EPIDEMIOLOGY : Mortality in diabetes

Mortality events amongst non-insulin-dependent diabetes mellitus patients in Orissa.

Das S, Mishra RK , Jena BB, Mishra BK, Misra KC, Sarangi B. Journal Association Physician, India 1991; 39:519-20

In a study over one year, it was observed that mortality amongst hospitalised patients with non-insulin-dependent diabetes mellitus (NIDDM) was nearly 20%. Those dying within 24 hours were classified as group A, between one and one week as B, between one week and one month as C and those after one month as D. There were 31 patients each in Groups A and B, 14 in C and 4 in D. The mean age of death was 61 years in the first three groups. The prevalence of cerebrovascular accident as a terminal event was similar i.e., 32.2, 35.5 and 35.7% in groups A,B and C respectively; 48% of patients in group A suffered from ischaemic heart disease. Diabetic ketoacidosis was equally prevalent amongst groups A, B and C. Infection was significantly more common in group B (45.2%) than A (P<0.55). Nephropathy was observed in 57% of patients in group C as compared to 22.5% in A (P<0.02). Cerebrovascular accident and infection were the major causes of mortality in groups B and C(80.7% and 71.4%). whereas ischaemic heart disease and cerebrovascular accident accounted for 80% of deaths in group A.

Prevalence of cerebrovascular accident in 4349 diabetic cases.

Patel JC. Indian Jour Med Sci 1989;43:59-70.

1. Prevalence of cerebrovascular accident in 4349 cases of diabetes admitted to Bombay Hospital, Bombay between 1967 and 1974 was in 411 (9.45%) cases. 2. Number of males predominanted, but was of no significance as compared to the occurrence of cerebrovascular accident in females. 3. Highest number of cases were in the age group 61-70 years (statistically significant), which was a decade higher than the age(51-60 years)of maximum number of admitted cases in 4349 cases. Mortality increases with age, highest in the age above 70 years-staistically significant. 4. They type and site of cerebrovascular accident has no relation to the age group or sex, duration and severity of diabetes. 5. Cerebrovascular accident was much less in last three months of the year and was highest in the month of June, and is of no statistical significance. 6.Cerebrovascular accident was prevalent in all types of blood pressure, but had highest mortality in severe hypertension. 8. Occurences of CVA had no relation with the duration of diabetes.

Mortality and health service utilization amongst Melanesian and Indian diabetics in Fiji.

Sicree RA, Ram P, Zimmet P, Cabealwala S, king H. Diabetes Res Clin Pract 1985; 1 : 227-34.

A population- based survey of the biracial population of Fiji conducted in 1980 showed non-insulin-dependent diabetes (NIDDM) prevalence to be high amongst urban Melanesians and Asian Indians. Follow-up of the cohort of urban residents has been conducted at the major sites of health service delivery in Suva, and surveillance now encompasses 4 years of such attendances.

Age-adjusted mortality rates for diabetic subjects were increased compared with normal subjects (relative risks for 4 year mortality being 4.6 for Indians i.e. P< 0.01 and 1.5 for Melanesians i.e. P>0.1). Inpatient admission rates were also increased amongst diabetic subjects, but only significantly for the females. The relative risk for admission was 3.1 for Melanesian and 2.6 for Indian females (both significant at P>0.05). These results suggest that NIDDM in these populations is associated with several adverse health outcomes, and confirms for developing country populations the association of NIDDM with excess mortality noted amongst developed country populations

Diabetic death.

Nanda KC, Samal KC, Tripathy B, J Diabetic Assoc India 1978; 18 : 175-8

Among 71 diabetic deaths, vascular causes were found to be account for 62%; cerebrovascular accident, coronary heart disease and real angiopathy were equally common in this series. In this, hospital deaths due to non-vascular causes, except diabetic coma, has gone down. There are differences in the causes of death among diabetics between eastern part of the country and northern part where coronary heart disease takes the major toll of life. Geographical variation and undernutrition may contribute towards the lower incidence of coronary heart disease peculiar to this part. The cause of this difference requires further probing. Collaborative attempts at the national level should be organized to have a prospective analysis of causes of death among diabetics by improving diagnostic procedures.

Diabetes mellitus in penninsular Malaysia : ethic differences in prevalence and complications.

Mustaffa BE, Ann Acad Med Singapore 1985; 14 :272-6.

Estimated prevalence of diabetes mellitus in Malaysia was about 2%. Diabetes was most common in Indians especially males and least common in Chinese. There was a slight male preponderence seen in Malays too. Positive family history was obtained in 14% of cases most commonly in Malays, almost 1/3 of whom had more than one family member with diabetes. Familial association was uncommon in Chinese. Over 50% of the patients were overweight. Obesity was noted in nearly 70% of female Malays and Indians while the majority of Chinese were not overweight. More than 80% of patients were non-insulin requiring. Youth onset diabetes was considered rare; those 10 years and below were estimated to be only 0.4% and below 20 years of age between 2-4% of the diabetic population. Females were twice as common than males in this type of diabetes and familial association was greater. Malnutrition-related diabetes and pancreatic calcification were not well documented but youth-onset non-insulin requiring diabetics with mild symptoms but a strong family history of diabetes were observed. More than half of hospital based patients had evidence of complications, mainly amongst Malays and Indians. Hypertension was the most frequent associated disease followed by foot ulcers and ischaemic heart disease. Hypertension usually associated with chronic renal failure was most common amongst Malays while gangrenic ulcers and heart diseases were seen mainly in Indians. The major causes of death were chronic renal failure, myocardial infraction, ketoacidosis, stroke and septicaemia related to gangrene.

We acknowledge the assistance of the Medical Research Division, Glaxo Laboratories for allowing access to their abstract service.

International Variations in Mortality Amongst Diabetic Patients.

WHO multinational study of a vascular disease in diabetes.

Head J. Fuller JH and the WHO, MNSUO Group, 1990

Mortality among 4740 diabetic men and women aged 35-55 years participating in the WHO multinational sudy of vascular disease in diabetics has been studied. Ten of the original centres (Warsaw, Berlin, Havana, Arizona, Oklahoma,Hong Kong, Switerzerland, London, Tokyo, Zagreb) were able to identify the life/death status of their study participants on 1st January 1983, giving an average follow-up period of upto six to seven years. All-cause mortality rates in males varied about 3-fold among the ten participating centres with the highest rates in Warsaw, Berlin and Havana and the lowest rates in Tokyo and Zagreb. All-cause mortality rates for females varied about 4-fold with the highest rates in Warsaw and Oklahoma and the lowest rates in Tokyo. The proportion of deaths ascribed to circulatory disease varied among the centres ranging from 32% for males and 0% for females in Tokyo to 67% for males and 47% for females in London. There was an excess all- cause mortality in males compared to females for all centres except Zagreb. This excess also applied to circulatory diseases in general, ischaemic heart disease in particular and occured in both insulin-dependent and non-insulin-dependent diabetic patients. Death rates for insulin-dependent diabetic patients were generally higher than those for non-insulin- dependent diabetic patients.

Declining mortality among Type 1 (insulin-dependent) diabetic patients in Denmark

Eshoj O, Borch Johnsen K, Green A, Beck-Neilsen H, EASD 1994, Düsseldort, abstract no. 95

We describing the 5 year mortality in a cohort of Type 1 (insulin-dependent) diabetic patients, ascertained from insulin prescriptions (estimated completeness:97%) and comprising all subjects living in the Funen County, Denmark, on July 1, 1987 who had diabetes diagnosed before age 30 years and who accepted a subsequent clinical examination (n=357 men and 281 women, 69% of all eligible patients). Median age at examination was 33.4 years (range 5-79) and duration of diabetes 16.5 years (range 0-63). After 5 years from the date of examination, 36(5.6%) had died. The mortality was 3.6 times higher (P< 0.0001) than expected from the general Danish population, after adjustment for current age and sex. Except for the age class 50-59 years all age specific relative mortalities were statistically significant higher than expected, ranging from 3.3 in age class 20-39 years to 7.3 in age class 40-49 years. The major causes of death were uremia and myocardial infarctions. Compared with previous Danish mortality studies the relative mortality in Type 1 diabetic patients with onset before the age of 30 years has delined. We conclude that even though the relative mortality in Type 1diabetes has declined during the last decades, the disease is still associated with a considerable excess mortality which is mainly attributable to cardiovascular and renal complications.

Long-term glycaemic control relates to mortality in NIDDM.

Dan KG, Anderson Suardsudd, EASD 1994,Düsseldorf, abstract no 603.

In order to study the influence of long-term glycaemic control on mortality we studied 411newly detected NIDDM individuals diagnosed between 1972 and 1987. They represented all new NIDDM cases in a geographically defined population.They were folowed until December 31,1989. Long term glycaemic control was measured as annual averages of fasting blood glucose(FBG) values during eight randomly selected years. Mortality data were obtained from official registers together with mortality data for 'control group' of 3180 non-iabetic persons. 161diabetic persons died during a mean follow up time of 7.4 years. In univariate analyses average FBG and age at diagnosis were positively and duration of diabetes and body mass index negatively related to mortality. Type of diabetes treatment or having a diagnosis of hypertension were not related to mortality. In a multiple logistic regression analysis average FBG and age at diagnosis were independently related to all cause (P< 0.0001), cardiovascular(P=0.0001) and ischaemic heart disease mortality (P=0.015). Weighting for diabetes duration strengthened the associations between average FBG and all cardiovascular types of mortality and all cause mortality. No correlations between glycaemic control and non-cardiovascular deaths was found. Diabetic subjects with average FBG < 7.8 mmol/L had two times and subjects with average FBG> 7.8 mmol/L three times the mortality of the non-diabetic control group. In conclusion, long term hyperglycaemia was related to survival in NIDDM subjects independent of age at diagnosis and type of diabetes treatment. The unfavourable effect of hyperglycaemia was further augmented by long diabetes duration. However, even diabetes patients mortality than non-diabetics individuals.

Trends in mortality of childhood-onset insulin-dependent diabetes mellitus in Leicestershire 19-40-1991.

McNally PG, Raymong NT, Burden ML, Burton PR, Botha JL, Swift PGF, Burden AC , Hearnshaw JR, Diabetologia 1994

There have been no comparative studies of mortality in juvenile-onset IDDM in the United Kingdom. Therefore, the relative risk of death by calendar date of diagnosis was investigated in a population- based incident cohort of 845 (463M : F382) Type 1, (insulin-dependent) diabetics diagnosed in Leicestershire before the age of 17 years between 1940 and 1989. The mortality status of 844(99.9%) patients was determined as of December 31, 1991, representing 14,346 person-years of risk

Trends in relative risk of death were investigated using Cox proportional hazards modeling for within cohort comparisons and age/sex and calendar time adjusted standardized mortality ratios(SMR) using generalized linear modeling for external comparisons. Median age at diagnosis was 10 years(range 3 months to 16 years); median duration of diabetes 14 years (range 1 to 51 years).

Forty-four patients had died (5.2%; median age at death 31 years, range 11-51 years). A further four patients died at presentation (within 24 hours) from ketoacidosis and are excluded from all analyses. Calendar date of diagnosis was to be an important predictor of mortality. Adjusting for attained age there was evidence of a decline in relative risk of death with calender date of diagnosis of 3.4% (95% Cl,0.005-6.9%) per annum, equivalent to a 32 per cent fall per decade (95% Cl, 5-51%) or 84 per cent (95% Cl,21-97) from 1940-89. Neither sex nor age at diagnosis were significant predictors of mortality. Over the study period 1940-89 the SMR (male and female combined) fell from 981 (581-1656) to 238 (60-953) relative to the general population.

This population based study shows that the prognosis for Type 1 (insulin-dependent) diabetes mellitus has improved markedly over the period 1940-1991.

UK prospective diabetes study XII : Differences between Asian, Afro-Caribbean and White Caucasian Type 2 diabetic patients at diagnosis of diabetes.

UK Prospective study Group.

Diabetic Medicine 1994; 11: 670-7.

Clinical and biochemical variables and prevalence of complications at diagnosis of diabetes were assessed in 5098 Type 2 diabetic patients in the UK Prospective Diabetes Study of whom 82% were white Caucasian, 10% Asian of Indian origin and 8% AfroCarribean. The Asian patients were(P< 0.001) younger than (mean age 52.3, 470, 51.0 years), less obese (BMI 29.3, 26.7, 27.9 kg/m^2), had a greater waist-hip ratio, lower blood pressure (systolic 145,139,144 diastolic 87, 86, 89 mmHg) and prevalence of hypertension. They were more often sedentary 19, 39, 15%), more often abstained from alcohol(21, 55, 25%) and had greater prevalence of first degree relaitves with known diabetes(36,44, 34%). The Afro-Caribbean patients had (p< 0.001) higher fasting plasma glucose (11.9,11.3, 12.5 mmol/L), more severely impaired ß-cell function (45,35, 28% normal) and less impaired insulin sensitivity (23, 19, 27% normal) by homeostasis model assessment, lower triglyceride (1.8, 1.8,1.3 mmol/L), and higher HDL-cholesterol (1.05, 1.03, 1.17 mmol/L). Prevalence of a history of myocardial infraction, stroke or intermittent claudication at diagnosis was similar. The prevalence of ischaemic ECG (Minnesota code), microalbuminuria (urine albumin > 50 mg/L), retinopathy('191' grading of retinal photographs), and neuropathy (abnormal vibration perception threshold or absent leg reflexes) was also similar. At diagnosis of Type 2 diabetes, there were no differences in prevalence of complications between white Caucasian, Asian, and Afro-Caribbean patients although differences were found in other clinical and biochemical variables.

AETIOLOGY

Autiantibodies against a novel 51 kDa islet antigen and glutamate decarboxylase isoforms in autoimmune polyendocrine syndrome Type 1

Velloso LA, Winqvist O, Gustafsson J.Kampe O, Karlsson FA, Diabetologia 1994 ; 37:61-9.

Beta-cell function and islet cell antibodies were studied in six patients with autoimmune polyendocrine syndrome Type 1. All suffered from mucocutaneous candidiasis, five had adrenocortical insufficiency and three hypoparathyroidism. All sera contained high titres of antibodies staining islets of Langerhans. Reactivity against glutamate decarboxylase, predominantly the 65 kDa isoform, was detected by immunoprecipatations and Western blots in five of the six sera, and all six sera immunoprecipitated a 51 kDa antigen from [35S]-methionine labelled rat islet cell lysates. No reactivity against this latter antigen was found in sera of patients with Type 1 (insulin-dependent) diabetes mellitus (n=9), Graves' disease (n=5), idiopathic Addison's disease (n=7), or stiff-man syndrome (n=2). The 51 kDa antigen was also detected by Western blots using homogenates of rat islets and autoimmune polyendocrine syndrome Type 1 patient sera, whereas no such reactivity of testes, adrenals, small intestine spleen, exocrine pancreas or brain. Moreover, the 51 kDa antigen was present in the rat insulinoma cell line RINm 5F but not in the SV 40 tranformed, monkey kidney cell line COS, when examined by immunoprecipitations of [35S]-methionine labelled cell lysates and by Western blots. None of the patients with autoimmune polyendocrine syndrome Type 1 had symptoms of diabetes and their insulin responses to glucose challenge were normal. The data illustrate that pateints with autoimmune polyendocrine syndrome Type 1 present an autoimmune response against islets of Langerhans, which is apparently different from that associated with classic Type 1 diabetes.

A high weight gain early in life is associated with an increased risk of Type 1 (insulin-dependent) diabetes mellitus

Johansson C, Samuelsson U, Ludvigsson J, diabetologia 1994; 37: 91-4.

Growth during the first years of life in relation to type of feeding infancy was retrospectively studied in an unselected population-based group of 297 children who had been diagnosed with type 1 (insulin-dependent) diabetes mellitus before the age of 15 years (probands) and 792 individually-matched referent subjects. Reliable data were collected from child welfare clinics. Probands weighed slightly less at birth but their weight gain at 6,9,18 and 30 months of age was significantly greater (p< 0.02) than that of referent children. The weight gain of children who had never been breast-fed was more marked than that of breast-fed children; this was found for both probands and referent. But also among exclusively breast-fed children (> 2 months), probands gained significantly more in weight from birth up to 18 and 30 months of age than exclusively breast-fed referent children. Early weight gain appears to be a risk factor for development of Type 1 diabetes. The lower weight gain in breast-fed compared to non-breast feeding against Type 1 diabetes observed in several studies.

The natural history of pre-Type 1 (insulin-dependent) diabetes mellitus in patients with autoimmune endocrine diseases.

Betterle C, Presotta F, Margin L, Pedini B, Moro L, Caretto A, Zanchetta R, Diabetologia 1994;34 : 95-103.

An 11-year prospective study was carried out in 180 non-diabetic patients with organ-specific autoimmune diseases to evaluate islet cell antibodies were charaterised according to titres, persistence, complement-fixing ability, and pattern. During follow-up, 14 or 46 patients with islet cell antibodies persistently greater than 5 Juvenile Diabetes Foundation Units (JDF-U) (30.4%), none of 23 with islet cell antibodies between 2.5 and 5 JDF-U of fluctuating, and 3 to 109 without islet cell antibodies (2.7%), developed diabetes. The cumulative risk of developing diabetes was 70%, 0% and 4%, respectively. All the patients who developed diabetes were females. Eight progressed to insulin-dependence acutely, four showed a transient period of insulin-dependence acutely, while two were still insulin-free. No difference was found in titres of islet cell antibodies for the risk of diabetes. Complement-fixing islet cell antibodies enhanced the cumulative risk of diabetes in patients with conventional islet cell antibodies at low-middle (> or = 2.5-40 JDF-U). but not at high (> or = 80 JDF-U) titres. Forty-two pateints with islet cell antibodies were investigated for the whole or the selective pattern. In the presence of the whole pattern the cumulative risk for diabetes rose to 100%, while with the selective pattern it declined to 34%. The whole pattern was found in 83% of patients who developed Type 1 diabetes acutely. In patients with organ-specific autoimmune diseases, the whole islet cell antibody pattern greatly enhances the prediction for diabetes.

Lymphocyte subset abnormalities, auto-antibodies and their raltionship with HLA DR types in children with Type 1 (insulin-dependent) diabetes and their first degree relatives.

Peakman M, Warnock T, Vats A, McNab GL, Underhill J, Donaldson PT, Vergani D. Diabetologia 1994; 37: 155-65.

Type 1 (insulin-dependent) diabetes mellitus is associated with abnormalities of circulating lymphocyte subsets and autoantibodies. To investigate the prevalence of these in non-diabetic siblings and non-diabetic patients of children with Type 1 diabetes, we analysed T-cell subsets of function and activation in 31 families with an index case of Type 1 diabetes and related these to autoantibodies and HLA DR type. Using two and three colour cytofluorimetry, we studied total and activated(HLA DR+)CD3+, CD4+, CD8+, lymphocytes and on CD4+ lymphocytes the CD45RA/RD "native" and "memory" cell phenotypes.DIiabetic children (mean duration of disease 3.1 years) had reduced total lymphocyte count ($p< 0.05$), their non-diabetic siblings a reduced CD4+ T- helper cell count ($p< 0.05$), and their parents a reduced percentage and number of CD3+ T-helper- cell count ($p< 0.05$), and their parents a reduced percentage and number of CD3+ T cells, ($p< 0.01$ and $p< 0.05$) compared with age-matched control subjects. Diabetic children, their siblings and parents all had significant over-expression of the CD45RA "naive" cell marker and significantly increased levels of activated CD4+ T-helper cells ($p< 0.01$, $p<0.05$ and p7lt;0,01). In diabetic children and their siblings there was a significant over-expression of the CD45RO "memory" cell marker and significant under-expression of the CD45RA "naive" cell marker, whilst these were normal in the parents. Islet cell antibody positive diabetic children had significantly higher levels of CD45RO -expressing CD4+ lymphocytes than those who were islet cell antibody negative ($p< 0.05$). Amongst the siblings and parents, possession of HLA-DR4 was associated with lower percentages of CD8+ T cells. These findings extend current knowledge about the role ofimmunoregulatory CD45RA/RO cells in Type 1 diabetes. In addition, they demonstrate lymphocyte abnormalities in unaffected family members, some of which may be influenced by HLA DR alleles.

Enzymatic, metabolic and secretory patterns in human islets of Type 2, (non-insulin-dependent) diabetic patients.

Fernandez-Alvarez J. Conget I, Rasschaert J,Sener A,Gomis R,Malaisse WJ. Diabetologia 1994; 37:177-81.

Islets were isolated by automatic digestion from non-diabetic cardaveric organ donors and from Type 2 (non-insulin-dependent) diabetic subjects. The activity of FAD-glycerophosphate dehydrogenase, but not that of either glutamate dehydrogenase, glutamate-oxaloacetate transaminase or glutamate-pyruvate transaminase, was lower in Type 2 diabetic patients than control subjects. Hexokinase, glucokinase and glutamate decarboxylase activities were also measured in islets from control subjects. The utilization of D-[5-3H] glucose, oxidation of D-[6-14C] glucose and release of insulin evoked by D-glucose were all lower in Type 2 diabetic patients than control subjects. The secretory response to the combination of L-leucine and L-glutamine appeared less severely affected. Islets from Type 2 diabetic patients may thus display enzymatic, metabolic and secretory anomalies similar to those often observed in animal models of Type 2 diabetes, including a deficiency of beta-cell FAD-linked glycerophosphate dehydrogenase, the key enzyme of the glycerol phosphate shuttle.

Pancreatic islet cell toxicity of amylin associated with Type 2 diabetes mellitus.

Lorenzo A. Razzaboni B, Weir GC, Yankner BA, Nature 1994; 368:756-60.

The 37-amino-acid polypeptide amylin is the principal constituent of the amyloid deposits that form in the islets of Langehans in patients with Type 2 diabetes mellitus, but its role in the pathogenesis of this disease is unresolved. In view of the fact that the beta-amyloid protein that forms fibrils in Alzheimer's disease is toxic to neurons, we have investigated whether amylin fibrils could be pancreatic islet cells. We show here that human amylin is toxic to insulin-producing beta- cells of the adult pancreas of rat and humans. This toxicity is mediated by the fibrillar form of the amylin peptide and requires direct contact of the fibrils with the cell surface. The mechanism of the cell death involves RNA and protien synthesis and is characterized by plasma membrane blebbing, chromatin condensation and DNA fragmentation, indicating that amylin induces islet cell apoptosis. These findings indicate that amylin fibril formation in the pancreas may cause islet cel dysfunction and death in Type 2 diabetes mellitus.

HLA-DQB1-associated susceptibility that distinguishes Hashimoto's thyroiditis from Graves' disease in Type 1 diabetic patients.

Santamaria P, Barbosa JJ, Lindstrom AL, Lemke TA, Goetz FC, Rich SS. Journal of Clincal Endrocrinology and Metabolism 1994; 78:878-83.

Insulin-dependent diabetes mellitus (IDDM) is frequently associated with autoimmune thyroid disease (ATD) within families. In these families, HLA polymorphism may modulate the susceptibilty to each disease. Families with IDDM were further categorized as to the presence of ATD. IDDM-affected subjects from families without ATD were compared with subjects with ATD or with IDDM and ATD from IDDM/ATD families and with a control group. IDDM susceptibility in IDDM/ATD families was negatively associated with the presence of DQB1*0602 [relative risk (RR)=0.038;P=0.0001; corrected P(Pc)=0.0005] and *0301(RR=0.3;P=0.0001; corrected P(Pc)=0.01) and positively associated with the presence of DQBI*0201 (RR-3.4;P=0.0007;Pc=0.0035) and *0302(RR=5;P=0.0001;Pc=0.0005), regardless of ATD. Compared with the IDDM-only group, the ATD -only group had an increased frequency of subjects with DQBI-0602(RR=0.14;P=0.031), suggesting that the known IDDM-protective effect of this allele may be independent of susceptibility to ATD; however, this difference was not significant when the P value was correlated for the number of alleles tested. In these families, susceptibility to ATD was only associated with DQB1*0201(RR=5.71;P=0.0043;Pc=0.021). Among subjects with DQB1* 0201, there was a weak negative association between the presence of DQB1*0302 on the second haplotype and the presence of DQB1*0302 on the second haplotype and Hashimoto's thyroiditis(RR=0.237; P= 0.026; Pc>0.05). We conclude that in IDDm/ATD families, IDDM-affected subjects are at a risk for ATD, especially those carrying DQB1*0302. This risk may be influenced by the alleles carried on the second haplotype, with DQB1*0302 (or a closely linked gene) protecting from Hashimoto's thyroiditis and favoring Graves' disease.

PATHOPHYSIOLOGY, DIAGNOSIS

Presentation and progress of childhood diabetes mellitus: a prospective population-based study. The Bart's-Oxford Study Group.

Pinkley JH, Bingley PJ, Sawtell PA, Dunger DB, Gale EA. Diabetologia 1994; 37: 70-4.

We surveyed the clinical presentation, initial management and subsequent course of a prospectively registered, population-based cohort of 230 patients with Type 1 (insulin-dependent) diabetes mellitus diagnosed before 21 years in the Oxford Regional Authority area in 1985 and 1986. Clinical details from the time of diagnosis were available on 219 patients. Thirty-four (16%) were in severe ketoacidosis with pH less than 7.10 or plasma bicarbonate less than 10mmol/L and 21(10%) had mild to moderate ketoacidosis with pH 7.10-7.35 or plasma bicarbonate 10-21mmol/L. One child died in ketoacidosis. Presentation in severe ketoacidosis was most common in children($0.05<p<0.01$) and those with a parent or sibling with diabetes($p<0.01$). Within 4 years of diagnosis, 55 of 211 patients (26%) experienced severe hypoglycaemia, which in 31(15%) led to one or more admissions. Readmission for unstable glycaemic control excluding acute hypoglycaemia occurred at least once within 1 year of diagnosis in 13% and within 4 years in 28%, and was more common in girls, in children aged les than 10 years at diagnosis, and those with a history of severe hypoglycaemia. A second cohort of 97 similar patients was recruited in 1990. The rates of admission at diagnosis (79%), severe ketoacidosis (13%) and mild to moderate ketoacidosis (13%) did not differ from the 1985/1986 cohort.

Determinants of insulin sensitivity and consequences on lipoproteins and blood pressure in subjects with non-insulin-dependent diabetes mellitus.

Blonk MC, Jacobs MA, Friedberg CE, Nauta JJ, Teerlink T,PoppSnijders C, Heine RJ, Metabolism: Clinical and Experimental 1994; 43 : 501-8

The aim of the present study was to investigate the possible determinants of insulin sensitivity and the relationships of these determinants and insulin sensitivity to lipoprotein levels and blood pressure in patients with non-insulin-dependent diabetes mellitus (NIDDM).We studied 46 patients (26 women, 20 men) treated either with diet alone or in combination with sulfonylureas. Insulin sensitivity was assessed as the insulin-mediated glucose uptake rate (M value) with the hyper insulinaemic euglygaemic clamp technique. In a multiple regression model, only percent body fat, waist hip ratio (WHR), and resting energy expenditure (REE) emerged as significant independent determinants of the M value, with a multiple R2 for the model of 44%, whereas age, haemoglobin, A1c(HbA1c) level, thyroid function, fitness level, smoking status, alcohol consumption, and dietary habits did not contribute significantly. The M value was independently and negatively associated with the concentrations of triglycercide (TG) and very low density lipoprotein (VLDL) cholesterol and positively associated with high density lipoprotein (HDL) cholestrol subfractions and apolipoprotien A1. In our predominantly normotensive subjects, we found no association between the M value and blood pressure. Moreover, fasting insulin contributed directly, i.e., independent of the M value , to the varition of TG, but not to the other lipoproteins and not to blood pressure. The results suggest that in NIDDM (1) insulin sensitivity is determined by percentagebody fat and REE, (2) the insulin level determines the TG level directly,whereas the lipoproteins are influenced indirectly as a reflection of the degree of insulin resistance, and (3) insulin sensitivity is not related to blood pressure in a normotensive population.

DIET, NUTRITION

Effects of dietary protien restriction on glucose and insulin metabolism in normal and diabetic humans.

Lariviere F, chiasson JL, Schiffrin A, Taveroff A, Hoffer LJ, Metabolism: Clinical and Experimental 1994; 43:426-7.

We determined whether the amount of protein in the diet can affect insulin requirements in subjects with diabetes mellitus and glucose metabolism in normal subjects. Seven normal weight volunteers with uncomplicated, intensively controlled, Type 1 (insulin-dependent) diabetes and 12 similar non-diabetic subjects were studied in a metabolic ward before and after consuming a maintenance-energy but protein- free diet for 10 days. Blood glucose levels of diabetic subjects were measured seven times daily in response to insulin administration by continuous subcutaneous infusion. The plasma glucose appearance rate (Ra) was measured in seven normal subjects and all diabetic subjects using a primed-continuous infusion of D-[6,6-2H2] glucose. After adaptation to the protein-restricted diet, diabetic subjects experienced a 30% decrease in average preprandial and average daily blood glucose concentrations ($P > 0.01$); this occurred despite a concurrent 25% decrease in both basal and bolus insulin dosages ($P<0.01$). Protein restriction decreased the post-absorptive glucose Ra ($P < 0.05$) and insulin concentrations ($P < 0.01$) of normal subjects by 20% and increased their fasting glucagon concentrations by 24% ($P < 0.01$). We conclude that severe protein restriction decreases insulin requirements in Type 1 diabetes and fasting hepatic glucose output and basal insulin levels in normal subjects. This effect appears to be mediated in part by decreased hepatic gluconeogenesis, but a contributory influence of increased insulin sensitivity is not ruled out.

TREATMENT: GENERAL

Suppression of non-esterified fatty acids to treat type A insulin resistance syndrome.

Kumar S, Durrington PN, Bhatnagar D, Laing I, Lancet 1994; 343: 1073-4.

A patient with type A insulin resistance syndrome, presented with severe hyper-triglycaemia and diabetes. Fasting insulin and non-esterified fatty acids (NEFA) were very high (41 mU/I and 3.3 mmol/L). A low fat diet failed to correct hyperglycaemia and diabetes. suspected suppression of NEFA with slow-release acipimox for 8 weeks resulted in substantial reduction of serum fasting NEFA (0.31mmol/L). Glucose tolerance became normal and insulin sensitivity increased from 7% to 32%. The glucose fatty-acid cycle may operate in patients with severe insulin resistance and hyperglycaemia: high serum NEFA aggravates insulin resistance and hyperglycaemia by inhibiting glucose uptake and utilisation.

INSULIN THERAPY : GENERAL ASPECTS

Expression of glycogen synthanse and phosphofructokinase in muscle from Type 1(insulin-dependent) diabetic patients before and after intensive insulin treatment.

Vestergaard H, Anderson PH, Lund S, Vedel, P, Pederson O. Diabtologia 1994; 37: 82-90.

The aim of the present study was to determine whether short-time appropriate insulinization of Type 1 (insulin-dependent) diabetic patients in long term poor glycaemic control (HbA1C > 9.5%) was associated with an adaptive regulation of the activity and gene expression of key proteins in muscle glycogen storage and glycolysis: glycogen synthase and phosphofructokinase, respectively. In nine diabetic patients biopsies of quadriceps muscle were taken before and 24-hour after intensified insulin therapy and compared to findings in eight control subjects. Subcutaneous injections of rapid acting insulin were given at 3-hour intervals to improve glycaemic control in diabetic patients (fasting plasma glucose decreased from 20.8+0.8 to 8.7+0.8 mmol/L whereas fasting serum increased from 59+8 to 173+3 pmol/L). Before intensified insulin therapy, analysis of muscle biopsies from diabetic patients showed a normal total glycogen synthase activity but 48% decrease(p=0.006) in glycogen synthase fractional velocity (0.1 mmol/L glucose 6-phosphate) (FVO.1) and a 45% increase (p=0.001) in the half maximal activation constant of glycogen synthase(AO.5). The activity of phosphofructokinase were similar in the two groups. The 2.8 fold increase in serum insulin levels and halving of the plasma glucose level for at least 150-hour were associated with a normalization of glucose level for at least 150- hour were associated with a normalization of glycogen synthase fractional activity (FVO.1) and of the half-maximal activation constant (AO.5) whereas the enzyme activity of phosphofructokinase and the mRNA and protein levels of both glycogen synthase and phosphofructokinase remained normal.

TRANSPLANTATION

Insulin independence in a Type 1 diabetic patient after encapsulated islet transplantation.

Soon-Shiong P, Heintz RE, Merideth N, Yao QX, Zheng T, Murphy M, Moloney MK, Harris M, et al. Lnacet 1994;343:950-1.

Identification of a biocompatible immunoprotective membrane to prevent graft rejection remained elusive until the development of macrocapsules formulated in alginate high in guluronic acid.we report insulin independence in a Type 1 diabetic patient after encapsulated islet transplantation. Encapsulated human islets were injected intraperitonealy in a diabetic patient with a functioning kidney graft. Insulin independence with tight glycaemic control was demonstrated 9 months after the procedure. These results warrant a trial of a high dose of encapsulated islets in early-onset diabetic patients.

PREGNANCY

Glucokinase gene in gestational diabetes mellitus: population association study and molecular scanning.

Chiu KC, Go RC, Aoki M, Riggs AC, Tanizawa Y, Acton RT, Bel DS, Goldenberg RL, Roseman JM, Permutt MA. Diabetologia 1994;37:104-10.

Mutations of the glucolinase gene result in early onset familial Type 2 (non-insulin-dependent) diabetes mellitus, and several members of teh mutant glucokinase kindreds were originally diagnosed as having gestational diabetes. This study examined teh glucokinase gene in 270 American Black women, including 94 with gestational diabetes whose diabetes resolved after pregnancy (gestational diabetes only), 77 with gestational diabetes who developed Type 2 diabetes after pregnancy (overt diabetes), and 99 normal control subjects who were recruited during the peripartum period.Two simple sequence repeat polymorphisms flanking either end of the glucokinase gene were evaluated. No association was found between flucokinase alleles and gestational diabetes only or overt diabetes, after adjustment for multiple comparisons. To detect single base changes, all 11 exons and proximal islet and liver promoter regions were examined by polymerase chain reaction plus single stranded conformational polymorphism analysis in 45 gestational diabetic patients who had not yet developed Type 2 diabetes. Nine coding region variants were identified: Ala 11(GCC) to Thr11 (ACC) in islet exon 1, and 8 variants either in untranslated regions or in the third base of a condon. Four variants sites were found in introns, but none in slpicing consensus sequences. Analysis of the promoter regions revealed two common variants, G->A at islet -30 (24%), and G->A at liver -258 (42%). The frequencies of the promoter variants, determined by allele specific polymearase chain reaction analysis, but did not differ among the three groups. Thus, no significant coding sequence glucokinase mutations were found in 90 alleles from 45 patients with gestational diabetes.

Intensified versus conventional management of gestational daibetes

Langer O, Rodriquez DA, Xenakis EM, McFarland MB, Berkus MD, Arrendondo F, American Journal of Obstetrics and Gynaecology 1994; 170:1036-47.

Objective: We tested the hypothesis that intensified management of gestational diabetes mellitus on the basis of stringent glycaemic control, verified glucose data, and adherence to an established criterion for insulin initiation results in near normoglycaemic control and reduction of adverse outcomes.

Study Design: A prospective, population-based study compared the effect on perinatal outcome of conventional (n=1316) and intensified (n=1145) management. Group assignment was based on availability of memory-based reflectance meters at entry to the program. A contemporaneous randomized control group (non-diabetic, n=4922) was selected.

Results: The diabetic groups were comparable in demographic characteristic and in factors associated with higher risk for adverse pregnancy outcome, such as previous macrosomia, previous gestational diabetes mellitus, and family history of diabetes. The control group was younger, less obese, and had a lower rate of previous macrosomia. The intensified management group had rates of macrosomia, caesarean section, metabolic complications, shoulder dystocia, stillbirth, neonatal intensive care unit days, and respiratory complications lower than those in the conventional management group and comparable to those of the non-diabetic controls. Other maternal complication rates, such as for preeclampsia, chronic hypertension, and infection, were similar for the three groups. Mean blood glucose levels were a good predictor of perinatal outcome. Gestational age at delivery, previous history of macrosomia, and overall mean blood glucose levels were the only significant predictors of birth weight percentile in both diabetic groups (logistic regression).

conclusion: The intensified management approach is significantly associated with enhanced perinatal outcome. This management strategy clarifies the relationship between glycaemic control and neanantal outcome.

COMPLICATIONS, FOOT ASPECTS

The contirbution of non-insulin-dependent diabetes to lower extremity amputation in the community.

Humphrey LL, Palumbo PJ, Butters MA, Hallet JW Jr, Chu CP, O'Fallon WM, Ballard DJ. Archives of Internal Medicine 1994; 154:885-92.

Background: Despite the significant public health burden of lower extremity amputations in diabetes mellitus, few data are available on the epidomiology of lower extremity amputations in diabetes mellitus in the community.

Methods:A retropective incidence cohort study based in Rachester, Minn, was conducted.

Results: Among the 2015 diabetic individuals free of lower extremity amputation at the diagnosis of diabetes mellitus, 57 individuals underwent 79 lower extremity amputations (incidence, 375 per 100,000 persons/years; 95% confidence interval, 297 to 467). Among teh 1826 patients with non-insulin-dependent diabetes mellitus, 52 underwent 73 lower extremity amputations, and the subsequent incidence of lower extremity amputation among these residents was 388 per 100,000 persons/years (95% confidence interval, 304 to 487). Of the 137 insulin-dependent diabetic patients, four subsequently underwent five lower extremity amputations (incidence, 238 per 100,000 persons/years; 95% confidence interval, 92 to 659). Twenty-five years after the diagnosis of diabetes mellitus, the cumulative risk of one lower extremity amputation was 11.2% in insulin-dependent diabetes mellitus and 11.0% in non-insulin-dependent diabetes mellitus. When compared with the lower extremity amputation rates for Rochester residents without diabetes, patients with non-insulin-dependent diabetes mellitus were nearly 400 times more likely to undergo an initial transphalangeal amputation(rate ratio, 378.8) and had almost two fold increased risk of a below-knee amputation (rate ratio, 11.8). In this community, more than 60% of lower extremity amputations were attributable to non-insulin-dependent diabetes mellitus

Conclusions: These population-based data document the magnitude of the elevated risk of lower extremity amputation among diabetic individuals. Efforts should be made to identify more precisely risk factors for amputation in diabetes and to intervene in the process leading to amputation.

COMPLICATIONS, GASTROPARESIS

Diabetic gastroparesis. What to do when gastric emptying is delayed?

Clarke DW, Nowak TV, postgraduate Medicine 1994;95;195-8,201-4

Diagnostic evidence or symptoms of gastroparesis develop in about 20% to 30% of patients with long-standing diabetes. Diabetic gastroparesis is likely to be caused by autonomic neuropathy involving the nerves that regulate gastric motor function The following are necessary for diagnosis: through history taking and physical examination to eliminate factors that might further delay gastric emptying; oesphageusgastroduodenoscopy or barium contrast studies to exclude structural abnormalities; and a radionuclide gastric emptying study. The three main agents available for therapy in the United States are metoclopramide (Mexolon, Octamide, Reglan), erythromycin, and cisapride (Propulsid). All have been shown to offer benefit in improving gastric emptying and symptoms, although use of metoclopramide is limited by significant incidence of side effects. Surgical intervention should be avoided if possible.

COMPLICATIONS, RENAL

Reduction of erthyocyte(Na(+)-K+)ATPase activity in Type 2 (non-insulin-dependent) daibetic patients with microalbuminuria.

Mimura M, Makino H, Kanatsuka A, Asai T, Yoshida S, Hormone and metabolic Research 194;26:33-8

In order to elucidate the casual relationship between (Na(+)-K+)ATPase and diabetic nephropathy,we studied the erthyrocyte (NA(+)-K+)ATPase activity in Type 2 diabetic patients, 20 with microalbuminuria and 27 without microalbuminuria and in 16 control subjects. (Na(+)-K+)ATPase activities in microalbuminuria patients (0.237+0.012 mumol Pi/mg protein/hr, mean+SE) were siginificantly reduced compared with those patients without microalbuminuria (0.308 +0.011 mumol Pi/mg protein/hr $P < 0.05$) and control subjects (0.33+0.011 mumol Pi/mg protein/hr,$p < 0.01$) Microalbuminuric patients had a higher systolic blood pressure (133+3 vs 124+3 mmHg, $p < 0.05$) and greater frequency of parental hypertension (50% vs 19%, $p < 0.05$) than those without microalbuminuria.(Na(+)-K+)ATPase activities in diabetic patients without parental hypertension. There was no difference in erythocyte Na+ content between with and without microalbuminuria or hypertension or parental hypertension in diabetic patients. Erythrocyte Na+ content was significantly negatively correlated with (Na(+)-K+)ATPase activity in control subjects ($r=-0.619$. $p <0.05$), but not in diabetic patients ($r=-0.194$). Plasma digitalis-like substances showed no correlation with (Na(+)-K+)ATPase activities in diabetic patients with microalbuminuria or hypertension or parental hypertension. We conclude that the reduction of erythrocyte (Na(+)-K+)ATPase activity may be related to a familial predisposition to arterial hypertension and may partly be responsible for the development of diabetic nephropathy in Type 2 diabetic patients

Glomerular size and charge selectivity in Type 2 (non-insulin-dependent) diabetic patients with diabetic nephropathy.

Gall MA, Rossing P, Kofoed-Enevoldsen A, Nielsen FS, Parving HH. Diabetologia 1994;37:195-201.

In an attempt to evaluate the mechanisms of proteinuria in diabetic kidney disease, we measured the renal clearance of albumin, total lgG, and lgG4 in 20 male Type 2 (non-insulin-dependent) diabetic patients with diabetic glomerulosclerosis (biopsy proven), in 10 male Type 2 diabetic patients without nephropathy (urinary albumin excretion rate < 30mg/24h), and in 10 healthy male subjects. The fractional clearance of albumin was increased in patients with nephropathy; 659 (42-4355) x10(-6)[median(range)]. compared to 2.6(0.2-14.2)x10(-6) in patients without nephropathy and 2.3 (0.4-4.2)x10(-6) in healthy subjects. The fractional clearance of total lgG (neutral) and of lgG4 (anionic) was 40-50 times higher in patients with nephropathy compared to the other groups. The lgG/lgG4 selectivity index was not significantly different in the three groups bring 1.12(0.06-5.65),1.16(0.45-3.72) and 1.35(0.65-3.34) in patients with nephropathy, patients without nephropathy and healthy subjects, respectively. The lgG/albumin selectively index was decreased in patients with nephropathy: $0.27(0.0^{1-1}.26)$ compared to 1.29(0.07-2067)($p < 0.05$) and 1.23 (0.76-7.84)($p <0.001$) in patients without nephropathy and healthy subjects, respectively. No significant change in lgG/albumin selectivity index was observed between patients without nephropathy and healthy subjects. The systolic blood pressure was elevated in the patients with nephropathy: 164+21 mmHg

(mean +SD) compared to patients without nephropathy: 145+/-20 mmHg ($p < 0.05$) and to healthy subjects:133+19mmHg ($p < 0.005$).

De novo diabetic glomerulosclerosis in a renal allograft recepient.

Sharma UK, Jha V, Gupta KL, Joshi K, Sakhuja V . American Journal of Kidney Diseases 1994;23:597-9

Posttransplant diabetes mellitus is a well recognized complication of renal transplantation. Although such patients are at risk for the development of de novo diabetic glomerulosclerosis with increasing graft survival, this has rarely been reported We describe a patient with posttransplant diabetes mellitus who developed end-stage renal failure due to diabetic glomerulosclerosis 12 years after renal transplantation.

PSYCHOLOGICAL ASPECTS, EDUCATION, MOTIVATION

Effect of advertising on awareness of symptoms of diabetes among general public : the British Diabetic Association Study.

Singh BM, Prescott JJ, Guy R, Walford S, Murphy M, Wise PH, BMJ. 1994;304:632-6.

Objective: To determine the impact of posters advertising symptoms of diabetes on public knowledge of these symptoms.

Design: Structured street interviews of members of the general public before, at the end of, and 10 weeks after a campaign advertising the main symptoms of diabetes.

Setting: Basingstoke and Wolverhampton.

Subjects: Three samples of 1000 members of the general public were interviewed. Samples were selected randomly but stratified to match the local population's age (20-75), sex, social class, and racial characteristics.

Main Outcome Measures: Knowledge of symptoms of diabetes; perceived seriousness of diabetes; and induction of anxiety about symptoms in the target population.

Results: Advertising significantly raised knowledge (without prompting) of symptoms: thirst, 245 before v 411 at end of campaign ($P < 0.0001$) v 341 after ($P=0.0012$ v before); polyuria, 72 v 101 ($P=0.0211$) v 92 ($P=0.5169$); lethargy, 180 v 373 ($P < 0.0001$) v 28 ($P < 0.0001$); knowledge of weight loss and visual disturbance was unaffected. The number of subjects lacking knowledge of any symptoms were reduced from 550 to 388 ($P < 0.0001$). The perceived seriousness of diabetes was unaffected (mean 7.6 in each phase on a scale of 1 (not) to 10 (very). Before advertising, 449 (45%) claimed to have one or more symptoms of diabetes, but this number fell at the end of the campaign (403; $P=0.0419$) and 10 weeks afterwards (278; $P < 0.0001$).

Conlusions: An advertising campaign raised public knowledge of diabetes symptoms without inducing fear of diabetes or anxiety about symptoms. Its potential fro achieving earlier detection of non-insulin dependent diabetes should be evaluated.

Effectiveness and cost-benefit analysis of intensive treatment and teaching programmes for Type 1(insulin dependent) diabetes mellitus in Moscow - blood glucose versus urine glucose self-monitoring.

Starostina EG, Antsiferov M, Galstyan GR, Trautner C, Jorgens V, Bott U, Muhlhauser I, Berger M, Dedov II. Diabetologia 1994;37:170-6.

In a prospective controlled trial the effects of a 5-day in-patient treatment and teaching programme for Type 1(insulin-depedent) diabetes mellitus on metabolic control and health care costs were studied in Moscow. Two different intervention programmes were compared, one based upon urine glucose self-monitoring (UGSM, n=61) and one using blood glucose self-monitoring (BGSM, n=60). Follow-up was 2 years A control group (n=60) continued the standard treatment of the Moscow diabetes centre and was followed-up for 1 year. Costs and benefits with respect to hospitalizations and lost productivity (according to average wage) were measured in November 1992 rubles(Rb), with respect to imported drugs and test strips in 1992 German marks (DM). In the intervention groups there were significant decreases of HbA1 values [UGSM:12.5% before, 9.4% after 1 year, 9.2% after 2 years($p <0.0001$); BGSM:12.6% before, 9.3% after 1 year 9.2% after 2 years($p<0.0001$) compared to no change in the control group (12.2% before 12.3% after 1 year)], and of the frequency of ketoacidosis. The frequency of severe hyoglycaemia wsa comparable between the UGSM(10 cases during 2 years),BGSM(10 cases during 2 years), and the control group(8 cases during 1 year).

Helath care expenditures for people with diabetes mellitus.

Rubin RJ, Altman WM, Menselson DN, Journal of Clinical Endocrinology and Metabolism. 1994; 78:809A-809F.

The purpose of this report is to estimate diabetes prevalence and annual health care costs for people with diabetes in 1992, compare average annual costs for diabetes and non-diabetics, and estimate the portion of total U.S. health care expenditure incurred by the people with the disease. Data from the 1987 National Medical Expenditure Survey were used to estimate diabetes prevalence and health care expenditures for diabetics in 1992. Diabetics were identified based on self-reports of a physicians diagnosis of diabetes, a history care system specifically related to diabetes. Identified diabetics were classified as confirmed if they had a history of taking diabetic medications, had a diabetes-specific encounter with the health care system, or purchased diabetic equipment. Estimates of diabetes prevalence and health care expenditures were calculated separately for identified and confirmed diabetics using the National Medical Expenditure Survey Database. Total health care expenditures included costs associated with inpatient hospital care, outpatient hospital care, office visits to a physician or other provider, emergency room visits, home health care, prescription drugs, dental care, and durable medical equipment purchases. We estimate that percapita annual health care expenditures in 1992 were more than three times greater for diabetics($9,493) than for nondiabetics($2,604). Percapita expenditures for confirmed diabetics ($11,157) were more than four times greater than for nondiabetics. In 1992, diabetics constituted 4.5% of the U.S. population but accounted for 14.6% of total U.S. health care expenditures($105 billion). Confirmed diabetics constituted 3.1% of the U.S. population but accounted for 11.9% of total U.S. health care expenditures ($85 billion). This study found that health care expenditures for people with diabetes constituted about one in seven health care dollars spent in 1992. Health care reform and insurers should take note of these findings and structure benefit packages to promote care likely to reduce costs of caring for diabetics.