Clinical Factors Associated With Resistance to Microvascular Complications in Diabetic Patients of Extreme Disease Duration

The 50-year Medalist Study

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Duration of diabetes and degree of hyperglycemia have consistently been identified as predictors of retinopathy and nephropathy (1–6). Multiple studies have concluded that nearly all individuals with type 1 diabetes will develop some level of retinopathy within 20 years of diagnosis (2,4,5,7,8). However, the study by Bain et al. (9) described the Golden Years study group of type 1 diabetic patients with ≥50 years of diabetes duration who appeared to be protected against nephropathy and large vessel disease but not against retinopathy. However, the associations of glycemic control, duration of disease, and vascular complications were not evaluated (9). This report characterizes the prevalence of complications and associated risk factors in a large number of individuals who have been insulin dependent for ≥50 years.

RESEARCH DESIGN AND METHODS

— The 50-Year Medal Program of the Joslin Diabetes Center (JDC) was initiated to recognize JDC or non-JDC patients who survived ≥50 years with type 1 diabetes. This was documented by either medical record or family report. This was a survey-based cross-sectional study of subjects living in the U.S. who were awarded the Joslin Medal between 1997 and 2003. The Committee on Human Subjects at the JDC approved this study. The patients were questioned regarding the presence and absence of eye, kidney, and peripheral neuropathy.

Clinical validation of retinopathy

Self-reported retinopathy was validated by comparing retinal clinical examination and fundus photography (seven-standard field), in a subset (n = 92, 28%) of the 326 subjects, to the questionnaire, with the worse eye used for analysis. Grading was performed by two experienced ophthalmologists and discrepancies adjudicated by consensus. Descriptive analyses were performed using the Statistical Analysis System (version 8.2; SAS, Cary, NC). The Cochran-Armitage test was used to test for trends of categorical variables. Logistic regression was used to estimate the association of microvascular complications with risk factors.

RESULTS

— A total of 405 (81%) out of 500 subjects responded to the initial questionnaire; the remaining 95 (19%) questionnaires were returned because of incorrect addresses. Of those who returned the original questionnaire, 21 (62%) individuals did not wish to participate; 7 (5.1%) were too ill, 13 (33.3%) were not interested, and 1 (4.7%) did not provide a reason. As of January 2004, 326 of 405 (81%) questionnaires had been completed, with 21% of subjects receiving regular care from JDC.

Of the 326 respondents, 54.7% were female. The mean ± SD ages at the time of completing the questionnaire and at diagnosis of type 1 diabetes were 69.5 ± 8.4 and 12.6 ± 7.1 years, respectively. The mean BMI was 24.5 ± 4.0 kg/m^2. The median of the most recent physician-reported A1Cs was 7.0% (range 4.7–10.8), and the average insulin dose was 0.5 ± 0.2 units/kg.

Microvascular complications

A total of 174 (53.4%) individuals reported microvascular complications (Table 1). Triglycerides (P = 0.05), insulin dose per kilogram (P = 0.02), and insulin dose ($P < 0.05$) were higher among subjects who reported a complication (retinopathy, nephropathy, or neuropathy) compared with those among subjects not reporting any microvascular problems (Table 1). Age, diabetes duration, age at onset of diabetes, A1C, BMI, total cholesterol, and LDL cholesterol did not differ significantly between groups or for each microvascular complication. HDL cholesterol levels were higher in subjects who did not report any microvascular complications (71.6 ± 30.9 vs. 64.5 ± 25.0 mg/dl, P = 0.06).

Current regular physical activity was associated with a reduced risk of complications (odds ratio [OR] 0.3 [95% CI 0.13–0.54]) and was independently associated with decreased risk of retinopathy (0.48 [0.26–0.92]), nephropathy (0.33 [0.13–0.87]), and neuropathy (0.27 [0.14–0.53]). Exercise was not protective among those with an HDL cholesterol level greater than the median (65 mg/dl) (0.35 [0.11–1.08]). However, regular exercise was associated with significantly

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Abbreviations: JDC, Joslin Diabetes Center.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Characteristics of medalists broken down by complication status*

	Retinopathy			Nephropathy			Neuropathy			Any		
	Yes	No	*P*	Yes	No	*P*	Yes	No	*P*	Yes	No	*P*
n	139	151		22	304		164	145		174	152	
Male/female	62/77	72/79	0.69	7/15	144/160	0.16	80/84	63/82	0.30	83/91	68/84	0.6
Age (years)	67.7 ± 7.5	71.3 ± 8.9	<0.01	66.4 ± 7.7	69.8 ± 8.4	0.08	69.0 ± 8.0	70.1 ± 8.7	0.30	68.8 ± 7.9	69.1 ± 8.0	0.75
Duration of diabetes (years)	56.1 ± 5.6	58.1 ± 6.3	<0.01	57.5 ± 5.7	57.2 ± 6.0	0.87	56.9 ± 5.9	57.6 ± 6.1	0.30	57.0 ± 5.9	57.3 ± 5.9	0.70
Age at onset (years)	11.9 ± 7.1	13.6 ± 7.4	0.06	9.8 ± 6.1	12.8 ± 7.2	0.05	12.7 ± 6.9	12.6 ± 7.3	0.90	12.4 ± 6.7	11.9 ± 6.9	0.64
BMI (kg/m^2)	24.9 ± 3.8	24.1 ± 4.2	0.31	27.0 ± 3.3	24.4 ± 4.0	<0.01	24.6 ± 3.8	24.4 ± 4.2	0.59	24.7 ± 3.8	24.4 ± 4.3	0.56
Daily insulin dose (units)	33.8 ± 15.2	32.3 ± 14.6	0.4	41.2 ± 18.8	32.2 ± 14.2	0.01	34.9 ± 16.0	30.3 ± 12.7	0.008	34.9 ± 15.8	30.2 ± 12.9	<0.01
Insulin dose (units/kg)	0.5 ± 0.2	0.4 ± 0.2	0.7	0.53 ± 0.2	0.4 ± 0.2	0.3	0.5 ± 0.2	0.4 ± 0.2	0.02	0.5 ± 0.2	0.4 ± 0.2	0.02
A1C (%)	7.1 (5.5–9.9)	7.0 (4.7–10.8)	0.28*	7.4 (5.7–9.5)	7.0 (4.7–10.8)	0.21*	7.1 (5.2–9.9)	7.0 (4.7–10.8)	0.11*	7.0 (5.2–9.9)	7.0 (4.7–10.8)	0.38*
HDL cholesterol (mg/dl)	74.5 ± 32.7	66.2 ± 70.4	0.6	53.8 ± 19.5	68.5 ± 28.0	0.01	64.3 ± 25.1	71.7 ± 30.4	0.04	64.5 ± 25.0	71.6 ± 30.8	0.06
Triglyceride (mg/dl)	90.3 ± 57.8	76.4 ± 43.6	0.04	142.6 ± 79.3	79.1 ± 46.5	<0.01	91.6 ± 58.0	72.3 ± 39.0	0.002	90.9 ± 57.6	72.6 ± 39.4	0.05
Hypertension (%)	52.5	53.6	0.85	61.9	50.5	0.30	56.9	48.7	0.02	56.8	45.1	0.2

Data are means ± SD or median (25th–75th percentile range). *Nonparametric test *P* value.

lower risk among those with HDL cholesterol levels below the median (0.22 [0.07–0.70]). Prevalence of retinopathy, nephropathy, and neuropathy did not differ across quartiles of A1C.

Retinopathy

A total of 139 (47.9%) subjects reported diabetic retinopathy (see online appendix [viewable at http://dx.doi.org/10.2337/dc06-2222] for assessment). Those without diabetic retinopathy were older ($P < 0.01$), had longer diabetes duration ($P < 0.01$), and had lower triglyceride levels ($P = 0.04$) than those with diabetic retinopathy (Table 1). Retinopathy prevalence declined with increasing duration. Reported prevalence of diabetic retinopathy was 50% (107 of 213), 44% (29 of 66), and 27% (3 of 11) for diabetes durations of 50–59, 60–69, and >69 years, respectively.

Nephropathy

A small number of subjects reported nephropathy ($n = 22$, 6.7%). Affected individuals were younger at diagnosis ($P = 0.05$); had higher BMI (<0.01), lower A1C levels ($P = 0.01$), and higher triglycerides ($P < 0.01$); and more frequently reported heart problems ($P = 0.05$) than those who did not report nephropathy.

Neuropathy

Over one-half of subjects reported neuropathy ($n = 164$). Compared with subjects without neuropathy, these patients had a higher insulin dose per kilogram ($P = 0.02$), lower HDL cholesterol levels ($P = 0.04$), higher triglycerides ($P < 0.01$), and more heart disease ($P < 0.01$).

Validation

Of the patients studied for validation ($n = 92$), 99% correctly reported their diabetic retinopathy status. In these individuals, 42 (51.9%) had no, mild, or moderate evidence of retinopathy, and 39 (48.1%) had proliferative diabetic retinopathy. Six individuals without diabetic retinopathy self-reported the complication, and only five individuals with diabetic retinopathy reported no retinopathy. The mean historical corrected A1C values had a strong correlation with a patients' current A1C level ($P < 0.01$, $R = 0.7$).

CONCLUSIONS — The subjects demonstrated several unexpected vascular findings. Close to one-half (46.8%) did not report any significant microvascular complications. Only ~50% of those with 50–60 years' diabetes duration re-

ported diabetic retinopathy, and this decreased to only 44 and 27% at 60–69 and ≥70 years of diabetes, respectively. This is in contrast with the literature that reports that >90% of type 1 diabetic patients will eventually develop retinopathy (2,4,7). Another unexpected finding is the lack of association between glycemic control and prevalence of reported microvascular complications in subjects, which was not addressed by Bain et al. (9). Most studies involving diabetes have shown that the risk for microvascular complications is strongly associated with glycemic control (3–6,10–12). The Medalist Study data suggest that individuals with extreme duration of type 1 diabetes are either protected from or have markedly slower progression of diabetic retinopathy. These novel findings might result from either a reduction in factors that promote the disease, such as hyperglycemia, or an increase in factors inhibiting the disease. Another possible reason, a reporting bias toward the complication-free group, is unlikely because validation studies showed close approximation of fundus photography with reported retinopathy.

A mean HDL cholesterol level of 67.7 ± 27.6 mg/dl in the subjects is high for type 1 diabetic patients, but this is consistent with the Golden Years Study (9). In the Cardiovascular Health Study, healthy aging men with HDL cholesterol levels of ≥60.4 mg/dl were found to be at lower risk for many common causes of death (13,14). HDL cholesterol levels are influenced by multiple factors, including genetics and physical activity (14–16). In this study, exercise was associated with reduced microvascular complications but not in those with HDL cholesterol above the median. These results suggest that exercise may be an important protective factor, especially when HDL cholesterol levels are not elevated. Genetic factors may also be important, since the mean age of death was 73.6 ±13.6 years for the fathers and 78.4 ±14.2 years for the mothers of subjects. The life expectancy for this birth cohort (ca. 1900) was 47.6 years for Caucasians of both sexes (17).

The Medalist Study showed that significant numbers of diabetic patients could live without severe complications for an extreme duration of the disease, suggesting that they may possess factors that can neutralize the adverse effects of hyperglycemia.

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