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DIABETES RESEARCH

UK PROSPECTIVE DIABETES STUDY 6. COMPLICATIONS IN NEWLY DIAGNOSED TYPE 2 DIABETIC PATIENTS AND THEIR ASSOCIATION WITH DIFFERENT CLINICAL AND BIOCHEMICAL RISK FACTORS*

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SUMMARY The prevalence of various diabetic complications, their association with each other and with many risk factors, has been assessed in 2,337 newly diagnosed Type 2 diabetic patients. The patients entered into the UK Prospective Diabetes Study were aged between 25 and 65 (mean age 52 yr) and 33% had either an abnormal ECG or retinopathy. Different macrovascular complications such as strokes, heart attacks or abnormal ECG, and peripheral vascular disease showed little association one with another, and each was associated predominantly with different risk factors, e.g., strokes with hypertension, heart attacks with hypertriglyceridaemia and peripheral vascular disease with smoking and a low HDL cholesterol. Retinopathy was associated with reduced vibration perception but not with other complications. Reduced vibration perception and absent reflexes were associated with absent foot pulses and ischaemic skin changes, raising the possibility of a macrovascular, as well as microvascular, contribution to peripheral neuropathy. Microalbuminuria was associated with hypertension, which might be a factor predisposing to renal microvascular disease or be a consequence of it. Microalbuminuria was also associated with an abnormal ECG. Retinopathy, with exudates and or haemorrhages rather than just microaneurysms, was associated with hyperglycaemia. The occurrence of a particular complication in a diabetic patient is probably dependent on a combination of specific risk factors, many of which are related to, and probably affected by, potentially avoidable factors such as hyperglycaemia, obesity, smoking and hypertension.

Key words: Type 2 diabetes, complications, retinopathy, angina, myocardial infarct, stroke, neuropathy, peripheral vascular disease, hyperlipidaemia, hypertension, hyperglycaemia, microalbuminuria

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Introduction

At the time Type 2 diabetes is diagnosed, patients may already have various macrovascular, microvascular and neuropathic complications. The inter-relationships between different diabetic complications have been studied mainly in Type 1 rather than Type 2 diabetic patients (1). A high prevalence of diabetic complications has been found in newly diagnosed predominantly Type 2 diabetic patients recruited in the UK Prospective Diabetes Study, and we have assessed the degree to which different complications are related to many clinical and biochemical risk factors. Analyses include the inter-relationship between the various complications, and their relationship to potentially treatable risk factors such as hypertension, obesity, hyperlipidaemia or hyperglycaemia.

Subjects, Materials and Methods

We report on the initial 2,337 patients entered into the UK Prospective Diabetes Study (UKPDS) (2). In 15 centres, newly diagnosed patients aged 25–65 inclusive, with a fasting plasma glucose (fpg) >6 mmol/l on two occasions were considered for inclusion in the Study. 83% had a fpg >8 mmol/l, the mean fpg concentration being 11·8 mmol/l. If reasonable, diuretics and oestrogen therapy were stopped before assessment. Patients were excluded if they had ketonuria, a history of myocardial infarction in the previous year, current angina or heart failure, more than one major vascular episode, serum creatinine >175 μmol/l, severe retinopathy requiring photocoagulation, malignant hypertension, an uncorrected endocrine abnormality, an occupation which would not allow randomization to insulin therapy (e.g., heavy goods vehicle driver), a severe intercurrent illness likely to limit life (e.g., cancer) or requiring extensive systemic treatment (e.g., ulcerative colitis), or inadequate comprehension to allow co-operation. Patients were invited to join the study, which has been approved by the Ethics Committee in each centre. Details regarding patients' age, sex, obesity, fasting plasma glucose and estimated beta cell function and insulin sensitivity have been reported (3, 4).

All patients entered into the study had a detailed questionnaire on their medical history, a detailed physical examination, blood taken for biochemistry and a chest X-ray and an ECG were taken. Where there was a history of myocardial infarction, confirmation was obtained either by a demonstrable ECG abnormality or by appropriate plasma enzyme rises described in a hospital discharge summary. Transient ischaemic attacks were defined as more than one episode of weakness with a neurological deficit lasting for less than 24 hr, a minor stroke as symptoms or signs for less than one month, and a major stroke as symptoms or signs for more than one month. Intermittent claudication and angina were defined by the WHO criteria of symptoms including precipitating and relieving factors (5). Males were asked if they had any sexual difficulty or impotence, but it is known than many will not admit to impotence at the initial medical consultation. The usual physical activity of subjects was assessed in most patients on a scale of sedentary (rarely takes exercise), moderately active (on their feet less than half the day or moderate exercise two days per week), active (on their feet more than half the day, or regular exercise three or more times a week) or fit (manual worker or regular vigorous exercise three or more times per week) (4).

Blood pressure was measured with the patient rested for at least 2 min. It was measured in the arm with a mercury sphygmomanometer and auscultation without masking of readings, usually with a regular size inflatable cuff, unless the arm circumference was greater than 33 cm when a large cuff was used. The diastolic pressure was taken at the Korotkoff phase 5. Hypertension was diagnosed using the WHO criteria if either the patient was on antihypertensive drugs or the blood pressure was >160 mmHg systolic and/or >95 mmHg diastolic.

Obesity was assessed from the weight at presentation as a percentage of the ideal body weight (ibw) given for the middle of the medium frame for the patient's height and sex by the Metropolitan Life Insurance Tables (6).

Assessment of macrovascular disease included a routine 12-lead ECG which was performed on all patients and classified according to the Minnesota Code (7). All ECGs were read by two independent observers and differences were adjudicated by a third. A final ECG code was expressed as normal, as probable ischaemia, "2" (Codes 1-1, 1-2, 7-1) or possible ischaemia, "1" (Codes 1-3, 4-1, 4-2, 4-3, 4-4, (if also abnormal 4-1, 4-2 or 4-3), 5-1, 5-2, 5-3). Cardiomegaly was assumed if the cardiac/chest ratio was more than 0·5 on a chest X-ray taken at diagnosis. Peripheral vascular disease was assessed by palpation for dorsal pedis and posterior tibial pulses, two or more absent pulses on either side being taken as abnormal. Any visible features on the feet thought to signify ischaemia were noted i.e., shiny or discoloured skin, loss of hair or thick nails.

Retinopathy was assessed in 1,232 patients by retinal colour photographs taken using a 30° camera through maximally dilated pupils (8, 9). Four horizontal fields, macula, temporal to macula, disc and nasal to disc were taken of each eye. Only photographs taken within six months of diagnosis were used, and for the purpose of this paper minimal retinopathy was defined as one or more microaneurysm in either eye and more severe retinopathy as haemorrhage and/or exudates in either eye in addition to microaneurysms.

Peripheral neuropathy was assessed by measuring the vibration threshold at both the great toes and medial malleoli using a biothesiometer (Biomedical Instrument Company, Ohio, USA). The instrument is a hand-held mains-operated unit with a constant frequency vibrator button, whose amplitude can be gradually increased until vibration is first detected by the patient. The threshold was classified as abnormal when the reading was greater than two standard deviations from the normal age corrected mean (10) or >50, the maximum reading on the biothesiometer scale. Knee and ankle reflexes were tested with the patient supine, and with reinforcement by the patient pulling on his interlocked hands if initially a reflex was not obtained. Absence of two or more reflexes was taken to be abnormal.

A fasting blood sample taken at the intitial clinic visit was analyzed for plasma glucose in each centre to confirm the diagnosis of diabetes. Quality control was assessed by each centre measuring four plasma samples sent monthly from Oxford. Additional plasma and blood samples were sent to Oxford at 4°C in specially designed polystyrene boxes for analysis of HbA1 by electrophoresis (Corning electro endomosis) (11), plasma total cholesterol (12) HDL and LDL cholesterol (13, 14), triglyceride (15). N-acetyl-glucosaminidase (16) and insulin (17). Plasma creatinine was measured locally in each centre by routine methods and variation between creatinine measurements assessed by comparing the means of all samples in each centre, and linearly adjusting results from each centre to the overall mean, 83 μmol/l. A single urine sample was taken on attending a morning out-patient clinic. Urinary albumin was measured by radio-immunoassay (18) and urinary creatinine spectrophotometrically on a Cobas-Bio (19) and the albumin/creatinine ratio expressed as g/mol (20).

Data Analysis

Data analysis was carried out using the Statistical Package for the Social Sciences (SPSS) (21) on the Oxford University ICL 2988 computer. Chi square test was used for statistical analyses of significant associations between presence or absence of complications and the chi square value is quoted with Yates correction and one degree of freedom. Analysis of variance was used for the investigation of continuous variable risk factors in the presence or absence of complications with age and percent ideal body weight as co-variates. Pearson correlation coefficients were calculated to analyze associations between continuous variables, taking into account age and obesity as co-factors and r values are quoted. All

results are reported after checking that the data were normally distributed. We report all analyses for associations between complications and risk factors for all ethnic groups together. Similar results were obtained for caucasian subjects alone. Analysis of associations between all different risk factors was done, but we report fully only those related to clinical variables which are potentially treatable. Further analyses are available on request. Calculations on triglyceride, insulin, N-acetyl-glucosaminidase and albumin/creatinine ratio data were done after log transformation to ensure a normal distribution.

Results

Prevalence

Of the 3,232 newly diagnosed patients referred for inclusion in the study, 51 (2%) patients had had a myocardial infarct, 86 (3%) had angina and 37 (1%) had had a stroke. Eight hundred and ninety-five (28%) of 3,232 patients were excluded by pre-determined criteria from entry to the study and from further analyses (Table 1). The groups of patients who had angina, recent myocardial infarcts or cancer tended to be older, mean age at 55–56 yr, compared with the mean age of 52 yr of all those referred, whereas the patients who were ketotic and needed immediate insulin, tended to be younger, mean age 41 yr. The main exclusion groups, those unable to attend the clinic or who had an occupation precluding insulin therapy e.g., Heavy Goods Vehicle Driver, had similar age, obesity and fasting plasma glucose to those who entered the study.

The prevalence of complications in the 2,337 patients, who entered the study is given in Table 2 and includes 33 with a myocardial infarct more than one year previously and 30 with a previous stroke or TIA. The different ethnic groups had a similar prevalence of complications, except that Asians had less frequent hypertension and abnormal ECG. They were also slightly younger and less obese than the other ethnic groups (Table 5).

Females had a higher prevalence of hypertension, abnormal ECG and absent foot pulses than males, whereas males had a greater prevalence of impaired vibration perception and raised plasma creatinine. Otherwise the two genders had a similar prevalence of both microvascular and macrovascular complications, and a similar cumulative prevalence of complications, when expressed in order of degree to which complications are likely to be due to diabetes and are precise measurements (Table 3). 20% of males admitted to impotence.

30% of women who had been pregnant had diabetes suspected in pregnancy either by glycosuria or a baby more than 9 lb birth weight. They had the same prevalence of complications as the women in whom diabetes had not been suspected.

Inter-relation between Complications

Macrovascular diseases Hypertension was associated with strokes ($p < 0{\cdot}001$), an abnormal ECG ($p < 0{\cdot}001$) and cardiomegaly ($p < 0{\cdot}001$), but not with previous myocardial infarct or peripheral vascular disease (Table 4). There were few associations between the three major types of macrovascular disease, i.e., strokes, myocardial infarcts and peripheral vascular disease (assessed by three

Table 1 Reasons for exclusion to entry into the prospective study with the number of patients in each group expressed as a percentage of all referrals. The mean age and fasting plasma glucose of those excluded is given. These data are included in prevalence of macrovascular complications at presentation in the text

	Number of patients	*% of all referrals*	*Mean age (yr)*	*Mean fasting plasma glucose (mmol/l)*
Angina	86	3		
Recent or multiple myocardial infarcts	18	0·5		
Recent stroke	7	0·2		
Generalized vascular disease	7	0·2	56	12·0
Heart failure	9	0·3		
Cardiac valve disease	7	0·2		
Uncontrollable hypertension	8	0·2		
Proliferative retinopathy or maculopathy	10	0·3	50	9·0
Plasma creatinine > 175 μmol	2	0·06	—	—
Cancer or other major disease	73	2	55	9·6
Uncorrected endocrine disturbance or pregnancy	17	0·5	56	14·3
Ketotic needing insulin therapy	76	2	41	19·6
Started therapy by GP	64	2	52	15·4
Heavy goods vehicle driver	103	3	48	11·3
Unable to attend or cooperate with study	408	13	51	11·4
Total excluded	895	28	51	11·8
Total entered in study	2,337	72	52	11·6

Table 2 Complications at presentation according to gender and ethnic groups.

The proportion of patients with each complication entered into the study according to gender and ethnic groups. The significant differences between the sexes and ethnic groups are given by * $p<0.05$, † $p<0.01$, ‡ $p<0.001$. Seven patients, classified as other ethnic groups, were excluded from the latter analysis

		Prevalence in sexes			*Prevalence in ethnic groups*			
	All	*Male*	*Female*	*p value*	*European*	*Afro Caribbean*	*Asian*	*p value*
Number of patients	2,337	1,387	950		1,948	202	180	
Retinopathy (>1 microaneurysm)	21%	22%	18%	ns	20%	26%	23%	
Abnormal ECG	18%	14%	23%	‡	19%	17%	6%	‡
Myocardial infarct	1%	2%	1%	*	2%	0%	0%	*
Intermittent claudication	3%	3%	3%	ns	3%	3%	3%	ns
Stroke or transient ischaemic attacks	1%	1%	2%	ns	1%	2%	0%	ns
Absent foot pulses (2 or more)	13%	10%	17%	‡	13%	13%	7%	*
Ischaemic skin changes feet	6%	6%	7%	ns	7%	5%	2%	*
Impaired reflexes (2 or more)	5%	4%	5%	ns	5%	7%	2%	ns
Abnormal vibration threshold	7%	9%	4%	‡	7%	3%	5%	*
Plasma creatinine >120 μmol/l	3%	4%	1%	‡	3%	4%	1%	ns
Hypertension	35%	27%	45%	‡	36%	32%	19%	‡
Impotence	20%	20%	—	—	20%	16%	20%	ns

different indices, intermittent claudication, absent foot pulses and ischaemic appearance of feet) except for an association between myocardial infarct and intermittent claudication ($p<0.001$), and between absent foot pulses and an abnormal ECG ($p<0.05$).

Neuropathic Disease, Retinopathy and Peripheral Vascular Disease

Some neuropathic indices were associated with each other e.g., impotence with both reduced reflexes ($p<0.05$) and abnormal vibration threshold ($p<0.001$), but abnormal vibration threshold and reduced reflexes were not associated with each other. However there was also an association between ischaemic complications and neuropathy in that abnormal vibration threshold and reduced reflexes were both associated with absent foot pulses ($p<0.001$ and <0.01 respectively) and ischaemic skin changes ($p<0.05$). Abnormal vibration threshold was also strongly associated with retinopathy ($p<0.001$). These associations might indicate both a microvascular and macrovascular ischaemic contribution to diabetic neuropathy.

Table 3 The cumulative total of patients with any complication is given in a group of 1,232 patients in whom retinal photographs and all data was available. The significant differences between male and female groups is given by * $p<0.05$ and ‡ $p<0.001$

	Cumulative prevalence			
	All	*Male*	*Female*	*p value*
Number of patients	1,232	728	504	
Retinopathy (>1 microaneurysm)	21%	22%	18%	ns
Abnormal ECG	33%	32%	35%	ns
Myocardial infarct	34%	33%	36%	ns
Intermittent claudication	37%	36%	38%	ns
Stroke or transient ischaemic attacks	38%	37%	40%	ns
Absent foot pulses (2 or more)	45%	42%	48%	*
Ischaemic skin changes feet	46%	44%	49%	ns
Impaired reflexes (2 of more)	49%	46%	52%	ns
Abnormal vibration threshold	51%	50%	54%	ns
Plasma creatinine >120 μmol/l	52%	51%	54%	ns
Hypertension	65%	60%	72%	‡
Impotence	—	66%	—	—

Microalbuminuria, Hypertension and Abnormal ECG

Increased microalbuminuria (expressed as albumin/creatinine ratio >2·5 g/mol) was associated with hypertension and with abnormal ECG. When assessed as a continuous variable with analysis of variance, the relation with abnormal ECG remained significant ($p<0.001$) after taking blood pressure into account as a co-variate.

Risk Factors

Various risk factors and biochemical indices were compared between the genders and ethnic groups (Table 5). Females were more obese and had a higher prevalence of systolic blood pressure as previously reported (3, 22) and also a higher plasma cholesterol (total, HDL and LDL). The males and females had similar absolute triglyceride values, but when corrected for obesity males had a significantly higher triglyceride than females (geometric mean 2·19 and 1·95 mmol/l respectively). A slightly younger Asian group had a lower blood pressure, weight and fasting plasma glucose. They had a higher fasting plasma insulin concentration and taking into account the degree of obesity, the Asians also had a higher plasma triglyceride than the Europeans.

The Analysis of Risk Factors in Relation to the Presence or Absence of Complications

Analysis of variance calculations were performed on

Table 4 Cross tabulation of association between different complications that have occurred at the time of diagnosis. Chi square values are quoted and significance is denoted by * $p<0.05$, † $p<0.01$, ‡ $p<0.001$. The boxes enclose expected associations, either because variables relate to the same disease process, i.e., cardiac, peripheral vascular disease, peripheral neuropathy, or because of previously reported associations i.e., hypertension/stroke and reduced vibration sense/retinopathy

		Macrovascular disease				*Peripheral vascular disease*			*Peripheral neuropathy*			*Microvascular disease*	
Chi squares	*Hypertension*	*Stroke or TIA*	*Cardiomegaly*	*Myocardial infarct*	*Abnormal ECG*	*Absent foot pulses*	*Intermittent claudication*	*Ischaemic skin changes*	*Impotence*	*Impaired reflexes*	*Reduced vibration*	*Retinopathy*	*Albumin/creatinine > 2·5 g/mol*
Hypertension	–	‡ 18·8	‡ 38·0	ns	‡ 72·0	ns	ns	ns	ns	ns	ns	ns	‡ 31·4
Stroke or transient ischaemic attack	‡ 18·8	–	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Cardiomegaly	‡ 38·0	ns	–	† 5·1	‡ 13·6	ns	ns	ns	ns	ns	ns	ns	* 4·9
Myocardial infarct	ns	ns	† 5·1	–	‡ 37	ns	‡ 11·8	ns	ns	ns	ns	ns	ns
Abnormal ECG	‡ 72·0	ns	‡ 13·6	‡ 36·9	–	* 5·0	ns	ns	ns	ns	ns	* 4·1	‡ 14·5
Absent foot pulses	ns	ns	ns	ns	* 5·0	–	‡ 31·8	‡ 106·8	ns	‡ 11·1	† 8·0	ns	ns
Intermittent claudication	ns	ns	ns	‡ 11·8	ns	‡ 31·8	–	‡ 34·3	ns	ns	ns	ns	ns
Ischaemic skin changes in feet	ns	ns	ns	ns	ns	‡ 106·8	‡ 34·3	–	* 4·4	* 6·2	* 4·6	ns	ns
Impotence	ns	ns	ns	ns	ns	ns	ns	* 4·4	–	* 6·5	‡ 20·3	ns	* 4·9
Impaired reflexes	ns	ns	ns	ns	ns	‡ 11·1	ns	* 6·2	* 6·5	–	ns	ns	ns
Abnormal vibration threshold	ns	ns	ns	ns	ns	† 8·0	ns	* 4·6	‡ 20·3	ns	–	‡ 15·9	ns
Retinopathy	ns	ns	ns	ns	* 4·1	ns	ns	ns	ns	ns	‡ 15·9	–	ns
>1 microaneurysm Albumin/creatinine > 2·5 g/mol	‡ 31·4	ns	* 4·9	ns	‡ 14·5	ns	ns	ns	* 4·9	ns	ns	ns	–

the continuously variable data to examine the relationships between known risk factors and the presence of complications taking into account age and obesity (Table 6). There was a significant increase in plasma triglyceride levels in patients with myocardial infarcts ($p<0.01$), abnormal ECG ($p<0.001$) and hypertension ($p<0.001$) as compared with patients without these complications. These associations were more marked in males than females i.e., mean values for males with and without myocardial infarct 2·5 and 1·5 mmol/l ($p<0.01$) and females 1·7 and 1·5 mmol/l respectively, and similarly for males with and without an abnormal ECG 1·8 and 1·4 mmol/l ($p<0.01$) and females 1·6 and 1·5 mmol/l respectively. Patients with abnormal ECG also had a significant increase in LDL cholesterol ($p<0.01$) and this association was more marked in females, mean values with and without abnormal ECG 3·5 and 3·2 mmol/l ($p<0.01$) than males 3·0 and 2·9 mmol/l respectively. Those patients with intermittent claudication showed a reduced HDL cholesterol ($p<0.01$) which was not present in either myocardial infarct or abnormal ECG patients.

Fasting plasma glucose levels were significantly raised both in patients with impotence ($p<0.05$) and in patients with more severe retinopathy ($p<0.01$). Fasting plasma insulin was associated with an abnormal ECG in males ($p<0.001$) but no association was found in females.

Table 5 The mean values for risk factors and biochemical variables is given for all patients, and according to gender and ethnic groups. Significant differences between the genders and ethnic groups are given by * $p<0.05$, † $p<0.01$, ‡ $p<0.001$

	All	*Male*	*Female*	*p value*	*Caucasian*	*Black*	*Asian*	*p value*
BP systolic (mmHg)	141	137	146	‡	142	140	129	†
BP diastolic (mmHg)	86	85	87	ns	86	88	82	‡
Age (yr)	52	52	53	†	53	51	47	‡
Obesity (% ideal body weight)	130	122	142	‡	131	126	115	‡
HbA1 (%)	11·6	11·4	11·8	‡	11·6	12·2	11·1	†
Fasting plasma glucose (mmol/l)	11·6	12·3	12·1	‡	11·6	12·4	10·8	†
Fasting plasma insulin (mU/l)	9·8	9·3	10·2	†	9·8	7·2	12·0	‡
Plasma N-acetyl-β-D-glucosaminidase (nmol/ml/hr)	1,357	1,324	1,407	ns	1,373	1,119	1,510	‡
Cholesterol (mmol/l)	5·1	4·9	5·3	‡	5·1	4·9	4·9	ns
HDL cholesterol (mmol/l)	1·3	1·2	1·3	‡	1·3	1·4	1·2	‡
LDL cholesterol (mmol/l)	3·1	3	3·3	‡	3	2·9	2·9	ns
Triglyceride (mmol/l)	2·1	2·1	2·1	†	2·2	1·3	2·1	‡
Packed cell volume (%)	45	46	43	‡	45	43	45	‡
Creatinine (μmol/l)	84	—	—	—	83	88	84	‡
Uric acid (mmol/l)	0·3	0·3	0·3	‡	0·3	0·3	0·3	ns
Albumin/creatinine (g/mol)	2·9	3·0	2·8	ns	3	2·9	2·7	ns

The percentage of smokers, whether current or previous, was significantly higher among patients with previous myocardial infarcts ($p<0.001$), and intermittent claudication ($p<0.001$).

Microalbuminuria, Hypertension, Retinopathy

Microalbuminuria (expressed as albumin/creatinine ratio) was associated with hypertension ($p<0.01$), but not with the presence of retinopathy defined as any microaneurysms (Table 6). It was weakly associated with more severe retinopathy ($p<0.05$), defined as the presence of haemorrhages and/or exudates, but the presence of retinopathy was not associated with hypertension.

The Inter-relationship between Risk Factors

The degree of hyperglycaemia, after taking into account obesity and age, correlated positively with the blood pressure ($p<0.001$), plasma cholesterol ($p<0.001$), LDL cholesterol ($p<0.001$), triglyceride, ($p<0.001$) and albumin/creatinine ratio ($p<0.001$) (Table 7). Obesity, after taking age into account, was associated with high blood pressure ($p<0.001$), plasma insulin ($p<0.001$), and albumin/creatinine ratio ($p<0.001$). Taking into account the degree of hyperglycaemia made little difference to these associations. Whilst an increased LDL cholesterol and triglyceride were associated with each other ($p<0.001$, $r=+0.25$) both were negatively associated with the HDL cholesterol ($p<0.001$, $r=-0.12$; $p<0.001$, $r=-0.32$ respectively).

Smoking was associated with a raised plasma triglyceride ($p<0.001$) and lower HDL cholesterol ($p<0.001$) after taking into account age and obesity. A low amount of exercise was associated with obesity ($p<0.001$), hyperglycaemia ($p<0.001$), hypertriglyceridaemia ($p<0.001$), and a raised plasma insulin ($p<0.01$).

Plasma N-acetyl-glucosaminidase was raised in relation to age, obesity and hyperglycaemia but was not associated with a raised albumin/creatinine ratio or any vascular disease (Table 7).

Discussion

Half of the newly presenting Type 2 diabetic patients already have one or more complications at diagnosis, with 18% having an abnormal ECG and 25% retinopathy. Females had a similar prevalence of macrovascular and microvascular complications to males and there were few differences between ethnic groups. If one includes hypertension and impotence as complications, in the order of 65–70% have a complication at presentation. Other studies of newly-diagnosed Type 2 diabetic patients had a similar prevalence of complications. The UGDP study (23) included similarly age patients (mean age 52 yr) within 1 yr of diagnosis but had a female predominance. With slightly different definitions of complications they had a similar prevalence of absent foot pulses (13%), intermittent claudication (5%) and hypertension (31%) but a lower prevalence of ECG abnormalities (3%) and a higher incidence of retinopathy (58%). In Finland, which has a high prevalence of coronary artery disease in the general population, newly diagnosed diabetic patients had an 18% prevalence of myocardial infarction in both sexes and, if angina and an abnormal ECG were included, 32% men and 42% women had coronary heart disease, which was higher than in a control population (24).

Klein *et al.* (25) found a 29% prevalence of retinopathy in 1,370 Type 2 diabetic patients within 5 yr of diagnosis, which is in accord with the 25% we found at diagnosis. Should a prospective study show that improved blood glucose control prevents complications, it would be im-

Table 6 Risk factors.

A tabulation of association of different complications and risk factors calculated by a two-way analysis of variance of the complication with covariates age and weight (except for age where % IBW is the only covariable). + indicates those patients with the complications and − those without. Significance is denoted by * $p<0.05$, † $p<0.01$, ‡ $p<0.001$. A blank space indicates the comparison was not significant.

Quoted are the mean or geometric mean values.

Smoking is compared with the complications by chi square analysis. All the complications correlated positively with age

Complication		*Patient numbers*	*Triglyceride (mmol/l)*	*Total cholesterol (mmol/l)*	*HDL cholesterol (mmol/l)*	*LDL cholesterol (mmol/l)*	*Uric acid (μmol/l)*	*Albumin/ creatinine (g/mol)*	*Packed cell volume (%)*	*Fasting plasma glucose (mmol/l)*	*HbA1 (%)*	*Smokers (%)*
Hypertension	+	805	1·6	5·2	1·3	3·2	0·32	2·4	45·2	12·0	11·7	63
	−	1,532	1·4 ‡	5·0 †	1·3	3·0	0·29 ‡	1·8 ‡	44·8 *	11·4 †	11·5	67
Myocardial infarct	+	33	2·2	5·6	1·2	3·4	0·3	1·5	45·2	11·7	11·7	97
	−	2,285	1·4 †	5·0 *	1·3	3·1	0·3	2·0	44·9	11·6	11·6	66 ‡
Abnormal ECG	+	371	1·7	5·3	1·3	3·2	0·31	2·6	44·9	12·0	11·6	65
	−	1,721	1·4 ‡	5·0 †	1·3	3·1 †	0·30 ‡	1·8 ‡	45·0	11·5 *	11·5	66
Absent foot pulses (2 or more)	+	298	1·6	5·1	1·3	3·1	0·30	2·0	44·9	12·2	11·9	68
	−	2,018	1·4	5·0	1·3	3·1	0·30	2·0	44·9	11·5 *	11·5	66
Intermittent claudication	+	74	1·8	5·3	1·1	3·4	0·29	1·7	45·9	11·7	11·4	85
	−	2,244	1·4	5·0	1·3 †	3·1	0·30	2·0	44·9 †	11·6	11·6	65 ‡
Impotence	+	254	1·4	4·8	1·2	2·9	0·30	2·1	46·7	11·6	11·5	83
	−	1,026	1·4	4·9	1·2	3·0	0·31	1·6 *	46·0 †	11·1 *	11·4	75 *
Abnormal vibration threshold	+	137	1·5	5·1	1·2	3·1	0·29	2·0	44·7	11·9	11·2	74
	−	1,621	1·5	5·1	1·3	3·1	0·30	1·6	45·0 *	11·6	11·6	65
Retinopathy (microaneurysms plus hard exudates or haemorrhages)	+	158	1·6	5·2	1·3	3·2	0·29	2·9	44·8	12·6	12·1	61
	−	966	1·5 *	5·0	1·2	3·1	0·30	2·2 *	44·8	11·6 †	11·5 *	67

Table 7 Relationship of biochemical indices to age and to potentially treatable risk factors.

Cross tabulation of correlations between potentially treatable risk factors and biochemical variables calculated using partial correlation coefficients controlling for age and % ideal body weight (except for age where controlling only for %IBW and %IBW controlling only for age). Correlation coefficient is expressed as a percentage.

Analysis of variance is used to compare the effects of smoking and exercise on risk factors with age and body weight as co-variates. The mean value of the variable is quoted.

Significance is denoted by † $p<0.01$, ‡ $p<0.001$

	By partial correlation coefficients				*By ANOVA*			
					Smoking		*Exercise*	
	Age	*Diastolic BP (mmHg)*	*Obesity %IBW*	*Plasma glucose (mmol/l)*	*Non smoker*	*Smoker*	*Sedentary mod. active*	*Active and fit*
Diastolic blood pressure	‡ 12%	–	‡ 24%	‡ 9%	‡ 86·5	83·7	ns	
Fasting plasma glucose	‡ 8%	‡ 9%	ns	–	ns		‡ 11·9%	11·3%
Fasting plasma insulin	ns	ns	‡ 38%	ns	ns		‡ 10·2%	9·1%
Plasma N-acetyl glucosaminidase	‡ 17%	ns	‡ 20%	‡ 17%	ns		ns	
Cholesterol	ns	‡ 10%	ns	‡ 20%	ns		ns	
HDL cholesterol	ns	ns	‡ 10%	ns	‡ 1·3	1·2	ns	
LDL cholesterol	ns	† 7%	† 8%	‡ 17%	† 3·0	3·2	ns	
Triglyceride	ns	† 7%	‡ 23%	‡ 19%	‡ 1·9	2·3	‡ 2·2	1·9
% Packed cell volume	ns	ns	ns	ns	‡ 44·5	45·7	ns	
Plasma creatinine	‡ 12%	ns	‡ 11%	† 6%	ns		ns	
Urate	‡ 16%	ns	‡ 13%	‡ 22%	† 0·3	0·29	ns	
Albumin/creatinine ratio	† 7%	‡ 14%	‡ 8%	‡ 23%	ns		ns	

portant to screen the general population to detect diabetes before these complications occur. One third of parous female patients in the UK Prospective Diabetes Study had had diabetes suspected in pregnancy or had had a baby weighing more than 9 lb, and thus might later have been screened as patients particularly at risk from development of complications.

When carrying out multiple statistical analyses, as with the present data, it is important to recognize that a proportion of "significant" associations would occur by chance. Whilst the number of associations were greater than would be expected, one cannot determine which reflect pathological processes and which might be chance occurrences.

Although the statistically significant results reflect only a small proportion of the observed variance, this does not necessarily mean that the association is trivial or clinically insignificant. These results are from a cross sectional study with biochemical variables measured on one occasion only. The clinical complications are classified according to defined but arbitary presence or absence, which do not necessarily identify the extent of pathology. The relationships in these analyses allow the generation of hypotheses, which can be re-examined prospectively during the follow-up of patients in the study.

Macrovascular Disease

Few associations between the different types of macrovascular disease (i.e., stroke, myocardial infarction and peripheral vascular disease) were found other than myocardial infarct with intermittent claudication. The data suggest that each particular complication may be dependent on several specific and different risk factors. The associations found are similar to those in non-diabetic populations, including strokes with hypertension (26) peripheral vascular disease with smoking (27), a low HDL cholesterol (28), and a low packed cell volume (29), and heart disease with hypertriglyceridaemia (30, 31). In diabetes, hypertriglyceridaemia appears to be a more important risk factor than a raised LDL cholesterol and this may reflect the greater frequency with which hypertriglyceridaemia occurs in diabetic patients than in the normal population. Several of these risk factors were associated with other abnormalities such as hypertension, hyper-

glycaemia, obesity, smoking and a sedentary life-style, all of which are potentially avoidable. The therapy of Type 2 diabetes should probably be directed as much to eliminating these risk factors as to improving blood glucose control. Indeed, the blood glucose concentration itself was not shown to be directly associated with the occurrence of macrovascular disease.

A raised fasting plasma insulin is a known risk factor for cardiovascular disease in the normal population (32), but an association with abnormal ECG was only found in male and not female patients. The fasting plasma insulin correlated with hypertriglyceridaemia independently of obesity and hyperglycaemia, and this is in accord with the known association of hypertriglyceridaemia with insulin resistance (33).

Neuropathic, Microvascular and Macrovascular Associations

Retinopathy was associated with reduced vibration sense, which may also be microvascular in origin. Indices of neuropathy, such as reduced vibration sense and absent knee jerks, were also found to be significantly associated with indices of peripheral vascular disease, such as absent foot pulses and ischaemic appearing feet. This suggests the possibility of both a microvascular and macrovascular contribution to neuropathy. In accord with a vascular pathology is the demonstration of fibrin deposition in vessels in biopsies of affected nerves (34). Experiments on rats have shown that the peripheral nerves of diabetic animals are particularly susceptible to ischaemic damage (35). Diabetic neuropathy may result from a combination of biochemical disturbances, e.g., reduced myoinositol concentrations, and ischaemia from macrovascular and microvascular disease.

Renal Disease and Microvascular Disease

Microalbuminuria was increased in patients with hypertension. It was not associated with retinopathy defined as the presence of microaneurysms alone, but was associated with more severe retinopathy defined as at least the presence of haemorrhages and/or exudates as well as microaneurysms. The association primarily with hypertension might either indicate that hypertension *per se* increases glomerular damage and albumin excretion (36) or that the hypertension is secondary to renal microvascular disease, which may not necessarily be associated with retinopathy. Reducing the blood pressure has been reported to reduce albumin excretion (37) and hypertension may be an important factor in the development of renal disease.

Microalbuminuria was associated with hyperglycaemia and hypertriglyceridaemia, suggesting renal disease may be multifactorial in origin.

The lack of association of retinopathy with hypertension suggests hypertension is not a major factor in its early development. The association of more severe retinopathy with hyperglycaemia is in keeping with the reported association in Type 1 (38) and Type 2 (39) diabetic patients.

The association of microalbuminuria with an abnormal ECG may reflect a microvascular contribution to cardiac ischaemia. It is in accord with the high cardiac mortality in patients with microalbuminuria (40, 41).

A raised plasma N-acetyl-glucosaminidase is common in diabetes, and has been associated with hyperglycaemia and retinopathy (42). It is not known why plasma lysosomal enzymes should be raised in diabetes, or from which organ they arise. Plasma N-acetyl-glucosaminidase was not associated with any macro- or microvascular complications, although it was increased in relation to hyperglycaemia, obesity, and a raised fasting plasma insulin.

Potentially Avoidable Risk Factors

Potentially avoidable risk factors such as hyperglycaemia, obesity and smoking had several associations with known biochemical risk factors. Hyperglycaemia and obesity were rarely associated directly with the different complications, but they were both associated with risk factors such as a raised LDL cholesterol, triglyceride and microalbuminuria. Obesity was associated with a low HDL cholesterol and high plasma insulin. Smoking was associated with a low HDL cholesterol, high triglyceride, high packed cell volume, a sedentary life-style and high plasma insulin. The occurrence of a particular complication in a diabetic patient is probably the result of an interaction of several risk factors, many of which might improve by simple change of dietary, smoking and exercise habits and by improving glucose control. Treatment of hypertension in diabetes would be expected to prevent strokes, as in the normal population (26) and may help to prevent associated renal disease, as suggested by the association with microalbuminuria.

In summary, there was little association between different types of complications in a Type 2 diabetic population. Macrovascular and microvascular complications appeared to have different associated risk factors. The occurrence of a complication in a particular patient is probably multifactorial and dependent on the interaction of several pathological mechanisms. Several risk factors are associated with potentially avoidable insults such as obesity, hyperglycaemia, smoking, hypertension and hyperlipidaemia and avoidance of these might help to prevent complications. In view of the complexity of the pathological processes, it is unlikely that therapy directed solely at a specific variable, such as the blood glucose, is likely to prevent the complications of diabetes.

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