Contribution of Diabetes Duration Before Puberty to Development of Microvascular Complications in IDDM Subjects

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The contribution of diabetes duration, both pre- and postpuberty, to the development of microvascular complications and mortality in diabetic subjects was investigated in three study populations from the Children's Hospital of Pittsburgh Insulin-Dependent Diabetes Mellitus (IDDM) Registry. Life-table analyses by total and postpubertal IDDM duration were used to evaluate differences in the prevalence of microvascular complications and diabetes-related mortality in subjects diagnosed before and during puberty, as defined by an age at IDDM onset marker of 11 yr for girls and 12 yr for boys. The prevalence of retinopathy and overt nephropathy in 552 White adult diabetic subjects (population 1, mean IDDM duration 20.8 yr) was significantly greater in subjects diagnosed during puberty compared with those diagnosed before puberty. However, similar analyses by postpubertal duration showed no difference in microvascular complication prevalence between the two groups. These findings did not appear to be due to a confounding effect of age. Additional analyses of 239 adolescent diabetic subjects (population 2, mean duration 8.3 yr) revealed the same trend for the prevalence of retinopathy. Finally, results concerning the risk of diabetes-related mortality in a cohort of 1582 subjects (population 3, mean duration 12.9 yr) indicated that postpubertal duration of IDDM may be a more accurate determinant of the development of microvascular complications and diabetes-related mortality than total duration, and it is suggested that the contribution of the prepubertal years of diabetes to long-term prognosis may be minimal. *Diabetes Care* **12:686–93, 1989**

Researchers have speculated that the years of diabetes before puberty do not contribute to the risk of diabetes complications (1,2). Evidence for this is based partially on the observation that retinal microvascular abnormalities do not typically occur before puberty in the diabetic child (1–4). However, the short duration of insulin-dependent diabetes mellitus (IDDM) before the onset of puberty could also explain this observation.

Studies that have investigated the existence of a puberty effect on prognosis by comparing the overall prevalence of early microvascular complications in prepubescent diabetic children with that of pubescent diabetic children with similar IDDM duration have reported a higher prevalence of complications in pubertal compared with prepubertal subjects (5–7). Moreover, in cohorts of diabetic adolescents and adults, a higher prevalence of retinopathy and nephropathy was reported in pubertal-onset IDDM subjects compared with prepubertal-onset IDDM subjects at a given duration (8–11). It was not clear, however, whether these findings were confounded by significant differences in age or whether the advent of puberty contributed to the development of diabetic microvascular disease. In addition, these studies were based on small cohorts of young diabetic subjects and did not address the question whether the proposed puberty effect influenced the onset of late complications and their consequences, such as mortality.

Although duration of IDDM has been shown to be a

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determinant of retinopathy (12–16) and nephropathy (16,17), the aforementioned studies suggest that the effect of diabetes duration on complications is not uniform and appears to be influenced by puberty status. This study evaluated the independent relationship of pre- and postpubertal IDDM duration to diabetes-related morbidity and mortality. In addition, the potentially confounding effect of attained age was addressed in these analyses. Three diverse populations of adolescent and adult IDDM subjects from the Children's Hospital of Pittsburgh (CHP) IDDM registry enabled an investigation of various end points in many subjects across a wide age range.

RESEARCH DESIGN AND METHODS

The relationship between complications and puberty was assessed by evaluating three populations of White diabetic subjects identified from the CHP IDDM registry. Subjects were included in the registry if they were *1*) <17 yr of age at diabetes onset, *2*) on insulin therapy at the time of discharge from the hospital, and *3*) seen at CHP within 1 yr of diagnosis for a diabetes evaluation between 1950 and 1981.

POPULATION 1: PARTICIPANTS OF EPIDEMIOLOGY OF DIABETES COMPLICATIONS (EDC) STUDY

Population 1 consisted of 593 White participants in the prospective EDC study who had undergone a baseline examination between 30 April 1986 and 31 December 1988. Participants in the EDC study were registered subjects of the CHP IDDM registry who had been diagnosed between 1950 and 1979 and were living within 100 miles of Pittsburgh at baseline. An additional eligibility criterion for the EDC study was that participants had to have a duration of IDDM >5 yr at baseline to allow for the development of diabetes complications. The initial examination, which consisted of a clinical evaluation of diabetes complications and an assessment of risk factors and host characteristics, will be repeated at 2-yr intervals for 10 yr.

The presence of retinopathy was determined by stereofundus photographs, as assessed by masked observers. Abnormalities were classified with the modified Airlie House classification system (18). Retinopathy status of 96% of the subjects was determined at time of baseline examination. The presence of retinopathy, determined by an Airlie House grading of ≥20 in the more severely involved eye, was used as the outcome variable for this study.

Diabetic nephropathy was defined as *1*) an albumin excretion rate (AER) of >200 μg/min on two of three urine collections including a 24-h, an overnight, and a 4-h timed collection or *2*) diabetes-related end-stage renal failure. Participants reporting a kidney transplant were also included in this category. Nephropathy status of 92% of the subjects was determined at baseline. In these analyses, subjects with diabetic nephropathy were compared with those with microalbuminuria (AER 20–200 μg/min) or normal albumin excretion (AER <20 μg/min).

POPULATION 2: CHP IDDM REGISTRY SUBJECTS WHO RECEIVED FLUORESCEIN ANGIOGRAPHY AT CHP

Population 2 was drawn from 389 White diabetic patients who have had fluorescein angiograms at CHP since the initiation of the procedure at the hospital in 1980. Angiograms were usually performed on the recommendation of a physician or as part of a research protocol. The 255 subjects in this group who were also part of the CHP IDDM registry were selected for population 2. The eligibility criteria of the CHP IDDM registry were outlined previously. The cohort was restricted to subjects in the CHP IDDM registry to develop a representative subgroup of IDDM subjects (i.e., by eliminating children who may have attended CHP solely for the treatment of IDDM complications) for epidemiological analyses. Although 108 of the subjects in population 2 were also participants in the EDC study (population 1), the diagnosis of eye disease in this population was independent of previous or subsequent testing.

Diabetic retinopathy was diagnosed by one of two masked retinal specialists and defined by the presence of microaneurysms and/or intraretinal microangiopathic changes. The disease outcome variable for these analyses was based on the presence of any retinopathy in the more severely involved eye.

POPULATION 3: CHP IDDM REGISTRY AND MORTALITY FOLLOW-UP, 1950–1981

Population 3 was composed of subjects who were part of the CHP IDDM registry of 1966 subjects. The mortality status of 1796 White subjects of this large representative population was determined on 1 January 1982 via mailed questionnaires or telephone interviews. The mortality patterns of this cohort have been described previously (19). Copies of death certificates were obtained to ascertain the cause of death. The outcome variable for these analyses was based on mortality commonly attributed to diabetes, such as renal and cardiovascular disease and deaths coded as diabetes related on the death certificate. Mortality due to other causes of death was not evaluated in these analyses. To investigate the relationship between postpubertal duration and long-term complications, deaths occurring within the 1st yr of diabetes were excluded.

Assessment of puberty. Puberty status at IDDM onset was defined by age: girls diagnosed with IDDM at ≥11 yr of age and boys diagnosed at ≥12 yr of age were considered pubertal at onset, because their age at diagnosis was either during or after the average onset of puberty (20). Those diagnosed at an earlier age were considered prepubertal at diagnosis of diabetes. Although more precise measurements of puberty, such as Tanner staging, were not available for the three populations, previous analyses of subjects from the CHP IDDM registry who were diagnosed between 1979 and

1981 revealed that age was a good predictor of puberty, and that delayed puberty was uncommon in these diabetic children (21). Because the focus of this study was to investigate the effect of puberty on subsequent complications and mortality, the 11 subjects in population 1, 16 subjects in population 2, and 214 subjects in population 3 who were prepubertal at follow-up were excluded from the analyses.

Analyses. Student's *t* tests were conducted to evaluate the difference in means of demographic characteristics with the SPSS statistical package (22). To ensure that the results would be easily interpreted and directly comparable, mortality and cross-sectional morbidity data were analyzed with the same statistical method. Kaplan-Meier survival analyses were used to determine the prevalence of microvascular complications (populations 1 and 2) and mortality (population 3) in the prepubertal- and pubertal-onset groups by total duration of diabetes with the BMDP statistical software package (23). Total IDDM duration was calculated from diabetes onset until examination (populations 1 and 2) or follow-up (population 3). To evaluate the independent influence of duration after puberty, survival analyses were repeated with postpubertal duration as the time scale. Postpubertal duration was computed from puberty onset until examination (populations 1 and 2) or follow-up (population 3). These analyses were used to permit evaluation of diabetes-related morbidity and mortality in the two comparison groups by the postpubertal years of IDDM.

Because all subjects in population 1 had to have a duration of diabetes of at least 5 yr, none of the participants with a pubertal onset had a postpubertal duration of ≤5 yr, whereas 30 prepubertal-onset subjects did. Therefore, in an effort to make the two groups comparable in terms of postpubertal duration, analyses of population 1 were limited to subjects with >5 yr duration postpuberty to eliminate a potential bias in the comparison groups.

Birth cohort analyses were also used to evaluate the consistency of the relationship between postpubertal duration and long-term complications, while accounting for potential confounding by age. Populations 1 and 3 were stratified into two birth cohorts, the first containing diabetic subjects born between 1940 and 1959 and the second containing those born between 1960 and 1979. Because population 2 was small and consisted of subjects born between 1960 and 1979, birth cohort analyses were not conducted. Life-table analyses were repeated by both total duration and postpubertal duration to see whether the relationships were uniform in both age strata.

RESULTS

Demographic characteristics of study populations. The demographic characteristics of the three study populations were compared by morbidity (Tables 1 and 2) and mortality status (Table 3). Diabetic subjects with retinopathy or nephropathy were significantly older, had a longer total duration of diabetes, and a longer diabetes duration after puberty compared with those without microvascular complications ($P < .001$). Similar relationships were found between the deceased and subjects who were still alive ($P < .001$). There was no difference in mean age at diabetes onset by morbidity status in population 1. Although diabetic subjects with retinopathy were significantly younger at onset than those without eye disease in population 2 ($P < .05$), deceased diabetic subjects in population 3 were older at IDDM onset than subjects who were still alive ($P < .05$).

POPULATION 1

Overall, the prevalence of microvascular complications was similar between prepubertal- and pubertal-onset groups. Three hundred sixty-three (93.8%) prepubertal-onset subjects had retinopathy compared with 136 (91.9%) pubertal-onset subjects. Diabetic nephropathy was found in 96 subjects (26.1%) from the prepubertal-onset group and in 35 subjects (24.8%) from the pubertal-onset group.

As shown in Fig. 1*A*, subjects diagnosed during or

TABLE 1
Demographic characteristics of diabetic subjects in population 1 by microvascular complication status

	Status			
	Retinopathy		Nephropathy	
	Disease	No disease	Disease	No disease
n	499	36	131	378
Attained age (yr)	29.6 ± 6.7	23.1 ± 5.7*	31.6 ± 6.2	28.5 ± 6.9*
IDDM duration (yr)	21.1 ± 6.9	14.8 ± 5.2*	23.3 ± 6.6	19.9 ± 7.0*
Postpubertal duration (yr)	17.6 ± 6.7	11.3 ± 5.9*	19.6 ± 6.2	16.5 ± 6.8*
Age at IDDM onset (yr)	8.5 ± 4.0	8.5 ± 4.4	8.3 ± 4.1	8.6 ± 4.0

Values are means ± SD. IDDM, insulin-dependent diabetes mellitus. Retinopathy status of 17 subjects and nephropathy status of 43 subjects was unknown.
*$P < .001$ was significant.

TABLE 2
Demographic characteristics of diabetic subjects in population 2 by retinopathy status

	Retinopathy status	
	Disease	No disease
n	101	136
Attained age (yr)	16.5 ± 2.3	15.5 ± 1.7*
IDDM duration (yr)	9.5 ± 3.5	7.6 ± 3.4*
Postpubertal duration (yr)	4.9 ± 1.8	3.8 ± 2.2*
Age at IDDM onset (yr)	7.0 ± 3.5	7.9 ± 3.5†

Values are means ± SD. IDDM, insulin-dependent diabetes mellitus. Retinopathy status of two subjects was unknown.
*$P < .001$ was significant.
†$P < .05$ was significant.

after puberty had a higher prevalence of retinopathy at a given IDDM duration compared with those diagnosed before puberty, as demonstrated by the significantly different morbidity curves ($P < .001$). In contrast, Fig. 1*B* shows the cumulative cross-sectional prevalence of retinopathy by postpubertal duration of IDDM. At all postpubertal durations, diabetic subjects with onset during or after puberty had a morbidity experience similar to that of the prepubertal-onset group ($P = .06$).

A similar trend was observed for the prevalence of diabetic nephropathy in subjects diagnosed with IDDM before and during puberty (Fig. 2*A*). The morbidity curve for diabetic nephropathy in subjects diagnosed during or after puberty was significantly different from the curve of diabetic subjects diagnosed before puberty ($P < .001$). When nephropathy was evaluated by postpubertal duration, the prevalence in the pubertal-onset group was similar to that in the prepubertal-onset group ($P = .57$; Fig. 2*B*).

Population 1 was stratified for birth cohort analyses as previously indicated. There were 305 subjects born between 1940 and 1959 and 247 born between 1960 and 1979. The results of the life-table analyses of the prevalence of retinopathy and overt nephropathy by total and postpubertal duration were consistent for the two birth cohorts (data not shown) and resembled the overall trends shown in Figs. 1 and 2.

TABLE 3
Demographic characteristics of diabetic subjects in population 3 by diabetes-related mortality status

	Mortality status	
	Deceased	Living
n	96	1486
Attained age (yr)	26.2 ± 7.5	22.9 ± 7.5*
IDDM duration (yr)	17.3 ± 6.6	14.1 ± 7.8*
Postpubertal duration (yr)	10.0 ± 6.7	5.8 ± 8.3*
Age at IDDM onset (yr)	9.3 ± 3.7	8.4 ± 3.8†

Values are means ± SD. IDDM, insulin-dependent diabetes mellitus.
*$P < .001$ was significant.
†$P < .05$ was significant.

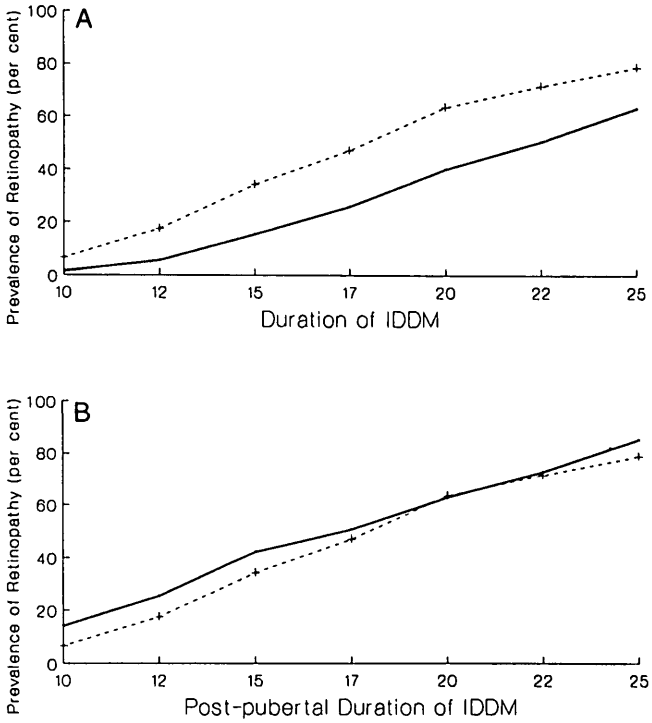

FIG. 1. Population 1: cumulative cross-sectional prevalence of retinopathy by duration of insulin-dependent diabetes mellitus (IDDM) (*A*; yr) and postpubertal duration of IDDM (*B*; yr). Prepubertal (*solid lines*) versus pubertal (*dashed lines*) subjects at IDDM onset.

To investigate whether the observed findings could be attributed to an effect of puberty on prognosis, population 1 was stratified by decreasing age at onset markers that would not likely be associated with puberty and the analyses were repeated. The curves generated from analyses of population 1 stratified by age at onset markers of 10 yr (girls) and 11 yr (boys) resembled the curves shown in Figs. 1 and 2. However, at younger age at onset markers, we could not demonstrate the trends reported above. Although the prevalence of microvascular disease was significantly increased in the pubertal-onset group compared with the prepubertal-onset group for all durations of IDDM, there was still a significant difference in morbidity between the two groups when analyzed by postpubertal duration (data not shown). This suggests that the observed relationship shown in Figs. 1 and 2 is related to puberty, and indicates an important biologic effect on the prognosis for diabetic subjects.

POPULATION 2

Of the subjects with onset of IDDM before puberty, 44% were identified as having retinopathy. A slightly smaller proportion (26%) of subjects diagnosed during or after puberty were found to have retinopathy ($P = .10$).

The cumulative cross-sectional prevalence of retinop-

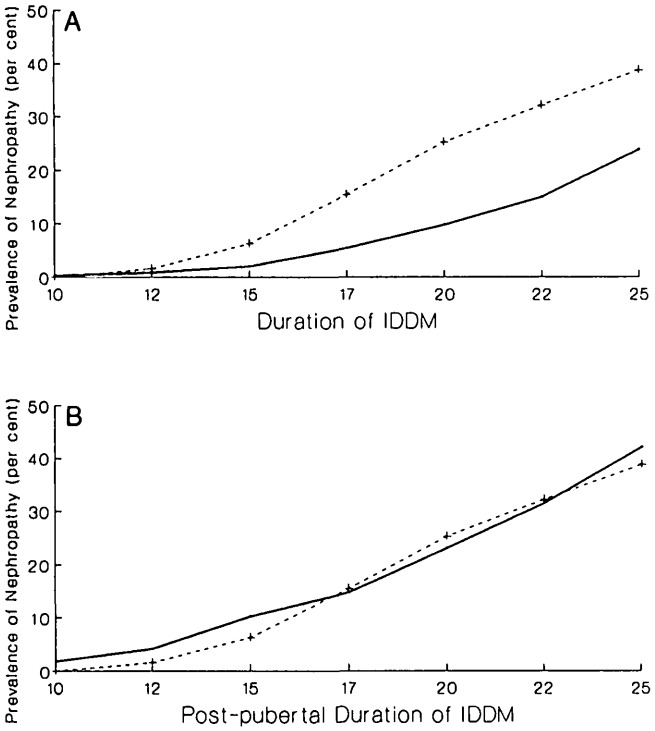

FIG. 2. Population 1: cumulative cross-sectional prevalence of nephropathy by duration of insulin-dependent diabetes mellitus (IDDM) (*A*; yr) and postpubertal duration of IDDM (*B*; yr). Prepubertal (*solid lines*) versus pubertal (*dashed lines*) subjects at IDDM onset.

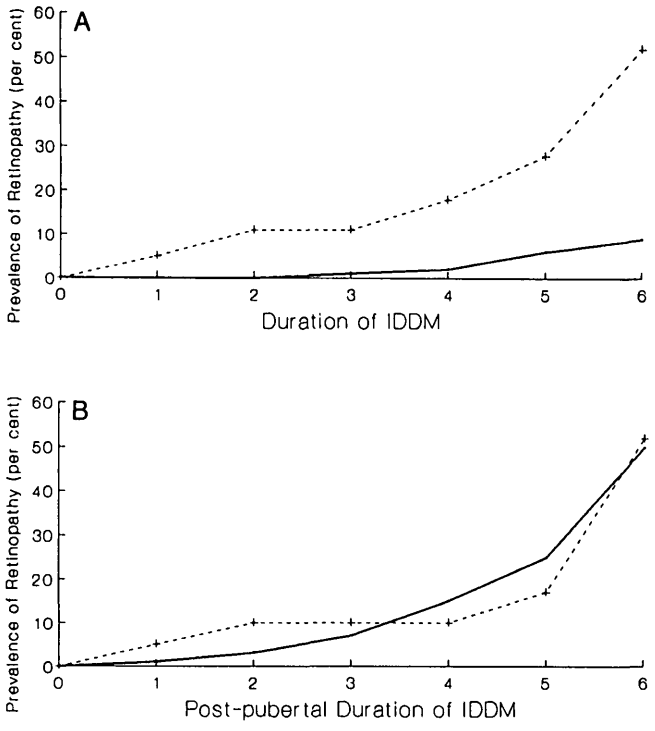

FIG. 3. Population 2: cumulative cross-sectional prevalence of retinopathy by duration of insulin-dependent diabetes mellitus (IDDM) (*A*; yr) and postpubertal duration of IDDM (*B*; yr). Prepubertal (*solid lines*) versus pubertal (*dashed lines*) subjects at IDDM onset.

athy was plotted by total duration of IDDM, as shown in Fig. 3*A*. Subjects diagnosed with IDDM during or after puberty had a higher prevalence of retinopathy than those diagnosed earlier at a given duration, as demonstrated by the significantly different morbidity curves ($P < .001$). However, the prevalence of retinopathy in the two groups was similar when plotted by postpubertal duration ($P = .07$; Fig. 3*B*).

POPULATION 3

Approximately 8% of diabetic subjects who were diagnosed during or after puberty died from diabetes-related causes compared with 5% of the subjects diagnosed before puberty.

Diabetic subjects diagnosed during or after puberty experienced significantly greater mortality at a given duration than those diagnosed before puberty (Fig. 4). At 20 yr duration, 5% of the prepubertal-onset group was deceased compared with 18% of the pubertal-onset group ($P < .001$). In contrast, the pubertal-onset group had a mortality experience similar to that of the prepubertal-onset group compared with postpubertal duration ($P = .70$; Fig. 4*B*).

Population 3 was divided into birth cohorts and life-table analyses were repeated to examine the influence of age on the above findings. In population 3, there were 880 diabetic subjects born between 1940 and 1959 and 702 diabetic subjects born between 1960 and 1979. Results of the life-table analyses of diabetes-related mortality in subjects born between 1940 and 1959 revealed a trend consistent with that shown in Fig. 4, in which mortality was similar in the comparison groups when postpubertal duration was used as the time scale. Only one diabetes-related death occurred in the second birth cohort, making it impossible to evaluate the effect of total and postpubertal duration on mortality in subjects born between 1960 and 1979.

DISCUSSION

The data suggest that the effect of duration on diabetes complications is not uniform. At a given duration, diabetic subjects diagnosed during or after puberty had a significantly increased prevalence of microvascular complications and mortality compared with those diagnosed before puberty. However, the prevalence of microvascular complications and mortality in these two groups was similar when postpubertal IDDM duration was examined. Moreover, results of the birth cohort analyses indicate that attained age did not appear to be a principal determinant of microvascular complications or mortality in these analyses. Therefore, the effect of prepubertal duration on the risk of complications appears to be minimal.

This investigation was unique in that several different

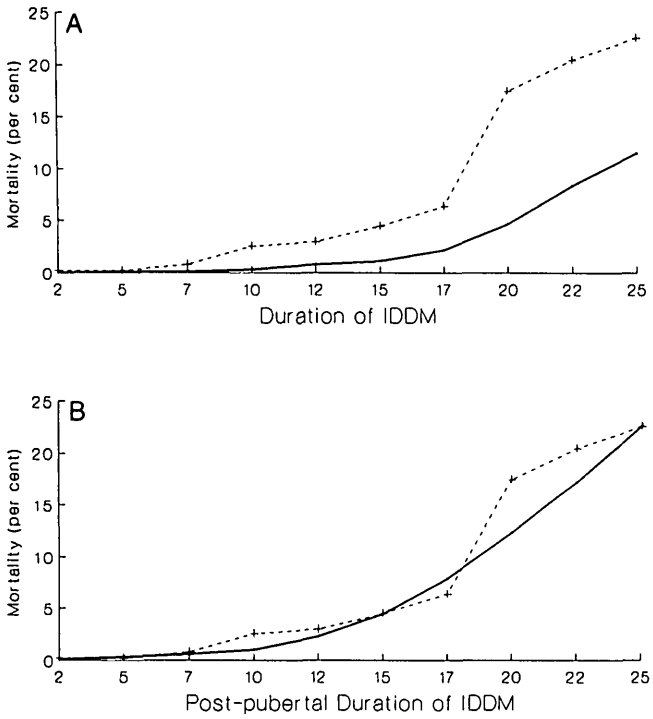

FIG. 4. Population 3: cumulative diabetes-related mortality by duration of insulin-dependent diabetes mellitus (IDDM) (*A*; yr) and postpubertal duration of IDDM (*B*; yr). Prepubertal (*solid lines*) versus pubertal (*dashed lines*) subjects at IDDM onset.

end points were evaluated in large populations of subjects covering a wide range of ages. With the use of three study populations from the same target group to examine this issue, the individual strengths of the various IDDM subgroups of CHP were combined. Because similar results regarding the influence of pre- and postpubertal duration on the risk of microvascular complications and mortality were found in the three separate cohorts, consistency of the pubertal effect was demonstrated.

The subjects in population 1 were volunteers and may have been an unusually healthy sample. Nonetheless, the puberty effect was consistently observed in a survivor cohort such as population 1, which was drawn from a living subgroup of the CHP registry. Because the data were collected at a baseline examination, no record of the actual time of onset of the microvascular complication was available. Nevertheless, an investigation of this magnitude has not been previously conducted on a cohort of postadolescent adults and offers valuable information concerning the influence of puberty on the risk of late diabetes microvascular complications.

It is possible that the criteria used to select population 2 resulted in a study population with an overrepresentation of retinal disease, because patients with retinal abnormalities were more likely to be tested at CHP than those without abnormalities. However, because these diabetic subjects were younger than those in population 1, the prevalence data for retinopathy in population 2 were more likely to resemble incidence data of early retinal abnormalities. Also, this cohort of adolescents was similar in age to that of previous studies, which allowed for a more direct comparison with the existing literature.

The investigation of diabetes-related mortality in population 3 was limited by the potential inaccuracies of the death certificate data and the danger of combining various disease processes into one end point. However, the consistency of results with both diabetes-related morbidity and mortality data indicate the strength of the observed relationship.

The wide age distribution of diabetic subjects in populations 1 and 3 suggested that the relationship between puberty, duration, and diabetes-related morbidity and mortality could be confounded by differences in attained age. Therefore, study populations were divided into two groups by year of birth and reanalyzed, a method typically used to account for the effect of age. The consistency of results in each birth cohort suggested that age did not have a strong confounding influence on the results.

Literature on a potential puberty effect on complications has suggested that diabetic retinopathy is related to altered hormonal levels and physiological changes associated with puberty (2). Increased skeletal muscle capillary basement membrane width, a common abnormality found in diabetic subjects that may serve as an early marker of microvascular disease, has been shown to be correlated with postpubertal duration of IDDM (24,25). Markers of diabetes control, such as glycosylated hemoglobin and fasting blood glucose levels, were positively related to capillary basement membrane width in postpubertal but not prepubertal subjects, which suggests an interaction between diabetes control and puberty (26). Moreover, an association between skeletal muscle capillary basement membrane width and bone age, which is primarily dependent on sex hormone levels after puberty, has been reported (27).

Growth hormone actions are thought to be mediated by somatomedin C, and blood levels have been correlated with increased basement membrane thickening and diabetic angiopathy (28–32). The relationship between these growth-related factors and diabetic eye disease is suggested in reports observing a reduced prevalence of retinopathy in diabetic growth hormone–deficient dwarfs (28) and higher somatomedin C levels in subjects with proliferative retinopathy (33). The increase in circulating growth hormone and somatomedin C concentrations during puberty suggests a relationship between these hormones and sex steroids (34,35). Moreover, increased sex hormone levels have been directly linked to the vascular structural abnormalities associated with diabetes complications by their capacity to increase polyol metabolism in the basement membrane in experimental animals (36,37).

Another mechanism by which puberty might exert its effect on morbidity and mortality risk is through behav-

ior. Psychosocial factors associated with adolescence may contribute to poor glycemic control (38). Individuals with diabetes diagnosed during adolescence may not accept their disease as well as those diagnosed before puberty, thus interfering with the development of healthy control habits. Without good glycemic control habits, the individual with diabetes onset during or after puberty may thus be at higher risk for diabetes complications than those diagnosed before puberty.

The minimal influence of prepubertal duration on the prevalence of microvascular complications and diabetes-related mortality was demonstrated by this study. Interpretations of these results are many and should be acted on with caution in the clinical setting. However, these findings indicate a need for future prospective studies investigating the factors related to puberty that initiate the development of microvascular complications and mortality in IDDM subjects.

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