of plasma lipoproteins and hormones during pregnancy in normal and diabetic women

Montelongo A., Lasuncion M.A., Pallardo L.F. and Herrera E. Diabetes 1992; 11: 1651-9.

Plasma lipoproteins were studied longtitudinally at the 1st, 2nd, and 3rd trimester of gestation and at postpartum and postactation in 12 age-matched PGDM women, 9 GDM women, and 12 healthy control subjects. FPG and HbA_{1c} were higher in every case in PGDM women than in control subjects, whereas in GDM patients, glucose was augmented only after parturition. FFA and β-hydroxybutyrate levels were higher in both PGDM and GDM patients than in control subjects during gestation but not after partutrition. Total TGs and VLDL, LDL, and HDL TGs increased with gestational time in the three groups and declined at postpartum, and although total cholesterol and VLDL, LDL and HDL cholesterol followed a similar trend, their rise was less pronounced, and the decline after parturition was slower than that of the TGs in the three groups, with no difference among them. The VLDL TG/cholesterol ratio declined in the three groups at the 3rd gestational trimester, whereas in both LDL and HDL, the TG/cholesterol ratio but, not the cholesterol/phospholipid ratio, increased during gestation in the three groups, indicating a specific enrichment of TGs in these particles. The increase in apoA-1 and apoB with gestation was parallel to the respective changes in HDL and LDL cholesterol and, again, no difference was observed between the three groups. Plasma levels of β-oestradiol, progesterone, and prolactin increased sharply with gestation and declined at postpartum in the three groups, but absolute values of β- oestradiol and prolactin, at the three trimesters of gestation, were lower in PGDM patients, but progesterone levels were lower than controls in GDM women only at the 3rd trimester. The logarithm for each of these hormones correlated linearly with VLDL, LDL, and HDL TGs, and the highest correlation coefficient value corresponded to the regression between β-oestradiol and HDL TGs. Because oestrogens are known to increase VLDL production, decrease hepatic lipase activity, and increase HDL TG levels, we propose that the decreased oestradiol levels in our diabetic patients impede an exaggerated rise of circulating lipoproteins above the normal range. We also propose that the development or lack of development of a dyslipidaemic condition in diabetic pregnancy depends on the balance between the metabolic control and the level of sex hormones.

GENERAL AND MISCELLANEOUS

A rapid and sensitive radioimmunoassay for the measurement of proinsulin in human serum

Bowsher R.R., Wolny J.D. and Frank B.H. Diabetes 1992; 41: 1084-90.

RIA methodology is used widely to measure proinsulin in human serum. However, some RIAs lack the sensitivity necessary to quantify proinsulin in unextracted serum and require long incubation periods. We developed an RIA with a sensitivity of 3.5 pM that permits the routine meausurement of proinsulin in <48 h. This was accomplished by using a nonequilibrum binding reaction at room temperature and PEG-assisted second antibody precipitation as the method for separating bound and free proinsulin. We obtained a specific antiproinsulin antibody by adsorbing the initial goat antiserum with human C-peptide-agarose. Proinsulin produced 50% displacement of tracer at 25.6 pM, whereas both human insulin and C-peptide failed to displace tracer at concentrations as much as 1 μM. We evaluated several cleaved derivatives of proinsulin for cross-reactivity with the antibody. B-chain-C-peptide cleaved derivatives (<50% cross-reactivity) were more potent than A-chain-C. Peptide cleaved derivates (<5% cross-reactivity). However, all derivatives cleaved in the region from 56-60 failed to cross-react with the antiserum. These data indicate that a major antigenic determinant is present on the C-peptide region of proinsulin adjacent to the A-chain-C-peptide junction. After administration of an oral glycaemic challenge, the mean fasting serum concentration of proinsulin in normal adults rose from 4.1 ± 0.28 to 23.6 ± 3.8 pM. We found a significant difference in the proinsulin concentrations in 6 adults before and after a glycaemic challenge. When two different antibodies were used in the RIA. Based on the antibodies different specificity for proinsulin, we concluded that B-chain-C-peptide junctional split forms of proinsulin comprise a significant portion of circulating proinsulin material after a glycaemic challenge.

Noninvasive detection of cardiac sympathetic nervous dysfunction in diabetic patients using [^{123}I] metaiodobenzylguanidine

Mntysaari M., ; Kuikka. J., Moustonen J., et al. Diabetes 1992; 41: 1069-75.

The association between clinical autonomic dysfunction and myocardial MIBG accumulation was investigated. The study groups comprised 6 male diabetic patients with autonomic neuroapthy (ANP + group), 6 male diabetic patients without autonomic neuropathy (ANP-group), and 6 male nondiabetic control subjects. The mean age was comparable in all groups, and the subjects had no evidence of coronary heart disease. Reduced heart-rate variation in a deep-breathing test was used as a criterion for autonomic neuropathy. Immediately after injection, the peak net influx rate of MIBG to

myocardum was significantly (P <0.05) reduced in both diabetic groups. At 6 hr after MIBG injection , the MIBG uptake of the myocardium was significantly (P < 0.05) smaller in the ANP + group than in the control groups. In the ANP-group, the MIBG uptake of the myocardium was between that of the ANF + group and that of the control group. Our data show that reduced myocardial MIBG accumulation is associated with autonomic dysfunction in diabetic patients, but it can occur to a lesser extent also in diabetic patients without apparent autonomic neuropathy. The measurement of the myocardial MIBG accumulation is a promising new method to detect cardiac sympathetic nervous dysfunction in diabetic patients.

A new method for qualification of islets by measurement of zinc content

Jindal RM. , Taylor R.P., Gray W.W.R. , Esmeraldo R., and Morris P.J. Diabetes 1991;41: 1056-62

The ability to quantify the yield of pancreatic islet tissue after isolation is important for interlaboratoy comparisons and for the assessment of islet yield prior to clinical transplantation. Because pancreatic islets contain a much higher concentration of zinc than other tissues, we investigated the analysis of zinc as a measure of islet tissue yield. Rat islets of standard diameter 250 µm were hand-picked into samples containing 10-80 islets. The zinc content was measured by EAAS and showed a linear correlation with islet number. A zinc binding flurorescent dye, TSQ, was investigated as a way of simplifying the zinc measurement for routine use. Samples of 10-80 islets of 250 µm were sonicated in 3 ml zinc-free water, 0.18 µmol TSQ was added, and the TSQ-zinc fluorescence was measured at 480nm. A linear correlation was observed. Exocrine contamination up to 50% barely affected the results. Islet zinc content also was shown to be correlated linearly with islet number for freshly isolated human islets. Measurement of zinc by TSQ fluorescence is a rapid, cheap and objective measure of islet tissue content.

Pentosidine formation in skin correlates with severity of complications in individuals with long-standing IDDM.

Sell D.R., Lapolla A., Odetti P., Fogarty J. and Monnier V.M. Diabetes 1992;41: 1286-92.

Pentosidine is an advanced glycosylation end product and protein cross-link that results from the reaction of pentoses with proteins. Recent data indicate that long-term glycation of proteins with glucose also leads to pentosidine formation through sugar fragmentation. In this study, the relationship between the severity of diabetic complications and pentosidine formation was investigated in collagen from skin-punch biopsies from 25 nondiabetic control subjects and 41 IDDM patients with diabetes duration > 17 yr. Pentosidine was significantly elevated in all IDDM patients versus control subjects (P <0.0001). It correlated strongly with age (P < 0.0001) and weakly with duration (P <0.082). Age-adjusted pentosidine levels were highest in grade 2 (severe) versus grade 1 and 0 complication in all four parameters tested (retinopathy, proteinuria, arterial stiffeness, and joint stiffness). Significant differences were found for retinopathy (P <0.014)and joint stiffness (P <0.041). The highest degree of association was the cumulative grade of individual complication (P <0.005), determined by summing indexes of all four parameters. Pentosidine also was significantly elevated in the serum of IDDM patients compared with control subjects (P< 0.0001) , but levels were not significantly correlated with age, diabetes duration, complication, or skin collagen pentosidine (P > 0.05). A high correlation, between pentosidine levels and long-wave collagen-linked fluorescence also was observed, suggesting that pentosidine is a generalized marker of accelerated tissue modification by the advanced glycosylation/Maillard reaction, which is enhanced in IDDM patients with server complications.

Effects of Gemfibrozil on Triglyceride levels in patients with NIDDM

Vinik A.L. and Colwell J.A., Diabetes Care 1992; 15: 37-44.

Objective- Patients with NIDDM have a two-to-fourfold increased risk of macrovascualr disease. The constellation of elevated TGs and decreased HDL cholesterol are recognized as risk factors and constitute the major dislipidaemic in NIDDM. We therefore sought to determine if gemfibrozil (600mg b.i.d) was effective in correcting the dyslipidaemia of NIDDM.

Research Design and Methods0- After 8 wk of placebo stabilization, 442 patients from 46 study centers were randomized to double-mlid treatment ; in designated 2:1 ratio, 295 received gemfibrozil and 147 received placebo for 20 wk. The primary end point was plasma TG; secondary end points were TC, LDL cholesterol, VLDL cholesterol, HDL cholesterol, and HbA_{1c}. No baseline differences were noted between group in sex, age, weight, type of diabetic therapy, fasting plasma levels of TGs, HbA_{1c} or C-peptide. About two-thirds received oral hypoglycaemic drugs, one-third insulin.

Results- TG fell 26.4% in gemfibrozil group and rose 7.4% in the placebo group ($P < 0.023$), by and intent-to-treat analysis. When patients who were noncompliant or with inadequate data were excluded, similar results were found-a 30.4% fall with gemfibrozil and a 4.8% increase with placebo ($P < 0.0001$): TG levels fell within 4 wk and remained low for 20 wk ($P < 0.001$). Mean HDL cholesterol rose by 4 wk and increased further at 12 wk (8-12%), $P < 0.0001$. TC fell. We observed a significant rise in LDL cholesterol in both gemfibrozil – and placebo-treated groups, with no significant differences between these groups. Changes in HbA_{1c} were similar in gemfibrozil and placebo groups. No differences were observed in responses in groups treated with insulin and or oral hypoglycaemic drugs. Overall AEs that were clinically; important occurred in 6.1% in the gemfibrozil group vs. 2.0% in the placebo group (NS).

Conclusions – We conclude that gemfibrozil is an effective and safe agent in combating the dyslipidaemia of NIDDM, irrespective of type of diabetic therapy.

α Glucosidase inhibition by miglitol in NIDDM patients

Kingma P.J., Menheere P.P.C.A, Sels J.P. and Kruseman A.C.N. Diabetes Care 1992; 15:478-83.

Objective – To determine the efficacy of the α-glucosidase inhibitor miglitol (BAYm 1099) regarding the starch content of food.

Research Design and Methods - Thirty-six non-insulin-dependent diabetes mellitus (NIDDM) subjects were studied in a double-blind randomized study comparing treatment with a single dosage of 100 mg miglitol or placebo and a single-blind crossover comparison of three test meals in which the carbohydrate contained either 30,50 or 70% starch, and quantities of fat and protein were kept constant.

Results – Postprandial blood glucose excursions were reduced by ~50% with miglitol after all test meals. In contrast, after miglitol treatment, maximum postprandial serum C-peptide and insulin values reached the some levels as after placebo treatment, although the time to reach these maximum levels was delayed. Free fatty acid value decreased after both miglitol and placebo similarly. Twenty-eight untoward events in 15 patients were reported in the miglitol treatment group and 11 events in 7 patients in the placebo treatment group.

Conclusion. - Miglitol reduces postprandial blood glucose excursions independent of the starch content of the meal. Because no effects, were found on international postprandial maximal levels of serum insulin and C-peptide, it may be that miglitol exerts, in additional to a delay of intestinal carbohydrate absorption, extraintestinal effects as well, particularly effects on disposition of glucose or anti-insulin counterregulatory factors.

Accuracy of home blood glucose monitors

Tate P.F., Clements C.A. and Walters J.E. Diabetes Care 1992; 15: 536-8.

Objective – To determine the accuracy of live home blood glucose monitors (HBGM) in reference to a standard laboratory reference method.

Research Design and Methods - The study took place in the laboratory of a 350-bed private acute care hospital. Subjects were a sample of convenience of 207 diabetic and nondiabetic adult and paediatric patients scheduled for fasting blood work that included a blood glucose test. Venous blood samples were collected for laboratory determination of blood glucose level. A separate sample was collected for testing on two each of five HBGMs: AccuChek II M, Tracer II, Exac Tech, Glucometer II with Memory, and One Touch.

Results – Multiple regression analysis showed that all 110 monitors could be used to predict laboratory blood glucose values. The monitors with the highest predictabilities were One Touch, Tracer II, and AccuChek II M. Consistency between monitors of the same brand was lowest with One Touch AccuChek II M had the smallest SD between the 2 monitors used in the study.

Conclusions - HBGM can be used to predict actual laboratory values of blood glucose. However, the controlled environment of the study should be considered and patient education made a high priority when recommending monitors.

Early sonographic evaluation for foetal growth delay and congenitl malformations in pregnancies complicated by insulin-requiring diabetes

Brown Z.A. Mills J.L., Metzger B.E., et al. Diabetes Care 1992; 16: 613-9.

Objective – It has been reported that early foetal growth retardation may be a useful marker for

congenital malformations in diabetic pregnancies. To test this hypothesis, diabetic and nondiabetic women were sonographically evaluated during the first trimester.

Research Design and methods - Foetal crownrump lengths were measured sonographically at least once during the first 15 wk of pregnancy in 329 nondiabetic and 312 diabetic women. Of these, 289 nondiabetic and 269 diabetic women had sonograms before 10 wk gestation and 283 nondiabetic and 269 diabetic women had songrams between 10 and 15 wk of gestation. Early foetal growth delay was defined as a sonographic gestational age of ≥6 days less than menstrual gestatinal age.

Results - The mean crown-rump lengths at 8 wk were 17.9 ± 4.6 mm in the diabetic and 18.7 ± 4.9 mm in the nondiabetic groups (P = 0.13): At 12 wk, the mean foetal crown-rump length was 58.5 = 8.8 mm for diabetic subjects and 60.6 = 8.7 mm for nondiabetic subjects (P = 0.04). Between 5 and 9 wk, 28 of 289. (9.7%) foetuses of nondiabetic subjects, 34 of 259 (13.1%) normal foetuses of diabetic subjects, and 2 of 10 (20%) malformed foetuses of diabetic subjects demonstrated growth delay (P= 0.31, normal vs. malformed diabetic). Between 10 and 15 wk of gestation, 28 of 283 (9.9%) foetuses of nondiabetic subjects, 32 of 256 (12.5%) normal foetuses of diabetic subjects, and 4 of 13 (30.8%) malformed foetuses of diabetic subjects demonstrated growth delay (P = 0.06, normal vs. malformed diabetic). Early foetal growth delay did not predict a reduced birth weight at term.

Conclusions – Among insulin-dependent diabetic subjects who were moderately well controlled at conception statistically significant but mild early foetal growth delay was present but did not appear to be useful clinically in predicting congenital malformations. Recommendations that growth delay demonstrated on early ultrasound be used as a predictor of congenital malforamtion require careful reexamination.

Glycosylated serum protein levels assayed with highly sensitivity Immunoradiometric assay accurately reflect glycaemic control of diabetic patients

Gordon A., Glaser B., Wald M., et al. Diabetes care 1992; 15: 645-50.

Objective- To develop a sensitive and reliable immunoradiometric assay to measure glycosylated lysine residues on serum proteins (GSP) and to evaluate its efficacy in monitoring glycaemic control.

Research Design – The effect of acute and chronic in vitro and in vivo changes in glucose levels on GSP concentration was evaluated. GSP determinations from insulin-dependent diabetic(IDDM) patients, non-insulin-dependent diabetic (NIDDM) patients, and control subjects were correlated with other indices of glycaemic control.

Results- The GSP levels were unaffected by acute glucose changes after food or intravenous glucose administration but increased during storage at 20°C due to in vitro glycosylation by endogenous glucose. Immediate acidification of the serum prevented this, permitting long-term storage despite high ambient glucose levels. In randomly selected diabetic patients, 96% of GSP values were greater than the man +BSD of nondiabetic control subjects. In diabetic patients, GSP levels correlated with mean plasma glucose concentrations (Kendall correlation statistics 0.47, P < 0.001), fasting plasma glucose levels (Kendall statistics 0.42 , P < 0.001), and glycosylated haemoglobin (GHb, Kendall statistics 0.30, P < 0.005). Induction of near normal glycaemia with a half time of disappearance of 4.7 ± 0.4 day. GSP levels remained elevated in 6 of 10 well-controlled NIDDM patients, despite normal GHb concentrations. Chronic hypoglycaemic states, like pregnancy and hyper-insulinaemic hypoglycaemia, were associated with significantly low GSP levels.

Conclusions- We describe a reproducible and sensitive immunoradiometric asay for GSP that closely reflects the degree of glycaemic control in diabetic patients. Further studies are needed to determine whether this assay may be useful in screening for glucose intolerance or gestational diabetes.

In vivo demonstration of insulin-receptor defect with ^{123}L-labelled insulin and scintigraphic scanning in severe insulin resistance.

Dozio N., Micossi P., Calimberti G., et al. Diabetes Care 1992; 15: 651-6.

Objective- Insulin-receptor function in humans is usually studied in vitro on readily available cells, e.g. erythrocyters and fibroblasts. Although these cells are not metabolically important targets for insulin action, information derived from them are often taken as representative of other tissues. The aim of this study was to investigate insulin receptors

in vitro on erythrocytes and in vivo on one of the main insulin-target organs, the liver.

Research Design and Methods- A 16-yr-old girl affected by severe insulin resistance was identified. Insulin receptor binding was measured on the erythrocytes of the patient and of 6 nondiabetic volunteers. The biodistribution of ^{123}l -labelled insulin was studied in vivo by scintigraphic scanning in the insulin-resistant patient and in 10 nondiabetic volunteers.

Results- Erythrocytes of this patients displayed a markedly reduced [^{125}I] insulin binding. In vivo ^{123}I-insulin biodistribution was characterized by lack of hormone uptake by the liver (4 vs. 21% of the injected dose in control subjects) contrasting with intense accumulation of radioactivity in the kidneys.

Conclusion – Our studies show that defects of insulin binding can be directly demonstrated in vivo on liver receptors with a noninvasive technique with low radiotoxicity.

Granulocytes and three-phase bone scintigraphy for differentiation on diabetic gangrene with and without osteomyelitis

Ritter M.M., Richter W.D., Leinsinger G., Kirsch C.M. and Schwandt P. Diabetes Care 1992; 15: 1014-9.

Objective - In diabetic gangrene, concomitant osteopathy and soft-tissue infection often render laboratory and roentgenographic signs unreliable as indicators of osteomyelitis. In this situation, scintigraphic methods can be helpful.

Research Design and Methods – Relying on the long-term clinical course as the final indicator of presence or absence of osteomyelitis, we prospectively compared in 31 patients three-phase bone scintigraphy with either indium-labelled autologous granulocytes (n=20) or ^{123}I-labelled antibodies against granulocytes (n = 11).

Results - Three-phase bone scintigraphy and imaging with indium-labelled autologous granulocytes yielded sensitivities and specificities of 95 and 70% for bone scintigraphy and 77 and 100% for granulocyte scintigraph respectively. One patient with severe angiopathy and proved osteomyelitis had a negative bone scintigraphy but a positive scintigraphy with labelled antibodies against granulocytes. One patient with aseptic bone necrosis presented with a formally false positive results with both methods.

Conclusion - In contrast to former retrospective studies, three-phase bone scintigraphy compares very well with granulocyte scintigraphy. The care of most patients can be managed with clinical data and this widely available scintigraphic method.

Intermeddiate HbA_{1c} results

Marrero D.G., Vandagriff J.E., Gibson R. et al. Diabetes Care 1992; 15:1045-9.

Objective – This study compared the performance of a new device that use an IA to measure HbA_{1c} in 9 mm with a l-µl capillary blood sample with AC and CE methods in both nondiabetic and diabetic paediatric patients.

Research Design and Methods – Two hundred seven paediatric subjects (103 nondiabetic, 10^4 with insulin-dependent diabetes mellitus) had HbA_{1c} measured with the IA method and compared with total GHb values determined by AC and HbA_1 by the CE method with the same whole-blood capillary aliquot. Glucose values were also obtained from the same blood samples.

Results - Correlations and regression analyses show excellent correspondence between the three assays. The correlation between the AC and CE methods is 0.98 ($P<0.001$) with a slope of 1.615 ± 0.0125 and intercept of 4.00 ± 0.20. The correlation between the IA and AC methods is 0.99 ($P < 0.001$) with a slope of 0.608±0.007 and intercept of 1.326±0.066. The correlation between the IA and CE methods of 0.97 ($P < 0.001$), with a slope of 0.983±0.018 and intercept of 1.122 ± 0.153. The average difference and average percentage difference between methods were also significant ($P < 0.001$), reflecting the differences in GHb components measured. There was a significant correlation ($P < 0.001$) between each method and glucose values CA r = 0.72, AC r = 0.70, CE r = 0.73). Within run precision for IA ranged from 1.7 to 3.5% and between-run precision 2.7 to 4.1%.

Conclusion – Study results suggest that the IA method gives extremely accurate and reliable values over the clinical range of interest. The instrument is small, portable, easy to use, and provides information within 9 min for both physicians and patients.

Hyperfibrinogenaemia

Ganda O.P. and Arkin C.F. Diabetes Care 1992: 15; 1245-50.

Objective – To evaluate the deteminants of elevated fibrinogen levels and the impact of hyper-

fibrinogenaemia on vascular complications in diabetes.

Research Design and Methods – Plasma fibrinogen, glucose, $HbA_{1,}$ and lipids were measured in 116 ambulatory type I and type II diabetic patients with (n = 59) or without (n = 57) clinical evidence of micro-or macrovascular complications. In 56 of these patients, factor VII activity and CRP also were measured. Univariate and multivariate data analyses were conducted.

Results – Overall mean ± SE fibrinogen levels in patients (339 ± 7.3 mf/dl) were elevated markedly compared with control subjects (248 ± 9.1 mg/dl). Fibrinogen levels were elevated disproportionately in patients with type II diabetes ($P < 0.0001$), hypertension ($P = 0.0001$), obesity ($P < 0.0001$), and vascular complications ($P < 0.0001$). Fibrinogen was correlated significantly with age ($P < 0.001$) cholesterol ($P=0.002$), CRP ($P<0.001$), and factor VII activity ($P = 0.032$), but not with plasma glucose, triglycerides, HDL cholesterol, or disease duration. Stepwise multiple regression analyses revealed that type II diabetes and presence of vascular complications were major determinants of fibrinogen. For vascular complications, fibrinogen emerged as one of only three independent predictors, the other two being diabetes duration and hypertension.

Prevalence of glucose intolerance in Asian Indians

Ramachandran A., Snehalaths C., Dharmaraj D., Viswanathan M. Diabetes Care 1992; 15: 1348-55.

Objective - To evaluate the prevalence of NIDDM and IGT in the urban and rural areas in southern India.

Research Design and Methods – Two populations of the same ethnic background, but different socioeconomic background were chosen for this study. Nine-hundred urban people and 1038 rural subjects were studied. Fasting and 2-h post-glucose capillary blood samples after a 75g oral glucose load (WHO criteria) were obtained in these randomly selected adults (≥ 20 yr of age).

Results – Using the WHO criteria, the prevalence of NIDDM, adjusted to the age of the respective general population, was 8.2% in the urban and 2.4% in the rural populations. The prevalence was 8.4 and 7.9% , respectively, in urban men and women, and2.6 and 1.6% in rural men and women. The age-adjusted prevalence of IGT was 8.7 and 7.8% in the urban and rural areas , respectively. The prevalence of IGT was 8.8% in urban men and 8.3% in women; the corresponding values for rural men and women were 8.7 and 6.4%. The prevalence of NIDDM increased with age, markedly so in the urban people. The urban-rural difference was significant for NIDDM ($x^2 = 29.4$, $P < 0.001$) but nor for IGT. In the urban population, 65% of the NIDDM patients were known cases, whereas in the rural area, the known cases accounted for only 24% Bivariate analysis showed an association of BMI, STR, and WHR with prevalence of NIDDM plus IGT. In the multiple logistic regression analysis, age BMI, STR, and WHR were associated significantly with glucose intolerance in the urban population, whereas only age was significant in the rural population. The best predictors of NIDDM were age, BMI, WHR, and urbanization.

Conclusion – The study showed a high prevalence of NIDDM in the urban southern Indian population. The prevalence of NIDDM in the same ethnic group in rural areas was significantly lower. The prevalence of IGT was similar in both populations., Upper body adiposity was a significant predictor of NIDDM in this population with low rates of obesity.

Relationship between absorption of radiolabelled soluble insulin, subcutaneous blood flow, and anthropometry

Vora J.P., Burch A., Peters J.R. and Owens D.R. Diabetes Care 1992; 15: 1484-93.

Objective – To evaluate the interrelationships between the rate of absorption of soluble insulin, SCBF and anthropometry in normal subjects.

Research Design and Methods- In 12 normal men (age range 23-30 yr , BMI 18.2 – 41.3 kg/m^2), simultaneous assessment of the absorption of ^{125}I-labelled soluble insulin and SCBF (^{99m}TC clearance) was performed, on separate study days, for the anterior abdominal wall, anterior midthigh, and the upper arm sites. Each site was examined in a randomized order on two separate occasions. Absorption of ^{125} I-soluble insulin was determined by external monitoring of residual radioactivity levels at the injection site for 6 h postinjection. Residual radioactivity level-time curves, including the characteristic early phase of slow absorption of soluble insulin (the lag phase), were described using two-and three-parameter biexponential models. Anthropometric measurements included BMI, ultrasonic measurement of the subcutaneous adipose tissue layer, and caliper skin fold thickness at the anterior abdominal wall biceps, triceps, anterior midthigh and subscapular sites.

Results- A highly significant positive relationship was observed between the rate of absorption of ^{125} I-soluble insulin and SCBF (r_s = 0.44-0.52; P < 0.01-0.001). The duration of the lag phase was inversely correlated with SCBF (r_s = -0.34-0.51; P < 0.01-0.001). Inverse relationships also were observed for ht subjects' degree of adiposity with the rate of soluble insulin absorption (rs=-0.43-0.71; P<0.001) and SCBF (r_s = -0.27-0.62; P < 0.05-0.001). Significantly shorter lag phase was observed for the abdominal site compared with thigh and arm injection sites (P < 0.05-0.01)

Conclusions - The rate of absorption of soluble insulin, including during the lag phase, is positively correlated with SCBF. Increasing adiposity prolongs the duration of the early lag phase and reduces the rate of absorption of soluble insulin and SCBF.

Leucocyte scanning with ^{111}In is superior to magnetic resonance imaging in diagnosis of clinically unsuspected ostemyelitis in diabetic foot ulcers.

Newman L.G., Waller J., Palestro C.J. et al. Diabetes Care 1992; 15: 1527-30.

Objective- To compare the accuracies of MRI and leucocyte scanning in diagnosing clinically unsuspected osteomyelitis in diabetic foot ulcers.

Research Design and Methods- A prospective study of 16 diabetic foot ulcers in 12 patients , including both ambulatory and hospitalized patients , was performed at a university medical center. Pedal images were obtained by leucocyte scanning with [^{111}In] oxyquinoline and MRI. Definitive diagnosis of ostemyelitis then was determined by bone biopsy for culture and histology.

Results – Biopsy-proven osteomyelitis was present in 7 (44%) of the 16 foot ulcers. The diagnosis was suspected clinically in 0%. Leucocyte scanning was 100% sensitive, whereas MRI was only 29% sensitive in diagnosing osteomyelitis in diabetic foot ulcers. Specificities were 67 and 78%, respectively. The positive and negation predictive values (70 and 100%, respectively) for the leucocyte scan also were greater than those of MRI (50 and 58%, respectively).

Conclusion – Leucocyte scanning is superior to MRI in detecting clinically unsuspected osteomyelitis in diabetic foot ulcers.