Factors Associated With Avoidance of Severe Complications After 25 Yr of IDDM

Pittsburgh Epidemiology of Diabetes Complications Study I

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To identify characteristics associated with long-term avoidance of insulin-dependent diabetes mellitus (IDDM) complications, subjects taking part in an epidemiologic natural history study of childhood-onset IDDM, with a duration of disease ≥25 yr, were studied. Nineteen percent of 175 subjects had avoided overt nephropathy, definite cardiovascular and peripheral vascular disease, clinical neuropathy, and proliferative retinopathy. Approximately half of the nonrenal complications occurred in the absence of renal disease. Subjects free of these advanced complications were characterized by a longer duration of disease ($P < 0.05$), better lipid profile and blood pressure ($P < 0.01$), and considerably lower glycosylated hemoglobin levels ($P < 0.001$). Health-related behaviors, including recent medical contact, regular glucose monitoring, physical activity in youth, and avoidance of cigarette smoking, did not relate to complication status, although regular (at least weekly) alcohol consumption was more prevalent ($P < 0.05$) in those without complications. We conclude that a lower mean glycosylated hemoglobin level is strongly related to the avoidance of all IDDM complications. *Diabetes Care* 13:741–47, 1990

Although it has long been recognized that the complications of insulin-dependent diabetes mellitus (IDDM) affect virtually all patients, a subset appears to fare particularly well and avoid major problems. A series of reports in the 1950s and 1960s described such patients and provided valuable insights, particularly the suggestion that good glycemic control was a predominant feature of such patients (1–4). However, the populations were very selective, the methodology for determining complications and risk factors understandably limited by today's standards, and, in general, these studies lacked a comparison group, as did a more recent study by Paz-Guevara et al. (5). In 1970, Chazan et al. (6) reported on a group of IDDM patients from the Joslin Clinic, all of whom had diabetes for >25 yr (mean 36 yr), and felt that a low prevalence of smoking, as well as good glycemic control and regular physical activity, were important for survival without major complications. However, in addition to lacking a true comparative population, this sample may be biased in terms of health care and socioeconomic characteristics, because 35% had a close relative in the medical profession. A follow-up of patients awarded the Joslin Quarter Century Victory Medal for survival without complications suggested that parental longevity was another beneficial characteristic (7). In contrast, Oakley et al. (8), in 1974, found no convincing evidence of a relationship between either parental longevity or good glycemic control and long-term survival, although the absence of hypertension was a striking feature of his study group. Two studies from Steno Clinic have provided more recent data concerning mortality, including a comparative analysis of those dying before 35 yr of IDDM with survivors after 40 yr (9,10). Male sex, poor glycemic control, and less frequent attendance at the clinic were adverse risk factors (10). This particular study, although providing valuable information, was limited by the use of a clinic popula-

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tion and data that did not include neuropathy measures. In this report, which extends the above findings, all four major complications (retinopathy, neuropathy, nephropathy, and macrovascular disease) are examined in a representative cohort of childhood-onset IDDM patients who have survived ≥25 yr of diabetes. Current risk factors, HLA-DR type, and historical health behaviors are compared in subjects with and without advanced complications in the hope that further insights that may lead to preventive strategies are discovered.

RESEARCH DESIGN AND METHODS

All subjects are childhood-onset (<17 yr) IDDM patients seen at or within a year of diagnosis at Children's Hospital of Pittsburgh between 1 January 1950 and 31 May 1980. If seen between 1 January 1950 and 13 February 1979, they had to have taken part in a questionnaire survey of morbidity (response rate 96%) conducted between 1981 and 1985. All subjects (979) living within 100 miles of Pittsburgh were sent a letter inviting them to take part in this study, followed by a phone call to schedule an appointment. If after repeated attempts the participant still refused to take part (or after repeated failure to keep the appointment), he/she was asked to complete the questionnaires and return them in the mail.

Two weeks before the scheduled appointment, participants were mailed three questionnaires and containers (with detailed instructions) for the collection of 24-h and separate overnight urine samples, which were kept refrigerated or frozen until clinic appointment. The questionnaires comprised *1*) medical history and health behavior (smoking habits, alcohol intake, diabetes management and monitoring, family history of diabetes, cardiovascular disease and hypertension, and the Rose Questionnaire for angina and claudication; 11); *2*) physical activity questionnaire (Paffenbarger Questionnaire on leisure activities; 12), and further details on worktime activities and a lifetime history of leisure activity (13); and *3*) psychosocial questionnaires (including quality-of-life, coping, personality types, and Beck Depression Inventory; 14–18).

On arrival at the clinic in the fasted state, subjects underwent sitting blood pressure measurement with a random zero sphygmomanometer according to the Hypertension Detection and Follow-Up Program Protocol, with the mean of the second and third blood pressures used in analyses (19). Blood samples were then taken for the following determinations: lipids, lipoproteins, apolipoproteins, serum glucose, glycosylated hemoglobin (saline incubated), full blood count, spontaneous whole-blood platelet aggregation, serum creatinine and albumin, and fibrinogen. Thyroid function testing and B_{12} and folate levels were also measured if clinically indicated. A urine sample was collected on arrival and ~4 h later at the end of the clinic visit. The three timed urine samples (24 h, overnight, and 4 h) were assayed for albumin and creatinine to calculate the albumin excretion rate, glomerular filtration rate, and albumin-creatinine ratio. After taking their insulin and receiving breakfast, the participants had a 12-lead electrocardiogram and three-field stereofundus photography after mydriasis and a measurement of intraocular pressure. A standardized medical history and clinical examination were performed by a trained internist to assess neuropathy (Diabetes Control and Complications Trial Protocol) and cardiovascular disease (including the presence of angina) (20). Systolic blood pressure was then remeasured in the right arm (or left arm if the pressure in the left arm had been >10 mmHg higher than in the right arm). Bilateral supine ankle pressures were then recorded with Doppler blood flow signals at the dorsalis pedis and tibialis posterior arteries. Two cycles of such blood pressures were taken with an additional measurement of the arm pressure at the end of the second cycle. Ankle-arm blood pressure ratios were then calculated with the use of the arm pressure closest in time to the ankle pressure. If any of the ankle-arm blood pressure ratios were <0.8, the subject was considered to have peripheral vascular disease. In addition, if the ankle pressure was >100 mmHg higher than the arm pressure, arterial calcification was suspected. In the absence of these conditions and any contraindications to exercise, a treadmill test consisting of walking on an 8% incline at 1.5 mph for 30 s followed by 2 mph for the next 4.5 min was performed. Ankle-arm blood pressure ratios were then determined with one ankle pressure per leg at 1, 3, and 5 min after exercise. A nutritional food-frequency questionnaire (Harvard-Willett) was then administered, and after a final urine collection, the exam ended with an exit interview with the physician (21).

DEFINITIONS OF COMPLICATION END POINTS

Nephropathy. Overt nephropathy was defined on the basis of *1*) the presence of renal failure (serum creatinine >440 μM or on dialysis or status postrenal transplant), *2*) increased albumin excretion rate (>200 μg/min in 2 of 3 timed urine samples), or *3*) in the absence of urine collections, a serum creatinine >180 μM.

Microalbuminuria was defined as an albumin excretion rate between 20 and 200 μg/min in two or three of the urine samples. In the few subjects with urine samples of questionable completeness, a previously validated albumin-creatinine urinary ratio was used (i.e., 0.03–0.3 mg/mg for microalbuminuria and >0.3 for overt nephropathy; 22). Cases of nephropathy due to nondiabetic causes were excluded from analyses.

Neuropathy. Distal symmetrical polyneuropathy was considered to be present if, in the opinion of the examining physician, at least two of the following three criteria were present and not due to a nondiabetic cause: symptoms consistent with distal symmetrical polyneuropathy, decreased (i.e., requiring reinforcement) or absent tendon reflexes, and signs of sensory

loss. Although symptoms of autonomic neuropathy and symptoms and signs of motor neuropathy were documented, the frequency of these abnormalities was insufficient to permit further analysis.

Retinopathy. Stereo fundus photographs were taken of fields one, two, and four with a Zeiss camera and were read by the Fundus Photography Reading Center at the University of Wisconsin in Madison. Readings were classified according to the modified Airlie House System (23) and grouped into four categories: no retinopathy (grade 10 in both eyes), early background retinopathy (highest grade from either eye 20 or 30), advanced background retinopathy (highest grade 40 or 50), and proliferative retinopathy (grade ≥60 in at least one eye). Individuals without fundus photographs were graded on the basis of a confirmed history. Scattered photocoagulation scars and a retinopathy grade of <60 were coded as proliferative retinopathy if the history suggested that laser therapy was for proliferative retinopathy.

Macrovascular disease. Definite macrovascular disease was considered to be present if any of the following criteria were met: *1*) peripheral vascular disease: an ankle-arm blood pressure ratio <0.8 either at rest or after exercise or a history of amputation for peripheral vascular disease, or *2*) cardiovascular disease: a history of myocardial infarction that was confirmed by electrocardiographic changes (i.e., pathological Q waves) at time of examination or if review of previous hospital records met the criteria for definite myocardial infarction of the Community Cardiovascular Surveillance Project Study (24), or a history of angina was elicited and confirmed by the physician, or a history of stroke.

Laboratory determinations. Glycosylated hemoglobin (GHb) was originally determined with saline-incubated blood samples and microcolumn cation-exchange chromatography (Isolab, Akron, OH). On 26 October 1987, the GHb technique was changed to high-performance liquid chromatography (Diamat, Bio-Rad, Hercules, CA). Extensive duplicate samples were run with both techniques, and no systematic differences were seen. Readings with the two methods were shown to be almost identical (r = 0.95; Diamat [HbA_1] = −0.18 + 1.00 Isolab [HbA_1]). The absolute difference between the means of the two methods was 0.158 (% HbA_1). Urinary C-peptide was determined in the 24-h sample with radioimmunoassay (Novo, Copenhagen). Serum cholesterol and triglyceride levels were determined enzymatically (25,26). High-density lipoprotein cholesterol was determined by a heparin and manganese procedure with modification of the Lipid Research Clinics methodology (27,28). Low-density lipoprotein cholesterol was calculated with the Friedewald equation if triglycerides were <4.5 mM (29). This equation has previously been validated in our laboratory for IDDM subjects (30). Apolipoproteins A-I and B were determined with a rocket immunoassay and lipoprotein A-II with an enzyme-linked immunosorbent assay methodology (31,32). Apolipoprotein E phenotyping was determined with isoelectric focusing and immunoblotting (33). Blood glucose was determined with a YSI analyzer (Yellow Springs, OH). Spontaneous whole-blood platelet aggregation was determined immediately after the blood draw by calculating the percentage fall in a single platelet count after 15 min shaking or magnetic stirring of citrated samples in a warm-water bath (37°C). A Clay Adams Ultraflo 100 platelet counter was used for these determinations, and the values were subtracted from a previously determined platelet count in an EDTA blood sample (34). Fibrinogen levels were performed via a biuret colorimeteric procedure and a clotting method and creatinine with an autoanalyzer (Ectachem 700xr, Kodak, Rochester, NY). Albumin was determined immunonephelometrically (35,36). HLA-DR typing was performed serologically (37).

Statistical analysis. Student's t test was used for continuous variables, except for the variables (e.g., spontaneous whole-blood platelet aggregation) where a normal distribution could not be achieved despite data transformations, when Wilcoxon's rank-sum test was used. For dichotomous variables, the χ^2-test was used. Multiple logistic regression was used to examine the relationship between the binary dependent variable and the independent variables. Each full model was analyzed with backward stepping, where nonsignificant variables leave the model and the coefficients for the remaining variables are recomputed.

RESULTS

One thousand eight hundred patients registered in the Children's Hospital registry had been diagnosed or seen within a year of diagnosis from 1 January 1950 to 31 May 1980 (Table 1). Of the 979 eligible participants, 67% attended the clinic and a further 13% supplied

TABLE 1
Epidemiology of diabetes complication study: recruitment tree based on Children's Hospital of Pittsburgh registry from 1 January 1950 to 31 May 1980

	n	%
Seen within 1 yr of diagnosis	1800	
Deceased	192	11
Out of area	419	23
No survey/not traced	204	11
Ineligible	6*	
Eligible	979	100
Participated	788	80
Full participation	657	67
Questionnaire	131	13
Nonparticipation	191	20
Refused	170	17
Not traced	21	2

*Participants in Diabetes Control and Complications Trial, 2; with severe retardation, 3; institutionalized, 1.

TABLE 2
Participants and nonparticipants and selected characteristics from previous survey

	Seen	Forms only	Refused/not traced	Total nonparticipants
*n**	618	109	181	290
Mean age (yr)	24	24	25	25
Male (%)	50.8	45.0	52.5	49.7
Mean duration of diabetes (yr)	16	16	17	16
Laser therapy (%)	18.5	26.9	15.6	19.8
Proteinuria (%)	18.8	16.3	15.2	15.6
Saw physician in last year (%)	83.2	80.7	75.7	77.6
Some college education (%)†	47.8	38.0	36.4	37.0

Based on ref. 9.
*Seventy-one not eligible for previous survey.
†Includes only ≥18-yr-old subjects.

questionnaire information for a total response rate of 80%. Over 95% of the subjects were seen between May 1986 and September 1988. To determine if our examined sample differed from the questionnaire and nonparticipant group, certain demographic variables were compared according to responses given in the 1981–1985 morbidity and mortality survey (Table 2). The full participants were similar to nonparticipants regarding age, sex, duration of diabetes, reported laser therapy ($P = 0.7$), and proteinuria/renal disease ($P = 0.3$). However, participants were more likely to have attended college ($P = 0.003$) and marginally more likely to have seen their physician in the last year ($P = 0.05$). Thus, it is concluded that the full participants are fairly representative of all those eligible.

Table 3 shows the age, sex, and duration of diabetes of the 175 subjects with a duration of ≥25 yr. This group should have a high probability of having developed those complications that they are going to develop. Thirty-three subjects (19%) had none of the advanced complications (i.e., proliferative retinopathy, distal symmetrical polyneuropathy, definite macrovascular disease, or overt nephropathy). Only 11 (6%) had all four complications. Forty-nine percent of subjects with proliferative retinopathy, 52% with neuropathy, and 63% with macrovascular disease did not have overt nephropathy.

Subjects free of advanced complications did not differ from those with complications by age or sex; however, those with complications did have a longer duration of diabetes (29.6 vs. 28.3 yr, $P < 0.05$; Table 4). Table 4 also shows a marginal difference in the frequency of high-risk HLA-DR types (3 or 4) by complication status, whereby subjects free of complications were less likely to have the high-risk HLA-DR types. Those health-related behaviors, which may reflect status before complication development, were generally not related to complication status. These include avoidance of cigarette smoking ($P = 0.22$), testing for glucose at least weekly ($P = 0.32$), physical activity in young adult life, and recent medical contact. Regular alcohol consumption (i.e., at least 1 alcoholic drink/wk) was, however, significantly ($P < 0.05$) more common in subjects without complications. Table 5 shows other risk factor differences by complication status for this subgroup. The lipoprotein and blood pressure profiles (including hypertension status) were significantly better in the complication-free group, whereas GHb was significantly higher in the complication group ($P < 0.001$). Urinary C-peptide did not differ either when examined by concentration or secretor status.

Multiple logistic regression analyses revealed GHb (β-coefficient 0.48, $P < 0.01$) to be the only independent predictor of complication status when health behavior variables were included in the model (Table 4). Low-density lipoprotein cholesterol ($\beta = 0.025$, $P < 0.01$) and hypertension ($\beta = 2.9$, $P < 0.01$) contributed equally to the model along with GHb ($\beta = 0.55$, $P < 0.01$) if all significant variables were available for modeling.

TABLE 3
Participants with ≥25 yr duration of diabetes

			Duration of diabetes (yr)		
	Male	Female	25–29	>30	Total
n	88	87	106	69	175
Age (yr)					
<35	40	33	49	17	37
>35	60	67	51	83	63
Overt nephropathy	48	25	32	44	37
Proliferative retinopathy	75	53	57	75	64
Neuropathy	63	54	50	72	59
Cardiovascular disease	7	9	7	10	8
Peripheral vascular disease	9	28	17	20	18
Microalbuminuria	27	22	22	29	25

Values other than *n* are percentages.

TABLE 4
Univariate correlates of complication-free status at ≥25 yr postdiagnosis of insulin-dependent diabetes mellitus (host and health behavior characteristics)

	Complication status		
	Free	Present	*P*
n	33	142	
Age (yr)	35.9 ± 4.8	36.9 ± 4.6	NS
Duration of diabetes (yr)	28.3 ± 2.4	29.6 ± 3.1	<0.05
Male	49	51	NS
Absence of high-risk HLA-DR type (3/4)	13	4	<0.09*
Ever smoked	42	56	NS
Alcohol consumption	48	25	<0.05
Seen physician in last year	84	83	NS
Test for glucose weekly	77	66	NS
Physical activity (17–23 yr of age; high)	65	67	NS

Values are percentages.
*Fisher's exact test.

DISCUSSION

These findings provide additional support to the hypothesis that good glycemic control is associated with avoidance of major complications and confirm the results of other studies based on less comprehensive examinations of select populations (1,2,6,9,10). The role of tight control of blood glucose, however, is still controversial. The Diabetes Control and Complications Trial is examining the hypothesis that intensive therapy reduces complication risk (20). The current study, by carefully determining all major complications, avoids the pitfall of assessing control in subjects with one specific complication and comparing them to subjects without that complication but who may have another unmeasured complication that is equally related to control.

Our data do not confirm the reported benefits of medical contact in terms of complication avoidance (9). However, the measure available (seeing a physician for diabetes care in the last year) is different from attendance at the Steno Clinic, which reports a benefit from regular medical contact (9). Clearly, subjects with complications and motivated subjects without complications are both more likely to be in recent medical contact, making the attenders a mixed population.

The second Steno report also focuses on survival and compares patients dying within 35 yr of diagnosis of IDDM with those surviving >40 yr (10). Again, regular clinic attendance and better diabetes control were favorable factors. In addition, there were more deaths among men in the early deceased group where renal disease was a major cause of death. Our findings of greatly increased renal disease in men ($P < 0.001$) and our previously reported greater overall early mortality in men in this cohort may explain in part why our survivors at 25 yr of age no longer exhibit a sex effect on complication status (38; Table 3).

To extend previous findings relating clinical findings to antecedent health-related behaviors, we examined smoking (lifetime status), drinking (current), physical activity in young adult life, and regular testing for glucose. Lifetime avoidance of cigarette smoking and regular testing for glucose were both more frequent (although insignificantly so) in the complication-free group. This may partly reflect sample size and both may be important. Because we have shown smoking to be a powerful predictor of death in IDDM in women, its benefit may be muted in this analysis of living cases (39). Regular glucose testing is associated with better control in this population (GHb 9.9 vs. 10.8%, $P < 0.01$) and therefore of likely benefit. In subjects free of complications, GHb did not differ significantly in those who tested regularly (GHb 9.0%) compared with subjects who did not test regularly (GHb 9.8%, $P = 0.18$). This suggest that this subgroup has additional factors acting to improve control, as even nontesting subjects without complications had lower mean GHb levels than regular testers with complications.

We found no relationship between historically documented physical activity at ages 17–23 yr and complications status. This age-group was chosen to maximize exercise measures and to ensure that it pre-

TABLE 5
Univariate correlates of complication-free status at ≥25 yr postdiagnosis of insulin-dependent diabetes mellitus (risk factors)

	Complication status		
	Free	Present	*P*
n	33	142	
Low-density lipoprotein cholesterol (mM)	2.8 ± 0.7	3.4 ± 1.0	<0.01
High-density lipoprotein cholesterol (mM)	1.5 ± 0.4	1.4 ± 0.3	<0.05
Triglycerides (mM)	1.0 ± 0.8	1.6 ± 1.2	<0.01
Systolic blood pressure (mmHg)	112 ± 10	122 ± 21	<0.001
Diastolic blood pressure (mmHg)	71 ± 7	75 ± 12	<0.01
Hypertensive (%)	3	33	<0.01
Fibrinogen (g/L)	2.7 ± 0.8	3.1 ± 0.9	<0.05
Urinary C-peptide (% >5 mg/h)	4	18	NS
Spontaneous whole-blood platelet aggregation (%)	9.1 ± 7.0	9.5 ± 8.0	NS
Glycosylated hemoglobin (%)	9.3 ± 1.0	10.4 ± 2.0	<0.001

Values are means ± SD.

ceded any effect of the complications. Again, it is possible that the effect is muted in this survivor group because of the earlier mortality associated with lack of activity; we have previously shown participation in team sports to be a protective factor in men (40).

The final intriguing finding is that regular alcohol consumption (at least 1 drink/wk) is more frequent in subjects without complications; unfortunately, we do not have data on lifetime exposure. However, alcohol consumption does relate to better control (GHb 9.7 vs. 10.3%, $P < 0.05$) in this population, which may explain its benefit, particularly because alcohol did not contribute to the multiple logistic analysis independent of GHb. Alcohol is known to induce hypoglycemia and has been shown to improve glucose tolerance in both diabetic and nondiabetic subjects, although this is far from a consistent finding (41–48). Long-term alcohol intake and glucose tolerance have not been well studied, although in nondiabetic subjects, nondrinkers had higher 1-h serum glucose values after a glucose challenge (49). Among drinkers in the overall study population, we could find no evidence for a dose-response relationship between alcohol and GHb. Other potential benefits might include alcohol's vasodilator and other cardioprotective effects. Because these data are cross sectional, and those with complications may drink less because of the complications, caution is advised in interpreting these data.

In conclusion, avoidance of complications is strongly related to good glycemic control in this cross-sectional analysis, an outcome that may be aided by regular glucose testing and alcohol consumption. Because increasing alcohol intake in the IDDM patient may be a risky intervention, prospective follow-up studies that confirm these findings are needed before this action is recommended.

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