Abstract Service

EPIDEMIOLOGY

Rising prevalence of NIDDM in an urban population in India.

Ramachandran A, Snehalatha C, Latha E, Vijay V, Viswanathan M. Diabetologia. 1997; 40(2): 232-7.

A survey conducted in 1988-1989, in the city of madras, south India, showed that the prevalence of diabetes mellitus in adults was 8.2% and prevalence of impaired glucose tolerance (IGT) was 8.7%. The present survey was another cross-sectional study conducted 5 years later in the same urban area to study the temporal changes in the prevalence of diabetes and IGT. The two sample populations surveyed were similar in age structure and socioeconomic factors. In the second survey in 1994-1995, a total of 2,183 subjects and 1,081 men and 1,102 women, with a mean age of 40 ± 12 years were tested by an oral glucose tolerance test; fasting and 2-h post-glucose plasma glucose were measured. Anthropometric measurements, details of physical activity and clinical history of diabetes were recorded. Age-standardised prevalence of diabetes had increased to 11.6% from 8.2% in 1989 and IGT was 9.1%, similar to 8.7% in 1989. Multiple regression analysis showed age, waist : hip ratio, body mass index (BMI) and female sex were correlated to diabetes. Family history of diabetes showed interaction with age and BMI. Prevalence of IGT correlated to age, BMI and waist: hip ratio. This study highlights the rising trend in the prevalence of non-insulin-dependent diabetes (NIDDM) in urban Indians. The persistent high prevalence of IGT may also be a predictor of a further increase in NIDDM in the future. No significant differences in the anthropometric data were noted in this compared to the previous study.

Risk for diabetes and persistent impaired glucose tolerance among middle-aged Finns.

Qiao Q, Keinanen-Kiukaanniemi S, Rajala U, Uusimaki A, Kivela SL. Diabetes Research and Clinical Practise. 1996; 33(3) : 191-8.

Among 183 middle-aged Finnish subjects with impaired glucose tolerance (IGT) defined according to the 1985 World Health Organization (WHO) criteria) who were retested on average 2.1 years after the first examination, diabetes developed in 14 (7.7%), persistent IGT in 54 (29.5%), and IGT was transient in 115 (62.8%). The odd ratio for diabetes was 4.4 (95% Confidence Interval (CI): 1.3 – 15.3) among subjects with a body mass index (BMI) of 30 Kg/m^2 or more, compared with those with a BMI of less than 30 kg/m^2. the increased in BMI during the follow-up period was also and independent risk predictor for diabetes. The odd ratios of having peristent rather than transient IGT were 3.0 (95% CI : 1.2 – 7.8) and 4.3 (95% CI : 1.5 – 12.6), among subjects with fasting insulin levels of 8.1 – 12.9 mU/1 and 13.0 mU/1 or more, respectively, compared with subjects with a fasting insulin level of no more than 8.0 mU/I. The degree of glucose intolerance and the diagnosis of hypertension at the initial examination were predictive of persistent IGT. It is evident from the present data that fasting hyperinsulinaemia forms an essential basis of persistence of IGT and diabetes, and that obesity plays a precipitating role for the deterioration from IGT to diabetes. Efforts to prevented diabetes should be focused on ways to reduce insulin resistance and obesity.

ETIOPATHOGENESIS

A higher proinsulin response to glucose loading predicts deteriorating fasting plasma glucose and worsening to diabetes in subjects with impaired glucose tolerance.

Inoue I, Takahashi K. katayama S.Harada Y, Neigishi K, Ishii J, Shibazak S, Nagai M, Kawazu S. Diabetic Medicine. 1996; 13(14:330-6.

To evaluate the clinical significance of proinsulin in determination, we measured glucose, insulin, C-peptide and proinsulin during 75-g oral glucose loading in 59 patients. In a 2.5-year follow-up study of 37 subjects with impaired glucose tolerance (IGT) at the initial test, 11 patients changed from IGT to a normal state and 5 patients showed worsening to overt Type 2 diabetes with elevation of fasting plasma glucose; 21 patients remained unchanged. Although our data showed that both fasting (IGT: p=0.4523) and 120-min plasma glucose (IGT: p=0.8168) values at the initial test were not significantly correlated with increased fasting plasma glucose levels in a 2.5-year follow-up study, subjects with a higher 120-min proinsulin response to glucose during the initial OGTT showed a significant correlation (IGT: p<0.0001) with increased fasting plasma glucose levels after follow-up period and developed Type 2 diabetes. The present finding suggest that the proinsulin response to glucose loading might be a useful indicator for predicting worsening to diabetes in subjects with impaired glucose tolerance.

Difference in the influence of maternal and paternal NIDDM on pancreatic beta-cell activity and blood lipids in normoglycaemic non-diabetic adult offspring.

Kasperska-Czyzyk T, Jedynasty K, Bowsher RR, Holloway DL, Stradowska I, Stepien K, Nowaczyk R, Szymczak W, Czyzyk A. Diabetologia. 1996; 39(7) : 831-7.

The 75-g oral glucose test was performed in 38 normoglycaemic (World Health Organization criteria) non-diabetic volunteers, aged 31-40 years, of whom 20 had a non-insulin dependent diabetic (NIDDM) mother and 18 had an NIDDM father. At the time of the study the offspring of NIDDM mothers had a somewhat higher body mass index (BMI) (males: 26.5± 1.0(mean± SEM), females: 27.5± 1.5 kg/m2) than the offspring of NIDDM fathers (males: 23.4± 0.9, females 24.2± 1.2kg/m2). There was no difference in the time-course of glycaemia; however the serum concentrations of immunoreactive insulin (IRI), C-peptide and proinsulin were significantly higher in offspring of NIDDM mothers than in offspring of NIDDM fathers; area under the curve (AUC) serum IRI: 0.928± 0.091 vs 0.757± 0.056 nmol.1-1.h-1, p+0.019; serum C-peptide: 6.379 ± 0.450 vs 4.753 ± 0.242 nmol. 1-1.h-1, p = 0.008). Serum IRI correlated with BMI, but C-peptide and proinsulin did not, and after accounting for BMI by covariance analysis they remained significantly higher in offspring of NIDDM mothers. In this group serum proinsulin was significantly higher in offspring of NIDDM mothers. In this group serum proinsulin was significantly higher in male than in female offspring (AUC serum proinsulin: 289± 68 vs 77± 27 pmol.I.h-1, P=0.015). Male offspring of NIDDM mothers also had significantly higher serum triglyceride levels than female of the same group and than offspring of NIDDM fathers. The offspring (male and female) of NIDDM mothers had slightly lower serum apolipoprotein A-I levels than the offspring of NIDDM fathers. Significant correlations were found between serum triglycerides. HDL-cholesterol and apolipoprotein B, and serum concentrations of pancreatic beta-cell peptides, mostly in the offspring of NIDDM mothers; however, they did not display

unequivocal association with gender within this group. The data are consistent with clinical observations of a greater risk of NIDDM transmission from the mother than from the father, and may suggest that male offspring are more exposed to this risk than female offspring.

Perinatal determinants among children who later develop NIDDM.

Diabetes Care. 1994; 17(10): 1154-7.

OBJECTIVE—The aim of this study was to investigate whether children who develop insulin-dependent diabetes mellitus (IDDM) differ in some aspects from a matched control group at the time of birth.

RESEARCH DESIGN AND METHODS—We studied all children who were born in Denmark during the period 1973-1977 and admitted to a Danish hospital with a diagnosis of IDDM during 1978-1989. The study was conducted by combining two nationwide registries, The National Patient Registry and The Birth Registry.

RESULTS — The criteria were fulfilled by 837 children. Data regarding the age of the parents, the number of previous pregnancies of the mother, the month of birth, and the birth weight and length of the children who developed IDDM were compared with the data of an age- and sex-matched control group of 837 children without IDDM. We did not detect any significant differences between the two groups with respect to the parameters studied.

CONCLUSIONS—Nod differences in perinatal determinants could be demonstrated among Danish children who develop IDDM compared with children without diabetes.

Short-term oestrogen replacement therapy improves insulin resistence, lipids and fibrinolysis in postmenopausal women with NIDDM.

Brussaard HE, Gevers Leuven JA, Frolich M, Kluft C. Krans HM. Diabetologia. 1997;40(7): 843-9.

Oestrogen replacement therapy is associated with a decreased risk of cardiovascular disease in postmenopausal women. Patients with non-insulin dependent diabetes mellitus (NIDDM) have an increased cardiovascular risk. However, oestrogen replacement therapy is only reluctantly prescribed for patients with NIDDM. In a double blind randomized placebo controlled trial we assessed the effect of oral 17 beta-estradiol during 6 weeks in 40 postmenopausal women with NIDDM. Glycated haemoglobin (HbA1c), insulin sensitivity, suppressibility of hepatic glucose production, lipoprotein profile and parameters of fibrinolysis were determined. The oestrogen treated group demonstrated a significant decrease of HbA1c and in the normotriglyceridaemic group a significantly increased suppression of hepatic glucose production by insulin. Whole body glucose uptake and concentrations of non-esterified fatty acids did not change. LDL-cholesterol and apolipoprotein B levels decreased, and HDL-cholesterol, its subfraction HDL2-cholesterol and apolipotrotein A1 increased. The plasma triglyceride level remained similar in both groups. Both the concentration of plasminogen activator inhibitor-1 antigen and its active subfraction decreased. Tissue type plasminogen activator activity increased significantly only in the normotriglyceridaemic group. Oestrogen replacement therapy improves insulin sensitivity in liver, glycaemic control, lipoprotein profile and fibrinolysis in postmenopausal women with NIDDM.

For a definite answer as to whether oestrogens can be more liberally used in NIDDM patients, long term studies including the effect of progestogens are necessary.

Total immunoreactive proinsulin, immunoreactive insulin and specific insulin in relation to conversion to NIDDM: the Mexico City Diabetes Study.

Haffner SM, Gonzlez C, Mykkanen L, Stern M. Diabetologia. 1997; 40(7): 830-7.

Although insulin resistance and decreased insulin secretion are characteristic of established non-insulin-dependent diabetes mellitus (NIDDM), which of these metabolic abnormalities is the primary determinant of NIDDM is still controversial. A disproportionate increase in the proinsulin to insulin ratio has been proposed as a marker of compromised insulin secretion. We examined the association of fasting immunoreactive insulin (which cross-reacts with proinsulin), specific insulin (which does not cross-react with proinsulin), total immunoreactive proinsulin (or insulin precursors), and the fasting proinsulin/specific insulin ratio to the risk of developing NIDDM in the 3.25-year follow-up of the Mexico City Diabetes Study. These measurements were made in 85 subjects who subsequently converted to NIDDM (prediabetic subjects) and in 85 age and gender matched subjects who remained non-diabetic at follow-up (control subjects). Immunoreactive insulin, proinsulin and the proinsulin/specific insulin ratio were significantly higher in prediabetic than in control subjects. However, the relation between specific insulin and the development of NIDDM was weaker than for proinsulin or immunoreactive insulin. After further adjustment for obesity, body fat distribution and glucose tolerance status, proinsulin and the proinsulin/specific insulin ratio, but not specific or immunoreactive insulin, predicted conversion to NIDDM. A high proinsulin/specific insulin ratio predicted conversion to NIDDM both in subjects normal and those with impaired glucose tolerance at baseline. We conclude that in prediabetic subjects increased proinsulin, a marker of islet cell distress or compromised insulin secretion, is associated with rapid conversion (within 3.25 years) to NIDDM even in obese populations.

Prevalence of NIDDM and impaired glucose tolerance in a rural and an urban population in Cameroon.

Mbanya JC, Ngogang J, Salah JN, Minkoulou E, Balkau B. Diabetologia. 1997; 40(7): 824-9.

The adoption of Western lifestyles is known to lead to increasing prevalence of non-insulin-dependent diabetes mellitus in Africa, yet epidemiological studies using standardised methods are rare. The prevalence of diabetes and impaired glucose tolerance was determined in a rural and an urban community in Cameroon using the 75-g oral glucose tolerance test and the World Health Organization diagnostic criteria in 719 rural (292 men, 427 women) and 1048 urban (458 men, 590 women) subjects aged 24-74 years. The response rate was 95 and 91% for the rural and urban population; respectively. The age-standardized prevalence of diabetes in the rural and urban population was respectively 0.9% (95% confidence interval (0.2-2.7) and 0.8% (0.2-1.8) for men and 0.5% (0.1-1.6) and 1.6% (0.7-3.1) for women, and that of impaired glucose tolerance was 5.8% (3.3-9.4) and 1.8% (0.9-3.2) for men, and for women, 2.2% (1.0 – 4.0) and 2.0% (0.6-4.5). Although for both men and women the body mass index was higher at all ages in the urban than in the rural area, the 2-hr plasma glucose, even after adjustment for age and body mass index, the 2-hr plasma glucose, even after adjustment for age

and body mass index, was significantly higher in the rural than in the urban area ($p<0.005$, $p<0.002$ for men and women, respectively). There was a female excess of diabetes in the urban area and an equal sex distribution in the rural area. In the rural area 67% (4 of 6) of diabetic subjects were unknown before the survey, compared with 57% (8 of 14) in the urban area. These data indicate a low prevalence of diabetes in Cameroon; however, the prevalence of impaired glucose tolerance suggests an early stage of diabetes epidemic.

Autoantibodies associated with presymptomatic insulin-dependent diabetes mellitus in women.

Whittingham S, Byron SL, Tuomilehto J, Zimmet PZ, Myers MA, vidgren G, Rowley MJ, Feeney SJ, Koskela P, Tuomilehto-Wolf E, Mackay IR. Diabetic Medicine. 1997;14(8): 678-85.

Presymptomatic autoantibody markers of insulin-dependent (Type 1) diabetes mellitus (IDDM) are less well characterized in adults than in children. We quantitated anti-GAD, anti-ICA512 and ICA by titration to endpoint and compared frequencies and levels in 139 Finnish women from who 390 serum samples had been archived during antecedent pregnancies for 10 years before and up to 1 year after diagnosis of diabetes. Also, we compared the autoantibody status in adults with IDDM with that of children with newly diagnosed IDDM. Of the 35 women seropositive for 1 or more autoantibodies 77% developed IDDM, 11% non-insulin-dependent (Type 2) diabetes mellitus (NIDDM), 9% gestational diabetes mellitus requiring insulin (GDM-ins) and 3% GDM controlled by diet. The frequency of antibodies during the 10-year presymptomatic period was 83% for anti-glutamic acid decarboxylase (GAD), 52% for anti-ICA512 and 41% for islet cell antibodies (ICA) for those who developed IDDM, 25%, 17%, and 0% for NIDDM, 12%,4%, and 8% for GDM-ins and 1%,0%, and 1% for GDM-diet, Anti-GAD was found most consistently in early samples: 13 of 15 with a single autoantibody at their first test had anti-GAD. Among those who developed IDDM, the frequency of anti-GAD was constant, anti-ICA512 increased threefold,and ICA increased slightly before diagnosis. Levels of the autoantibodies varied between subjects, but were relatively stable in individual subjects. Comparison of tests on the women, and children after diagnosis of IDDM, showed the frequencies and levels to be the same for anti-GAD but lower for anti-IGA512 and ICA in adults. Our observations show in women the long latency of seropositivity before overt IDDM, the predominance of anti-GAD among these serological markers, and the presence of these markers in NIDDM presumably representing a NIDDM phase of autoimmune insulitis.

Diabetes in British South Asians: nature, nurture, and culture.

Greenhalgh PM. Diabetic Medicine. 1997; 14(1): 10-8.

Diabetes mellitus and its complications account for a high proportion of avoidable morbidity and premature mortality in people of South Asian origin living in the UK. This review examines available of evidence as to why this might be and what can be done to address the problems. The sources for data were a Medline search by MeSH terms, free text and key authors by name, and relevant references, searched by hand, from all review articles in the AIM journals, up to April 1996. Most trials identified were epidemiological surveys. The high instance of diabetes and some of its complications do not have a single explanation. The early incidence of diabetes and its link with coronary heart disease may be partially explained by the central adiposity-insulin resistance syndrome. Predisposition to this is probably largely genetic but exacerbated by other factors such as diet, immuneinflammatory changes, and physical activity levels. There is less evidence to support conventional dietary risk factors and some for potentially deleterious effects of traditional Western dietary advice in this population. The impact of the genetic and environmental influences is exacerbated by suboptimal use of health services. The contribution of economic deprivation to the poor outcome of diabetes in these patients may be substantial. There is a considerable impact of psychosocial stress on morbidity, supporting the view that a narrow biomedical model will neither fully explain the problem nor provide solutions. To be successful, strategies for the secondary prevention of diabetes complications in British South Asians need to be incorporate a number of paradigms: genetic physiological, psychological, anthropological, and sociological. Recommendations for a multidimensional approach to this important clinical issue are proposed.

Abnormal regulation of hepatic glucose output in maturity-onset diabetes of the young caused by a specific mutation of the glucokinase gene.

Tappy L, Dussoix P. Iynedjian P, Henry S, Schneiter P, Zahnd G, Jequier E, Philippe J. Diabetes. 1997; 46(2): 204-8.

A subtype of maturity-onset diabetes of the young (MODY) is caused by mutations of the glucokinase gene, an enzyme expressed in pancreatic beta-cells and the liver. To assess the consequences of a functional alteration of glucokinase at the level of the liver, endogenous (hepatic) glucose production and glucose cycling (an indirect, assessment of hepatic glucose production and glucokinase activity) were measured with 2-2H glucose and 6, 6-2H glucose in patients who developed MODY because of the V203A mutation of glucokinase, and in control subjects at similar levels of glycemia. Measurements were performed in the postabsorptive state and after ingestion of 13C-labeled glucose. In the postabsorptive state, MODY patients had normal glucose production (10.9± 1.3 vs. 11.3± 0.6 micromol x kg (-1) x min (-1)) but decreased glucose cycling (0.6± 0.3 vs. 1.5± 0.3 micromol x kg(-1) x min(-1); $P<0.05$) when compared with control subjects. However, at plasma glucose and insulin levels similar to those observed in MODY patients, control subjects' glucose production was markedly lower (3.2± 1.5 micromol x kg(-1) x min(-1). After glucose ingestion, endogenous glucose production was reduced by only 29% in MODY patients compared with 80% in control subjects the V203A mutation of glucokinase results in decreased activity of glucokinase in liver cells. Thus endogenous glucose production is inadequately inhibited by hyperglycaemia in MODY patients, possibly as a result of impaired hepatic glucokinase activity. These alterations contribute to the pathogenesis of hyperglycemia.

Childhood size is more strongly related than size at birth to glucose and insulin levels in 10-11 year-old children.

Whincup PH, Cook DG, Adshead F, Taylor SJ, Walker M, Papacosta O, alberti KG. Diabetologia. 1997; 40(3): 319-26.

In adults low birthweight and thinness at birth are associated with increased risk of glucose intolerance and non-insulin-dependent diabetes mellitus. We have examined the relations between size at birth (birthweight, thinnes at birth) and levels of plasma glucose and serum insulin in children, and compared them with the effects of childhood size. We performed a school-based survey of 10-11-year-old British children (response rate 64%) with measurements made after an overnight fast. One

group of children (n=591) was studied fasting while the other (n=547) was studied 30 min after a standard oral glucose load (1.75 g/kg). Serum insulin was measured by a highly specific ELISA method. Birthweight was assessed by maternal recall and thinness at birth using birth records. Neither fasting nor post-load glucose levels showed any consistent relationship with birthweight or ponderal index at birth. After adjustment for childhood height and ponderal index, both fasting and post-load insulin levels fell with increasing birthweight. For each kg increase in birthweight, fasting insulin fell by 16.9% (95% confidence limits 7.1 – 25.8%, p=0.001) and post-load insulin by 11.6% (95% confidence limits 3.5 – 19.1%, p=0.007). However, the proportional change in insulin level for a 1 SD increase in childhood ponderal index was much greater than that for birthweight (27.2% and -8.8%, respectively, for fassting insulin). We conclude that low birthweight is not related to glucose intolerance at 10-11 years, but may be related to the early development of insulin resistance. However, in contemporary children obesity is a stronger determinant of insulin level and insulin resistance than size at birth.

Association between neonatal blood pressure and umbilical cord insulin concentration.

Simmons D. Diabetic Medicine. 1997; 14(3): 196-9.

The aetiology of the metabolic syndrome remains unknown. This study investigated whether two components of this syndrome, higher blood pressure and higher plasma insulin concentrations, are related at birth. Neonates in the study were from 23 European,25 Maori, 22 South Asian, and 25 Pacific Islands women having normal singleton pregnancies as well as 6 Maori, 5 Indian, and 19 Pacific Islands women with gestational diabetes (diagnosed by a 3 h 100 g oral glucose tolerance test at 28-32 weeks). Additional fasting glucose and fructosamine concentrations were measured at 36-38 weeks. Umbilical cord blood was taken for insulin, C-peptide, fructosamine and insulin-like growth factor I. Neonatal anthropometry and blood pressure were measured 24 h after delivery. Compared with those with a lower systolic blood pressure (SBP), neonates with a higher SBP had higher umbilical cord insulin (45.6 (39.6 – 52.8) vs 63.0 (54.6 – 72.6) pM, p<0.01), C-peptide (0.22(0.20 – 0.25) vs 0.28(0.26 – 0.30) nmol I-1, p<0.001) and fructosamine concentrations, higher maternal fructosamine concentrations and heavier placentas. These data suggest that neonatal hyperinsulinaemia, possibly driven by minor elevations in maternal glycaemia, may be linked to a higher neonatal SBP.

Identification of 14 new glucokinase mutations and description of the clinical profile of 42 MODY-2 families.

Velho G, Blanche H, Vaxilaire M, Bellanne-Chantelot C, Pardini VC, Timsit J, Passa P, Deschamps I, Robert JJ, Weber IT, Marotta D, Pilkis SJ, Lipkind GM, Bell GI, Froguel P. Diabetoloigia. 1997; 40(2): 217-24.

Mutations in glucokinase are associated with defects in insulin secretion and hepatic glycogen synthesis resulting in mild chronic hyperglycaemia, impaired glucose tolerance or diabetes mellitus. We screened members of 35 families with features of maturity-onset diabetes of the young for mutations in the glucokinase gene and found 16 different mutations. They included 14 new mutations in the glicokinase gene: 9 missence mutations (A53S, G80A, H137R, T168P, M210T, C213R, V226M, S336L and V367M); 2 nonsense mutations (E248X and S360X); a deletion of one nucleaotide resulting in a frameshift (V401del1); a substitution of a conserved nucleaotide at a splice acceptor site (L122-1G→ T); and a 10 base pair deletion that removed the GT of the splice donor site and the following eight nucleotides (K61+2del10). In addition, we found two previously identified mutations; R186X and G261R. Study of 260 subjects with glucokinase deficient hyperglycaemia from 42 families with 36 different GCK mutations made it possible to define the clinical profile of this subtype of non-insulin-dependent diabetes mellitus (NIDDM). Hyperglycaemia due to glucokinase deficiency is often mild (fewer than 50% of subjects of overt diabetes) and is evident during the early years of life.

MANAGEMENT

GENERAL

Improved biocompatibility but limited graft survival after purification of alginate for microencapsulation of pancreatic islets.

De Vos P, De Haan BJ, Wolters GH, Strubbe JH, Van Schilfgaarde R. Diabetologia. 1997; 40(3): 262-70.

Graft failure of alginate-polylysine microencapsulated islets is often interpreted as the consequence of a non-specific foreign body reaction against the microcapsules, Initiated by impurities present in crude alginate. The aim of the present study was to investigate if purification of the alginate improves the biocompatibility of alginate-polylysine microcapsules. Alginate was purified by filtration, extraction and precipitation. Microcapsules prepared from crude or purified alginate were implanted in the peritoneal activity of normoglycaemic AO-rats and retrieved at 1,2,3,4,6,9, and 12 months after implantation. With crude alginate, all capsules were overgrown within 1 month after implantation. With purified alginate, however, the portion of capsules overgrown was usually less than 10%, even at 12 months after implantation. All recipients of islet allografts in capsules prepared of purified alginate became normoglycaemic within 5 days after implantation, but hyperglycaemia reoccurred after 6 to 20 weeks. With intravenous and oral glucose tolerance test, all recipients had impaired glucose tolerance and insulin responses were virtually absent. After graft failure, capsules were retrieved (80-100%) by peritoneal lavage. Histologically, the percentage of overgrown capsules was usually less than 10% and maximally 31%. This small portion cannot explain the occurrence of graft failure. The immunoprotective properties of the capsules were confirmed by similar if not identical survival times of encapsulated islet allo-and isografts. Our results show that purification of the alginate improves the biocompatibility of alginate-polylysine microcapsules. Nevertheless, graft survival was still limited, most probably as a consequence of a lack of blood supply to the encapsulated islets.

INSULIN THERAPY

Effects of short-acting insulin analog [Lys(B28), Pro(B29)] on postprandial blood glucose control in IDDM.

Torlone E, Pampanelli S, Lalli C, Del Sindaco P, Di Vincenzo A, Rambotti AM, Modarelli F, Epifano L, Kassi G, Perriello G, Brunetti P, Bolli G. Diabetes Care. 1996; 19(9): 945-52.

OBJECTIVE: To establish the effects of the short-acting insulin analog Lispro versus human regular insulin (Hum-R) on post-prandial metabolic control in IDDM.

RESEARCH DESIGN AND METHODS: Four studies were performed in 10 C-peptide-negative IDDM patients. Lispro or Hum-R+NPH were injected subcutaneously 30 min (Hum-R) or 5 min (Lispro) before lunch. Preprandial plasma glucose intravenous insulin.

RESULTS: After subcutaneous Lispro injection, plasma free insulin (FIRI) was greater between 0 and 2 h (233 ± 22 pmol/l) than after Hum-R (197 ± pmol/l) but lower between 2.25 and 7 hr (81± 10 vs. 104± 13 pmol/l, p<0.05). After Lispro, PG was lower versus Hum-R for 3 h (7.4± 0.6 vs. 8.3± 0.9 mmol/l) but subsequently increased more than after Hum-R (3.25-7h, 11.3± 1 vs. 9.6± 1.2 mmol/l), resulting in a 7-h FIRI to 110± 11 pmol/l and decreased the 3.25-to 7-h PG to 7.7± 0.8 pmol/l, resulting in 0-to 7-hr PG (7.3± 0.3 mmol/l) lower than after Hum-R+NPH (7.9± 0.5 pmol/l) (P<0.05).

CONCLUSIONS: At meals, in order for Lispro to improve post-prandial blood glucose not only at 2-hr, but also over a 7-hr period in C-peptide-negative IDDM, basal insulin must be optimally replaced.

ISLET TRANSPLANTATION

Islet transplantation in IDDM patients.

Secchi A, Socci C, Maffi P, Taglietti MV, Falqui L, Bertuzzi F, De Nittis P, Piemonti L, Scopsi L, Di Carlo V, Pozza G. Diabetologia. 1997; 40(2): 225-31.

This single-centre study investigated parameters that positively correlated with the success rate after islet allotransplantation in insulin-dependent diabetic (IDDM) patients. Twenty-one intrahepatic, fresh islet transplantations were performed in 20 IDDM patients (one patient had two transplants), after or simultaneous with kidney transplantation. The correlation between number and purity of transplanted islets and final outcome was investigated. One patient died of a cardiac arrest several hours after islet transplantation; this patient was not included in the follow-up analysis. Three patients (15%) experienced acute, irreversible, early failure of islet function, which was considered as a 'presumed rejection'. Nine patients (45%) achieved either complete insulin-independence (seven cases) or a reduction (>50%) of exogenous insulin requirement'. Nine patients (45%) achieved either complete insulin-independence (seven cases) or a reduction (>50%) of exogenous insulin requirement (two cases), with sustained serum C-peptide secretion (0.89 ± 0.04 nmol/l; duration: 21 ± 7 months, range 2-58 months). Liver biopsy, performed 3 years after transplantation in one successful case, showed normal islets within the hepatic parechyma. eight cases (40%) did not show any metabolic effect of islet transplantation, with low serum-petide levels ('presumed function exhaustion'). Metabolic investigations performed in successful cases showed an early phase of insulin release after arginine, mild and reversible postprandial hyperglycaemia and normal HbA1c levels. Success of islet transplantation positively correlates with the number (p<0.05) of the transplanted islets. Islet transplantation is a safe procedure, with 45% success rate, in terms of insulin-independence or relevant reduction of exogenous insulin requirement, although success can be transient.

MONITORING CONTROL

Self monitoring of blood glucose in blind diabetic patients.

Windecker R, Heinemann L. Sawicki PT. Diabetic Medicine. 1997; 14(8): 703-6.

Blind diabetic patients face particular difficulties in blood glucose self monitoring (BGSM). We investigated the quality of BGSM in blind and severely visually impaired diabetic patients and assessed the effects of training in BGSM using a blood glucose meter with voice edition of values and a modified test strip holder for easier placement of blood samples on the strip (One Touch II talk (OT II). Twenty-six insulin-treated diabetic patients (23 IDDM and 3 NIDDM) participated. At baseline the quality of BGSM was checked in 14 patients who already regularly performed BGSM without external help. Thereinafter all 26 patients received an extensive instruction in BGSM for blind patients. At re-examination, after a mean period of 41 days, the quality of BGSM performed by the patients without assistance was checked in three different blood samples. Blood glucose was measured in the same sample by a routine laboratory method. At baseline the mean absolute difference between BGSM and the reference method was –0.3mmol I(1) (range; ± SD) (-7.7-4.8; ± 2.6mmol I(-1); 74% of BGSM measurements deviated by more than 10% from the reference values and 43% by more than 20%. At follow-up all 26 patients reported daily BGSM without external help. The mean absolute difference between BGSM and the reference method was –0.1 (-2.7 – 2.8; ± 0.9mmol I(-1); 25% of BGSM measurements deviated by more than 10% from the laboratory reference values and 5% by more than 20%. The results of this study suggest that a substantial number of blind diabetic patients do not perform BGSM on their own at all and in those who do the reliability of the results is poor. However, after extensive instruction, the majority of blind diabetic patients should be able to perform BGSM and to obtain reliable results.

COMPLICATIONS

GENERAL

The effect of glycaemic control and the introduction of insulin therapy on retinopathy in non-insulin-dependent diabetes mellitus.

Henricsson M, Nilsson A, Janzon L, Groop L. Diabetic Medicine. 1997: 14(2): 123-31.

To study the progression of diabetic retinography in relation to diabetes treatment and glycaemic control in patients with non-insulin dependent (Type 2) diabetes mellitus (NIDDM), we performed a prospective study in cohort of 1378 diabetic patients, aged > or =40 years at diagnosis, of who 333 were treted with insulin, and 1045 with oral antihyperglycaemic agents or diet alone. In the latter group 174 patients changed to insulin therapy during follow-up. We used the Wisconsin scale to grade retinopathy, recorded blindness (visual acuity < or = 0.1) and visual impairment (visual acuity 0.2 – 0.4), and measured the average HbA1c for each patient during a mean 3.1 year study period. In a multivariate analysis, patients who changed treatment from oral agents or diet alone to insulin therapy had a relative risk of 2.0 (95% confidence interval 1.7 – 2.3) for progression of retinopathy > or = 3 levels compared with all other patients in the study. The increase in risk remained even after controlling for mean HbA1c (relative risk 1.6; 95% confidence interval 1.3 – 1.9). Progression > or = 3 levels was significantly associated with a higher incidence of macular oedema and deterioration of visual acuity (p < 0.001). The relative risk for blindness/visual impairment due to retinopathy was 2.7 (95% confidence interval 1.8 - 4.0) in the group with changed treatment compared with all the other patients in the study. Poor glycaemic control (Hba1c%) before the start of insulin therapy and any retinopathy at baseline were significant risk factors for progression in the group with changed treatment (both p<0.01). In the whole study group, poor glycaemic control was significantly associated with retinopathy progression > or = 3 levels; the relative risk for those having mean HbA1c above the median being 1.7 (95% confidence interval having mean HbA1c value below the median. Moderate non-proliferative diabetic retinopathy at baseline was also associated with progression (relative risk 2.5; 95% confidence interval 1.4 – 4.5). In contrast, new insulin treatment at baseline was not associated with an increased risk

of retinopathy progression. In conclusion, while hyperglycaemia was a risk factor for the progression of retinopathy in all patients, change of treatment from oral drugs to insulin was associated with a 100% increased risk of retinopathy progression and a 3-fold increased risk of blindness/visual impairment.

Hypertension in Diabetes Study IV. Therapeutic requirements to maintain tight blood pressure control.

Anonymous. Diabetologia. 1996; 39(12): 1554-61.

We report the efficiency of therapy over 5 years follow-up in 758 non-insulin-dependent diabetic patients in a prospective, randomised controlled study of therapy of mild hypertension. Patients were recruited who on antihypertensive therapy had systolic blood pressure over 150mmHg or diastolic over 85mmHg. or if not on therapy had systolic blood pressure over 160mmHg or diastolic over 90mmHg. Their mean blood pressure at entry to the study was 160/94mmHg at a mean age of 57 years. They were allocated to tight control (aiming for systolic<150/diastolic<85 mmHg) or to less tight control (aiming for systolic <180/diastolic < 105mmHg). The tight control group were allocated to primary therapy either with a beta blocker (atenolol) or with an angiotensin converting enzyme inhibitor (captopril), with addition of other agents as required. Over 5 years, the mean blood pressure in the tight control group was significantly lower (143/82 vs 154/88mmHg, $p < 0.001$). No difference was seen between those allocated to atenolol or captopril. The proportion of patients requiring three or more antihypertensive therapies to maintain tight control in those allocated to atenolol or captopril increased from 16 and 15%, respectively at 2 years to 25 and 26%, respectively at 5 years, whereas in the less tight control group at 2 and 5 years only 5 and 7%, respectively required three or more therapies. There was no difference in the incidence of side effects or hypoglycaemic episodes between those allocated to atenolol or captopril, but those allocated to atenolol increased their body weight by a mean of 2.3 kg compared with 0.5 kg in those allocated to captopril ($p < 0.01$). Allocation to atenolol was also associated with small increase in triglyceride, and decreases in LDL and HDL cholesterol, which are of uncertain clinical relevance. The study is continuing to determine whether the improved blood pressure control, which was obtained, will be beneficial in maintaining the health of patients by decreasing the incidence of major clinical complications, pricipally myocardial infarction and strokes, and microvascular complications, such as severe retinopathy requiring photocoagulation and deterioration of renal function.

Thrombolytic therapy in diabetic patients with acute myocardial infarction.

Hansen HH, Khaergaard SC, Bulow I, Fog L, Christensen PD. Diabetes Care. 1996; 19(10): 1135-7.

OBJECTIVE: To compare the frequency of thrombolytic therapy in diabetic and nondiabetic patients with acute myocardial infarction (MI) and to examine why some diabetic patients do not receive thrombolytic therapy.

RESEARCH DESIGN AND METHODS: Retrospective study of all diabetic patients with acute MI admitted to the coronary care unit of Aalborg Hospital within a 3-year period.

RESULTS: Only 35% (43 of 123) of patients with diabetes compared with 47% (404 of 856) of patients without diabetes received thrombolytic therapy ($P < 0.002$). There was no difference in the percentage of patients thrombolyzed among patients admitted to the hospital within 12 hrs after onset of symptoms. Of diabetic patients who were not thrombolyzed, 60% (48 of 80) arrived at the hospital later than 12 hrs after onset of symptoms. Among patients who arrived late, 63% (35 of 56) had Q wave infarction and 84% (47 of 56) had symptoms typical of acute MI. Mortality was 29% (16 of 56) in this group. Only one patient did not receive thrombolytic therapy due to diabetic retinopathy.

CONCLUSIONS: Significantly fewer diabetic patients received thrombolytic therapy compared with patients without diabetes. The main reason diabetic patients did not receive thrombolytic therapy was late arrival to the hospital.

Glomerular hyperfiltration is associated with blood pressure abnormalities in normotensive normoalbuminuric IDDM patients.

Pecis M, Azevedo MJ, Gross JL. Diabetes Care. 1997; 20(8): 1329-33.

OBJECTIVE: To analyze the blood pressure patterns in normoalbuminuric IDDM patients with glomerular hyperfiltration.

RESEARCH DESIGN AND METHODS: a controlled cross-sectional study of 38 normotensive normoalbuminuric (urinary albumin excretion rate < 20 micrograms/min) IDDM patients (18 hyperfiltering [glomerular filtration rate > 134 ml. min- 1 1.73m-2] and 20 normofiltering) and 20 normal individuals matched for age, sex, and BMI was performed. The 24-hrs ambulatory blood pressure was monitored using an auscultatory technique (Pressurometer IV, Del Mar Avionics), the glomerular filtration rate was measured by 51Cr-labelled EDTA, and the 24-hrs urinary albumin excretion rate by radiommunoassay.

RESULTS: Mean nocturnal diastolic blood pressure was higher in hyperfiltering IDDM patients (70.4 ± mmHg), when compared with the control group; (65.1 ± 5.3mmHg, P=0.04). Diastolic blood pressure night : day ratio was higher in hyperfiltering IDDM patients (85.9 ± 8.6%), when compared with normofiltering IDDM patients (85.9 ± 4.8%) and control subjects (87.0 ± 6.8%, P=0.02). In IDDM patients, the glomerular filtration rate significantly correlated with the diastolic blood pressure night : day ratio (r=0.5, P=0.002), extracellular volume (r=0.04, P=0.002), and HbA1 (r=0.3, P=0.03). In stepwise multiple regression analysis, factors associated with glomerular filtration rate were diastolic blood pressure night : day ratio, extracellular volume, and HbA1 (adjusted r2 = 0.27, P = 0.003).

CONCLUSIONS: Glomerular hyperfiltration is associated with higher nocturnal diastolic blood pressure and with a blunted nocturnal decrease in diastolic blood pressure levels in normotensive and normoalbuminuric IDDM patients.

Healing rates of diabetic foot ulcers associated with midfoot fracture due to Charcot's arthropathy.

Lavery LA, Armstrong DG, Walker SC. Diabetic Medicine. 1997; 14(1): 46-9.

The aim of this study is to compare the effectiveness of total contact casts based on wound location in groups of patients with diabetes mellitus with neuropathic ulcerations under the forefoot and patients with midfoot ulcerations associated with acute Charcot's arthropathy. Twenty-five consecutive diabetic

patients with Meggitt-Wagner grade I neuropathic foot ulcerations (NU) and 22 consecutive diabetic patients with neuropathic ulceration and acute Charcot's arthopathy (CU) were selected for study. Larger wounds took longer to heal in both the CU ($p < 0.0001$) and NU groups ($p < 0.0001$). Duration of ulcer prior to treatment also was significantly associated with increased healing time in both groups ($p = 0.008$ NU, $p = 0.03$ CU). The CU group had larger wounds (10.3 ± 4.6 vs 7.7 ± 4.0 cm2, $p=0.04$) but took significantly less time to heal (28.4 ± 13.0 vs 38.8 ± 21.3 days, $p=0.001$). In this study, subjects with ulcerations secondary to acute charcot fractures healed more rapidly than in previous reports with healing times of forefoot neuropathic ulcers similar to previous studies. Every patient's ulcer healed. There were no cast-related ulcerations, infections, or hospitalizations. Concerns regarding the safety of total contact casts to treat well-vascularized superficial forefoot and midfoot plantar wounds appear to be unfounded.

Supplemental myo-inositol prevents L-fucose-induced diabetic neuropathy.

Sima AA, Dunlap JA, Davidson EP, Wiese TJ, Lightle RL, Greene DA, Yorek MA. Diabetes. 1997; 46(2): 301-6.

Nerve myo-inositol depletion, which has been implicated in the pathogenesis of acute experimental diabetic neuropathy, can be reproduced in normal rats by feeding diets enriched in L-fucose, a competitive inhibitor of sodium-dependent myo-inositor transport. Previously, we reported that L-fucose feeding for 6 weeks reproduces the effect of experimental diabetes on nerve Na+-K+-ATPase activity and conduction velocity, which can be prevented by simultaneous dietary myo-inositol supplementation. To further validate this model of myo-inositol depletion, we examined the effects of long-term (24-week) L-fucose feeding and dietary myo-inositol supplementation on nerve Na+-K+-ATPase, nerve conduction velocity, and myelinated nerve fiber pathology. After 24 weeks of L-fucose enriched (10 or 20%) diets, nerve conduction velocity, all of which were completely prevented by 1% dietary myo-inositol. Twenty percent L-fucose diet resulted in significant axonal atrophy, paranodal swelling ($P < 0.001$), and paranodal demyelination ($P < 0.005$), without increasing Wallerian degeneration or nerve fiber loss, a pattern qualitatively similar to that seen in early murine diabetic neuropathy. Dietary myo-inositol supplementation prevented these structural changes and increased nodal remyelination, supporting a role of myo-inositol depletion in the genesis of early diabetic neuropathy. The L-fucose model system may therefore serve as an experimental tool to elucidate the pathophysiological role of isolated myo-inositol depletion and its consequences in the multifactorial pathogenesis of diabetic neuropathy.

Polymorphism in the 5'-end of the aldose reductase gene is strongly associated with the development of diabetic nephropathy in Type 1 diabetes.

Heesom AE, Hibberd ML, Millward A, Demaine AG. Diabetes. 1997; 46(2): 287-91.

Recent studies suggest that the gene encoding aldose reductase (ALR2), the enzyme that converts glucose to sorbitol, may confer susceptibility to microvascular disease. DNA from 275 British Caucasian patients with Type 1 diabetes and 102 normal healthy control patients were typed for a (CA)n dinucleotide repeat polymorphic marker in the 5'-region of the ALR2 gene using polymorase chain reaction (PCR). A highly significant decrease in the frequency of the Z+2 allele was found in patients with nephropathy (nephropathy group) compared with those with no complications after a 20-year duration of diabetes (uncomplicated group) (12.7 vs 38.2%, respectively, $chi2 = 18.6$, $P < 0.00001$); this was accompanied by an increase in the Z-2 allele in the nephropathy group (32.0 vs 12.7% in the uncomplicated group). The nephropathy group also had a significant decrease in the Z/Z+2 genotype compared with the uncomplicated patients (10.7 vs. 44.7%, $chi2=16.0$, $P<0.0001$) and an increased frequency of the Z/Z-2 genotype. There as no significant association with diabetic retinopathy. These results demonstrate that the ALR2 gene may play a role in susceptibility to diabetic nephropathy; individuals with the Z+2 allele are more than seven times less likely to develop diabetic renal disease than those without this marker. This marker may prove valuable in screening for patients with diabetic nephropathy at diagnosis of diabetes.

Salt restriction reduced hyperfiltration, renal enlargement, and albuminuria in experimantal diabetes.

Allen TJ, Waldron MJ, Casley D, Jerums G, Cooper ME. Diabetes. 1997; 46(1): 19-24.

The effects of dietary salt restriction on the renin-angiotensin system, glomerular filtration rate (GFR), renal size, and albuminuria were assessed in streptozotocin diabetic rats. Two series of experiments were performed: one short-term with servere salt restriction and the second long-term with moderate salt restriction. The first studied the effect of a very-low-salt diet for 4 weeks on GFR, renal size, and plasma angiotensin II concentration in diabetic and control rats. Diabetes was associated with a 49% increase in GFR, a 34% increase in kidney weight, and an 85% reduction in plasma angiotensin II when compared with control rats ($P < 0.001$). Sodium restriction in diabetic rats reduced GFR, restored plasma angiotensin II to control values, and retarded kidney growth when compared with diabetic rats receiving a normal sodium diet. GFR correlated negatively with plasma angiotensin II ($r=-0.65$, $P < 0.001$) and positively with kidney weight ($r=0.66$, $P < 0.001$). In the second experiment, serial measurements of albuminuria and GFR were performed in control, diabetic, and salt-restricted (0.05% NaCI) control and diabetic rats over 24 weeks. Albuminuria showed a continuous rise in the diabetic rats when compared with control rats. Salt restriction attenuated the increase in albuminuria over the whole study period as well as reducing blood pressure and kidney weight in the diabetic rats. In conclusion, sodium restriction was associated with a lower GFR and kidney weight after 4 weeks and reduced levels of albuminuria, kidney weight, and blood pressure after 24 weeks in diabetic rats. Salt restriction may have an important role in the prevention and treatment of diabetic nephropathy.

Evaluation of risk factors for the development of nephropathy in patients with IDDM: insertion/deletion angiotensin converting enzyme gene polymorphism, hypertension and metabolic control.

Barnas U. Schmidt A. Illievich A. Kiener HP, Rabensteiner D, Kaider A, Prager R, Abrahamian H. Irsigler K. Mayer G. Diabetologia. 1997; 40(3): 327-31.

Diabetic nephropathy represents a major complication in patients with insulin-dependent diabetes mellitus (IDDM). Intervention trials using angiotensin-converting enzyme (ACE) inhibitors have pointed towards the important pathogenetic role of the reninangiotensin system. Recently and insertion/deletion (I/D) polymorphism for the gene encoding the ACE has been described, the deletion type being associated with higher plasma ACE levels. As the intrarenal renin-angiotensin system might also be activated in this setting, we determined the ACE

genotype together with other risk factors for the development of diabetic nephropathy in 122 patients with IDDM from a single centre with (n=63) and without (n=59) nephropathy. Long-term glycaemic control was evaluated using mean HbA1c values from the last 10 years. The two patient group were comparable with regard to duration of diabetes and glycaemic control as assessed by current HbA1c values. However, mean long-term HbA1c values were significantly higher in patients with diabetic nephropathy as was systemic blood pressure. The DD subgroup of patients who had diabetes for more than 20 years (n=90), the DD genotype was even more frequent in patients with nephropathy, and blood pressure and long-term HbA1c values were also higher in patients with renal disease. Logistic regression analysis revealed long-term glycaemic control, blood pressure and the ACE genotype to be independent risk factors for the prevalence of diabetic nephropathy.

Prevalence of diabetic retinopathy in children and adolescents with IDDM. A population-based multicentre study.

Kernell A, Dedorsson I, Johanson B, Wickstrom CP, Ludvigsson J, Tuvemo T, Neiderud J, Sjostrom K, Malmgren K, Kanulf P, Mellvig L, Gjotterberg M, Sule J, Persson LA, Larsson LI, Aman J, Dahlquist G. Diabetologia. 1997; 40(3): 307-10.

Vision-threatening diabetic retinopathy can be prevented if it is diagnosed before becoming too advanced. Since diabetic retinopathy has been reported to occur only rarely before the end of pubertal development, children and adolescents are seldom included in screening programmes. We invited 780 children and adolescents with insulin-dependent diabetes mellitus diagnosed before the age of 15.0 years (disease duration of < 12 years) and who were older than 9.0 years at the time of examination from eight regions of Sweden. Retinal examination was performed with sterioscopic fundus photograph. The photograph were rated according to a modified Airlie House classification. The dropouts (223/780, 28.6%) were significantly older and with a longer duration of diabetes than the examined children ($p < 0.001$ and 0.001, respectively). Photographs from 557 patients aged (median [interquartile range]: 14.6 [12.4 – 17.0]) years and with a diabetes duration of 8.0 (5.5 – 9.9) years were evaluated. Retinopathy was demonstrated in 81 patients (14.5%): 66 with background retinopathy, 2 with microaneurvsms and hard exudates, 12 with preproliferative retinopathy, 1 with proliferative retinopathy, Preproliferative retinopathy was diagnosed in a 12.8-year-old girl. Retinopathy was demonstrated in 6% and 18% of patients in pubertal stages 1 and 5, respectively. The overall prevalence of retinopathy in this population may even be higher since the dropouts were older and had a longer duration of diabetes. Since background and preproliferative retinopathy were found in children before puberty, we recommend including children and adolescents in screening programmes for diabetic retinopathy from the age of 10 years.

Increased serum levels of advanced glycation end products (AGEs) in children and adolescents with IDDM.

Berg TJ, Dahl-Jorgensen K, Torjesen PA, Hanssen KF. Diabetes Care. 1997; 20(6): 1006-8.

OBJECTIVE: To investigate whether the serum levels of advanced glycation end products (AGEs) are increased in IDDM children and adolescents and to study the effect of puberty on serum levels of AGEs (S-AGEs).

RESEARCH DESIGN AND METHODS: A total of 68 children and adolescent IDDM patients (age, 13.3 ± 4.0 years; duration of diabetes, 5.0 ± 3.6 years; HbA1c, 8.2 ± 2.0%; Tanner stage [public hair], 1 vs. 2-5, 24/42) recruited from the pediatric outpatient clinic at Aker University Hospital were compared with 25 healthy nondiabetic control subjects. SAGEs were measured by a fluoremetric immunoassay.

RESULTS: S-AGEs were significantly elevated in the diabetic group when compared with the control group (14.4 ± 3.5 vs. 11.7 ± 3.0 U/ml, $P < 0.002$). A significant correlation ($r=0.26$, $P<0.04$) was found between S-AGEs and HbA1c in the diabetic group but not in the control group. No significant correlation was found between S-AGEs and blood glucose concentration or age in either group. We found no difference between S-AGEs in boys and girls and in prepubertal and pubertal diabetic or control subjects.

CONCLUSION: S-AGEs are increased in young patients with diabetes before puberty. Since AGEs are linked to the pathogenesis of vascular complications, this observation suggests that the pathological processes leading to diabetic late complications start even before puberty.

Elevated plasma endothelin-1 levels as an additional risk factor in non-obese essential hypertensive patients with metabolic abnormalities.

Ferri C, Bellini C, Desideri G, Baldoncini R, De Siati L, Santucci A. Diabetologia. 1997; 40(1): 100-2.

Circulating endothelin-1 concentration was evaluated in 93 lean patients with essential hypertension, of whom 16 had impaired glucose tolerance and hyperlipidaemia, 25 had impaired glucose tolerance, 28 had hyperlipidaemia and 24 had no metabolic abnormalities; we also studied 22 control subjects. All groups were age- and sex-matched. Plasma endothelin-1 levels were higher ($p < 0.05$) in hypertensive patients with impaired glucose tolerance and hyperlipidaemia than in the remaining groups and were directly correlated with fasting insulin levels ($r = 0.506$, $p = 0.045$). Therefore, circulating endothelin-1 concentrations are elevated in hypertensive patients with a high-risk profile due to the presence of metabolic abnormalities, and might favour the development of vascular damage.

Carotid artery stenosis is related to blood glucose level in an elderly Caucasian population: the Hoorn Study.

Beks PH, Mackaay AJ, De Vries H, de Neeling JN, Bouter LM, Heine RJ. Diabetologia. 1997; 40(3): 290-8.

Cross-sectional associations between carotid artery stenosis (CAS) on the one hand, and parameters of glycaemia and specific insulin levels on the other, were investigated in an age, sex, and glucose tolerance stratified random sample from a 50-74-year-old Caucasian population. Subjects treated with insulin or oral hypoglycaemic agents were classified as having known diabetes mellitus (KDM) (n = 66). Using two oral glucose tolerance tests, and based on the World Health Organisation criteria, all other participants were classified as having a normal (NGT) (n=287), an impaired (IGT) (n=169) for a diabetic (NDM) (n=106) glucose tolerance, CAS was defined haemodynamically using duplex scanning. The crude prevalences of any moderate (16-49%) CAS were 6.6%, 7.1%, 5.7% and 12.1% in NGT, IGT, NDM and KDM subjects, respectively. For any severe (< or = 50%) CAS, crude prevalences were 2.8%, 4.7%, 9.4% and 7.6%. The prevalence of any severe CAS was higher in NDM ($p < 0.01$) and KDM

subjects (p=0.07) than in NGT subjects. The prevalence of a history of stroke or transient ischaemic attack was 1.7%, 1.8%, 2.8% and 1.5% in NGT, IGT, NDM and KDM, respectively. In univariate logistic regression analysis, HbA1c, serum fructosamine, fasting and 2-hr post-load glucose were significantly associated with any server CAS. In multivariate analyses controlling for other risk factors, only HbA1c and 2-hr post-load plasma glucose remained significantly associated (odds ratios: 1.29 per % and 1.09 per mmol/I, respectively) in separate models. No association could be shown between either fasting or 2-hr post-load specific insulin and any severe CAS in either univariate or multivariate analyses. In conclusion, HbA1c and 2-hr post-load plasma glucose are independently associated with any severe CAS, whereas specific insulin is not.

The effect of an angiotensin converting enzyme inhibitor on skin microvascular hyperaemia in microalbuminuric insulin-dependent diabetes mellitus.

Yosipovitch G, Schneiderman J, Erman A, Chetrit A, Milo G, Boner G, Van Dijk DJ. Diabetic Medicine. 1997; 14(3): 235-41.

Patients with longstanding insulin-dependent (Type 1) diabetes mellitus (IDDM) are reported to have microvascular complications in most capillary beds. The microvascular hyperaemia of the skin in normoalbuminuric and microalbuminuric IDDM patients and healthy volunteers was measured with laser Doppler flowmetry. The effect of 3 and 9 months of treatment with captopril, an angiotensin converting enzyme inhibitor, on hyperaemia in the microalbuminuric patients was studied. Mean (± SD) pretreatment duration of skin postocclusive reactive hyperaemia was longer in micoalbuminuric than in both normoalbuminuric patients and healthy volunteers (118.2 ± 34.4 vs. 57.8 ± 16.0 vs 63.3 ± 18.3 sec, respectively, $p < 0.00001$). After 3 and 9 months of captopril treatment the prolonged hyperaemia was shortened to 78.6 ± 45.6 s ($p < 0.01$) and 62.3 ± 55.6 s ($p < 0.03$), respectively. Urinary albumin excretion decreased from 63.9 ± 43.5 to 33.4 ± 28.1 mg 24 h-1 at 3 months treatment ($p < 0.002$) and 43.1 ± 38.5 mg 24 h-1 at the end of the study period ($p < 0.02$). A positive correlation between changes in urinary albumin excretion and the shortening of the skin postocculsive reactive hyperaemia was found. Blood pressure remained in the same range throughout. These results show that captopril affects skin blood flow, independent of its hypotensive effect. This action may reflect the influence of angiotensin converting enzyme inhibitor on vascular beds other than those of the kidneys.

Results and cost analysis of distal [crudal/pedal] arterial revascularisation for limb salvage in diabetic and non-diabetic patients.

Panayiotopoulos YP, Tyrrell MR, Arnold FJ, Korzon-Burakowska A, Amiel SA, Taylor PR. Diabetic Medicine. 1997; 14(3): 214-20.

In order to compare the outcome and costs of femorodistal grafting in diabetic and nondiabetic patients presenting with critical limb ischaemia we analysed a consecutive series of 109 femorodistal bypasses, 38 (35%) performed on people with diabetes and 71 (65%) on non-diabetic patients. The same aggressive revascularization policy was used in both groups with the decision to operate based on the presence of a calf or foot vessel on preoperative intra-arterial digital subtraction angiography (IADSA). Data were collected prospectively and the median follow-up was 15.4 months (range 0 to 42 months). There were no significant differences in 30-day (5.3% vs 4.2%) and in-hospital mortality (13.2% vs 14.1%) between the two groups. Life table curves at 3 years in diabetic and non-diabetic patients showed 48% vs 60% survival, 76% vs 72% knee salvage, 45% vs 56% limb salvage, and 35% vs 47% secondary patency. Although there was a trend for diabetic patients to perform less well, there was no statistically significant difference in these outcome measure. In cost comparison the only significant difference was found in the total hospital cost, which was pounds 9181 in diabetic, compared to pounds 6350 in nondiabetic patients ($p = 0.026$, Mann-Whitney). However, this cost was significantly less than that of primary amputation in either group (Pounds 15500 and Pounds 12040, respectively). Femorodistal reconstruction in both diabetic and non-diabetic patients, whenever feasible, is a cheaper option than primary amputation, even though vascular surgery may be more expensive in people with diabetes.

RETINOPATHY

The relation between accumulation of advanced glycation end products and expression of vascular endothelial growth factor in human diabetic retinas.

Murata T, Nagai R, Ishibashi T, Inomuta H, Ikeda K, Horiuchi S. Diabetologia. 1997; 40(7): 764-9.

Both advanced glycation end products and vascular endothelial growth factor are believed to play a role in the pathogenesis of diabetic retinopathy. It is known that vascular endothelial growth factor causes retinal neovascularization and a breakdown of the blood-retinal barrier; how advanced glycation end products affect the retina, however, remain largely unclear. The substance-Ne(carboxymethyl) lysine is a major immunologic epitode, i.e. a dominant advanced glycation end products antigen. We generated an anti-Ne-(carboxymethyl) lysine antibody to investigate the relationship between the localization of advanced glycation end products and that of vascular endothelial growth factor in 27 human diabetic retinas by immunohistochemistry. Nine control retinas were also examined. In all 27 diabetic retinas, Ne-(carboxymethyl)lysine was located in thickened vascular wall. In 19 of the 27 observed around the vessels. In all 27 diabetic retinas, vascular endothelial growth factor revealed a distribution pattern similar to that of Ne-(carboxymethyl)lysine. Vascular endothelial growth factor was also located in the vascular wall and in the perivascular area. Neither Ne-(carboxymethyl)lysine nor vascular endothelial growth factor immunoreactivity was detected in the 9 control retinas. Vessels with positive immunoreactivity for Ne-(carboxymethyl)lysine and/or vascular endothelial growth factor were counted. A general association was noted between accumulation of Ne-(carboxymethyl)lysine and expression of vascular endothelial growth factor in the eyes with non-proliferative diabetic retinopathy ($p < 0.01$) and proliferative diabetic retinopathy ($p < 0.05$).

NEUROPATHY

Postural stability of diabetic patients with and without cutaneous sensory deficit in the foot.

Simmons RW, Richardson C, Pozos R. Diabetes Research and Clinical Practice. 1997; 36(3): 153-60.

Postural stability was measured in 50 patients classified into two diabetic group: insulin-dependent diabetes mellitus (IDDM: n = 27), and diabetic patients with bilateral cutanoeus sensory deficit in the foot (CD: n = 23). All patients were matched to 50 non-diabetic controls on age, weight and gender variables. The integrity of cutaneous sensory information at the foot was assessed using monofilament test. Static and dynamic balance

was evaluated using an objective balance test involving computer-controlled dual force platforms enclosed by a visual surround. The apparatus provided six test conditions designed to systematically manipulate or eliminate visual, vestibular or somatosensory information. Scores for the six tests, and a derived composite balance score together with movement strategy scores were used for data analysis. For all six tests and composite score CD patients revealed significant postural instability compared to controls. Additionaly, the CD group recorded reduced strategy scores indicating an atypical shift from ankle to hip strategy movement as postural control was stressed. IDDM patient test scores were not significantly different from control data on any pairwise comparison. Results indicated significant balance loss associated with CD putting the individual at increased risk for falling and compromising foot-mechanics.

Evaluation of skin vasomotor reflexes in response to deep inspiration in diabetic patients by laser Doppler flowmetry. A new approach to the diagnosis of diabetic peripheral autonomic neuropathy.

Aso Y, Inukai T, Takemura Y. Diabetes Care. 1997; 20(8): 1324-8.

OBJECTIVE: To evaluate the peripheral sympathetic function in feet of NIDDM patients by means of laser Doppler flowmetry.

RESEARCH DESIGN AND METHODS: After deep inspiration, we measured the vasoconstrictor response in the feet of 51 patients with NIDDM, as compared with those of 20 healthy control subjects, using laser Doppler flowmetry. Subjects whose skin temperature was < 32 degrees C were excluded from our study because a skin temperature of approximately 34 degrees C is the optimal temperature for the evaluation of skin vasomotor reflexes in response to a deep inspiration by laser Doppler flowmetry.

RESULTS: The vasoconstrictor response to deep inspiration in the big toe was significantly decreased in NIDDM patients compared with healthy subjects (26.8 ± 2.0 vs. 48.3 ± 18.5%, P < 0.0001). In NIDDM patients, the vasoconstrictor response was positively correlated with the duration of diabetes, the median motor and sensory nerve conduction velocities, the coefficient of variation of the R-R interval at rest, and the postural fall in systolic blood pressure. The vasoconstrictor was inversely correlated with the vibratory perception threshold.
CONCLUSIONS: Vasomotor reflexes in the lower limbs were markedly impaired in NIDDM patients. The measurement of vasoconstrictor responses to deep inspiration by using laser Doppler flowmetrry is a novel and useful method for detecting peripheral sympathetic failure in diabetic patients.

A randomised controlled trial of topical glycopyrrolate, the first specific treatment for diabetic gustatory sweating.

Shaw JE, Abbott CA, Tindle K, Hollis S, Boulton AJ. Diabetologia. 1997; 40(3): 299-301.

The treatment of gustatory sweating in diabetes mellitus is usually with oral anti-cholinergic drugs, but these frequently lead to unacceptable side effects. Glycopyrrolate is an anti-muscarinic agent that can be applied topically and is efficacious in gustatory sweating occurring in other conditions. In a double-blind placebo-controlled crossover study, we assessed the value of glycopyrolate in 13 diabetic patients with gustatory sweating. Sweating was measured by a sweat challenge, and diaries recorded by the patients throughout the 2 weeks of each treatment period. Compared to placebo, glycopyrrolate reduced the sweat response to a challenge by 82% ($p < 0.01$). The frequency of episodes of gustatory sweating during the treatment period was also reduced by 51% ($p < 0.01$), with a nearly 100% reduction in the frequency of episodes of severe sweating ($p < 0.01$). In conclusion, topically applied glycopyrrolate is a very effective treatment in reducing both the severity and frequency of diabetic gustatory sweating.

Premature cell ageing and evolution of diabetic nephropathy.

Morocutti A, Earle KA, Rodemann HP, Viberti GC. Diabetologia. 1997; 40(2): 244-6.

The rate of development and progression of renal disease varies greatly in insulin-dependent diabetic (IDDM) patients. The cellular and molecular reasons for this difference are largely unknown but could be related to early cell differentiation, a phenomenon recently reported in IDDM patients with nephropathy. In this study we compared cell differentiation and cell volume between IDDM patients with and without nephropathy and investigated the cell ageing characteristics in relation to the rate of evolution of renal disease in the IDDM patients with diabetic nephropathy. Cell volume was larger and the percentage of post-mitotic fibrocytes was higher in skin fibroblasts derived from IDDM patients with diabetic nephropathy compared to those from IDDM patients without kidney disease (mean ± SD in arbitrary units 817.3 ± 25.7 vs 760 ± 32.8; $p = 0.005$; and mean ± SD% 33.6 ± 11.8 vs 20.8 ± 10; $p=0.02$ respectively). Analysis of the interaction of the time to proteinuria (TTP) and the rate of change of glomerular filtration rate (GFR) with glycaemic control, arterial blood pressure and cell volume and the state of cell differentiation showed that glycated baemoglobin and the percentage of post-mitotic fibrocytes were negatively correlated to TTP ($r = -0.68$; $p = 0.008$; $r = 0.52$; $p = 0.05$ respectively) and positively associated with the rate of change of GFR ($r=0.76$; $p=0.03$; $r=0.56$; $p=0.037$ respectively). Cell volume was negatively correlated to TTP ($r = -0.53$; $p = 0.05$). Diastolic blood pressure was also related to the rate of GFR change ($r=0.56$; $p=0.039$). In a multiple linear regression analysis glycated haemoglobin maintained its significance independent relationship with TTP at the 1% level, while the strength of the association between the percentage of post-mitotic cells and cell volume was reduced to the 11 and 9% level, respectively. Cultured skin fibroblasts from IDDM patients with nephropathy show signs of early differentiation. Glycaemic control is a key factor in the rate of onset of proteinuria and different rates of cell ageing appear to contribute to the rate of development and progression of diabetic nephropathy. Their intereaction may be responsible for the severity of renal involvement in susceptible IDDM patients.