ABSTRACT SERVICE

EPIDEMIOLOGY

Cost of predicting IDDM

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SUMMARY: Programmes aiming at prediction and prevention of insulin-dependent diabetes mellitus (IDDM), a multifactorial autoimmune disease, have been launched or are in the planning phase in several countries. We hypothesized that the costs of finding the correct target subjects for preventive interventions are likely to very markedly according to the prediction strategy chosen. Average direct costs accruing in the Finnish IDDM Prediction and Prevention Project (DIPP) were analysed from the health care provider's viewpoint. The genetically targeted strategy included costs of assessing genetic IDDM susceptibility followed by measurement of marker(s) of islet autoimmunity in the susceptibility restricted population at 3 to 6-month intervals. In the pure immunological strategy markers of autoimmunity were repeatedly analysed in the entire population. The data were finally exposed to sensitivity analysis. The genetically targeted predication strategy is cost saving in the first year if autoimmune markers are analysed as frequently as under the DIPP project, and in all circumstances later. The 10-year direct costs per child are US$ 245 (present value $ 217,5%% discount rate) if the genetically targeted approach is used and $733 (present value $ 619) if the pure immunological strategy is chosen. In sensitive analysis the 10-year costs (present value) per child of the genetically targeted strategy and of the pure immunological strategy varied from $ 152 to $ 241 and from $ 430 to $ 788, respectively. The genetically targeted IDDM prediction strategy is remarkably cost saving as compared with the pure immunological strategy mainly because fewer subjects will need retesting during the follow-up [Diabetologia (1998) 41: 79-85].

High Blood Glucose Concentration Is a Risk Factor For Mortality in Middle-Aged Nondiabetic Men. 20-year follow-up in the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study.

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OBJECTIVE: To assess the association between high but non-diabetic blood glucose levels and the risk of death from all causes, coronary heart disease (CHD), cardiovascular disease and neoplasms.

RESEARCH DESIGN AND METHODS: We studied the 20-year mortality of non diabetic working men, age 44-45 years, in three European cohorts known as the Whitehall Study (n=10.025), the Paris Prospective Study (n=6,629), and the Helsinki Policemen Study (n=631). These men were identified by their 2-h glucose levels following an oral glucose tolerance test and by the absence of a prior diagnosis of diabetes. As the protocol for the oral glucose tolerance test and methods for measuring glucose differed between studies, mortality was analysed according to the percentiles of the 2-h and fasting glucose distributions, using the Cox's proportional hazards model.

RESULTS: Men in upper 20% of the 2-h glucose distributions and those in the upper 2.5% for fasting glucose had a significantly higher risk of all-cause mortality in comparison with men in the lower 80% of these distributions, with age-adjusted hazard ratios of 1.6 (95% CL 1.4-1.9) and 2.0 (1.6-2.6) for the upper 2.5% For death from cardiovascular and CHD, men in the upper 2.5% of the 2-h and fasting glucose distributions were at higher risk, with age adjusted hazard ratios for CHD of 1.8 (1.4—2.4) and 2.7 (1.7-4.4), respectively.

CONCLUSIONS: If early intervention aimed at lowering blood glucose concentrations can be shown to reduce mortality, it may be justified to lower the levels of both 2-h and fasting glucose, which define diabetes.

The Epidemiology and Cost of Inpatient Care for Peripheral Vascular Disease, Infection, Neuropathy, and Ulceration in Diabetes.

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OBJECTIVE : To describe the epidemiology and costs of the acute care of peripheral vascular disease infection, neuropathy, and ulceration in a U.K. population with special consideration of those patients with diabetes.

RESEARCH DESIGN AND METHODS : Routine data describing inpatient care for a 4-year period were analyzed (financial years 1991/1992 to 1994/1995). These data had undergone record-linkage to draw together records from the same patients, and records of patients with diabetes were flagged. Cost estimates were determined by attributing a diagnosis-related group cost-weight to each record.

RESULTS : A total of 4,245 admission (1.2% of all admissions) had a primary diagnosis of peripheral vascular disease, infection, neuropathy, or ulceration, and 7,379 (2.1%) admission had these categories recorded in any one of six diagnostic fields. These figures were generated by 3,159 and 4,751 patients, respectively. This represented a range of crude annual incidence of admission of between 1.9 and 2.9 per 1,000 people Patients with diabetes accounted for 625 (15.4%) of primary admissions, a crude annual incidence of admission of 18.8 per 1,000. The age-standardized relative risk of admission for patients with diabetes to the non-diabetic population was 7.61 for men and 6.85 for women. The length of stay for patients with diabetes was almost twice that of the non-diabetic population (15.5 vs. 8.7 days). The relative risk of hospital mortality (diabetes vs. non-diabetes) was 2.83. Surgical procedures were carried out on 857 patients, 272 (31.2%) with diabetes. This represented an age-standardized relative risk of 31.19. The estimated cost of admissions for primary diagnose in these categories over 4 years was £ 6,128,211 ($ 9,743,855). Patients with diabetes accounted for £1,236,623 ($1,996,230), an excess of 87% attributable to the diabetic state.

CONCLUSION: Diabetes is confirmed as a significant risk factor for peripheral vascular disease, infection, neuropathy, and ulceration. The severity of these disorders in terms of increased risk of hospital mortality, length of stay, and risk of surgical procedure is also demonstrated for those patients with diabetes.

ETIOPATHOLOGY

Glucagon-Like Peptides

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Proglucagon contains the sequence of two glucagons-like peptides, GLP-1 and GLP-2, secreted from enter endocrine cells of the small and large intestine. GLP-1 lowers blood glucose in both NIDDM and IDDM patients and may be therapeutically useful for treatment of patients with diabetes. GLP-1 regulates blood glucose via stimulation of glucose-dependent insulin secretion, inhibition of gastric emptying, and inhibition of glucagons secretion. GLP-1 may also regulate glycogen synthesis in adipose tissue and muscle; however, the mechanism for these peripheral effects remains unclear. GLP- is produced in the brain, and intracerebroventricular GLP-1 in rodents is a potent inhibitor of food and water intake. The short duration of action of GLP-1 may be accounted for in part by the enzyme dipetidyl peptidase 4 (DPP-IV), which cleaves GLP-1 at the NH2-terminus; hence GLP-1 analogs or the lizard peptide exendin-4 that are resistant to DPP-IV cleavage may be more potent GLP-1 molecules in vivo. GLP-2 has recently been shown to display intestinal growth factor activity in rodents, raising the possibility that GLP-2 may be therapeutically useful for enhancement of mucosal regeneration in–patients with intestinal disease. This review discusses recent advances in our understanding of the biological activity of the glucagons-like peptides.

Molecular mimicry in diabetes mellitus: the homologous domain in Coxsackie's B virus protein 2C and islet auto antigen GAD_{65} is highly conserved in the Coxsackie's B-like enter viruses and binds to the diabetes associated HLA-DR3 molecule.

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SUMMARY: It has been proposed that molecular mimicry between protein 2C (p2C) of Coxsackie's virus B4 and the auto antigen glutamic acid decarboxylase (GAD_{65}) plays a role in the pathogenesis of insulin dependent diabetes mellitus (IDDM). In this study we show that the amino acid sequence in GAD_{65} (PEVKEE), is highly conserved in Coxsackie's virus B4 isolates as well as in different viruses of the subgroup of Coxsackie's B-like enter viruses. These are the most prevalent enter viruses and therefore exposure to the mimicry motif will be a frequent event throughout life. Presentation of the homologous peptides by HLA molecules is essential for T-cell reactivity. Therefore, we tested whether the PEVKEK motif can bind to the IDDM-associated HLA-DRl, -DR3 and –DR4 molecules. Synthetic peptides with sequences derived from p2C and GAD_{65} did bind to HLA-DR3 but not to HLA-DRl or – DR4. Replacement of amino acids within

the motif showed that the PEVKEK motif bind specifically to HLA-DR3. Moreover, both p2C and GAD_{65} peptides bind in the same position within the peptides bind in the same position within the peptide binding groove of the DR3 molecule which is an essential requirement for T-cell cross-reactivity. The results support molecular mimicry between p2C of Coxsackie's B-like enter viruses and GAD_{65}. However, this molecular mimicry may be limited to the HLA-DR3 positive subpopulation of IDDM patients. [Diabetologia (1998) 41:40-46].

Gender, Auto antibodies, and Obesity in Newly Diagnosed Diabetic Patients Aged 40-75 Years.

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OBJECTIVE: To evaluate the frequency of autoimmune markers (islet cell antibodies [ICA] and glutamic acid decarboxylase antibodies [GADA]) and clinical features in newly diagnosed people with diabetes aged 40-75 years.

RESEARCH DESIGN AND METHODS: Two hundred fifty-nine consecutive patients (aged 40-75 years) with newly suspected diabetes diagnosed during a 2-year period were studied. The diagnosis of newly discovered diabetes was confirmed in 203 patients. Gender, BMI, HbA_{1c}, fasting C-peptide, ICA, and GADA were evaluated. The frequency of obesity was estimated using two different sets of criteria1) National Diabetes Data Group (NDDG) criteria, and 2) criteria based on a Swedish reference population.

RESULTS: The annual incidence of diabetes was 106 per 100,000 people. The incidence of diabetes in those patients who were 40-54 years old was significantly higher in men than in women (odds ratio: 2.16; p=0.001). ICA were detected in 16 of 203 patients were positive for both ICA and GADA. Among the 203 diabetic patients, 19 (9.4%) were classified as having IDDM, giving an IDDM incidence of 10 per 100,000 people aged 40-75 years. The frequency of obesity in NIDDM was high but varied with its definition; the frequency of obesity was highest (p<0.001) when NDDG criteria, and not Swedish reference values, were used (57 of 75 [76%] vs. 40 of 75 [53%] for women and 66 of 109 [61%] vs. 45 of 109 [4%] for men).

CONCLUSION: A striking male preponderance was found among incident cases of diabetes in people aged 40-54 years. Autoimmune markers were detected in 10% of incident cases of diabetes in people aged 40-75 years. Using a conservative estimation, as many as 10 of 100,000 middle-aged and elderly subjects developed IDDM. The frequency of obesity in NIDDM was high but this was also the case in the reference population.

Induction of b -Cell Rest in Type 1 Diabetes. Studies on the effects of octreotide and diazoxide.

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OBJECTIVE : To evaluate the inhibitory effects of octreotide and Diaz oxide on insulin secretion in patients with type 1 diabetes and measurable levels of circulating C-peptide.

RESEARCH DESIGN AND METHODS : Diaz oxide was given to six patients during a 7-day period (100 mg three times daily), followed by a 3-week wash out. Subsequently, octreotide (50m g, three times daily) was administered subcutaneous for 7 days. Pre-and post-prandial blood glucose and serum C-peptide concentrations was measured before medication (control) and on day 7 of each medication period. Glucagons-stimulated C-peptide was determined in the morning before medication and on the day after each treatment period.

RESULTS : Diaz oxide inhibited glucagons-stimulated C-peptide secretion (mean increment 0.08 nmol/l vs. 0.18 nmol/l, $P < 0.05$), whereas octreotide had no such effect. Both reduced the pre- and postprandial serum C-peptide concentrations ($P < 0.05$), octreotide being the more potent in this respect. A reduction in basal and meal-related blood glucose was observed during octreotide treatment, whereas the glucose concentrations tended to be higher during treatment with Diaz oxide than during the 24-h control period.

CONCLUSIONS : The study indicates that the two drugs reduce insulin output by difference mechanisms. Diaz oxide inhibits hormonal release directly on the b -cells, whereas octreotide exerts its effect indirectly, presumably by multiple actions on insulin sensitivity and insulin-releasing hormones. The results suggest that each drug is capable of inducing b -cell rest in type 1 diabetes.

DIAGNOSIS

Variation of Postprandial Plasma Glucose, Palatability, and Symptoms Associated with a

Standardized Mixed Test Meal Versus 75 g Oral Glucose.

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OBJECTIVE: To compare with-subject variability of plasma glucose measured 2h after glucose tolerance test (GTT) with that of plasma glucose measured 2h after administration of a standardized test meal (diabetes screening product [DSP], Ceapro, Edmonton, Alberta, Canada) and to determine the relationship between the two sets of plasma glucose measurements.

RESEARCH DESIGN AND METHODS: Plasma glucose and insulin responses of 36 overnight-fasted subjects (10 lean normal, 9 obese normal, 9 with impaired glucose tolerance [IGT], and 8 with mild diabetes) were studied on eight different mornings after they consumed 75g oral glucose or 50g carbohydrate from the DSP. Each test meal was repeated four times by each subject. Within-subject coefficients of variation (CVs) (CV = 100 X SD/mean) of plasma glucose concentration 2h after administration of the GTT and DSP were compared by repeated measures ANOVA and linear regression analysis.

RESULTS: Mean plasma glucose 2h after administration of the DSP (D) was linearly related to that 2h after the GTT (G): G = 1.5 X D –1.6 ($r = 0.97$, $p < 0.0001$). The CV of 2h plasma glucose was significantly lower after administration of the DSP, 10.5 ± 1.0%, than after the GTT, 12.7±1.18% ($P = 0.025$). The effect of test meal on CV differed in different groups of subjects ($P = 0.018$), with the largest difference found in IGT subjects, in whom the CV after DSP administration was 47% less than after the GTT ($P = 0.0005$). The DSP was significantly more palatable and produced fewer adverse symptoms than the GTT.

CONCLUSION: Plasma glucose concentrations measured 2h after DSP administration are closely related to those measured 2h after the GTT but are more consistent than the 2-h post-GTT concentrations within the critical IGT range. This finding suggests that measurement of plasma glucose 2h after administration of the DSP may allow more precise discrimination among normal glucose levels, IGT, and diabetes than measurement of plasma glucose 2h after the GTT.

Biological Variation of Glycated Hemoglobin. Implications for diabetes screening and monitoring.

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OBJECTIVE: To assess the inherent potential of glycated hemoglobin as a screening test for type 2 diabetes by determining the biological variation in non-diabetic subjects.

RESEARCH DESIGN AND METHODS: HbA_{10} values were measured by high-performance liquid chromatography (HPLC) in 12 non-diabetic subjects (7 men and 5 women median age, 40 years [range, 21-55 years]) on 10 fortnightly occasions. The non-diabetic index of individuality (IOL) for HbA_{1c} (i.e., the square root of the ratio of intra-to inter individual variance) was determined. Any test with an IOl of 1.4 has the most potential in disease screening, while one of 0.6 will be of little value.

RESULTS: The analysis variance contributed to 9% of the total test variance, intra individual variance, 6%; and inter individual variance, 85%. The lOl was, therefore, only 0.27. Thus, non-diabetic HbA_{1c} values vary markedly between subjects, while values in the same individual change little with time. As such, to lie outside the assay reference range, the HbA_{1c} values of some non-diabetic subjects must exceed 12 SD from their usual mean value, while in others a change of only 2 SD would be sufficient.

CONCLUSIONS: This fundamental characteristic of HbA_{1c} means that even if analytical methods improve, glycated hemoglobin measurements will always be of limited value when screening for type 2 diabetes. If similar inter individual differences also exist in diabetic subjects, then patients with the same glycemic control may vary by at least 1-2%, which has implications in setting glycated hemoglobin targets.

TREATMENT

DIET

Lifestyle intervention in Overweight individuals with a family History of Diabetes.

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OBJECTIVE: To assess the effect of lifestyle intervention over 2 years on changes in weight, coronary heart disease (CHD) risk factors, and incidence of diabetes in overweight individuals with a parental history of diabetes.

RESEARCH DESIGN AND METHODS: Participants (n = 154), who were 30-100% over ideal body weight, had one or both parents with diabetes, and were currently non-diabetic, were randomly assigned to 2-year treatments focused on diet (decreasing calories and fat intake) exercise (goal of 1,500 kcal/week of moderate activity), or the combination of diet plus exercise or to a no-treatment control group. Subjects were reassessed at 6 months, 1 year, and 2 years.

RESULTS: At 6 months, the groups differed significantly on measures of eating, exercise and fitness: weight losses in the diet and diet-plus-exercise groups were significantly greater than in the exercise and control conditions. Weight losses were associated with positive changes in CHD risk factors. After 6 months, there was gradual deterioration of behavioral and physiological changes, so that at 2 years, almost no between-group differences were maintained. Differences between groups in risk of developing diabetes were of borderline significance (P = 0.08). Strongest predictors were impaired glucose tolerance at baseline, which was positively related to risk of developing, diabetes, and weight loss from baseline to 2 years, which was negatively related; in all treatment groups, a modest weight loss of 4.5 kg reduced the risk of type 2 diabetes by – 30% compared with no weight loss.

CONCLUSIONS: Although initially successful, the interventions studied here were not effective in producing long-term changes in behavior, weight, or physiological parameters. However, weight loss from 0 to 2 years reduced the risk of developing type 2 diabetes. Since modest weight loss significantly reduced risk of type 2 diabetes, further research is needed to determine how best to increase the percentage of subjects achieving at least a modest weight loss.

The Effect of Short Periods of Caloric Restriction on Weight Loss and Glycemic Control in Type 2 Diabetes.

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OBJECTIVE: To determine whether an intermittent very-low-calorie diet (VLCD) Improves weight loss and glycemic control more than moderate caloric restriction alone.

RESEARCH DESIGN AND METHODS: Individuals with type 2 diabetes (n = 54) who were [3] 20% over ideal body weight participated in a 20-week behavioral weight participated in a 20-week behavioral weight control program. Subjects were randomized to either a standard behavioral therapy (SBT) group or to one of two VLCD groups. SBT subjects received a 1,500-1,800 Kcal/day diet throughout. Both VLCD groups followed a VLCD for 5 consecutive days during week 2, followed by either intermittent VLCD therapy for 1 day/week for 15 weeks (1-day) or for 5 consecutive days every 5 weeks (5-day), with a 1,500-1,800 kcal/day diet at other times.

RESULTS: Both VLCD groups lost more weight than the SBT group over the 20 weeks (P = 0.04) Although the groups did not differ in fasting plasma glucose (FPG) changes at 20 weeks, more subjects in the 5-day group attained a normal HbA_{1c} when compared with the SBG group (P = 0.04). This benefit was independent of the effects of weight loss. The best predictor of over all change in FPG and HbA_{1c} was the FBG response during the first 3 weeks of the program.

CONCLUSIONS: Periodic VLCDs improved weight loss in diabetic subjects. A regimen with intermittent 5-day VLCD therapy seemed particularly promising, because more subjects in the group attained a normal $HbA_{1c.}$ Moreover, the glucose response to a 3-week period of diet therapy predicated glycemic response at 20 weeks, and it was a better predictor of the 20-week response than initial or overall weight loss.

Stimulation of Insulin Secretion by Fructose Ingested With Protein in People With Untreated Type 2 diabetes.

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OBJECTIVE: Ingested protein provides substrate for gluconeogenesis and strongly stimulates insulin and glucagons secretion, but it has little effect on the glucose concentration in people with type 2 diabetes. Ingested fructose also is a substrate for gluconeogenesis, modestly stimulates insulin and glucagons secretion, and has little effect on the

plasma glucose. Therefore, we were interested in determining if ingestion of fructose along with protein would result in an additive, greater than additive, or less than additive effect on circulating insulin, glucagons, and glucose concentrations.

RESEARCH DESIGN AND METHODS: Seven male subjects with untreated type 2 diabetes were fasted overnight and then were given either 25g fructose, 25g protein, 25g fructose plus 25g protein, or water only at 0800; Subjects also ingested 50g glucose on two separate occasions. Plasma glucose, insulin, C-peptide, glucagons, ???? amino nitrogen, urea nitrogen, non-esterifies fatty acids, and triglyceride concentrations were determined over the subsequent 5h.

RESULTS: The glucose concentration was only modestly increased and the area responses were similar when protein, fructose, or the combination was ingested. Thus, the glucose response to the combination was less than additive. The insulin area response to protein was 2.5-fold greater than to fructose, and the response to the two nutrients was additive and quantitatively smellier to the response to 50g glucose. The glucagons area response was less than additive, i.e. there was an interaction between the protein and fructose that resulted in a smaller than expected response.

CONCLUSIONS: When protein and fructose were ingested together, the insulin response was similar to that following ingestion of 50g glucose. It also was as expected based on the response to the individual nutrients. In contrast, the glucose and glucagons responses were significantly less than expected. These data may be useful in dietary planning for subjects with type 2 diabetes.

EXERCISE

The Association Between Diabetic Complications and Exercise Capacity In NIDDM Patients

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OBJECTIVE : Exercise capacity has been used as a noninvasive parameter for predicting cardiovascular events. It has been demonstrated previously in NIDDM patients that several risk factors (i.e., obesity, smoking, hypertension, and African-American race) are associated with an impaired exercise capacity. We studied 265 male and 154 female NIDDM patients who underwent graded exercise testing with expired gas analyses to determine the possible influences of diabetic neuropathy, nephropathy and retinopathy on exercise capacity.

RESEARCH DESIGN AND METHODS: Univariate and multiple linear regression analyses were performed to determine the relationship between diabetic neuropathy, urinary albumin excretion (UAE), and retinopathy with respect to peak oxygen consumption (VO_2). Neuropathy was assessed by neurological symptom and disability scores, autonomic function testing, and quantitative sensory exams involving thermal and vibratory sensation. Three categories of UAE were used: normal albuminuria (<20 m g/min), microalbuminuria (20-200 m g/min), and overt albuminuria (> 200 m g/min). Retinopathy was assessed by stereoscopic fundus photographs. Multiple linear regression analyses were then performed controlling for age, sex, length of diagnosed diabetes, duration of hypertension, race and ethnicity, GHb, BMI, and smoking to determine whether there was an independent effect of these diabetic complications on exercise capacity.

RESULTS : Univariate analyses revealed that the presence of diabetic retinopathy (P = 0.03), neuropathy (P = 0.002), microalbuminuria (P = 0.04), and overt albuminuria (P = 0.06) were associated with a lower peak VO_2. Multiple linear regression analyses were performed to determine independent relationships with peak VO_2. The results revealed that increasing retinopathy stage (Parameter estimate [PE] = -0.59 ± 0.3 ml. kg $^{-1}$. min-1; P = 0.026) and increasing UAE stage (PE = -0.62 ± 0.3 ml. kg^{-1}. min^{-1}; P = 0.044) were associated with a decrease in peak VO_2.

CONCLUSIONS : In the present study of NIDDM subjects, a significant independent association was demonstrated between diabetic nephropathy and retinopathy with exercise capacity. These results were obtained controlling for age, sex, length of diagnosed diabetes, hypertension, race, and BMI. Thus the finding in this large NIDDM population without a history of coronary artery disease indicate a potential pathogenic relationship between micro vascular disease and exercise capacity

INSULIN

Substitution of night-time continuous subcutaneous insulin infusion therapy for bedtime NPH insulin in a multiple injection regimen improves counter regulatory hormonal

responses and warning symptoms of hypoglycemia in IDDM.

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SUMMARY : In patients with insulin-dependent diabetes mellitus (IDDM) good glycaemic control confers an enhanced risk of hypoglycemia. Nocturnal hypoglycemia occurs frequently and contributes to the syndrome of hypoglycemia unawareness. In order to avoid nocturnal hypoglycemia we substituted night-time continuous subcutaneous insulin infusion (CSII) therapy in 14 patients with well-controlled IDDM using a multiple injection regimen for the more variable bedtime NPH insulin. During a stepwise hypoglycemic clamp we studied the effect of this regimen on counter regulatory hormonal responses, warning symptoms and cognitive function. In addition, we investigated the incidence of daytime hypoglycemia and the acceptability of night-time CSII treatment. CSII was associated with a lower frequency of hypoglycemia (mean ± SEM): 16.1 ± 3.1 vs. 23.6 ± 3.3) episodes during the last 6 weeks of treatment, p = 0.03 (CSII vs. NPH) with maintenance of good glycaemic control (HbA_{1c} 7.2 ± 0.2 vs. 7.1 ± 0.2%, p = 0.2). Hypoglycemic thresholds for the growth hormone response and for autonomic symptoms were lower for CSII treatment than for NPH treatment. Of 14 patients 6 decided to continue with the nocturnal CSII treatment. In conclusion, counter regulatory hormonal responses to hypoglycemia and is an acceptable treatment strategy for patients suffering from hypoglycemia unawareness; as demonstrated in this acute feasibility study. [Diabetology (1998) 41 : 322-329].

The Effect of the Insulin Analog Lispro on Nighttime Blood Glucose Control in Type 1 Diabetic Patients

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OBJECTIVE : Unmodified regular insulin has a long absorption tail, unlike the fast-acting insulin analog lispro, and may contribute to hypoglycemia in the early part of the night. A randomized crossover double-blind study was performed to compare blood glucose concentrations in the early part of the night in type 1 diabetic patients receiving lispro or unmodified regular human insulin, in random order, on 2 separate study days.

RESEARCH DESIGN AND METHODS : We studied 23 C-peptide-negative patients; 12 were using a premeal plus basal insulin regimen, and 11 were using twice-daily insulin injections. Patients were admitted to the investigation unit at 5:00 p.m. and received a single dose of lispro or unmodified regular human insulin before the evening meal. In both groups, the NPH insulin dose remained unchanged. Identical meals and snacks were eaten at the same time during both study days.

RESULTS : Average postprandial (6:00-10:00 p.m.) blood glucose concentrations were significantly lower after lispro therapy compared with human insulin (7.1 ± 0.4 [se] vs. 8.5 ± 0.4 mmol/l, P = 0.0002). Nighttime (midnight to 4:00 a.m.) blood glucose concentrations were significantly higher after lispro compared with human insulin (10.3 ± 0.4 vs. 9.1 ± 0.4 mmol/l, P = 0.02). This difference was greatest in patients on the premeal plus basal insulin regimen 11.6 ± 0.5 vs. 8.7 ± 0.4 mmol/l, P < 0.001). The incidence of nocturnal hypoglycemia (mid-night to 4:00 a.m., blood glucose < 3.5 mmol/l) was less with lispro compared with unmodified insulin (1 vs. 6 patients, P = 0.04). Nighttime (midtime to 4:00 a.m.) 3 – hydroxybutyrate (102 ± 13 vs. 51 ± 7 m mol/l, P = 0.000) and glycerol (52 ± 3 vs. 42 ± 2 m mol/l, p < 0.01) were significantly higher after lispro therapy compared with human insulin in patients on the premeal plus bolus insulin regimen.

CONCLUSIONS : Lispro can improve postprandial blood glucose control and reduce the incidence of nocturnal hypoglycemia at the expense of nocturnal hyperglycemia and hyperketonemia in patients using a premeal plus basal insulin regimen.

Optimal Time of Administration of Insulin Lispro Importance of meal composition.

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OBJECTIVE : To compare the glycodynamics of preand postprandial administration of insulin lispro using test meals of differing composition.

RESEARCH DESIGN AND METHODS : Twenty subjects with IDDM were studied on four separate occasions. Ten subjects ingested high-carbohydrate

and high-fat breakfasts with large liquid component, and 10 subjects ingested high-carbohydrate and high-fat break-fasts in a more solid form. With each meal, insulin lispro was injected 10 min preprandial one occasion and 20 min postprandial on another. The magnitude and temporal pattern of postprandial glucose excursions were observed.

RESULTS : With all meal types studied, postprandial blood glucose excursions were significantly smaller when insulin lispro was administered preprandially ($P < 0.05$). With both high-carbohydrate meals and the liquid high-fat meal, preprandial administration of lispro was associated with modest postprandial increments of blood glucose. With solid high-fat meal, preprandial lispro produced a cumulative decline in postprandial blood glucose, whereas blood glucose rose when lispro was administered postprandially.

CONCLUSIONS : For meals with a high carbohydrate content, the optimal time of administration of lispro is preprandial. However, for meals with a high solid fat content, post-prandial administration of lispro may be preferable.

COMPLICATIONS
GENERAL
Dietary antioxidant supplementation reduces lipid per oxidation but impairs vascular function in small mesenteric arteries of the streptozotocin-diabetic rat.

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SUMMARY : Impaired endothelium-dependent relaxation could underlie many of the vascular complications associated with insulin-dependent diabetes mellitus, and may be mediated by increased oxidative stress. The effect of antioxidants on vascular endothelial function and oxidative stress of streptozotocin-diabetic rats was assessed by dietary supplementation with vitamins E and C. Diabetic (i.v. streptozotocin, 45 mg/kg) male Sprague-Dawely rats were fed one of six supplemented diets containing 75.9 250, or 500 mg vitamin E/kg chow, 250 mg vitamin C/kg H_2), 250 mg vitamin E/kg chow plus 250 mg vitamin C/kg H_2O, or chow deficient in vitamin E, and then compared to standard-fed control rats. After 4 weeks, small mesenteric arteries were dissected and mounted on a small vessel myograph, concentration response curves were then constructed to nor adrenaline, acetylcholine and sodium nitroprusside. Acetylcholine-mediated relaxation was impaired in arteries from diabetic rats (pEC_{50} 6.701 ± SEM 0.120, n = 8) compared to controls (7.386 ± 0.078, n = 6; $p < 0.05$)./ the 500 mg/kg vitamin E diet further impaired maximum relaxation to acetylcholine (58.2 ± 10.5 vitamin E, n = 7 vs. 84.4 ± 5.3% standard, $p < 0.05$), and the combined vitamin E plus C diet impaired maximum relaxation to sodium nitroprusside (48.5 ± 4.1 in vitamin E + C, n = 8 vs. 75.6 ± 3.9% standard; $p < 0.01$). However, plasma 8-epi-prostaglandin (PG)F2a (measured as an estimate of oxidative stress) was dose-dependently decreased in rats on vitamin E supplemented diets. Dietary antioxidant supplementation did not reverse impaired endothelial function in this model of uncontrolled diabetes despite a concomitant decrease in oxidative stress. [Diabetologia (1998) 41 : 148-156].

NEPHROPATHY
Role of Glycemic Control and Blood Pressure in the Development and Progression of Nephropathy in Elderly Japanese NIDDM Patients.

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OBJECTIVE : To investigate the role of glycemic control and blood pressure in the development and progression of nephropathy and to suggest goals for glycemic control and blood pressure for the prevention of nephropathy in elderly Japanese NIDDM patients.

RESEARCH DESIGN AND METHODS : A total 123 age-and diabetes duration-matched elderly Japanese NIDDM patients (ages 60-75 years; 74 normoalbuminuric and 49 microalbuminuric) were retrospectivey studied for 6 years.

RESULTS : The group that developed microalbuminuria from normoalbuminuria (group NM: n = 24) showed a higher 6-year mean HbA_{1c} than the group that remained normoalbuminuric (group NN: n = 50; 9.0 ± 0.8 vs. 8.1 ± 0.8%, $P < 0.01$) in spite of no significant difference is 6-year mean blood pressure (MBP). On the other hand, the group that progressed from microalbuminuria to overt proteinuria (group MP: n = 26) showed a

higher 6-year MBP than the group that remained microalbuminuric (group MM: n = 23; 106 ± 5 vs. 95 ± 6 mmHg. P < 0.01) in spite of no significant difference in 8.5% (normal ranges £ 6.5%), and of MBP separating group MM from group MP was 100 mmHg.

CONCLUSIONS : Glycemic control is a more potent factor than blood pressure level on the development of microalbuminuria. However, as far as the progression of microalbuminuria to overt proteinuria is concerned, hypertension is the most crucial factor in elderly NIDDM patients. Suggested goals for glycemic control and blood pressure level for the prevention of nephropathy in elderly Japanese patients are an HbA_{1c}; of £ 8.5% (equivalent to 7.8% in the current measurement & stable HBA_{1c}; normal range £ 5.8%) and an MBP of £ 100 mmHG.

Meta-analysis of association of insertion/deletion polymorphism of angiotensin I-converting enzyme gene with diabetic nephropathy and retinopathy.

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SUMMARY : An insertion/deletion (I/D) polymorphism in the angiotensin-converting enzyme (ACE) gene has repeatedly been shown to be association of this genetic marker with diabetic microangiopathy is controversial. To assess the association of the genotypes with the development of diabetic nephropathy or retinopathy, we performed a meta-analysis of data from the literature, using Mantel-Haenzel method followed by the Breslow-Day test for assessing homogeneity among data. In a total of 4773 diabetic patients from 18 studies with (n = 2495) and without (n = 2278) renal complications, the D allele was significantly associated with diabetic nephropathy (P < 0.0001 in a dominant model (summary odds ratio 1.32, 95% confidence interval: 1.15 to 1.51). There was no significant evidence against homogeneity of the odds ratios (c 2 = 18.9, 20 df; P = 0.53). The association was significant both in non-insulin-dependent diabetes mellitus (p < 0.005) and in insulin-dependent diabetes mellitus (p < 0.05). Likewise, in a total of 2010 diabetic patients with (n = 1008) and without (n= 1002) retinopathy, there was no association of the I/D polymorphism with diabetic retinopathy. These data suggest that the ACE I/D polymorphism affects the risk for diabetic nephropathy, but not for diabetic retinopathy. [Diabetologia (1998) 41 : 47-53].

Heterogeneous nature of microalbuminuria in NIDDM: studies of endothelial function and renal structure.

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SUMMARY : Microalbuminuria (MA) is associated with microangiopathy (renal and retinal lesions) in insulin–dependent diabetic (IDDM) patients. In contrast MA does not reflect micro vascular damage in a substantial number of non-insulin-dependent diabetic (NIDDM) patients. MA predicts cardiovascular disease in NIDDM patients with increased von Will brand factor (vWF) plasma levels which are hypothesized to reflect endothelial dysfunction. However, it is not known whether MA is consequent to generalized endothelial dysfunction or to renal injury. Thus, this study evaluated vWF plasma levels in relation to renal and retinal structural abnormalities in NIDDM patients with MA. Kidney biopsies, fundoscopy and measures of vWF plasma levels were performed in 32 NIDDM patients with MA. These patients were allocated to two renal structural categories: A) Without renal structural abnormalities (C.I, n = 10): normal or near-normal renal structure, and B) With renal structural abnormalities (n = 22), further divided into: C II (n = 12) with typical diabetic nephropathology, predominantly glomerulopathy, and C lll (n = 10) with atypical patterns of renal injury (more advanced tubulo-interstitial and arteriolar than glomerular changes). vWF plasma levels were significantly higher in category B (C II: 195 ± 49% and C III: 119 ± 42%). (chi-square, p < 0.05). Diabetic retinopathy was also related to vWF plasma levels (ANOVA, p < 0.05). These data suggest that there are two types of MA in NIDDM: one associated with increased vWF levels, established renal injury and frequently retinopathy, and other characterized by normal vWF levels, normal renal structure and absent or mild diabetic retinopathy. We propose that vWF plasma levels in NIDDM patients with MA may help to identify patients with important renal structural changes, increased retinopathy risk and, perhaps, generalized endothelial dysfunction. Whether vWF plasma levels predict end-stage renal disease and

cardiovascular events deserves longitudinal studies. [Diabetologia (1998) 41 : 233-236].

Ethnic Differences in Correlates of Microalbuminuria in NIDDM. The role of the acute-phase response.

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OBJECTIVE : To investigate whether microalbuminuria is associated with markers of the acute phase response in NIDDM and whether there are ethnic differences in this association among the three main racial groups in Malaysia.

RESEARCH DESIGN AND METHODS : NIDDM patients of Chinese, Indian, and Malay origin attending a diabetic clinic in Kuala Lumpur, Malaysia, were matched for age, sex, diabetes duration, and glycemic control (n = 34 in each group). Urinary albumin-to-creatinine ratio was measured in an early morning urine sample, Biochemical measurements included markers of the acute-phase response: serum sialic acid, triglyceride, and (lowered) HDL cholesterol.

RESULTS : The frequently of microalbuminuria did not differ among the Chinese, Indian, and Malay patients (44, 41 and 47% respectively). In Chinese patients, those with microalbuminuria had evidence of an augmented acute-phase response, with higher serum sialic acid and triglyceride and lower HDL cholesterol levels; and urinary albumin-to-creatinine ratio was correlated with serum sialic acid and triglyceride. The acute-phase response markers were not different in Indians, with microalbuminuria being high in even the normoalbuminuric Indians; only the mean arterial blood pressure was correlated with urinary albumin-to-creatinie ratio in the Indians. Malay NIDDM subjects had an association of microalbuminuria with acute-phase markers, but this was weaker that in the Chinese subjects.

CONCLUSIONS : Microalbuminuria is associated with an acute-phase response in Chinese NIDDM patients in Malaysia, as previously found in Caucasian NIDDM subjects. Elevated urinary albumin excretion has different correlates in other racial groups, such as those originating from the Indian subcontinent. The acute-phase response may have an etiological role in microalbuminuria.

IATROGENIC

Effects of Glycemic Control on Protective Response against Hypoglycemia in Type 2 Diabetes.

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OBJECTIVE : To determine the effects of glycemic control on the counterregulatory responses to hypoglycemia in type 2 diabetes.

RESEARCH DESIGN AND METHODS : Seven poorly controlled type 2 diabetes controlled 2 diabetes patients (mean HbA_{1c}' 11.3 ± 1.1%) were studied by stepped hyperinsulinemic hypoglycemic clamp (nadir, 2.4 mmol/l) before and after improving glycemic control with insulin treatment. Counterregulatory hormones, symptoms, and four-choice reaction time were measured at each glucose plateau.

RESULTS : In patients with poorly controlled type 2 diabetes, counter regulatory hormone responses began at higher plasma glucose levels than did not those in healthy subjects (epinephrine, 4.4 ± 0.2 vs. 3.7 ± 0.2 mmol/l, P = 0.011). After significant improvement in glycemic control (mean HbA_{1c}' 8.1 ± 0.9%, P < 0.001) was achieved without severe hypoglycemia, hormonal responses started at much lower plasma glucose levels (e.g., epinephrine, 3.5 ± 0.3 mmol/l, P = 0.005) and were significantly reduced in magnitude (e.g., epinephrine, 3.5 ± 0.3 mmol/l, P = 0.005) and were significantly reduced in magnitude (e.g., area under epinephrine response curve, 306 ± 93 vs. 690 ± 107 nmol · min^{-1} · 1^{-1}, P = 0.012). This was accompanied from 3.6 ± 0.2 to 3.0 ± 0.2 mmol/l (P = 0.019). In contrast, the plasma glucose threshold at which four-choice reaction time deteriorated did not change significantly (3.1 ± 0.1 vs. 2.9 ± 0.1 mmol/l, P = 0.125).

CONCLUSIONS : Counter regulatory responses begin at normoglycemia in poorly controlled type 2 diabetes. Improving glycemic control with insulin therapy normalizes hormonal responses but lowers the plasma glucose levels at which hypoglycemic symptoms develop to levels associated with impairment of four-choice reaction time, a marker of cognitive function. This process potentially increases the risk of severe hypoglycemia, but to a lesser extent than occurs in type 1 disease.