Juvenile Diabetes Mellitus After Forty Years

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SUMMARY

Seventy-three patients with juvenile diabetes mellitus for a mean duration of 42.9 years were retrospectively studied on a multidisciplinary basis. Only three of this group of patients were socially disabled as a result of their long-standing illness. Of all the complications, insulin-induced hypoglycemia was most common. Although diabetic retinopathy was clinically evident in about 75 per cent of patients, only 50 per cent of these seventy-three patients had a significant visual impairment. Nephropathy was apparent in 59 per cent of patients, and neuropathy was demonstrable in half of them. Significant peripheral vascular system impairment was present in 40 per cent and major cardiac complication in 20 per cent. DIABETES *24*:559-65, June, 1975.

Since insulin was not available for general use until the mid-1920s, patients who have had juvenile-onset diabetes mellitus for more than forty years represent a unique group of patients. Seventy-three patients with juvenile diabetes mellitus with a duration of illness of at least forty years have been followed periodically at the Joslin Clinic. Their macro- and microvascular complications as well as their life as part of society were analyzed retrospectively.

MATERIALS AND METHODS

Juvenile diabetes mellitus is defined in this report as a form of diabetes mellitus with onset before age 15. Orginally planned as a prospective study, the present report is a retrospective clinical epidemiologic analysis.

From 1893 to 1967, a total of 6,594 juvenile diabetics were registered at the Joslin Clinic; 782 of these patients had their diabetes diagnosed before December 31, 1927. As shown in figure 1, 457 of these 782 patients had died at the time of this study and 194 patients had not been followed at the Clinic; the remaining 131 patients (16.7 per cent) were alive as of January 1, 1968. Of these 131 patients, seventy-three were regularly followed at the Joslin Clinic; the remaining fifty-eight could be contacted only by mail.

All these seventy-three patients have been under the care of one of us (P.W.) for many years, and records extending for more than fifty years were available for analysis. These patients were examined at least once in the period of 1966-67 during their regular clinic visit or for the study purpose. Detailed past histories of diabetes including the occurrence of ketoacidosis, insulin-induced hypoglycemia, and infections were obtained. Special attention was paid to their family history, social life, habits, occupation, physical activity, diets, and other specific health events during adolescence or adulthood. Complete physical examination was performed on each patient, with special attention to the presence of cataracts, arcus senilis, neuropathy, and peripheral vascular insufficiency. The eye examination of each patient was carried out independently by two ophthalmologists. Some patients had retinal photography and fluorescein angiography as part of a special study published elsewhere.[1] Laboratory studies, including fasting and/or two-hour postprandial blood glucose, serum urea nitrogen, cholesterol, creatinine, complete blood counts, urine analysis, and electrocardiogram, were performed at least once every six months between 1965 and 1967.

RESULTS

Causes of Death

The fatal cases studied were divided into two groups: those who died before (group A) and after (group B) August, 1922, when insulin became available in the United States (see figure 2). Among

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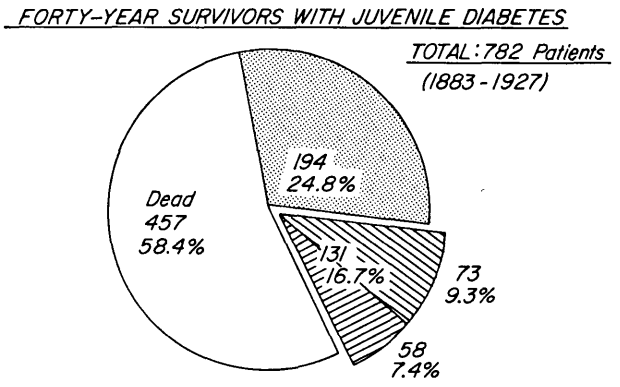

FIG. 1. Juvenile diabetic patients diagnosed at the Joslin Clinic between 1893 and December, 1927.

the 208 fatal cases in the preinsulin era, ketoacidosis accounted for 74 per cent of deaths; this was much higher than the next most common causes of death, infections and cardiovascular disease. Cardiovascular disease replaced ketoacidosis as the main cause of death in the 249 patients who died after insulin was available for the management of diabetes mellitus. They survived long enough to develop myocardial infarction, arteriosclerotic heart disease, and cardiac failure, which together accounted for 30.9 per cent of the deaths (figure 2). Renal failure became the second most common cause of death (22.8 per cent). As expected, 83.5 per cent of patients in group A died during the first decade of their disease, soon after the diagnosis of diabetes and development of ketoacidosis (figure 3). It should be noted that during the first ten years after insulin was available, ketoacidosis was still the most common cause of death (11.2 per cent). Infections, particularly tuberculosis, had been frequent cause of death during their second through fourth decades of the disease until chemotherapeutic

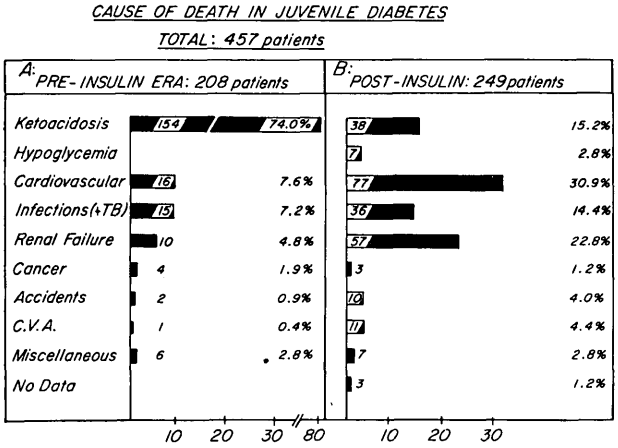

FIG. 2. Cause of death in 457 juvenile diabetic patients before (Group A) and after (Group B) 1922, when insulin became available.

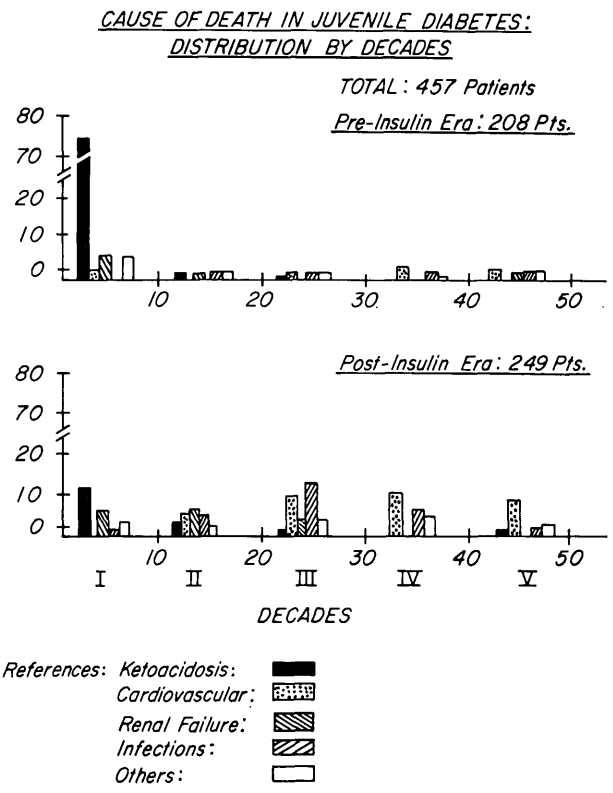

FIG. 3. Cause of death in 457 juvenile diabetics in each decade before and after insulin became available.

agents became available. The incidence of cardiovascular death increased progressively during the second and third decades, and it became the leading cause of death by the fourth and fifth decades.

Analysis of the Survivors

These seventy-three patients under study showed a classic presentation of juvenile diabetes[2] characterized by an acute onset of illness in early childhood, often with rapid progression to diabetic coma, a short period of remission, and establishment of permanent diabetes with a progressive increment in insulin requirement until the fourth or fifth decade of life, when the requirement for insulin showed a slight tendency to drop.[3]

The chronologic age, sex, and age of onset of their diabetes are depicted in figures 4 and 5. Their mean age at the time of this study carried out in 1967 was 51.2 years. The youngest patient was a forty-two-year-old, married office worker (R.S., J.C. no. 54591) who developed diabetes at eight months of age. Despite pyelonephritis and personality disorders at about age 25, he was still in good health. Only a few microaneurysms in the fundi and moderate peripheral neuropathy were detected. He has a strong family history of diabetes and had received life-long

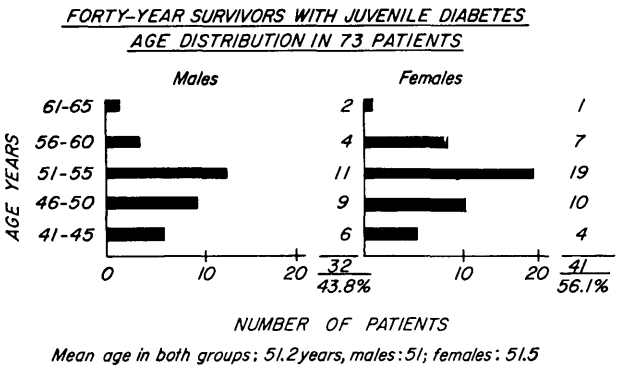

FIG. 4. Chronological age and sex of seventy-three juvenile diabetics who survived longer than forty years.

meticulous care and regulation of diabetes mainly by his mother, a compulsive nurse. The oldest patient among the group was a sixty-four-year-old housewife and active social worker (J.D., J.C. no. 5301) whose diabetes was detected in 1916 when she was thirteen. Although classified then as having ketosis-prone diabetes, she had survived to her seventh decade with few diabetic complications, mild peripheral neuropathy, and minimal nonproliferative retinopathy.

The duration of illness in these patients is illustrated in figure 6. Ten patients (13.6 per cent) among the group had diabetes for longer than forty-five years.

Twenty-one of the seventy-three surviving juvenile diabetics reached the expected life span (fifty-five years of age) for individuals born before 1930.[4]

Acute Diabetic Complications

Thirty-seven patients (50.6 per cent) had one or more episodes of ketoacidosis during their lifetime. In sixteen patients, ketoacidosis was the presenting feature of diabetes. Almost all patients showed mild to moderate acetonuria at some time, but ketoacidosis occurred in only half. Insulin-induced hypoglycemia was reported by all but two patients. The multiple episodes of hypoglycemia throughout their lives indicate a continous effort to control their hyperglycemia. The frequency of these acute complications further demonstrates that the patients in this cohort do not fit

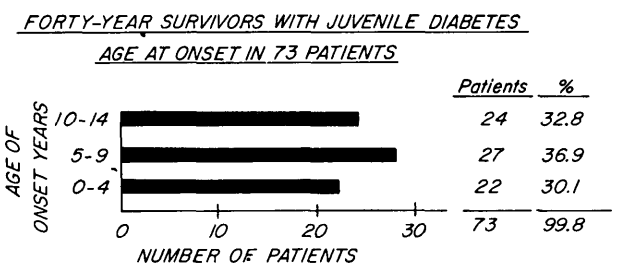

FIG. 5. Age at onset of seventy-three juvenile diabetics surviving longer than forty years.

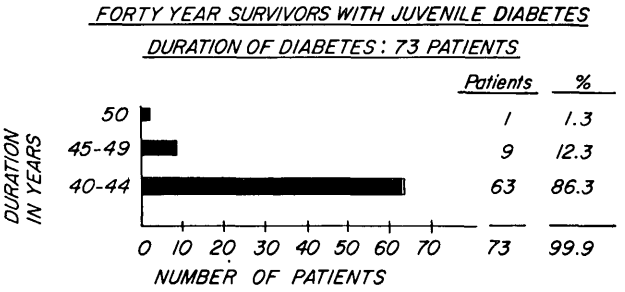

FIG. 6. Duration of diabetes in seventy-three patients surviving more than forty years.

into the category of adult-onset diabetes. On the contrary, these complications emphasize the severe and labile nature of their disease.

Chronic Complications

Retinopathy. Patients with diabetic retinopathy were divided into two groups: (A) those with nonproliferative or intraretinal retinopathy, which includes microaneurysms, hard and soft exudates, retinal edema, intraretinal microvascular abnormalities, and intraretinal hemorrhage; (B) those with proliferative retinopathy consisting of vascular proliferation, neovascularization, preretinal hemorrhage, and partial or total vitreous detachment. As shown in table 1, no diabetic retinal changes were demonstrable on funduscopic examination in about one fourth of our patients. However, the possibility of subtle changes had not been totally excluded by fluorescein studies in all patients. Forty-five per cent of the patients had nonproliferative retinopathy that impaired their vision only to a minor degree or not at all. Although progressive proliferative retinopathy was observed in twenty-two patients (30 per cent), only nine (12.3 per cent) were legally blind in one or both eyes. Combining the patients with well-preserved vision and those whose slight visual impairment was readily correctable by ophthalmological prescription shows that 87 per cent retained useful vision. Considering the dura-

TABLE 1

Forty-year survivors with juvenile diabetes

		Patients	%
Diabetic retinopathy			
Nonproliferative, background retinopathy		33	45.2
Proliferative retinopathy		22	30.1
No change		18	24.6
	Totals	73	99.9
Cataracts		13	17.8
Vision			
Good		39	53.4
Impaired		25	34.2
Legally blind		9	12.3
	Totals	73	99.9

tion of their diabetes, their visual functions were surprisingly well maintained.

Nephropathy

It is difficult to detect early diabetic glomerulosclerosis by noninvasive tests. Albuminuria may be difficult to demonstrate because the quantity of protein excretion may be small or vary in amount, in contrast to that found in other types of nephrosis. Mere demonstration of proteinuria or renal failure is not conclusive evidence of diabetic nephropathy, since diabetics, like other patients, are vulnerable to nephropathy of nondiabetic origin. Nevertheless, Johnsson's cirteria[5] were employed for the purpose of analysis. When proteinuria was found in more than half of all examinations performed in the preceding year, the patient was categorized as having diabetic nephropathy unless he had some other obvious type of nephropathy. Hypertension was considered a consequence of diabetic nephropathy unless another cause was apparent. As illustrated in table 2A, twenty-one patients (28.7 per cent) showed proteinuria, whereas nine (12 per cent) had arterial hypertension without evidence of renal involvement. Of those patients with proteinuria, six had hypertension and progressive renal failure. The remaining forty-three patients (59 per cent) were free of renal involvement and were normotensive. Chronic bacteriuria, not necessarily a complication of diabetes, was present in 16 per cent of the patients.

Cardiac Complications

Twelve patients (16 per cent) had a well-documented history of myocardial infarction with enzyme elevations and changes in electrocardiogram. Three patients complained of chest pain compatible with angina pectoris, but their electrocardiograms were normal. The rest of the fifty-eight patients (79 per cent) had no clinical evidence of coronary insufficiency (table 2B). Interestingly, ten of twelve patients who survived a myocardial infarction were females. Eighteen patients (24.6 per cent) had a history of congestive heart failure, some accompanied by arrythmias. In some instances, heart failure could be considered as comorbidity, not necessarily related to diabetes mellitus. One patient had rheumatic mitral valvular disease.

TABLE 2

Forty-year survivors with juvenile diabetes

A. Nephropathy

	Patients	%
No renal involvement	43	58.9
Proteinuria Normotensive:	15	20.5
Proteinuria Hypertensive: + BUN	6	8.2
Hypertension without proteinuria	9	12.3
Totals	73	99.9
Urinary tract infection	12	16.4

B. Cardiac Complications

	Sex M	Sex F	Totals	%
Myocardial infarction	2	10	12	16.4
Angina pectoris	1	2	3	4.1
No involvement	29	29	58	79.4
Totals	32	41	73	99.9

Eighteen patients (24.6 per cent) had history of cardiac failure.

Peripheral Major Vascular Involvement

Peripheral vascular patency was determined by physical examination of peripheral pulses and temperature and trophic changes and by arteriography in selected cases. As illustrated in table 3A, forty-four patients (60 per cent) had no clinical evidence of peripheral vascular insufficiency. Poor peripheral pulses were demonstrated in the remaining twenty-nine patients. Symptoms of intermittent claudication were present in eleven patients, and ten had a history of gangrene or required amputation. Nine patients had limited use of their lower extremities and needed crutches or a wheelchair. None, however, were completely bedridden because of their vascular involvement.

Neuropathy

Neurologic complications were determined by subjective complaints, testing of muscular strength, deep tendon reflexes, and sensation to touch, pinprick, vibration, and position. Criteria for neurologic involvement, as suggested by Knowles,[6] consisted of absent ankle jerks or marked motor weakness and loss

TABLE 3

Forty-year survivors with juvenile diabetes

A. Peripheral vascular insufficiency (PVI)

	Patients	%
Poor pulses (P.P.)	8	
PP + Intermittent claudication (I.C)	11	39.7
PP + IC + gangrene or amputation	10	
Patients with no detectable PVI	44	60.2
Totals	73	99.9

B. Neuropathy

	Patients	%
Peripheral neuropathy	26	
Neuropathic ulcer	5	
		47.3
Diabetic amyotrophy	1	
Autonomic nervous system involvement	3	
No neuropathy	38	52.0
Totals	73	99.3

of vibratory sense. On this basis, as depicted in table 3B, about half of the patients had no evidence of neuropathy. Neurologic involvement, most likely as a consequence of diabetes mellitus, was present in the remaining half. Five patients developed neuropathic ulcers, one had amyotrophy, and three had autonomic nervous system involvement (postural hypotension, diabetic gastropathy, and neurogenic bladder).

Heredity

Fifty-two (71.2 per cent) patients gave a family history of diabetes mellitus among their close blood relatives. Information was available on only forty-one of their offspring. Nine children (21.9 per cent) had developed diabetes mellitus at the time of the study.

Social Status and Psychologic Problems

Sixty-three patients (86 per cent) were married, and the majority of them enjoyed a pattern of life close to normal. Forty-one of sixty-three married patients have one to five children, and five patients have grandchildren. Emotional and behavioral problems are well known in juvenile diabetics[2,7] Fifteen patients (20 per cent) had personality disorders and required psychiatric counseling at one time or another. Feelings of inadequacy, fear of diabetic complications, depression, psychoneurosis, and anxiety were common problems.

Achievements

Only three out of seventy-three patients were unable to work because of diabetes mellitus and its complications; two patients were retired but were able to carry on useful forms of work. Surprisingly, the remaining patients were self-sufficient and socially productive (table 4). Their intellectual and vocational achievements were high; 20 per cent had graduated from college.

General Evaluation

For an over-all evaluation, we divided these patients into three classes:

1. *Good condition.* Patients had only minor complications of diabetes, such as scattered funduscopic microaneurysms or mild peripheral neuropathy that did not affect vital functions or interfere with an active and fruitful life.

2. *Fair condition.* Patients showed moderate to severe complications in any one of the four major categories, namely retinopathy, nephropathy, neuropathy, or heart involvement. Although clinically significant, these complications did not impair their activities, and the patients were self-sufficient.

3. *Poor condition.* Patients had multiple crippling complications that limited activities.

About one quarter of the patients were severely affected by the complications of the long-term diabetes and, therefore, fell into class three. Forty-six per cent were considered in good condition and the remaining 28 per cent in fair condition (table 4).

TABLE 4

Forty-year survivors with juvenile diabetes

	Patients	%
Achievements		
Active	68	93.1
Retired	2	2.7
Inactive	3	4.1
Totals	73	99.9
General evaluation		
Good	34	46.5
Fair	21	28.7
Poor	18	24.6
Totals	73	99.8

Diabetic Control

It was extremely difficult to estimate the degree of diabetic control. For example, dietary adherence could be assessed only by the patient's own statements. The degree of glycosuria was measured only during a hospital stay or visit to the Clinic; such values may not be representative of the patient's general pattern. Since similar limitations apply to blood glucose values, retrospective analysis of glucose homeostasis over a forty-year period would be not only impractical but misleading. Furthermore, some patients did not attend the Clinic regularly. Equally difficult to assess are other factors proposed to affect the rate of development of diabetic vascular disease. These range from internal metabolic disturbances to external influences, hormonal interactions, genetic disposition, and aging. For these reasons any attempt to measure diabetic control accurately and objectively over a period of forty years would be unrealistic.

DISCUSSION

The survival rate for juvenile diabetics forty years after the onset of their illness is 16.7 per cent in our study. However, those patients who died in the preinsulin era were included in our statistical analysis; thus, the survival rate of juvenile diabetics in the postinsulin period conceivably can be higher than 16.7 per cent. In the future, a forty-year survival for juvenile diabetics will probably be more common.

Since insulin became available, cardiovascular complications have clearly emerged as the leading cause of death. Among the survivors, ischemic heart disease is considered the major hazard of long-term diabetes. In our study, ten of twelve patients who survived a

myocardial infarction were females. It is not clear whether this reflects a higher incidence of myocardial infarction in the female diabetic, or female diabetics can tolerate and survive myocardial infarction better than men. A recent report by Oakley et al. also revealed that the over-all prevalence of ischemic heart disease in diabetics, including angina of effort and ECG abnormalities, was greater in women.[8]

A study of this nature clearly suffers from the drawback of being confined to survivors. The study of all diabetics, dead or alive, diagnosed forty years ago could reveal a significantly different result. However, the present study provides understanding of the natural history of the disease under the available therapy. It also proves that juvenile-onset diabetes is compatible with a long survival and minor complications.

One of the striking features of these seventy-three patients as a whole was the relatively low rate of macro- and microvascular complications despite their long-standing diabetes. There is general agreement among various authors that the incidence of angiopathy increases with the duration of diabetes mellitus.[9] Whether rigid control of their glucose homeostasis lowers the incidence of vasculopathy is still controversial. By the use of the fluorescein injection technic, the reversal of retinal vascular changes has been demonstrated when patients were subjected to a period of vigorous control of diabetes.[10] Similarly, the rapid development of malignant retinal lesions has been observed during a period of poor diabetic management.[2] These results suggest that close control of diabetes is beneficial while negligence in care may lead to rapid aggravation or appearance of vascular lesions: a large body of evidence supports this view.[11-16] However, it has not been resolved whether good control results from the mild nature of the diabetes itself or from the efforts exerted to bring the metabolic derangement under control.[17] Some reports and evidence support the thesis that the progression of diabetic vasculopathy is inherent to the severity of diabetes itself rather than to the control of the disease.[18-20] The fact that specific diabetic complications have been observed in patients without glucose intolerance[21,22] suggests that some of the manifestations are not complications but, rather, concomitants of the disease. The chemical components of the human glomerular basement membrane described by Spiro[23] might suggest the possibility of a biochemical basis of diabetic angiopathy. The demonstration of an abnormality in the glucose content of the diabetic basement membrane tends to support a cause-effect relationship between the metabolic derangement and the development of diabetic angiopathy. Kilo et al.[24] also suggested that the basement membrane thickening progresses with the duration of diabetes mellitus and is a result of a metabolic abnormality. These histochemical studies in conjunction with the clinical surveys would justify the recommendation for a more strict control of diabetes.

CONCLUSION

We do not conclude that the relative success in the long fight with diabetes in this group of patients is due exclusively to the control of their carbohydrate homeostasis throughout their lifetime. This group of patients demonstrates that juvenile diabetics can survive forty or longer years without crippling complications. We don't know precisely the reasons for their long survival. Multiple factors are probably involved, but a meticulous day-by-day care of their illness might have been an important one. Whether diabetics in poorer control can have the same degree of over-all achievement is not known. The fact that this group of patients successfully overcame forty years of diabetes with relatively minor complications is very encouraging. The outlook for juvenile-onset diabetics is better today than in the past. With new knowledge and proper management of this condition, it may be even better in the future.

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