ABSTRACT SERVICE

ETIOPATHOLOGY

Human Type 1 diabetes and the insulin gene, principles of mapping polygenes.

Bennett ST. Todd JA. Annual Review of Genetics, 1996; 30 : 343-70

We review the strategy used to identify a susceptibility locus (IDDM2) type 1 (insulin dependent diabetes mellitus. As type 1 diabetes is becoming the paradigm for dissecting multifactorial disease genetics, the approach described provides important general guideline for positional changing of human disease polygenes. Main topics include: 9a) historical constitutes of the mapping and identification of IDDM2 – a critical survey of the work leading up to the conclusion that IDDM2 most likely corresponds allelic variation at the insulin gene minisatellite (VNTR) locus;(b) the nature of allelic (length and sequence) variation at the VNTR locus, (c) gene interactions and disease pathogenesis; (d) mechanism of action of the INS VNTR in Type 1 diabetes-insulin gene expression, parent-of-origin effects (genomic imprinting). and (e) summary and future prospects – alleles of the insulin VNTR that are protective for Type 1 diabetes appear to encode susceptibility to Type 2 diabetes.

The harmony of the spheres : inducible nitric oxide synthase and related genes in pancreatic beta cells.

Eizirik Dl. Flodstrom M. Karlsen AE, Welsh N,. Diabetologia. 1996; 39(8) : 875-90.

The radical nitric oxide (NO) is a possible mediator of pancreatic beta-cell damage. In insulin-depender diabetes mellitus (IDDM) NO is produced by the enzyme nitric oxide synthase (NOS), in a reaction where arginine is the main substrate. There are different isoforms of NOS, but in the context of immune mediated beta-cell damage the inducible from of NOS (iNOS) is the most relevant. The beta-cell iNOS is similar and encoded by the same gene on chromosome 17 as the iNOS expressed in macrophages and other nucleated cells. iNOS activation depends on gene transcription and denovo enzyme synthesis and NO seems to induce a negative feedback on iNOS expression. While iNOS mRNA is induced by interleukin-1 beta (IL –1 beta) alone in rodent insulin-producing cells, a combination of two (IL-1 beta + interferon gamma) (IFN gamma) or three (IL – 1 beta + IFN gamma + tumour necrosis factor alpha) cytokines is required for iNOS activation in human pancreatic islet. The promoter region of the murine iNOS gene has at least 25 binging sites for different transcription factors, and the nuclear transcription factor kappa B is necessary for cytokine-induced iNOS transcription in both rodent and human pancreatic islets. The nature of other transcription factors relevant for iNOS regulation in these cells remains to be determined. Induction of iNOS is paralleled by induction of several other cytokine-dependent genes in beta cells, including argininosuccineate synthetase, cyclooxygenase and mangenese superoxide dismutase. Some of these genes may contribute to beta-cell damage, while others are probably involved in beta-cell defence and/or repair. Regulation of iNOS and other related genes in beta cells is complex, and differs in several aspects from that observed in macrophages. There are also important differences in iNOS regulation between rodent and human pancreatic islets. A detailed knowledge of the molecular regulation of these genes in beta cells may be instrumental in the development of new approaches to prevent beta- cell destruction in early IDDM.

Theory and practice of nicotinamide trials in pre-Type 1 diabetes.

Gale EA. Journal of Pediatric Endocrinology and Metabolism 1996; 9(3) : 375-9.

Autoimmune processes are involved in pancreatic beta cell destruction in Type 1 diabetes. Autoantibodies including islet cell antibodies (ICA), glutamic acid decarboxylase antibodies (GADA), and antibodies directed against protein tyrosine phosphatase/IA2 (IA2-AB) appear in the circulation years before clinical onset and permit increasingly precise disease prediction. Increasing knowledge of the pathogenesis of Type 1 diabetes in animal models and humans suggests that progression to disease is not inevitable in those with indications of autoimmune processes directed against islet beta cell, and that these processes may prove vulnerable to intervention. The condition therefore exist for screening g and attempted intervention in pre-type 1 diabetes. This review will discuss the theoretical and practical background to a major controlled trial using one of a number of interventions currently under consideration. Nicotinamide, a soluble B group vitamin, has for many years been known to protect beta cells against a variety of noxious stimuli. It is at high doses a free radical scavenger a potent inhibitor of the enzyme poly (ADP-ribose) polymerase (PARP), and prevents depletion of interventions NAD. Although its benefits have been marginal or absent in recently diagnosed patient, promising pilot studies have been performed in ICA positive first degree relatives and school children. No serious side effect to have been reported from its use at the doses proposed in man or other species. There is therefore a sound case for submitting this agents to a controlled clinical trial, which in view of the number involved, has necessarily been launched on an international collaborative basis.

Maturity onset diabetes of the young (MODY).

Fajans SS. Bell GI, Bowden DW, Halter JB, Polonsky KS. Diabetic Medicine. 1996; 13 (9 Supple 6). S90-5

MODY is a sub-type of NIDDM. It is characterised by an early age of onset and autosomal dominant mode of inheritance. These features, and the availability of large multigenerational pedigrees, make MODY useful for genetic studies of diabetes. In the large 5-generational RW pedigree, MODY is tightly linked to genetic markers on chromosome 20q. Affected subjects in this family show sbnormalities of carbohydrate metabolism, varying from impaired glucose tolerance (IGT) to severe diabetes. Approximately 30% of diabetic subjects become insulin-requiring, and vascular complications occur. MODY is also linked to the glucokinase gene on chromosome 7p and many different mutation associated with MODY have been identified in this gene. MODY, due to mutations in the glucokinase gene, is a relatively mild form of diabetes with mild fasting hyperglycae,oa and IGT in the majority clinical investigative studies indicated that the genetic or primary defect in MODY is characterized by deranged and deficient insulin secretion and not by insulin resistance. There are quantitative and qualitative differences in insulin secretary defects which

differentiate subjects with MODY due to mutation in the gene on chromosome 20q from those with glucokinase mutation. These differences correlate with the severity of diabetes between these two genetic forms of MODY.

Impaired glucose tolerance in Pima Indians.

Lilloja S. Diabetic Medicine. 1996; 13(9 Supple 6) S127-32.

More than 50% of Pima Indians develop NIDDM. This disorder is preceded by impaired glucose tolerance (IGT) and we tested the hypothesis that the elevated glucose tolerance (IGT) and we tested the hypothesis that the elevated glucose levels in IGT must be due to reduced beta-cell function. We first determined the plasma glucose/plasma insulin and plasma insulin/insulin resistance relationships in individuals with NGT relationships which by definition must be normal, and determined if these relationships were intact in individuals with IGT. We also compared Pimas and Caucasians with NGT or IGT. Subjects were assessed with an OGTT, and IVGTT, underwater weighting (for body composition), and a euglyucaemic clamp. The results showed that insulin concentration in Pimas with IGT were not lower than the levels predicted by the same degree of insulin resistance. These studies indicate that insulin resistance, and not beta-cell failure, is the principal lesion determining IGT in Pimas. NIDDM occurs when beta cell failure develops in the presence of insulin resistance. In some individuals of other races beta-cell functions may be less able to withstand insulin resistance, and presumably in these individuals beta-cell failure assumes a greater importance in the evolution to NIDDM.

Planning for gold; genome-wide scanning for linkage in Type 1 diabetes.

Todd JA, Farrall M. Human Molecular Genetics. 1996;1443-8

Genome – wide scans for linkage of chromosome regions to Type 1 diabetes in affected sib pair families have revealed that the major susceptibility locus resides within the major host compatibility complex (MHC) on chromosome 6p21 (Lambda S = 2.4). It is recognized that the MHC contains multiple susceptibility loci (referred to collectively as IDDM1), including the class II antigen receptor genes, which control the major pathological feature of the disease. Tlymphocyte-medicated autoimmune destruction of the insulin-producing pancreatic beta cells. However, the MHC genes, and a second locus, the insulin gene minisatellite on chromosome 11p15 (IDDM2; lambda S = 1.25). cannot account for all of the observed clustering of disease in families (lambda S = 15), and the scans suggested the presence of other susceptibility loci scattered throughout the genome. There are four additional loci for which there is currently sufficient evidence from linkage and association studies to justify fine mapping experiments: IDDM4 (FGF3/11q13), IDDM5 (ESR/6q22), IDDM8 (D6S281/6q27) and IDDM12 (CTLA-4/2q33) IDDM4, 5 and 8 were detected by genome scanning, and IDDM12 by a candidate gene strategy. Seven other named loci are not discounted but remain to be replicated widely. Multiple susceptibility loci were expected as genome-wide scans of the mouse model of type 1 diabetes which showed that although the MHC is the major mouse locus, at least 13 genes unliked to the MHC are involved in the development of disease. Genome-wide scans using 1000 affected sibpair families will be required to be confident that all genes with effects on familial clustering equivalent to the insulin gene locus (lambda S = 1.25) have been detected. The identification of aetiological determinants, requires exclusion of hitchhiking polymorphisms in regions of linkage disequilibrium, as demonstrated for the MHC and the insulin geneloci and functional studies implicating the disease-associated variants in pathogenesis. Ultimately, targeting of specific candidate mutation as in mice by homologous recombination and replacement will be necessary to prove the primary role of any candidate mutation.

Molecular mechanisms of beta-cell destruction in IDDM: the role of nicotinamide.

Gale EA. Hormone Research. 1996; 45 Suppl 1 : 39-43

Autoimmune processes are involved in pancreatic beta-cell destruction in Type 1 diabetes. Autoantibodies including islet cell antibodies (ICA), glutamic acid decarboxylase antibodies (GADA), and antibodies directed against the 37/40 K antigen appear in the circulation, years before clinical onset and permit increasingly precise disease prediction. A cellular immune response causes pancreatic infiltration, while macrophages and Th-cells appear to be implicated – via local release of cytokines – in beta-cell destruction. Generation of free radicals, DNA strand breaks, activation of the enzyme poly (ADP-ribose) polymerase (PARP), and depletion of intracellular nicotinamide adenine dinucleotide (NAD) appear to be common factors in beta cell death, whether mediated by oxygen radicals nitric oxide, or streptozotocin. Nicotinamide, a soluble B group vitamin which offers protection against these toxic stimuli, is at high doses a free radical scavenger, a potent inhibitor of PARP, and protects against depletion of intracellular NAD. A sound scientific rationale therefore exists for its use in human prediabetes, and promising pilot studies have been performed in ICA-positive first-degree relatives and school children. No serious side effects have been reported from its use at the doses proposed in man or other species. There is therefore a sound case for submitting this agent to a controlled clinical trial.

Prediction of Type 1 diabetes.

Seidel D. Ziegler AG. Hormone Research. 1996; 45 Supple 1 : 36-9

Prediction of Type 1 diabetes is largely based on islet cell antibodies, but may be improved by
combined analysis with other markers. We conducted a screening of first-degree relatives of Type 1 diabetic patients in Germany using islet cell antibodies (ICA, indirect immunofluorescence on human pancreas) and insulin autoantibodies (IAA, radioimmunoassy) as screening markers. Of 1460 relatives tested, 2.3% (n=33) were identified to be ICA+ (> or = 10 JDFu) and 1.9% (n=27) to be IAA+(> or = 50 nU/ml) in at least two subsequent serum sample. Of 44 antibody-positive relatives, 17 (39%) progressed to clinical insulin-dependent diabetes mellitus (IDDM) within 5 years. Life table analysis showed a 58% risk of IDDM for ICA=and 46% risk for IAA+ individuals. ICA combined with IAA gave a risk of 67% ($p<0.02$ compared with ICA- n.s. compared with (IAA-). Of all relatives who progressed to clinical IDDM, only one was negative for ICA, but 6 were negative for IAAT resulting in a sensitive were characterised for HLA DR and DO markers by genotyping. Relatives with 2 nonDR3/non-DR4 (DRx/x) alleles had no risk of IDDm, although they were consistently positive for one or more antibody specificities. We conclude that IAA screening is less sensitive than screening with ICA and relatives who lack ICA rarely progress to clinical disease. HLA analysis may be useful among antibody-positive relatives to define subgroups with a

low risk of progression to exclude those from future intervention trials.

Mouse and man: multiple genes and multiple auto antigens in the aetiology of Type 1 DM and related autoimmune disorder.

Gottlieb PA, Eisenbarth GS. Journal of Autoimmunity. 1996 (2) :277-81.

Autoimmunity to the pancreatic beta cell appears to be a chronic disorder which in some individuals progresses to overt Type 1 diabetes[1]. Studies of offspring or siblings of patients with Type 1 diabetes (IDDM) and discordant twins who have been followed for over 30 years are shedding new light on the disorder. Recent advances in molecular biological techniques have resulted in out ability to identify normal auto antigens and rapidly develop sensitivity and specific test's to detect beta cell autoimmunity. The ability to cost-effectively screen the general population for diabetes susceptibility is rapidly becoming a reality, Animal models of diabetes such as the non-obese diabetes.

Development and consequences of insulin resistance: lessons from animals with hyper-insulinaemia.

Shafrir E. Diabetes and Metabolism. 1996; 22(21: 122-31).

Studies involving genetically and nutritionally induced diabetes in animals indicate that early hyperinsulinaemia is the causative factor of tissue insulin resistance, leading to compensatory insulin over secretion and pancreatic beta-cell dysfunction. The models for this syndrome, which over in association with obesity (thus termed"diabesity" merely concern either species with a sturdy pancreas, capable of long-lasting oversecretion, or those with labile beta cell which cannot sustain the initial oversecretion due to genomic modifiers enhancing gluco-or lipotoxicity. Examples of the latter are db/db mice mutants and desert gerbils susceptible to overnutrition, i.e. Psammomys obesus (sand rats). The latter also comprise spiny mice (Acomys cahirinus) which do not manifest resistance. They are low insulin secretors and accumulate insulin in beta cells which may disintegrate, producing insulin-deficiency. P obesus is characterised by low insulin-receptor density. On a high energy diet, the capacity of insulin to activate receptor tyrosine kinase (TK) is reduced, concomitant with hyperinsulinaemia. With subsequent hyperglycaemia, a vicious circle of insulinaemia-glycaemia accentuates TK activation failure. This is attributable to multisite phosphorylation, including serine and threonine on the receptor b-subunit, which are inhibitory to TK activity. The compromised TK activation is reversible by diet restriction and normoinsulinaemia restoration. Similar receptor TK malfunction is seen in other animal species a variety of detrimental effects in vitro and in vivo. The beta-cell response to long-lasing stimulation and the receptor mulfunction in diabesity have implications for a similar etiology in human insulin-resistance syndrome and non-insulin-dependent diabetes mellitus, particularly in populations emerging into nutitional abundance. It is postulated that the "thrifty gene" is focused on receptor TK, whose reduced function is the primary phenotypic expression of protracted hyperinsulinaemia.

Candidate genes for insulin resistance.

Moller De, Bjorbaek C, Vidal-Puig A. Diabetes Care. 1996; 19(4) : 396-400.

Insulin resistance confers increased susceptibility to NIDDM, atherosclerotic cardiovascular disease, ovarian hyperandrogenism, and possibly hypertension. Insulin resistance is largely inherited, in rare cases as a monogenic disorder or more commonly as a complex trait. The search for insulin resistance gene relies mainly on two complementary approaches 1) positional cloning using random DNA markers present throughout the genome, and 2) the analysis of specific candidate genes. This report briefly summarizes the candidate gene approach to insulin resistance. Progress related to the analysis of genes encoding molecules that participate in insulin action is reviewed. In addition, the spectrum of potential genetic defects that might contribute to insulin resistance, both at the level of the target cell and secondarily (e.g. obesity genes) is discussed.

Fatty acids and insulin resistance.

Boden G. Diabetes Care. 1996; 19(4) : 394-5

We have demonstrated that physiological elevation in plasma free fatty acids concentration inhibit insulin-stimulated glucose uptake in a dose-dependent manner control subjects and in patients with NIDDM. Two possible mechanisms were identified: 1) a fat-related inhibition of glucose transport or phosphorylation that appeared after 3-4 hr of fat infusion and 2) a decrease in muscle glycogen synthase activity that appeared after 4-6 hr of fat infusion. We conclude that elevations of plasma FFAs caused insulin resistance and hence may play a significant role in the pathogenesis of insulin resistance in obesity and NIDDM.

Glucokinase mutations, insulin secretion, and diabetes mellitus.

Bell GI, Pilkis SJ, Weber IT, Polonsky KS. Annual Review of Physiology. 1996;58 : 171-86.

The glycolytic enzyme glucokinase plays a role in glucose sensing by the insulin-secreting pancreatic beta-cells, and mutations in the gene encoding this enzyme are common cause of maturity-onset diabetes mellitus characterised by autosomal-dominant inheritance and onset before 25 years of age. Twenty-eight different mutations in this gene have been identified in subjects with MODY. Clinical studies have shown that subject with MODY due to mutations in glucokinase have elevated fasting and postprandial glucose levels with normal first-phase insulin secretary responses to intravenous glucose and insulin secretion rate obtained during graded intravenous glucose infusions was shifted to the right in subjects with glucokinase mutations, indicating decreased sensitivity to glucose. In normal subjects, the beta-cell was most sensitive to an increase in glucose concentration between 5.5 and 6.0 MM, whereas in patients with glucokinase is an important component of the glucose-sensing mechanism of the beta-cell.

The relationship between cow's milk exposure and Type 1 diabetes.

Gerstein HC, VanderMeulen J. Diabetic Medicine. 1996; 13(1) 23-97.

Environmental factors are important for the development of Type 1 diabetes mellitus. They likely account for charges in the incidence of this disease over time, as well as the well-documented differences in incidence in ethnically and genetically similar people living in different parts of the

world. There is a relationship between early cow's milk exposure and the development of Type 1 diabetes in humans, and between early cow's milk exposure and the development of autoimmune diabetes in rodent models of type 1 diabetes. Moreover, some immunological studies have suggested a possible mechanism whereby exposure to cow's milk protein could result in beta-cell directed autoimmunity and subsequent Type 1 diabetes. Although provocative, the existence of alternative explanations for these epidemiological and biological observations, suggest that the data are insufficient to conclude that the observed associations represent causal relationships or to mandate changes in recommendations for infant feeding. The question of whether or not avoidance of cow's milk protein in infancy will prevent. Type 1 diabetes can, however, be tested in an international randomized clinical trial of infant diets, which is currently under review.

Lilly lecture 1995. Glucose transport pivotal step in insulin action.

Kahn BB. Diabetes 1996; 45(11) : 1644-54.

The effect of insulin to acutely stimulate glucose uptake into muscle and adipose tissue is essential for normal glucose homeostatasis. The GLUT4 glucose transporter is a major mediator of this action, and insulin recruits GLUT4 from an intracellular pool to the plasma membrane. An important pathologic feature of obesity, NIDDM, and to a lesser extent IDDM is resistance to insulin-stimulated glucose uptake. Investigations of the mechanisms have revealed tissue-specific regulation of GLUT4 with decreased gene expression in adipose cells but not in skeletal muscle. This has led to the hypothesis that alterations in the trafficking of the GlUT4 vesicle or in the exposure or activation of the Glut4 transporter may cause insulin resistance in skeletal muscle in obesity and diabetes. Exercise training increases GLUT4 expression in muscle in association with enhanced glucose tolerance in vivo. Transgenic mice have been created to investigate other approaches to improve insulin action on glucose transport. Over expression of GLUT4 in adiposities of transgenic mice result in increased GULT4 on the plasma membrane in the absence of insulin and increases insulin sensitivity in vitro and vivo. Thus, glucose transport is a pivotal step in whole-body insulin action. Strategies to increase the number of GLUT4 transporter that are functionally inserted in the plasma membrane in muscle and adiposities may lead to new therapies to treat or prevent NIDDM.

Role of the Maillard reaction in diabetes mellitus and diseases of aging.

Thorpe SR, Baynes JW. Drugs & aging. 1996; 9(2) : 69-77.

Advanced glucation and –products (AGEs) are formed by spontaneous chemical reactions between carbohydrates and tissue proteins. The accumulation of AGEs in long-lived proteins contributes to the age-related increase in brown colour, flourescence and insolubilisation of lens crystallins and to the gradual cross linking and decrease in elasticity of connective tissue cillagens with age. These nonenzymatic reactions, known collectively as Maillard or browning reactions, are also implicated in the development of pathophysiology in age-related disease such as diabetes mellitus, atherosclerosis, alzheimer's disease. And in dialysis-related amyloidosis. Oxygen and oxidation reactions accelerates Maillard reacrtions in vitro , and the structurally characterised AGEs that accumulates in long-lived tissue proteins are in fact gluoxidation products, formed by sequential glucation and oxidation reactions. In addition to their immediate effects on protein structure and function, AGEs also induce oxidative stress, leading to inflammation and propagation of tissue damage. Thus, glucation of protein , formation of AGEs and resultant oxidative stress which accelerate Maillard reactions, can initiate an autocatalytic cycle of deleterious reactions in tissues. Pharmacological inhibition of the Maillard reaction should improve the prognosis for a broad range of age-related diseases. The role of oxidative stress as a catalyst and the consequences of Maillard reaction damage in tissues suggests that antioxidant therapy may also retard the progression of age-related pathology.

COMPLICATIONS – GENERAL

Triglycerid – rich lipoproteins in non-insulin-dependent diabetes mellitus; post-prandial metabolism and relation to premature atherosclerosis.

De Man FH, Cabezas MC, Van Barlingen HH, Erkelens DW, De Bruin TW. European Journal of Clinical Investigation. 1996;26(2) : 89-108.

Non-insulin-dependent diabetes mellitus is frequently associated with premature atherosclerosis. Abnormalities in lipid and lipoprotein metabolism contribute to the increased risk of coronary heart disease. One of the most common lipid abnormalities in non-insulin-dependent diabetes mellitus is hypertriglyceridaemia. In the present paper, the authors review the metabolism of triglyceride – rich lipoproteins, with special emphasis on the post-prandial state. Several studies have demonstrated that levels of atherogenic post-prandial lipoproteins are increased in patients with non-insulin-dependent diabetes mellitus. An increased supply of glucose and free fatty acids contributes to overproduction of very low-density lipoproteins increasing the burden of triglyceride –rich lipoproteins on the common lipolytic pathway at the level of lipoprotein lipase. Low lipoprotein lipase activity and increased amounts of lipolysis –inhibiting free fatty acids further impair lipolysis of post-prandial lipoproteins. The clearances of atherogenic remnants is also delayed in non-insulin-dependent diabetes mellitus. There is evidence that a relative hepatic removal defect exists. Secondary to impaired remnant-receptor interaction and increased competition with very low density lipoprotein remnants. Correction of the increased post-prandial glycaemia in non-insulin-dependent diabetes mellitus is advisable, as if it may contribute to attenuation of the risk on premature atherosclerosis. When dietary measures and hypoglycaemic agents have failed to achieve acceptable lipid levels, lipid-lowering drugs should be advised. Fabric acids and hydroxymethyl-glutaryl coenzyme A (HMG CoA) reductase inhibitors are the drugs of choice.

Advanced glycation end-products and atherosclerosis.

Vlassara H. Annals of Medicine. 1996; 28(5) : 419-26.

The late rearrangements of the covalent non-enzymatic modification of proteins by glucose, called advanced glycation end-products (AGEs), have been shown to accumulate in diabetic and ageing tissue. AGEs elicit a wide range of cell-mediated responses leading to vascular dysfunction, matrix expansion and athero and glomerulosclerosis. Cellular responses are thought to be largely induced through and AGE-specific cell-surface receptor complex (AGEs). Interaction of AGE-modified proteins with these cells may serve diverse purposes, including disposal pf semescemt AGE-modified

molecules and initiation of tissue repair and protein turnover. In humans, the normal renal clearance rate for of the AGE-degradation products found in serum., Age peptides (AGEp), correlates inversely with renal creatinine clearance rate. Of note, circulating AGEp include reactive intermediates which readily attach covalently to either insoluble matrix collagen on serum proteins, e.g. low density lipoproteins (LDL), to form AGEp collagen and AGEp-LDL. Consistent with this diabetic and nondiabetic patients with renal failure (a group highly susceptible to accelerated atherosclerosis) exhibit markedly elevated AGE-modified serum LDL. In summary, in addition to glucose-derived AGEs, the endogenously produced degradation products, AGE peptides, can amplify tissue damage and thus account as distinct toxins. The effects may particularly accelerate glucose toxicity in certain individual that are genetically susceptible to diabetic renal extrarenal disease.

Will correction of dyslipoproteinaemia reduce coronary heart disease risk in patients with non-insulin-dependent diabetes? Need for trial evidence.

Pyorala K, Steiner G. Annals of Medicine. 1996 : 28(4) : 357-62

The incidence of atherosclerotic vascular disease is greatly increased in patients with non-insulin-dependent diabetes (NIDDM). The most frequent lipoprotein abnormalities in this type of diabetes are an increase in triglyceride-rich lipoproteins and a decrease in high-density lipoproteins. Hypertriglyceridaemia appears to be a stronger coronary heart disease risk factor in patients with NIDDM than in nondiabetic subjects. Plasma total and low-density lipoprotein cholesterol levels in NiDDM patients and nondiabetic , subjects do not differ. Hypercholesterolaemia is however, as powerful a predictor of coronary heart disease risk in diabetic patients as in nondiabetic subjects. In spite of this knowledge, there is to date no solid evidence to indicate whether correction of dyslipoproteinaemia in order to reduce coronary heart disease risk in patients with NIDDM is more equally, or less beneficial than it is in nondiabetic subjects. The only available data comes from the post-hoc subgroup analyses of the Helsinki Heart Study and the Scandinavian Simvastatin Survival Study (4S). Other trials including patients with diabetes are in progress. Only one intervention trial (currently in its treatment phase), the Diabetes Atherosclerosis Intervention Study (DAIS), is specifically designed to examine the lipid hypothesis in patients with NIDDM.

Diabetic neuropathy in elderly patients. What can be done?

Belmin J, Valensi P. Drugs and Aging. 1996;8(6) : 416-29

The prevalence of diabetes mellitus increases markedly with age. Furthermore, advancing age is a strong risk factor for diabetic neuropathy, independent of the duration of diabetes mellitus and glyucaemic control.

Several biological changes occurring during the aging process may account for the facilitating effect of age on diabetic neuropathy. These include an increase in the production of advanced glycosylation end-products (AGEs), a defect in the polyolpathway, nerve vascular alterations and impaired resistance to oxidative stress. The clinical diagnosis of diabetic neuropathy is often difficult in elderly patients. The relationship between symptoms and neuropathy and that between neuropathy and diabetes mellitus are more difficult to ascertain in elderly patients due to age-related changes in the peripheral and autonomic nervous system and associated disease frequently encountered in this population. Diagnosis of diabetic neuropathy is based on nerve conduction studies, vibratory perception threshold determination and assessment of autonomic functions. For most of these tests, reference values are markedly influenced by age and their interpretation should use careful age-adjusted reference intervals. Identification of peripheral diabetic neuropathy indicates a high risk of food complications, such a\ulcers and gangrene, often resulting in amputation , whereas cardiovascular autonomic neuropathy is associated with an increased rash of postural hypotension and coronary events. All these risks increase markedly with aging. Therapeutic trials in elderly patients with diabetic neuropathy are lacking. Treatment of diabetic neuropathy consists of achievement of better glycaemic control and treatment of symptoms related to neuropathy . Specific treatments capable of preventing or curing neuropathy are under investigation. The omterestomg results in patients with diabetes mellitus. Other metabolic approaches, like antioxidants and gamma-linolenic acid, seem promising. Clinical complications of diabetic neuropathy in the elderly are often severe. Early detection is required, since at the present time a preventive approach is the most effective way to avoid or postpone debilitating complications. More research is needed to make effective curative treatments of diabetic neuropathy available.

Current issues in treating the hypertensive patient with diabetes: focus on diabetic nephropathy.

Cziraky MJ, Mehra IV, Wilson MD, Bakris GL. Annals of Pharmacotherapy. 1996; 30(7-8) : 791-801.

OBJECTIVE: To review the pathophysiology of hypertension and complications in patients with diabetes mellitus, specifically focusing on diabetic nephropathy, to evaluate the current clinical literature regarding the appropriate management of hypertension in this patient group, and to offer treatment recommendations.

DATA SOURCES : A MEDLINE search of applicable English-language clinical studies, abstracts, and review articles pertaining to hypertension, diabetes and diabetic nephropathy.

STUDY SELECTION : Relevant studies on humans, examining hypertension, diabetes and diabetic nephropathy and the effects of drug therapy on these interrelated disease states.

DATA SYNTHESIS : Pathophysiology of hypertension in the patient with diabetes mellitus and the pathophysiology of diabetic nephropathy are discussed. Studies evaluating the therapeutic effect of certain antihypertensive agents, their effect on glucose control and insulin sensitivity and the progression of diabetic nephropathy are reviewed. Recommendations on the treatment of the patient with diabetes and hypertension are given.

CONCLUSIONS: The treatment of the patient with diabetes mellitus and hypertension remains complex. Intervention in this patient populations should not only decrease blood pressure, but also reduce the risk of both vascular and nonvascular complications. Data support the theory that by controlling a patient's hypertension, the incidence of albuminuria and the progression of diabetic nephropathy are slowed. Additionally, data are available to support the use of

pharmacologic interventions in nonhypertensive patients with diabetes and proteinuria. Drug therapies that have produced reductions in proteinuria in this patient population include angiotensin-converting enzyme inhibitors and non-dihydropyridine calcium-channel antagonists. Additional information is needed to better differentiate the individual agents within each of the antihypertensive drug classes regarding their individual effects on the patient with diabetes and hypertension, specifically effect on diabetic nephropathy and its progression to end renal disease.

Dyslipidemia in diabetes mellitus.

Yoshino G, Hirano T. Kazumi T. Diabetes Research and Clinical Practice. 1996;33(1) : 1-14.

Patients with diabetes mellitus have a higher rate of mortality than the general population. This higher mortality may be attributed mainly to cardiovascular disease. A high prevalence of dyslipidemia in diabetics can be one of the reasons for this. The most commonly recognized lipid abnormality in non-insulin-dependent diabetics (NIDDM) is hyper-triglyceridemia, which is known to be an independent risk factor for coronary heart disease in diabetics. Hypertriglyceridaemia can be produced by two mechanisms, increased synthesis of very low-density lipoprotein (VLDL), triglyceride and removal defect of always stimulates hepatic VLDL secretion but it is generally accepted that insulin deficiency results in an impairment of plasma triglyceride clearance. Considerable attention has recently been focused on the atherogenecity of postprandial hyperlipidemia, remnant lipoproteins, small, dense LDL, lipoprotein (a) [Lp(a)] and isolated hypoalphalipoproteinemia in NIDDM subjects. Several reports suggested that these atherogenic lipoprotein abnormalities are present in NIDDMs even if they are apparently normolipidemic. Association of visceral fat obesity, insulin resistance and nephropathy may aggravate the atherogenic lipoprotein profile. Therefore, we propose here that plasma lipid levels of diabetic subjects must be more strictly controlled than for the non-diabetic population in order to avoid an increased risk for coronary heart disease. If they are obese or associated with insulin resistance or nephropathy, these conditions should be carefully controlled.

COMPLICATIONS – RENAL

Macroalbuminuria in essential hypertension and diabetes mellitus.

Parving HH. Journal of Hypertension – 1996; 14(2) : s89-93-4

Definition : Macroalbuminuria is defined as abnormally elevated urinary albumin excretion below the level of clinical albuminuria (albustix). This represents a urinary alnumin excretion rate of 20-200 micrograms/min., equal to 30-300 mg/24 h. Urinary albumin excretion can vary as much as 40% with natural fluctuations, and so several tests should be done. Inexpensive radioimmunoassay, enzyme-linked immunosorbent assays or immunoturbidimetric assays are now routine in many clinical laboratories.

Prevalence: The prevalence of macroalbuminuria in essential hypertension and diabetes is about the same; 25% (range 14-31) and 20% (9-27), respectively.

Mechanism: Increased transglomerular passage is the major mechanism of macroalbuminuria in both the above-mentioned conditions increased hydraulic glomerular capillary pressure, and glomerular lesions probably both contribute. Macroalbuminuria is highly predictive of the development of diabetic nephropathy but the predictive power in relation to hypertensive nephropathy remains to be established. However, in both conditions macroalbuminuria is associated with an increased risk of retinopathy, left ventricular hypertrophy, fatal and non-fatal car-diovascular disease and all-cause mortality. The following mechanisms have been suggested as a link between macroalbuminuria and these finding; endothelial dysfunction, insulin resistance, and these finding; endothelial dysfunction, insulin resistance, hyperinsulinaemia, dyslipoproteinaemia and a procoagulant state.

Effect of antihypertensive treatment: Blood pressure lowering reduces microalbuminuria in essential hypertension and in diabetes millitus. Long-term studies in diabetes suggest that angiotensin converting enzyme inhibitors postpone, and may even prevent, progession to overt clinical naphropathy in noromotensive diabetic patients with persistent micoralbuminuria. So for, their have been no long-term comparative trials on the beneficial effects of different antihypertensive trugs in hypertensive patients with microalbuminuria.

Differing effects of antihypertensive agents on urinary albumin excretion.

Weir MR. American Journal of Nephrology 1996;16(3) : 237-45.

Increased urinary albumin excretion is a good predictor of future progression of renal disease in patients with both insulin-dependent and non-insulin-dependent diabetes mellitus. In addition, it is an independent predictor of cardiovascular morbidity and mortality in patients with essential hypertension and normal renal functions, remains to be determined. In patients with diabetic renal disease urinary albumin excretion is a good predictor for the future development of renal injury. Some antihypertensive agents are demonstrated abilities to reduce urinary albumin excretion either with or without a reduction in systemic arterial pressure. Whether abilities of these drugs to protect renal functions is related to their antihypertensive effects or antiproteinuric effects, or both, is unknown. This review will explore the influence of different antihypertensive agents on urinary albumin excretion in patients with and without essential hypertension, as well as in patients with non-diabetic antidiabetic renal disease.

Macroalbuminuria in patients with NIDDM : an overview

Alzaid AA Diabetes Care. 1996; 19(1) : 79-89.

We have come a long way in our understanding of the epideminology, pathophysiology, and clinical significance of albuminuria in patients with NIDDM. However, substantial gaps remain to be defined. NIDDM nephropathy is a serious and increasingly burdensome disease for both the diabetic individual and the society at large. Onset of macroalbuminuria, an early but common manifestation of NIDDM nephropathy, marks an ominous turn for the NIDDM patient, in whom its development forecasts a grave cardiovascular outcome. Interception of albuminuria with antihypertensive agents such as ACE inhibitors in otherwise healthy NIDDM subjects holds a significant promise but must first await further investigation.

TREATEMENT

Pharmacokinetic basis for the safety of glimepiride in risk groups of NIDDM patients.

Rosenkranz D. Hormone and Metabolic Research, 1996; 28(9) : 434-9.

The pharmacokinetics of the sulfonylurea, glimepiride, in risk groups of NIDDM patients are reviewed with regard to pharmacokinetic-effect relationships. A variety of factors, such as regulatory processes, glucose absorption, insulin sensitivity, might prevent the definition of clear concentration – effect relationship for abifonglureas. However, when these processes are minimized, as with the glucose clamp technique such relationship can be defined. This is true for glibenclamide or glimepiride, for which saturation of effect is apparent in the upper therapeutic does range in healthy subjects. However, pharmocokinetic – pharmacodynamic relationships are less readily defined during long-term treatment of NIDDM patients. In kidney or liver disease, the hypoglycaemic effect – of sulfonylurea can be increased and prolonged, mainly due to a decrease in insulin metabolism or of hepatic glucose output; the risk of hypoglycemia is increased. The pharmacokinetics of most sulfonylurea have not been well characterised in patients with kidney of liver disease. Generally, sulfonylurea are eliminated by renal excretion of metabolites, some of which have similar pharmacological activity to the parent drug e.g. glibenclamide, chlorpromazine, tolbutamide. In renal disease elimination of these metabolitic can be impaired. In 31 NIDDM patients with kidney disease, elimination of unchanged glimepiride was greater in patients with more severe renal disease, probably due to a decrease the plasma protein-bound fraction. Elimination of the really excreted metabolites was also impaired in the same group of patients. Twelve of 16 NIDDM patients with kidney disease who continued glimepiride treatment for 3 months maintained fasting blood glucose levels of less than 9.99 mmol/1 at a daily dose of 1-6 mg, the typical dose range for patients with normal renal function, Pharmacokinetics of glimepiride were similar to those of healthy volunteers. In conclusion, pharmacokinetics, pharmacodynamic and their relationship can be defined for glimepiride under controlled conditions. Such information is lacking for many commonly used sulfonylurea in risk group NIDDM of glimepiride are altered in renal disease but may not be seriously affected in patients with liver disease.

Effects of troglitazone on insulin sensitivity.

Henry RR. Diabetic Medicine. 1996; 13 : S148-50

Studies to date confirm that troglitazone has therapeutic benefits to NIDDM and can normalize IGT in those individuals at increased risk of developing NIDDM. Hyperinsulinaemia is reduced by such treatment in association with reduced insulin resistance and there are favorable effects on blood pressure with troglitazone therapy as well. Since insulin resistance and hyperinsulinaemia are usually present in obesity and impaired glucose tolerance (IGT), troglitazone may be useful in preventing the development of NIDDM in these susceptible populations.

The frequency of sever hypoglycaemia in children with insulin-dependent diabetes mellitus.

Clark WL, Gonder-Frederick L, Cox DJ. Hormone Research 1996; 45 Suppl 1 : 48-52.

The literature contains numerous reports of the frequency of sever hypoglycaemia in childhood insulin-dependent diabetes mellitus. Unfortunately, most of these data have been collected in such a manner as to make comparisons between them difficult. Most reports have used small, well-defined populations of children who were participants in larger, complex, clinical studies. Additional difficulties are encountered in the standardisation of the definition of sever hypoglycaemia. Some studies have required that the child lose consciousness while other also included children who required assistance with treatment. Even when studies clearly define the representative nature of their patient population and include universally acceptable criteria for identifying a severe hypoglycaemic episode, the frequency of severe hypoglycaemia must be qualified. Severe hypoglycaemia is generated by a series of complex biological, psychological, and behavioral process. Its frequency must be viewed not as a fixed value, but rather as a dynamic dependent variable.

Insulin treatment in elderly patients with non-insulin-dependent diabetes mellitus. A double-edge sword?

Niskanen L. Drugs and Aging. 1996; 8(3) : 183-92

Elderly patients with non-insulin-dependent (Type 2) diabetes mellitus (NIDDM) form one of the largest sectors of the diabetic population. Emerging evidence indicates that hyperglycaemia is associated not just with an increased risk of macro vascular complications but also with microvascular disease which remains the main cause of excess mortality in people with NIDDM. The treatment of hyperglycaemia in patients with NIDDM is notoriously difficult when diet, exercise and judicious use of oral antihyperglycaemic agents fail to maintain acceptable metabolic control. The treatment of hyperglycaemia in elderly patients is further hampered by age- or disease-related co-morbidity. Insulin therapy can ameliorate many metabolic abnormalities of NIDDM, with consequent reduction of hyperglycaemia. Moreover, insulin treatment induces antiatherogenic changes in serum lipids and lipoproteins and probably enhances general well-being. However, insulin therapy is associated with bodyweight gain and an increased risk of hypoglycaemia. An unresolved question is the relationship of exogenous insulin therapy to the development of cardiovascular disease. This most promising target in this respect has been the control of glucose overproduction long-acting insulin with or without oral antihyperglycaemic drugs. Intensive insulin therapy does not seem to have clear-cut benefits in elderly patients and can be hazardous. However, we can put regimens and therefore clinicians should use sound clinical judgement in choosing the appropriate therapy for an individual patient with NIDDM. Although we do not know at present whether we can, by our current modes of treatment, lower the frequency of vascular diseases, therapeutic nihilism, even in elderly patients with NIDDM, is outmoded.

Metformin : an antihyperglycaemic agent for treatment of Type 2 diabetes.

Melchior WR, Jaber LA. Annals of Pharmacotherapy. 1996;30(2) : 158-64.

OBJECTIVE : To review the comparative efficacy of metformin, sulfonylureas, and insulin in the treatment of patients with Type 2 diabetes.

DATA SOURCES : Articles were identified by a MEDLINE search of articles from 1966 to 1994, using the terms

metformin, sulfonylurea, chorpropamide, glipizide, glyburide, tolazamide, tolbutamide and insulin, published in English, French or German. Articles also were identified from bibliographies of pertinent articles.

DATA EXTRACTION: Effects of metformin therapy metabolic and cardiovascular risk factors were abstracted: weight, blood pressure, total and low-density lipoprotein cholesterol, triglycerides, fasting and postprandial glucose and glycosylated hemoglobin.

DATA SYNTHESIS : Metroymin is an antihyperglycaemic agent with a mean bioavailablity of 50-60%. It is eliminated primarily by renal filtration and secreation and has a half-life of approximately 6 hours in a patients with Type 2 diabetes. Although the half-life of metformin is prolonged in patients with renal impairment, no specific dosage adjustments have been recommended. This agents has no effect in the absences of insulin. Metformin is as effective as the sulfonylureas in treating patients with Type 2 diabetes and has a more prominent postprandial effect than the sulfonylureas or insulin. When combined with a sulfonylurea, metformin has been shown to exert antihyperglycaemic effects in addition to the sulfonylurea with which it is combined. Metformin decreases the elimination of metformin; therefore, the manufacturer recommends a reduced metformin dosage when these agendas are combined. The most frequently reported adverse effects of metformin are gastrointestinal in nature (diarrhoea, nausea, abdominal pain, and metallic taste, in decreasing order). Metformin has been used in Canada, Great Britain and the rest of Europe for more then 30 years and was approved for use in the US in December 1994.

CONCLUSIONS : Three trials comprise the Food and Drug Administration approval database (one foreign). Metformin will be most useful in managing patients with poorly controlled postprandial hyperglycaemia, as its postprandial effect is much greater than that of the sulfonylureas. In contrast, sulfonylureas or insulin are more effective for managing patients with poorly controlled fasting hyperglycaemia. Metformin should be considered a first-line agent, particularly in obese or hyperlipidemic patients.

Pancreas transplantation: a treatment option for insulin-de-pendent diabetes mellitus.

Larsen JL, Stratta RJ. Diabetes & Metabolism. 1996; 22(2) : 139-46.

The success with which pancreas trasplantation normalizes glucose concentration in patients with Type 1 diabetes mellitus has made it an important treatment option. Most pancreas transplant operations are performed in combination with a kidney transplant and neithere over all patient survival nor renal graft survival is compromised by the addition of a pancreas graft. Pancreas after kidney transplantation and isolated pancreas transplantation are performed less frequently since the pancreas graft success rate remains lower in these operations compared to combined pancreas-kidney transplantation. Pancreas transplantation improves the quality of life and stabilizes or reverses some diabetic microvascular complications, but its impact on the risk of atherosclerotic vascular disease is still unknown,. The relative risks and benefits of pancreas transplantation need to be carefully assessed for each candidate through a through screening process, regardless of which type of graft is being considered. However, patient counseling and selection will be greatly aided by further research assessing the long-term risks and benefits of all types of pancreas transplantation. Pancreas transplantation will probably remain an important treatment option for some patient with Type 1 diabetes mellitus until this disease can either be successfully prevented or alternative treatment strategies are developed that provide equal glycaemic control with less or no associated immunosuppression.

Sulphonylurea treatment of NIDDM patients with cardiovascular disease : mixed blessing?

Lelbowitz G, Cerasi E. Diabetologia 1996; 39(5) : 503 –14.

Non-insulin dependent diabetic (NIDDM) patients show a high incident of cardiovascular disease, with greater risk of recurrent myocardial infarction and less favorable clinical outcome than non-diabetic patients. The majority of NIDDM patients are treated Sulphonylurea (SU) derivatives. In the 1970's the university group diabetes program concluded that tolbutamide treatment caused increased cardiovascular mortality. The study, which led to curtailment of oral antidiabetic treatment in the USA, was received with scepticism in Europe. Later criticism of its methodology reduced the impact of the study ; however the question of the safety of SU in NIDDM patients with cardiovascular disease has been reopened in the face of new experimental data. The heart and vascular tissues do have prerequisites for SU actions, i.e. SU receptor and ATP-dependent K+ (K+ATP) channels. These channels play an important role in the protection of the myocardium against ischaemia-reperfusion damage , and their closure by SU could lead to reduction of post-infarct arrhythmias; the drug has also beer claimed to improve various atherosclerosis risk factors. The evidence for these beneficial effect of SU is also reviewed. We look at the major difficulties that hamper transfer of information from experimental studies to clinical decisions making :a) The affinity of SU for heart K+ATP channels is orders of magnitude lower than for beta-cell channels, it is reasonable to expect in vivo cardiac effects with therapeutic 'pancreatic' SU doses? B) Most studies utilized high doses of acutely administered SU; are effects similar in the chronic steady-state of the SU-treated diabetic patient? C) convincing SU effects have been demonstrated in acutely induced ischaemia? d) Ischaemia and modification of K+ATP channel activity induce complex events, some with opposing effects; what is the net result of SU action and do differently SU derivatives lead to different outcomes? E) In the chronic (and the clinically relevant) situation, how can direct (delereropis pr nemeficial) SU effects be spared from beneficial effects mediated by the metabolic action of the drug? Only large prospective clinical studies making use of advanced technology for assessment of cardiovascular functions, can answer these questions. Millions of NIDDM patients are treated with SU derivatives; many are in the age group where cardiovascular risk are extremely high. The question of whether WU derivatives are beneficial or deleterious for these patients much finally be settle unequivocally.

MANAGEMENT

Diabetes mellitus and traffic incidents.

Veneman TF, Netherlands Journal of Medicine. 1996; 48(1) : 24-8.

At present , no clear evidence is available that, as a group patients with diabetes mellitus are at increased risk of becoming involved in traffic accidents. However, accidents as

a consequence of hypoglycaemia do occur and the percentage of accidents in patients with insulin-dependent diabetes mellitus resulting from hypoglycaemia has been estimated at 5.2%. A recent study using computer-stimulation technique showed that during moderate hypoglycaemia (2.6 mol/l) driving performance deteriorated significantly.. Only one third of these subject were aware of it. Surprisingly, only half of them stated that they would not drive under such circumstances. Unawareness of hypoglycaemia forms a major risk factor. With the present efforts to improve metabolic control with intensive insulin therapies the incidence of unawareness and therefore of sever hypoglycaemic reactions is increasing. With intensive education hypoglycaemic reactions in\s increasing. With intensive education programs such as blood glucose awareness training (BGAT), introduced by Cox et al patients learn to estimate blood glucose concentrations and specifically to detect hypoglycaemia at an early stage. The first studies so that after BGAT, the incidence of hypoglycaemia decreases. Interestingly, after BGAT, patients were less frequently involved in traffic accidents (crash rates per 1000,000 miles 6.8 vs. 29.8 p=0.01). Therefore although many questions remain to be answered, BG At has proved beneficial in reducing hypoglycaemic episodes and in reducing traffic accidents.

Glucose monitoring as a guide to diabetes management. Critical subject reivew.

Koch B. Canadian Family Physician, 1996; 42 : 1142-6.

PURPOSE : To encourage a balanced approach to blood glucose monitoring in diabetes by a critical review of the history, power and cost of glucose testing.

DATA SOURCES : The Cambridge Data Base was searched and was supplemented by a random review of other relevant sources, including textbooks, company pamphlets and laboratory manuals.

STUDY SELECTION: Keywords used were "glucosuria diagnosis, "blood glucose self-monitoring," "glycosylated hemoglobin" and "fructosamine" for the 10 year period ending 1992, restricted to English language and human.

DATA EXTRACTION : About 200 titles were retrieved and reviewed according to the author’s judgment of relevance.

FINDINGS : "Snapshot test" (venous and capillary blood glucose) and "memory tests" (urine glucose, gyrated hemoglobin fractions and fructosamine) must be employed according to individual patients treatment goals, Day-to-day metabolic guidance is facilitated by capillary blood glucose testing for patients receiving insulin and by urine glucose testing for others. Capillary blood glucose testing is mandatory in cases of hypoglycaemia unawareness (inability to sense hypoglycaemia because of neuropathy) but is not a substitute for a knowledge of clinical hypoglycaemia self care. Criteria by reason (clinical judgement and cost effectiveness) must be separated from criteria by emotion (preoccupation with technology and marketing). No randomized studies show that any of these tests consistently improve clinical outcome. Optimal metabolic control and cost savings can be expected from a rational selection of tests.