Abstract Service

ETIOPATHOLOGY

Reversible insulin resistance in non-insulin-dependent diabetes mellitus.

Karam JH. Hormone and Metabolic Research 1996; 28(9) : 440-4.

Insulin resistance is a major component of non-insulin-dependent diabetes mellitus (NIDDM). While a genetic contribution is likely, as yet none of several proposed candidate genes have been incriminated in the typically obese patient with NIDDM to explain their insulin resistance. Accordingly, this review focuses on some recent advances in understanding three acquired factors contributing to insulin resistance: visceral obesity, glucotoxicity and lipotoxicity. Newer computerized tomography scans allow quantitation of fat accumulating in visceral organs including the mesentery and omentum. This visceral fat relates much more to the insulin resistance syndrome than does subcutaneous fat. Moreover, exercise, as performed by active Sumo wrestlers, is associated with low visceral fat, absent hyperglycemia and absent dyslipidaemia despite massive subcutaneous obesity. It remains to be seen whether exercise programs more moderate than Sumo wrestling will also mobilise visceral fat. A new metabolic pathway has recently been described whereby hexosaminea are formed by an increased flux of glucose into fat and muscle. These hexosamine products appear to explain how glucotoxicity results in insulin resistance. They act as a negative feedback system to limit further glucose transport by insulin target tissue during hyperglycemia. Lipotoxicity has previously been implicated in insulin resistance by its inhibitory effect on glucose uptake by muscle because of the Randle-fatty acid cycle. Recently the role of elevated fatty acids in producing "hepatic" resistance to insulin in NIDDM has also been documented, but the site of insulin resistance may be the fat cell rather than the hepatocyte. Therapy consists of mainly hygenic measures including caloric restriction and exercise, which can reverse three of these acquired forms of insulin resistance. In addition, pharmacologic measures to reduce hyperglycemia can reduce the glucotoxicity and liptoxicity. The use of insulin-sparing antihyperglycaemia drugs may be particularly useful in the insulin-resistant patient to avoid weight gain while correcting the hyperglycemia.

In vivo glucose metabolism, insulin secretion and insulin action in Europids with non insulin dependent diabetes mellitus (NIDDM) and their first-degree relatives.

Beck-Nielsen H, Henriksen JE, Alford F, Hother-Nielson O. Diabetic Medicine 1996; 13(9) Suppl (6) : S78-84.

In this review we will mainly concentrate on the most common form of NIDDM in Europe, namely the form linked to overweight, arterial hypertension dyslipoproteinaemia and coronary heart disease (CHD) – the Insulin Resistance Syndrome (IRS). This form of NIDDM seems to be growing epidemically world wide following the industrial growth or the 'cocacolanization', as it has been mentioned. Around 2-3% of the population in Europe suffers from this disease, but for subjects beyond 60 years of age the prevalence is 5-20%. Thus, we face an enormous economical, social and humanitarian challenge. Therefore it is important to continue the research on aetiology and pathologysiology of this syndrome. The results of treatment of NIDDM patients (often started at 60 years of age) have been rather disappointing; even properly treated NIDDM patients develop substantial complications, especially macroangiopathy. Coronary heart disease is the main cause of death in these patients and the overall mortality rate in NIDDM patients is 3-4 times higher than in comparable non diabetic-subjects. Furthermore, several complications may already be present at the diagnosis of the disease, which indicate that macroangiopathy may not be secondary to the diabetic state itself, but rather a part of the NIDDM phenotype. Based on these finding it seems obvious that the IRS must be diagnosed in the prediabetic states before macrogiopathy has started or reached a clinically manifest level. In this review, therefore, we will discuss the metabolic background of NIDDM and especially focus on the pathphysiological mechanisms leading to hyperglycemia, i.e. alterations in glucose effectiveness, insulin action and insulin secretion in prediabetic states.

Towards an integrated phenotype in pre-NIDDM.

Bergman RN. Watanable R. Rebrin K, Ader M, Steil G. Diabetic Medicine 1996; 13(9 Suppl 6) : 867-77.

The research for the genetic basis of NIDDM has magnified the need for an efficient representation of the pre-NIDDM phenotype. The overall goal is to relate specific mutations on the genome to specific changes in physiologic functions, which lead to NIDDM. Unfortunately, there is still not a clear understanding of the molecular cause of NIDDM in most individuals. Therefore, one must take an alternative approach: to express in quantitative terms the various tissue processes, which determine the ability to regulate the blood glucose in fasting and after carbohydrate administration. A minimal list of such processes includes the provision of glucose by the liver, insulin sensitivity, and insulin secretion and glucose effectiveness. The latter function is the ability of glucose per se to enhance glucose disappearance from blood, independent of a dynamic insulin response. Approaches to measuring the list of functions, which determine the glucose tolerance, are reviewed, they include the minimal model method, which quantitates insulin sensitivity (S1) and glucose effectiveness (SG), and a combined model approach, which measures insulin secretion. These methods are being developed for large populations. Such a development is important for elucidating the causes of reduced glucose tolerance in populations, and examining the relation between such causes and outcomes including diabetes and cardiovascular disease. Of particular importance for diabetes development is the characteristic hyperbolic relationship between insulin secretion and insulin action. This relationship, the "hyperbolic law of glucose tolerance" indicates that insulin secretion can only be assessed in terms of the ambient degree of insulin sensitivity. By applying this principle, it is clear that latent pancreatic islet-cell dysfunction has been underestimated, and may be significant even in subjects with impaired glucose tolerance. Finally, new explorations of insulin control of liver glucose output indicate that this process may be under the control of free fatty acids. The latter realisation indicates that the insulin effect on lipolysis is what is critical for determination of glucose output in the fasting state, and that insulin resistance at the level of the adipocyte may determine the extent of fasting hyperglycemia, and may be an important factor in the overall phenotype in prediabetic and NIDDM individuals.

Diabetes mellitus and impaired pancreatic beta-cell proliferation.

Sjoholm A. Journal of Internal Medicine 1996; 239(3) : 211-20.

The factors that normally regulate the proliferation of the insulin-producing pancreatic beta-cell largely remain elusive

although several factors have been identified that influence beta-cell growth in vitro. The adult beta-cell is normally virtually quiescent, but its replicatory activity can be enhanced in vitro by certain nutrients and growth factors and long-term alterations in beta-cell mass constitute an important means to accommodate an increased demand for insulin. Likewise, expansion of the beta-cell mass by recruitment of beta-cells to proliferate may constitute a means by which the organism can compensate for the loss or dysfunction of beta-cell occuring in diabetes. However, neither in human or animal models for Type 1 diabetes, nor in Type 2 diabetes, is beta-cell regeneration a noteworthy feature. Thus, if beta-cells could be induced to replicate at a higher rate, this may prove beneficial in maintaining normoglycaemia, since the beta-cell mass is a major determinant of the total amount of insulin that can be secreted by the pancreas. The present review will focus on the normal regulation of beta-cell mitogenesis and hormones production in vitro and in vivo and furthermore, will present evidence for an insufficient extent of beta-cell regeneration in different forms of diabetes mellitus. Additionally, the possibility of manipulating beta-cell proliferation by peptides and genetic engineering and the significance of beta-cell mitogensis in islet transplantation will be discussed in relation to treatments of diabetes mellitus.

Thrombogenic and fibrinolytic factor and cardiovascular risk in non-insulin-dependent diabetes.

Juhan-Vague l, Alessi MC, Vague P. Annals of Medicine 1996; 28(4) : 371-80.

Disturbances of the haemostatic system may favour the development of vascular damage and the final occlusion events in the progress of coronary heart disease (CHD). It has been shown recently in epidemiological studies, that increased concentration of several factors, mainly fibrinogen, factor VII, von Willebrand factor (vWf), and the fibrinolytic variables plasminogen activator inhibitor 1 (PAl-1) and it tissue plasminogen activator (t-PA), can be considered as risk factors for CHD. As morbidity and mortality through coronary atherosclerosis are higher in Type 2 diabetic patients than in nondiabetic subjects and as insulin resistance represents a situation which favours the development of atherothrombosis, evaluation of the haemostatic factors which are recognized as risk factors may be in interesting to consider in these situations. In fact, it has been shown that the fibrinolytic parameters PAl-1 and t-PA antigen are strongly related to the metabolic disorder of insulin resistance, whereas the link with fibrinogen, factor VII, and vWF remains weak. Many cross-sectional studies conducted in different populations have shown that PAl-1 and t-PA antigen (which represents t-PA/PAl-1 complexes) are strongly correlated with insulin, triglyceride, high-density lipoprotein (HDL) cholesterol, body mass index, waist-to-hip ratio and blood pressure and that the improvement of insulin resistance improves in parallel the metabolic abnormalities and the concentration of the fibrinolytic parameters. Attempts at explaining the elevated PASI-1 and t-PA antigen levels in the insulin resistance syndrome have involved many clinical and in vitro studies, in which the role of insulin, insulin propeptides, very low-density lipoprotein (VLDL) triglyceride, insulin resistance perse, glucose and adipose tissue have successively been analysed and the main results of these studies are presented in this review. Due to recent experimental data from animal models of thrombosis, a pathogenic role of decreased fibrinolytic activity or increased PAl-1 levels can be proposed and could play a role in the development of vascular disease in subjects with Type 2 diabetes or insulin resistance.

Cardiovascular risk factors and the prediabetic syndrome.

Haffner SM. Annals of Medicine 1996; 28(4) : 363-70.

Cardiovascular disease is increased 2- to 4-fold in non-insulin-dependent diabetes mellitus (NIDDM), yet in most studies, there is a relatively weak relationship between the frequency of coronary heart diseases (CHD) and the duration of diabetes and severity of hyperglycemia. A number of authors have suggested that the prediabetic stage may contribute to the risk of CHD in NIDDM. Hyperinsulinaemia and insulin resistance has been strongly associated with the development of NIDDM. Data are less conclusive about the relationship of hyperinsulinaemia to the development of CHD in nondiabetic subjects. Relatively little data are available on hyperinsulinaemia and/or insulin resistance to CHD in NIDDM subjects. Tight control of glycaemia with exogenous insulin improves cardiovascular risk factors in NIDDM subjects and therefore is unlikely to increase the risk of CHD. Although the relation of insulin to CHD in the general population is somewhat controversial, insulin is clearly related to multiple cardiovascular risk factors (especially elevated triglyceride, decreased high-density lipoprotein, small dense low-density lipoprotein, impaired glucose tolerance and increased plasminogen activator inhibitor 1 (PAl-1). However the relation of insulin resistance to hypertension remains controversial.

Intra-abdominal fat: is it a major factor in developing diabetes and coronary artery disease?

Kissebah AH. Diabetes Research and Clinical Practice 1996; 30 Suppl : 25-30.

Abdominal obesity has emerged as a strong and independent predictor for non-insulin dependent diabetes mellitus (NIDDM). Adiposity located centrally in the abdominal region and particular visceral as opposed to subcutaneous fat is also distinctly associated with hyperlipidemia, compared with generalized distributions of body fat. These lipoprotein abnormalities are characterized by elevated very low density lipoprotein (VLDL) and low density lipoprotein (LDL) levels, small dense LDL with elevated apolipoprotein B levels and decreased high density lipoprotein 2b (HDL2b) levels. This is the same pattern seen in both familial combined hyperlipidemia and NIDDM. The pronounced hyperinsulinemia of upper-body obesity supports the overproduction of VLDL and the increased LDL turnover. We have proposed than an increase in the size of the visceral fat depot is a precursor to the increased lipolysis and elevated free fatty acid (FFA) flux and metabolism and to subsequent overexposure of hepatic and extrahepatic tissues to FFA, which then, in part, promotes aberrations in insulin actions and dynamics. The resultant changes in glucose/insulin homeostasis, lipoprotein metabolism and vascular events then lead to metabolic morbidities such as glucose intolerance, NIDDM, dyslipidemia and increased risk for coronary heart disease.

Mitochondrial diabetes mellitus.

Rotig A, Bonnefont JP, Munnich A. Diabetes and Metabolism 1996; 22(5) : 291-8.

In the last few years, several mitochondrial DNA mutations and deletions have been described in association with various human disease. Mitochondrial disorders, though long regarded strictly as neuromuscular disease, may in fact involve non-neuromuscular symptoms. Diabetes mellitus has been reported in patients presenting with large mtDNA rearrangements (deletion, deletion-duplication) or in association with mtDNA point mutation, generally in tRNA (Leu(UUR)). Genetic studies have shown that these disorders occur in sporadic cases or can be maternally inherited. The main clinical feature of

mitochondrial diabetes is its nearly-consistent association with other symptoms (deafness, neurologic disorders, cardiac failure renal failure etc.) This paper provides a review of different types of mtDNA abnormalities associated with diabetes and a study of the prevalence of mitochondrial diabetes mellitus.

CLINICAL PRESENTATION

Clinical aspects of coeliac disease in children with insulin dependent diabetes.

Lorini R, Scaramuzza A, Vitali L, d'Annunzio G, Avanzini MA, De Giacomo C, Severi F. Journal of Pediatric Endocrinology and Metabolism 1996; 9 Suppl 1 : 101-11.

Coeliac disease (CD) is heterogeneous in its clinical presentation and pathological expression. Silent, latent and potential forms represent the submerged part of the so-called "coeliac iceberg". The association of insulin-dependent diabetes mellitus (IDDM) and CD has been widely reported. For the screening of CD and diabetic patients, antireticulin R1 (ARA-R1) and anti-endomysium (AEA) antibodies are more reliable markers than anti-gliadin (AGA) antibodies. Recent studies have reported an increased prevalence of CD in children with IDDM. In our experience intestinal biopsy confirmed a diagnosis of CD in 6 out of 172 diabetic patients, with a prevalence of 3.5%. Only occasionally does CD precede the onset of IDDM, more often CD is diagnosed shortly or sometimes years after the onset of diabetes. Typical gastrointestinal complaints of CD (such as diarrhoea, abdominal distension are rare in IDDM patients, while atypical isolated signs or symptoms of CD are more common, in particular sideropenic anemia, short stature, delayed puberty, epilepsy, hyper-transaminasemia, dyspeptic symptoms, herpetiform dermatitis, and recurrent aphthous stomatitis. It is recommended that all diabetic children, even those asymptomatic, should be screened yearly for CD, using a combination of AGA plus ARA-R1 and AEA.

Transient neonatal diabetes mellitus and macroglossia.

Battin M, Yong C, Phang M, Daaboul J. Journal of Perinatology 1996; 16(4) : 288-91.

Transient neonatal diabetes mellitus is an uncommon disorder. Macroglossia in association with transient neonatal diabetes mellitus has been reported only twice before. We report the case of a 21-day-old male infant referred from a peripheral hospital for management of hyperglycemia. The mother was a 21-year-old primigravid in good health. There was no history of diabetes or drug or alcohol exposure. The pregnancy was complicated by intrauterine growth retardation and oligohydramnios from 30 weeks' gestational and the birth weight at 38 weeks' gestation was only 1480 gm. Physical examination revealed dymorphic features and asymmetric growth retardation. The admission weight (1940 gm) and length (40.5 cm) were 5 SDs less than the mean and head circumference (32.5 cm.) was 1 SD less than the mean. Dysmorphic features included macroglossia, large fontaneless, hypospadias, umbilical hernia and bilateral inguinal hernias. Hyperglycemia had been noted on day 1 of life with an initial blood glucose value of 16 mmol/L (288 mg/dl). Despite treatment with regular insulin blood glucose control continued to be erratic. Therefore a regimen of daily NPH insulin was begun, which has a smoother action. Interestingly, from day 41 to day 47 the infant did not receive insulin and a crude control of the blood glucose was demonstrated. Peak levels of blood glucose in excess of 20 mmol/L (360 mg/dl) were followed by drops to levels less than 2 mmoI/L (36 mg/dl) without insulin administration. This abnormal pattern of glucose control may represent poorly regulated release of endogenous insulin. However, because of unsatisfactory glucose levels administration of daily NPH insulin was reintroduced. The infant was discharged from the hospital on day 50 and administration of insulin was discontinued uneventfully at 9 months. At 1 year the hemoglobin A1c level was still normal and the infant's weight was at the 10th percentile. Macroglossia was less pronounced. Development showed mild delay in gross motor milestones.

Changing needs of the patient with diabetes mellitus during the teenage years.

Gordon CM, Mansfield MJ. Current Opinion in Pediatrics 1996; 8(4) : 319-27.

The Diabetes Control and Complications Trial has established the role of chronic hyperglycemia in the development of retinal renal and neuropathic complications of insulin-dependent diabetes mellitus. This paper discusses the special physiological and control in adolescents. We also review the prevalence of eating insulin omission in this age group as well as nutritional, gynecological and contraceptive issues. We emphasize the importance of family support, promotion of self-esteem and the setting of realistic and attainable goals in improving long-term care for teenage patients with this disease

MANAGEMENT – GENERAL

Smoking and diabetes mellitus.

Dierkx Rl, van de Hoek W, Hoekstra JB, Erkelens DW. Netherlands Journal of Medicine 1996; 48(4) : 150-62.

The goal of this review is to determine the effects of smoking on diabetes mellitus, whether it aggressive diabetic complications or influences insulin metabolism and action. Also available anti-smoking programs applicable for diabetic patients have been studied. The prevalence of smoking among diabetic patients has been investigated by conducting a meta-analysis. Compared with normal subjects, the prevalence of smoking among diabetic patients is significantly higher (27 vs 33%, P<0.001), IDDM patients largely accounting for this difference. However, care must be used in interpreting these data. Smoking presents an extra risk for development of macro-and microvascular complications in these patients, contributing to increased cardiovascular morbidity and mortality. Smoking also increases the risk of diabetes itself. Neither acute nor habitual smoking causes substantial changes in insulin sensitivity in IDDM patients, whereas it does so in NIDDM. Studies in diabetic patients concerning anti-smoking strategies are scarce and only yield disappointing results. Making these patients abstain from smoking turns out to be extremely difficult, probably due to the considerable psychosocial stress experienced.

DIET

Fat replace: their use in foods and role in diabetes medical nutrition therapy.

Warshaw H, Franz M, powers MA, Wheeler M. Diabetes Care 1996; 19(11) : 1294-301.

The scientific literature demonstrates that fat replacers have a reasonable certainty of no harm. Whether they help produce desired health outcomes, i.e., decreased risk of coronary heart disease and certain types of cancer related to excess fat intake, weight reduction, changes in lipid profile, improved glycaemic control, etc., depends on how individuals use these foods to change food choices and eating behaviours. As Miller and Rolls

conclude, the use of fat-replaced foods alone should not be expected to produce spontaneous improvements in weight management. Such improvements will still be dependent on long-term behavioral changes that include not only modification in fat, but also modifications in overall energy intake and increase in energy expenditure. Though it has not been studies, one may conjecture that encouraging people with diabetes to use foods with fat replacer to achieve nutrition management goals requires sufficient education, continuous counseling, and an individual's conscientious commitment and readiness to change food habits.

Does diabetes mellitus increase the requirements for vitamin C?

Will JC, Byer T. Nutrition Reviews; 1996; 54(7) : 193-202.

This paper reviews the scientific evidence regarding the vitamin C status of people with diabetes mellitus and whether they might have increased dietary vitamin C requirements. English language articles published from 1935 to the present that either compare ascorbic acid concentrations of persons with and without diabetes mellitus or assess the impact of vitamin C supplementation on various health outcomes among persons with diabetes mellitus to have at least 30% lower circulating ascorbic acid concentrations than people without diabetes mellitus. Vitamin C supplementation had little impact on blood glucose concentrations, but was found to lower cellular sorbitol concentrations, and to reduce capillary fragility. Much of the past research in this area has been methodologically weak. To further understand the relation of ascorbic acid and diabetes mellitus, randomized clinical trials of ascorbic acid supplementation should be a high priority for research.

High-fat and high-carbohydrate diets and energy balance.

Shan M, Garg A. Diabetes Care 1996. 19(10) : 1142-52.

The current American Diabetes Association guidelines for nutrition recommend a moderate increase in monounsaturated fats and a reduced intake of carbohydrate inpatients with diabetes in which high-carbohydrate diets deteriorate glycemic control and lipoprotein levels. High-fat diets, however are believed to promote obesity, and some investigators may have reservations recommending such diets. This review thus investigates the role of diet composition in promoting obesity or achieving weight loss and its implication inpatients with diabetes. Epidemiological studies show some evidence that fat intake is more importantly related to body weight than carbohydrate intake, but conclusions are weak because confounding variables, such as physical activity, smoking, and energy intake, were generally not controlled for. Metabolic studies under isoenergic conditions report no change in energy balance when fat intake is increased, but report a negative fat balance with substantial increase carbohydrate intake. During overfeeding, excess fat intake is stored as fat, whereas excess carbohydrate is mostly oxidized in the short term but can lead to substantial gain in fat stores because of reduced fat oxidation and considerable denovo lipogenesis in the long term. Spontaneous energy intake, however, is higher on an unrestricted high-fat diet compared with a high-carbohydrate diet, but the long-term effects are not known. Weight-loss intervention studies show that a hypocaloric high-carbohydrate diet is not associated with more weight loss than a high-fat hypocaloric diet. In conclusion, a high- monounsaturated fat diet to control glycaemic control and lipoprotein levels in patients with diabetes should not affect weight loss or maintenance, provided that energy intake is carefully controlled.

INSULIN

Insulin lispro: its role in the treatments of diabetes mellitus.

Campbell RK, Campbell LK, White JR. Annals of Pharmacotherapy 1996; 30(11) : 1263-71.

OBJECTIVE: To introduce a rapid-acting human insulin analog, insulin lispro; to review its pharmacology, therapeutics, pharmacokinetics, does guidelines, adverse effects and drug interactions and to summarize the clinical trials of its efficacy and safety alone and in comparison with regular human insulin in the treatment of diabetes mellitus.

DATA SOURCES: A MEDLINE database search was completed to identify all relevant articles, including reviews; EliLilly and Co.; published articles and abstracts; and review chapters from medical textbooks.

STUDY SELECTION: Due to the relatively few citations listed in MEDLINE (12 as of December 1995), most of the studies reported were found from abstracts summarizing the clinical action, adverse effects, or pharmacokinetics of insulin lispro in healthy volunteers or patients with diabetes mellitus. A few of the studies used patients with diabetes mellitus in multicenter, randomized crossover trials of insulin lispro.

DATA EXTRACTION: All clinical trial that were available i.e. prior to submission of this manuscript for publication, including unpublished reports, was reviewed.

DATA SYNTHESIS: The human insulin analog insulin lispro, which is biosynthetically made by inverting the amino acid sequence of human insulin at B-28 and B-29, is more effective than regular human insulin in improving postprandial glucose control. Subcutaneous injections of insulin lispro result in decreased blood glucose peaks following meals and a potential decreased risk of hypoglycemic episodes, including night time hypoglycemia in patients with Type 1 diabetes. Insulin lispro in comparison with regular human insulin provides equal or slightly better blood glucose control. When compared with subcutaneous injections of regular human insulin, the peak serum insulin concentration of insulin lispro is three times higher, time to peak is 4.2 times faster, the absorption rate constant is double, and the duration of action is half as long. Insulin lispro is similar to regular human insulin with reference to dose, toxicity, adverse effects, drug interactions, and immunogenicity. When insulin lispro is mixed with human NPH (isophane) or Lente insulins, insulin lispro should be drawn into the syringe first, mixed with the long-acting insulin, and injected immediately after mixing. Patients using insulin lispro perceive an improvement in their well being and quality of life due to flexible injection times and less frequent hypoglycemic reactions. Insulin lispro is believed to be suitable for patients using insulin infusion pumps.

CONCLUSIONS: Insulin lispro is equipotent to human insulin and has a much more rapid onset and shorter duration of action than human insulin does, which may reduce the risk of hypoglycemia. In addition, insulin lispro improves the dosing convenience for patients with diabetes and provides a more natural control of blood glucose concentration. Insulin lispro is a useful new agent in the treatment of diabetes mellitus.

ORAL HYPOGLYCEMIC AGENTS

Acarbose: its role in the treatment of diabetes mellitus.

Campbell LK, White JR, Campbell RK, Annals of Pharmacotherapy 1996; 30(11) : 1255-62.

OBJECTIVE: To review the clinical pharmacology of acarbose, and alpha-glucosidase inhibitor and to summarize its role in the pharmacotherapy of diabetes mellitus.

DATA SOURCES: A MEDLINE search identified all relevant articles, including reviews; Bayer Pharmaceuticals.

STUDY SELECTION: Due to the large number of clinical trials available specific criteria were used to narrow the focus of this review: (1) randomized, double-blind, placebo-controlled, parallel-group study design; (2) a minimum of 25 patients enrolled per treatment arm; (3) a treatment duration of 90 days or more; and (4) adherence to Food and Drug Administration Good Clinical Practice guidelines.

DATA EXTRACTION: All clinical trials that were available up to December 1995 were reviews. Preliminary trials and unpublished reports were not reviewed.

DATA SYNTHESIS: Acarbose is effective in reducing postprandial hyperglycemia. It does not stimulate endogenous insulin secretion and therefore, will not cause hypoglycemia when used as monotherapy. The enhanced glycaemic control achieved with acarbose is additive to that of sulfonylures. It lowers postprandial serum glucose and insulin concentrations and dose not promote weight gain. Acarbose can be used as first-line therapy with diet and exercise, or it can be used in combination with sulfonylureas to lower haemoglobin A 1c concentrations an additional 0.5-0.9%. Acarbose is not a cure for diabetes, not is it a substitute to diet, exercise, oral hypoglycemic agents, or insulin. Adverse effects are gastrointestinal and can be diminished by starting with an initial dosage of 25 mg tid. Depending on patient response, the dosage can be increased up to a maximum of 100 mg tid over time.

CONCLUSIONS: Acarbose, through its unique mechanism of action, appears to be a safe and effective adjunctive agent to diet/exercise therapy or sulfonylureas therapy for treatment of non-insulin-dependent diabetes mellitus.

An overview of the safety and tolerance of glimepiride.

Hormone and Metabolic Research 1996; 28(9) : 413-8.

The objective of this paper is to obtain an overview of the safety and tolerance of glimepiride by presenting results from the clinical trials in patients with non-insulin dependent diabetes mellitus that were conducted during the development of this new product. A total of 21 clinical studies with a minimum duration of two weeks were conducted during the clinical development of glimepiride in the United States and Europe. This included fourplacebo-controlled, four active-controlled (with glyburide and glipizide) and three non comparative trials conducted in the United States and 10 European studies (eight active controlled and two non-comparative). All of the patients provided an extensive medial history, which included information on concomitant medications, underlying diseases, and ongoing adverse events. During the clinical studies, the patients were monitored for treatment-emergent signs and symptoms (TESS), clinical laboratory abnormalities, discontinuations, deaths and serious adverse events. Over 6,500 patients were included in the worldwide clinical trials with more than 4,200 of these patients treated with glimepiride, 1,500 of these patients were treated for at least 1 year. In controlled clinical trials in the United States, 2,013 subjects received glimepiride, 294 placebo, 322 glyburide, and 258 glipizide. In European studies, the duration of therapy ranged from 14 days to 2.8 years in the 1,489 patients who received glimepiride and the 1,247 control patients who were treated with either glyburide or gliclazide. In the Japanese studies, a total of 983 patients were treated, 718 on glimepiride.

Acarbose: an alpha-glucosidase inhibitor.

Martin AE, Montgomery PA. American Journal of Health-System Pharmacy 1996; 53(19) : 2277-90.

The chemistry, pharmacology, pharmacokinetics, and clinical efficacy of acarbose, a new antidiabetic agent, are reviewed. Acarbose reversibly inhibits intestinal alpha-glucosidases, enzymes responsible for the metabolism of complex carbohydrates into absorbable monosaccharide units. This action results in a diminished and delayed rise in blood glucose following a meal, resulting in a reduction in post-prandial hyperglycemia, area under the glucose concentration-time curve, and glycosylated hemoglobin. Other effects include a reduction in postprandial insulin and variable changes in plasma lipid concentration. In placebo-controlled trials, acarbose caused significant improvements in glycaemic control indicators, including glycosylated hemoglobin. Acarbose has demonstrated additional glycaemic control when added to other antidiabetic therapies, including sulfonylureas and insulin efficacy of a carbose appears to be comparable to or slightly less than that of sulfonylure as or metformin, although it has not been compared with maximal dose of these agents. The most commonly reported adverse drug reactions with acarbose are abdominal pain, diarrhea, and flatulence, which tend to lessen with time. Acarbose may affect the bioavailability of metformin and may be less effective when used in conjunction with intestinal adsorbents and digestive enzyme preparations. Concurrent use with hypoglycemic agents (sulfonyureas and insulin) may cause an increased frequency of hypoglycemia. Acarbose should not be used to individuals with certain intestinal disorders, including inflammatory bowel disease. The dosage should start at 25 mg one to three times daily given with the first bite of each main meal and should be adjusted to a maximum of 50 mg three times daily for patients weighing up to 60 kg or 100 mg three times daily for heavier patients. Acarbose may be considered for first-line antidiabetic therapy in certain patients and may be useful as combination therapy in certain patients and may be useful as combination therapy in selected instances. Acarbose is efficacious in improving metabolic control in non-insulin-dependent diabetes mellitus. Further evaluation of its effects on the long-term complications of diabetes is needed.

New treatments for patients with Type 2 diabetes.

Wolffenbuttel BH, Graal MB. Postgraduate Medical Journal 1996; 72(853) : 657-62.

In subjects with Type 2 diabetes, both defects of insulin secretion and insulin resistance contribute to the development of hyperglycemia. The Major goals of treatment are to optimise blood glucose control and normalise the associated lipid disturbances and elevated blood pressure. Pharmacologic treatment is often necessary. This paper discussed new forms of oral treatment for subjects with Type 2 diabetes. These include a new sulphonylurea compound glimpiride (Amaryl), which binds to a different protein of the putative sulphonylurea receptor than glibenclamide and seems to have a lower risk of hypoglycemia. A new class of drugs with insulin secretary capacity of which repaglinide (NovoNorm) is the leading compound, is now in phase III clinical trials. Alpha-glucosidase inhibitors reversibly inhibit alpha-glucosidase enzymes in the small intestine, which delay cleavage of oligo-and disaccharides to monosaccharides. This leads to a delayed and reduced blood glucose rise after a meal. Two compounds are in development or have been marketed, i.e., miglitol and acarbose (Glucobay).

Another new class of drugs is the thiazolidine-diones, which seem to work by enhancing insulin action. The 'insulin sensitising' effects of the leading compounds, troglitazone and BRL 49653C, do not involve any effect on insulin secretion. These drugs also seen to beneficially influence serum cholesterol and triglyceride levels Oral antihyperglycaemic agents can be used only during a limited period of time in most patients, after which the diabetic state worsens' and insulin therapy has to be started. In this light, two new forms of treatment which require subcutaneous injections are also discussed, the synthetic human amylin analogue AC137 (pramlintide) and glucagon like peptide-1 (7-36)-amide, a strong glucose-dependent stimulator of insulin secretion. It remains to be seen whether these compounds can be developed further for clinical use in patients with diabetes.

OHA AND INSULIN

Combined therapy with sulfonylurea plus evening insulin: safe, reliable and becoming routine.

Riddle MC. Hormone and Metabolic Research 1996; 28(9) : 430-3.

Whether a sulfonylures may be used together with insulin for treating NIDDM has been controversial. One view, based on older studies, has been that the additional benefit is too small or the level of glucose control achieved usually too poor to recommend this method. More recent studies of a more specific way of combining a sulfonylurea with insulin taken in the evening is added to a sulfonylurea at the time of secondary failure of the sulphonylurea alone, glycaemic control is quite simply and consistently restored to acceptable revels. At this time in the natural history of NIDDM, evening insulin combined therapy is more effective than a single injection of insulin alone and just as effective as a more complex multiple-injection regimen without an oral agent. A recent multicenter trial of a new sulfonylurea, glimepiride, in combination with a single injection of 70/30 insulin before dinner has confirmed that this approach is safe and more consistently effective than insulin alone for obese patients beginning insulin in a setting resembling clinical practice. The available evidence suggests this form of combined therapy is suitable for routine use.

COMPLICATION – GENERAL

The aetiology and management of erectile, ejaculatory and fertility problems in men with diabetes mellitus.

Dunsmuir WD, Holmes SA. Diabetic Medicine 1996; 13(8) : 700-8.

Erectile impotence is more common in the diabetic than the general population, occurs at a younger age, and is often associated with ejaculatory problems. For these, and possibly for other more subtle reasons, fertility may be a problem for men with diabetes. The symptoms of erectile and ejaculatory dysfunction are frequently not discussed between patient and doctor. Psychological factors are important but the vast majority of diabetic patients have an organic basis for their impotence. Both neurogenic and vascular factors are important in the pathogenesis of erectile failure. Autonomic neuropathy is almost certainly the cause of the ejaculatory failure that may be present in up to 40% of men with diabetes. The final biochemical mediator of erection within the penile erectile tissue is nitric oxide and a key enzyme in its degradation is phosphodiesterase (Type 5). Drugs that affect the metabolism of this enzyme are being developed to treat erectile failure. At present, the self injection of intra-cavernosal erectogenic agents (such as prostaglandin E1) provide the main form of therapy for erectile failure. Vacuum devices are a simple alternative and venous ligation surgery may be effective for a properly selected cohort of patients. Prosthetic implants are a final option for patients in whom all else has failed. Fertility problems, particularly when associated with ejaculatory failure can be overcome with modern assisted reproductive techniques. Nowadays, these will frequently involve gamete micromanipulation.

Infant of diabetic mother: a continuing challenge for perinatal-neonatal medicine.

Wu PY.Acta Paediatrica Sinica 1996; 37(5) : 312-9.

Current increase in the incidence of diabetes mellitus complicating pregnancy is of concern since it is associated with an increase in mortality and morbidity of the fetus and neonate. Pregnancy itself is diabetogenic causes by increased insulin resistance due to the production of hormones like estrogen, progesterone, cortisol, human chorionic somatom-ammotropin (HCS) and human placental lactogen (HPL). The latter increases lypolysis which provides free fatty acids and ketones as fuels for energy for the pregnant mother. This spares maternal blood glucose, amino acids and ketones which cross the placenta to the fetus. The influx of nutrients increases fetal insulin production which together with HPL induce somatogenesis. Maternal hyperglycemia and fetal hypoxemia are shown to be responsible for structural congenital anomalies of the rapidly developing organs of the fetus during the early weeks of gestation while continuing hyperglycemia and hypoxemia in the second and third trimester are factors related to the production of macrosomia, including cardiomyopathy, delay in lung maturation and polycythemia. Metabolic problems such as hypoglycemia, hypocalcemia, hypomagnesemia and hyper bilirubinemia are common neonatal morbiditeis. Follow-up of the infants of diabetic mothers indicates that these infants have a 20 fold increase in acquiring diabetes. Early identification of maternal diabetes with strict metabolic control prior to conception as well as throughout pregnancy together with careful fetal monitoring can reduce the incidence of congenital anomalies and morbidities in the fetus and neonate.

COMPLICATIONS : CARDIOVASCULAR

Myocardial alterations in diabetes and hypertension.

Factor SM, Borczuk A. Charron MJ, Fein FS, van Hoeven KH, Sonnenblick EH. Diabetes Research & Clinical Practice. 1996; 31 Suppl: S133-42.

Diabetes mellitus is a complex group of diseases that has hyperglycemia as a common metabolic abnormality. Although it is well-known that diabetic patients are susceptible to the effects of large vessel atherosclerosis with specific cardiac and cerebral complications, the association of diabetes mellitus with cardiac dysfunction caused by cardiomyopathy in the absence of significant coronary artery disease has been recongnized for many years. However, the pathogenesis of diabetic cardiomyopathy remains unknown and has been somewhat controversial. Specially, whether diabetes mellitus with its metabolic effects is sufficient to account for cardiomyopathy remains to be proven. This paper reviews the evidence for and against a metabolic etiology in addition, we review the clinical and experimental evidence that supports the view that diabetes mellitus acts together with hypertension to produce structural damage in the heart that manifests as ventricular dysfunction and ultimately congestive heart failure. The concomitant effects of the metabolic derangements of diabetes and the vascular abnormalities associated with hypertension may lead to microvascular induced tissue injury. Findings supporting this

hypothesis are presented, along with observations suggesting that treatment with vasodilating calcium channel blockers or angiotensin converting enzyme inhibitors may be beneficial in regard to tissue pathology and mortality in experimental models. Recent clinical studies also support a role for the microcirculation in diabetics. Finally, it is suggested that if the microcirculation is pathogenetically involved in diabetic cardiomyopathy, then agents that improve microcirculatory flow along with tight control of hypertension may be as beneficial in the treatment or prevention of diabetic cardiomyopathy as strict metabolic control of hyperglycemia.

Non-insulin dependent diabetes and reverse cholesterol transport.

Berthezene F. Atherosclerosis 1996; 124 Suppl : S39-42.

Quantative and qualitative changes are observed in high-density lipoproteins (HDL) in patients with non-insulin dependent diabetes mellitus (NIDDM) and more generally, in states of insulin resistance combined with central obesity. Reduced levels of HDL cholesterol are observed in patients with NIDDM, this decrease being correlated with the degree of insulin resistance. Qualitative changes in HDL are characterised by an increased triglyceride content, changes in the free cholesterol-phospholipid ratio and an increase in the number of glycosylated apolipoprotein A-1 molecules, giving rise to major variations in the viscosity of HDL particles. The transport of cholesterol is reduced when HDL is glycosylated and the transfer activity of cholesterol esters is increased. There is also a reduction in the level of HDL lipid peroxidation. These abnormalities in the lipid profile cause changes in reverse cholesterol transport which may be involved in the genesis of the accelerated atherosclerosis observed in patients with NIDDM.

PATIENT EDUCATION

The role of patient participation in the visit to the doctor. Implicaions for adherence to diabetes care.

Golin CE, DiMattao MR, Gelberg L. Diabetes Care 1996; 19(10) : 1153-64.

For patients, treatment of diabetes involves complex changes in basic behaviors and adherence to complicated regimens. Understanding the factors that enable patients to adhere to diabetes treatment is the first step to designing effective interventions. Researchers of diabetes care have postulated that increasing diabetic patients' participation in medical decision making during the doctor visit is likely to improve their adherence to self-care. However, a critical review of the impact of patient participation on diabetic patients adherence to self-care is absent from the literature. We review the subject of patient participation in medical decision making and its effect on adherence to self care for patients with diabetes. We introduce a model of the determinants of adherence to diabetes self-care that incorporates the effects of patient participation in medical decision making. In this model, we suggest three ways that patient participation can affect adherence to self-care: 1) it may have a direct effect; 2) it may affect adherence to self-care indirectly by affecting patients' understanding of their treatment regimen or the fit of their regimen with their lifestyle; and 3) perceived omissions of participation can affect adherence to self-care indirectly through an effect on patient satisfaction. Research is needed to identify more clearly which components of patient participation affect adherence to self-care and in what ways. Distinguishing patient and physician behaviors that contribute to the process of patient participation would provide a means to develop specific behavioral interventions.

PHYCHOLOGICAL ASPECTS

Psychological factors in intensive management of insulin dependent diabetes

Strauss GJ. Nursing Clinics of North America 1996; 31(4) : 737-45.

With the publication of the DCCT results in 1993, hope has been given to patients with Type 1 diabetes that blindness, kidney failure and neuropathies are not necessarily what awaits them. However, to assume that diabetes is simply a disease that can be controlled "if only the patient would be complaint" is an incredibly naïve way to approach treatment. Practitioners need to be keenly aware of not only the complexities of intensive management of Type 1 diabetes but perhaps more importantly the numerous psychological factors that determine whether treatment adherence will occur. Psychological issues such as patient perceptions of symptoms, fear, unawareness of symptoms because of autonomic dysregulation or cognitive decline, attitudes and control issues need to be assessed. These issues can be assessed quite easily with questionnaires, scales and interview schedules readily available to practitioners. Additionally, for those patients who may not be attuned to monitoring physiologic on cognitive cues, awareness training and other coping skills interventions are available that can be incorporated into existing diabetes education programs. A mutual effort by the patient and health-care provider team can lead to success in intensive management of IDDM.

PREVENTION

Prevention of insulin-dependent diabetes mellitus: an overview of three trials.

Schatz DA, Rogers DG, Brouhard BH. Cleveland Clinic Journal of Medicine 1996; 63(5) : 270-4.

Genetic, immune and metabolic testing can reveal a person's risk of developing insulin-dependent diabetes mellitus (IDDM), and three large clinical trials are planned or underway to see if interventions can prevent IDDM in persons at risk. Researchers in diabetes prevention trials are screening first-and second-degree relatives of probands with IDDM for islet-cell antibodies. In the Cow's Milk Avoidance Trial, infant siblings of probands with IDDM will be randomized to receive either a baby formula containing a non-antigenic protein hydrolyzate or a standard cow's milk-based formula. The Diabetes Prevention Trial-Type 1 is randomly assigning subjects at high risk (more than a 50% probability of developing IDDM) to either receive insulin injections or undergo observation alone; subjects at intermediate risk (25% to 50%) will receive either oral insulin or placebo. In the European Nicotinamide Diabetes Intervention Trial, subjects receive either nicotinamide or placebo. If any of these trials show that IDDM can be prevented, then large-scale screening of children for IDDM risk factors may prove beneficial.