Chapter 25

Therapy for Diabetes

Brian J. Fertig, MD; David A. Simmons, MD; and Donald B. Martin, MD

SUMMARY

The most recent information about use of diet, oral agents, and insulin by people with diabetes in the United States is from the 1989 National Health Interview Survey (NHIS). For all diabetic patients age ≥18 years, 43% were treated with insulin, 49% were treated with oral agents, and 64% reported they were following a diet for their diabetes. Of insulin-treated non-insulin-dependent diabetes mellitus (NIDDM) patients, 10% were using oral agents in addition to insulin. The proportion of NIDDM patients treated with insulin increased with longer duration of diabetes, from 22% at 0-4 years to 58% at ≥20 years. Concomitantly, the proportion treated with oral agents declined from 64% at 0-4 years duration to 37% at ≥20 years. Two or more insulin injections daily were taken by 61% of insulin-dependent diabetes mellitus (IDDM) patients and 48% of insulin-treated NIDDM patients; use of an insulin pump was rare.

Nutritional therapy is a challenging but necessary dimension in the management of diabetes. For children with IDDM, a goal is to match diet to insulin requirements to ensure normal growth and development. By contrast, in obese NIDDM patients, it is important to achieve and maintain a reasonable or realistic body weight. Successful long-term weight loss for obese NIDDM patients remains an elusive and difficult task. According to current guidelines, dietary protein intake should constitute 10%-20% of total daily calories. Saturated and polyunsaturated fat should each be limited to <10% of total daily calories, and the remaining 60%-70% of calories, composed of monounsaturated fat and carbohydrate, may be tailored to individual needs. Cholesterol should be limited to ≤300 mg daily. A large body of literature shows no significant difference in glycemic control from sucrose or complex carbohydrate forms. Soluble and insoluble dietary fiber is healthy for all individuals, and the recommended daily consumption is 20-35 g, which is two to three times the average daily consumption.

When optimal diet with weight reduction and exercise fail to restore adequate glycemic control in NIDDM patients, pharmacologic treatment should be considered. The sulfonylureas are the major group of oral hypoglycemic agents currently used in the United States, although the biguanide drug metformin recently was approved for use. The Diabetes Control and Complications Trial (DCCT) evaluated the effect of intensive insulin therapy in IDDM and found ~40%-70% risk reduction in retinopathy, nephropathy, and neuropathy, compared with conventionally treated subjects. However, there was also a threefold greater risk of hypoglycemia in the intensively treated patients.

Patient education can translate to increased self-management skills, including self-glucose monitoring, compliance with overall management, improved glycemia for insulin-treated diabetes, and reduction in complications. Despite these favorable effects, only 35% of people with diabetes in the United States have attended a diabetes education class or course, including 59% of those with IDDM, 49% of those with insulin-treated NIDDM, and 23% of those with NIDDM not treated with insulin. About 40% of IDDM and 26% of insulin-treated NIDDM patients self-test their blood glucose at least once per day, but this proportion is substantially lower for NIDDM patients not treated with insulin (5%).

Pancreatic transplantation in the United States is being performed with increasing frequency, with >2,700 cases reported by 1992. Pancreatic transplant is the only treatment for IDDM capable of establishing an insulin-independent state with euglycemia and normal glycosylated hemoglobin.

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INTRODUCTION

Diet, insulin, and oral hypoglycemic agents have remained the mainstays of therapy for the diabetic patient for decades. Despite this, there have been major advances in surgical alternatives for individuals with IDDM and an emerging increase in the available medical options for both IDDM and NIDDM. This chapter provides an overview of current concepts and data regarding approaches to managing diabetes, including not only medical therapies but, perhaps as important, patient education and self-care practices.

CURRENT THERAPIES USED BY DIABETIC PATIENTS

The most recent information about diet, oral agents, and insulin use by U.S. diabetic patients is from the 1989 NHIS diabetes supplement[1]. This questionnaire was administered to a representative sample of 2,405 persons who reported having been diagnosed by a physician as having diabetes. Questions about duration of diabetes, duration of insulin use, height, and weight permitted differentiation of diabetic subjects into IDDM and NIDDM[2]. Criteria for IDDM were age <30 years at diabetes onset, continuous insulin use since diagnosis, and percent desirable weight ≤120. All other subjects were considered to have NIDDM, and these were differentiated into those who did and did not use insulin. Characteristics of these subjects are shown in Table 25.1. Some insulin-treated NIDDM patients with diabetes onset at age ≥30 years may have IDDM (see Chapter 2). This has been estimated to be ~7% of all adults with diagnosed diabetes[3]. In addition, some patients with NIDDM may have slowly evolving IDDM. No reliable estimate of this type of diabetes is available for the United States.

Subjects' responses to questions about diabetes therapies in the 1989 NHIS are shown in Table 25.2. For all persons age ≥18 years, 42.8% were treated with insulin, 49.2% were treated with oral agents, and 63.8% reported they had been given a diet for their diabetes and were following this diet. For patients with NIDDM, the proportions treated with insulin and oral

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Table 25.1

Characteristics of Persons with Diabetes, Age ≥18 Years, U.S., 1989

Characteristic	IDDM	NIDDM, insulin-treated	NIDDM, not insulin-treated
Mean current age (years)	34.1	60.6	62.6
Men (%)	53.4	41.4	41.8
Non-Hispanic white (%)	92.0	63.4	73.7
Non-Hispanic black (%)	3.7	26.6	16.0
Mexican American (%)	0	5.6	4.2
Other race (%)	4.3	4.5	6.1
Median income (in $1,000)	35-40	17-18	16-17
Median education (years)	13	12	12
Mean age at diabetes diagnosis (years)	16.2	47.1	53.8
Mean duration of diabetes (years)	17.9	13.4	8.6
History of diabetes in mother or father (%)	14.6	44.3	40.9
Mean body mass index—men	23.0	27.4	27.7
Mean body mass index—women	21.3	29.3	28.5
Regular doctor for diabetes (%)	87.9	91.3	91.0
Had diabetes education class (%)	58.6	48.9	23.7
Has health insurance (%)	89.6	92.6	91.9

Body mass index, weight (kg) divided by height (m^2); percent with a regular doctor for diabetes is based on response to question, "Is there one doctor you usually see for your diabetes?"; percent with a diabetes education class is based on responses to questions about whether information about diabetes had been obtained from a diabetes education class, whether the subject had ever taken a course or class in how to manage diabetes, and whether the subject had attended any other education program or class about diabetes; health insurance includes Medicare, private health insurance, military health coverage, Medicaid, and coverage through any public assistance programs.

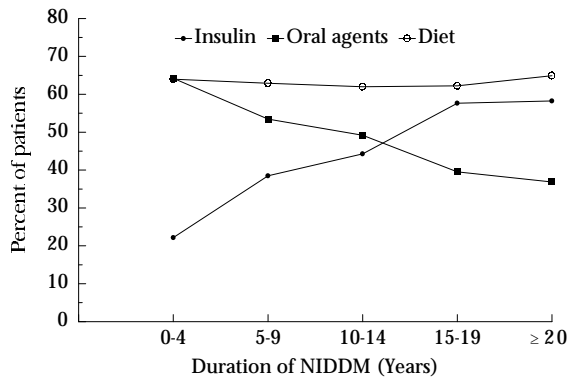*Source*: Reference 1, 1989 National Health Interview Survey

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Table 25.2

Percent of Adults with Diabetes Who Report Using Diabetes Therapies, Age ≥18 Years, U.S., 1989

Type of diabetes and age (years)	Use insulin (%)	Use oral agents (%)	Follow a diabetes diet (%)
All diabetic subjects			
≥18	42.8	49.2	63.8
18-34	74.9	6.4	65.8
35-44	53.8	36.9	58.9
45-54	41.7	48.0	57.3
55-64	44.0	51.3	65.8
65-74	37.3	57.4	64.7
≥75	32.7	56.2	67.7
IDDM			
≥18	100.0	1.6	72.7
18-34	100.0	1.6	69.3
35-44	100.0	2.7	75.8
≥45	100.0	0.0	77.2
NIDDM			
≥18	39.4	52.0	63.3
18-34	50.8	11.1	62.6
35-44	44.0	44.2	55.3
45-54	39.1	50.0	56.2
55-64	43.6	51.7	65.6
65-74	37.1	57.6	64.8
≥75	32.7	56.2	67.7

Data on following a diet are the percent who answered that they had been given a diet for their diabetes and that they were now following this diet all or most of the time.

Source: 1989 National Health Interview Survey

Figure 25.1

Percent of Adults with NIDDM Who Report Using Diabetes Therapies, by Years Since Diagnosis of Diabetes, Age ≥18 Years, U.S., 1989

Source: 1989 National Health Interview Survey

agents were relatively constant across the entire age range. The proportion of IDDM subjects who reported they were following their diabetes diet (72.7%) was slightly higher than that of NIDDM subjects (63.3%).

Although for NIDDM subjects there was little relationship of insulin and oral agent use with age, there was a strong relationship with duration of diabetes. As shown in Figure 25.1 and Table 25.3, the proportion of NIDDM patients treated with insulin increased with longer duration of diabetes, from 22.2% at 0-4 years duration of diabetes to 58.3% at ≥20 years duration. Concomitantly, the proportion treated with oral agents declined with increasing time since diagnosis of diabetes, from 64.2% at 0-4 years duration of diabetes to 36.9% at ≥20 years duration. The proportion who stated that they had been given a diet for their diabetes and were following this diet all or most of the time was relatively constant across the range of diabetes duration. Appendix 25.1 provides further information on diabetes therapies by duration of diabetes and age.

Table 25.4 presents additional information on diabetes therapy for IDDM, insulin-treated NIDDM, and NIDDM not treated with insulin[4]. For both insulin-treated groups, the average insulin dose was about 50 units per day and use of an insulin pump was rare. Two or more insulin injections daily were taken by 61.8% of IDDM and 47.8% of insulin-treated NIDDM patients. Thus, a substantial proportion of insulin-treated diabetes patients were not using multiple daily insulin injections. About 1.6% of IDDM and 9.6% of insulin-treated NIDDM patients reported using oral agents in addition to insulin. Combined insulin and

oral hypoglycemic agents (e.g., BIDS—bedtime insulin to better attenuate early morning counterregulatory response, and daytime sulfonylurea to improve insulin sensitivity) is a more recent form of diabetes therapy. About 40% of IDDM and 26% of insulin-treated NIDDM patients reported self-testing their blood glucose at least once per day, but this proportion was substantially lower for NIDDM patients not treated with insulin (5.3%). Frequent hyperglycemia and glycosuria were reported by about one-fourth of diabetic subjects who self-tested or knew the results of tests that their physicians had performed[4].

TRENDS IN DIABETES THERAPY

Questions on use of diabetes therapies have been included in several NHIS surveys and in the 1976-80 Second National Health and Nutrition Examination Survey (NHANES II). Figure 25.2 shows information on the proportion of diabetic persons who reported they used insulin, oral agents, or dietary therapy in these national surveys[2,5-9]. Appendices 25.2 and 25.3 provide these data and also information from some community-based studies of large populations[2,5-14].

Table 25.3

Percent of Adults with Diabetes Who Report Using Diabetes Therapies, by Duration of Diabetes, Age ≥18 Years, U.S., 1989

Duration of diabetes (years)	Use insulin (%)	Use oral agents (%)	Follow a diabetes diet (%)
All diabetic subjects			
0-4	23.5	63.2	64.5
5-9	41.1	51.4	63.6
10-14	46.8	47.0	61.3
15-19	61.3	36.1	62.6
≥20	64.3	31.8	66.7
IDDM			
0-14	100.0	2.3	70.0
≥15	100.0	1.2	73.7
NIDDM			
0-4	22.2	64.2	64.0
5-9	38.5	53.5	62.9
10-14	44.3	49.2	62.0
15-19	57.7	39.5	62.2
≥20	58.3	36.9	64.9

Data on following a diet are the percent of persons who answered that they had been given a diet for their diabetes and that they were now following this diet all or most of the time.

Source: 1989 National Health Interview Survey

Table 25.4
Diabetes Therapies and Medical Care for Patients with Diabetes in the U.S., 1989-91

	IDDM	NIDDM, insulin-treated	NIDDM, not insulin-treated
Characteristics of diabetes therapy			
Mean age at diabetes diagnosis (years)	16.2	47.1	53.8
Mean diabetes duration since diagnosis (years)	17.9	13.4	8.6
Mean duration of insulin use (years)	17.9	8.0	
Mean units insulin/day	47.1	50.7	
Ever used insulin pump (%)	5.5	1.1	
Currently using insulin pump (%)	0.7	0.2	
≥2 insulin injections/day or insulin pump (%)	61.8	47.8	
≥3 insulin injections/day or insulin pump (%)	14.2	3.3	
Taking oral agents (%)	1.6	9.6	79.5
Following diet for diabetes (%)	72.7	64.4	62.5
Percent desirable weight ≥120 (%)	0.0	61.2	60.1
Blood glucose checked by health professional ≥ twice in past 6 months (%)	52.9	70.4	67.0
Urine glucose checked by health professional ≥ twice in past 6 months (%)	37.8	50.9	48.5
Self-test blood glucose ≥ once/day (%)	39.5	25.8	5.3
Self-test urine glucose ≥ once/week (%)	29.3	32.4	20.1
High blood glucose always/most of the time	17.4	25.9	26.6
Glucose in urine always/most of the time	26.1	29.9	26.0
Medical care characteristics			
≥4 visits to diabetes physician in past year (%)	36.1	65.0	57.1
Visit to dietitian/nutritionist in past year (%)	20.8	24.5	18.6
Has had diabetes education class or course (%)	58.6	48.9	23.7
Mean patient education hours	15.7	13.3	9.1
Visit to cardiologist in past year (%)	4.7	26.7	22.4
Visit to ophthalmologist in past year (%)	54.4	50.8	39.8
Dilated eye examination in past year (%)	56.9	54.6	43.6
Visit to podiatrist in past year (%)	7.9	22.5	14.0
Health professional has checked feet ≥ twice in past 6 months (%)	24.4	38.8	25.3
	Percent of all physician visits for diabetes		
Physician specialty for diabetes visits			
Internal medicine	37.2		
General practice	14.4		
Family practice	20.0		
Diabetology/endocrinology	7.9		
All other specialties	20.5		

IDDM was defined as diabetes onset at age <30 years, continuous insulin use, and percent desirable weight <120; data on high blood glucose and urine glucose were reported by 80% (blood glucose) and 61% (urine glucose) of subjects based on self-tests and results of physician tests for blood and urine glucose.

Source: Reference 4, 1989 National Health Interview Survey, and 1990-91 National Ambulatory Medical Care Survey
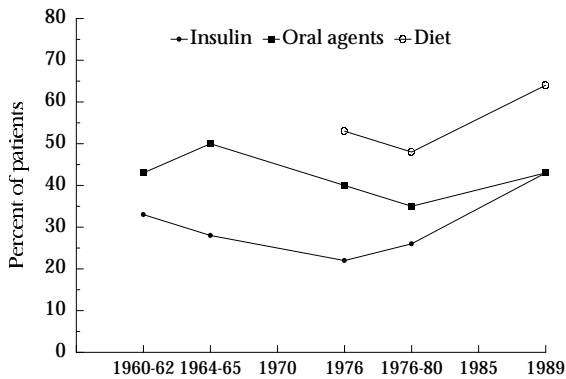
In 1981, an assessment of diabetes care was made in four large and four small randomly selected Michigan communities. This study was repeated in these communities in 1991; Figure 25.3 shows information from the two studies[14]. A much higher proportion of all diabetic subgroups in 1991 compared with 1981 reported they self-monitored their blood glucose and adjusted their insulin dose based on these tests. Patients with IDDM and insulin-treated NIDDM were more likely to use multiple injections and various types of insulin in 1991 than in 1981.

DIETARY THERAPY

Nutritional therapy is a challenging but necessary dimension in managing diabetes. For IDDM and NIDDM patients, goals for dietary management are the same but also very different. For both groups, a major objective is to optimize glycemic control and blood lipid levels and to prevent and treat acute hypoglycemic events and chronic diabetic complications including nephropathy, hypertension, cardiovascular

Figure 25.2

Time Trends in the Proportion of Diabetic Subjects in National Surveys Who Report Using Diabetes Therapies, U.S., 1960-89
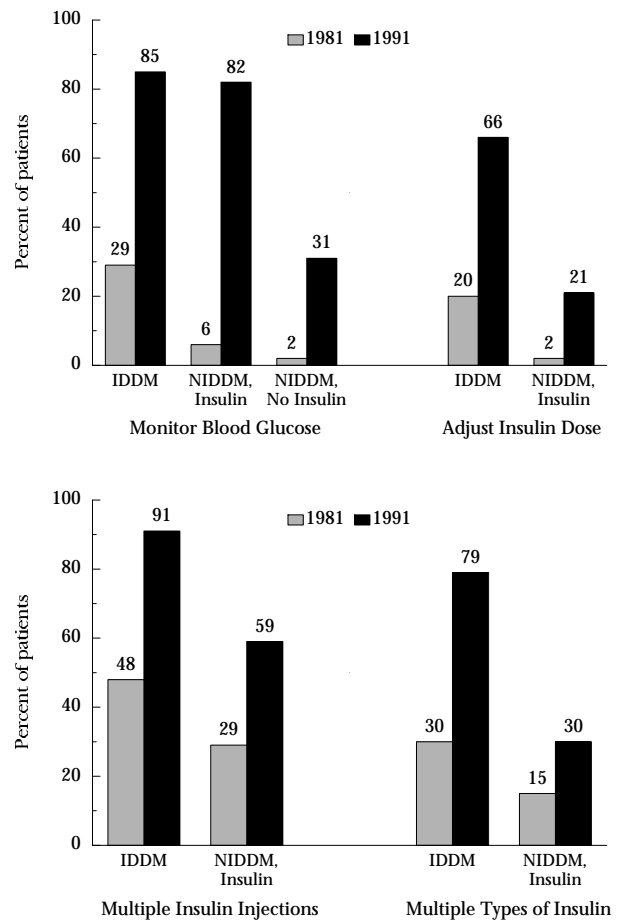
Figure 25.3

Percent of Diabetic Patients in Eight Michigan Communities, According to Diabetes Care Practices, 1981 and 1991

disease, and autonomic neuropathy. For individuals with IDDM, an additional goal is to match diet to insulin requirements to ensure normal growth and development for adolescents and children[15]. By contrast, in obese NIDDM patients, it is important to achieve and maintain a reasonable or realistic body weight (as opposed to a desirable or ideal body weight)[16] and to maximize the success of oral hypoglycemic therapy. Attainment of nutritional goals is best achieved through the coordinated efforts of a diabetes educator, nutritionist, physician, and occasionally, behavioral and exercise specialists. This has been substantiated by the DCCT[17]. However, in practice this set of health practitioners is often not available to the patient, probably for logistic and financial reasons (Table 25.4). Insulin therapy should be integrated into the usual dietary and exercise patterns of the individual. For the highly motivated patient, using multiple daily insulin injections or an infusion pump allows marked flexibility in these patterns.

As shown in Table 25.2, ~64% of all diabetic subjects in the 1989 NHIS reported having been given a diet for their diabetes and that they were following this diet all or most of the time. In response to a question about whether diet is important in controlling their diabetes, 87% answered yes. Subjects who reported they were not following a diabetes diet or were able to follow their diabetes diet most or some of the time, rarely, or never, were asked about particular situations that they found difficult. These data are shown in Table 25.5. A variety of situations were problematic for these subjects, most notably the desire to eat foods that are not on the diabetes diet. Of importance, two situations were not issues for these patients: lack of support from family and friends and being unsure about what foods they should eat. In general, difficulties with following a diet for diabetes were expressed less frequently as age increased.

Successful long-term weight loss for the obese NIDDM patient remains an elusive and difficult task. It is best achieved by a 250-500 kcal decrease in daily caloric intake, with less dietary fat (especially saturated fat) consumption and an increase in regular physical activity[18]. Because ideal body weight may be impractical to achieve or maintain, a more mild-to-moderate weight reduction to a reasonable body weight is encouraged, as it has been shown to improve metabolic control, increase insulin sensitivity, and reduce hepatic glucose output[19-22]. Other useful strategies include spacing nutrient intake with more frequent meals[23-25], as well as behavioral and attitude changes in the patient. For refractory morbid obesity,

	Age (years)			
	≥18	18-44	45-64	≥65
Difficulty				
Eating at restaurants	48.4	53.7	50.3	44.1
At parties and social events	43.4	55.1	45.7	36.1
When busy with other activities	35.4	52.3	37.4	26.2
When going on trips	41.3	48.7	44.2	35.3
When feeling upset or angry	42.8	56.9	46.0	33.7
When feeling sad, depressed, or blue	40.6	53.9	41.2	34.3
When feeling bored	38.0	46.9	41.0	31.3
Because foods you should eat do not taste good	31.4	27.3	30.8	33.7
Because you crave foods not on your diet	58.2	64.5	56.9	57.0
Because your have to prepare food separately for yourself	18.6	23.7	22.3	12.7
Because of lack of support from your family or friends	8.4	12.5	8.0	7.1
Because you are unsure about what foods you should eat	7.4	6.9	8.9	6.2
Believe that what you eat or drink is very important in controlling your diabetes	87.4	89.8	90.8	83.3

People never given a diet for their diabetes (5%), who had not tried to follow a diabetes diet (12%), or who stated that they are always able to follow their diabetes diet (23%) were not asked questions about difficulties.

Source: 1989 National Health Interview Survey

more radical management may include appetite suppression or gastric bypass surgery; however, their long-term safety and efficacy remain to be established[26].

The subject of protein intake in diabetic patients is controversial. Adequate intake is required to achieve metabolic control and nutritional sufficiency. However, excess protein ingestion has been linked to progression of diabetic nephropathy. According to current guidelines, dietary protein intake should constitute 10%-20% of total daily calories, except in the presence of nephropathy, when the recommended daily allowance (RDA) for protein is 0.8 g/kg body weight/day or ~10% of total daily calories[27].

When 10%-20% of total daily calories derives from dietary protein, the remaining 80%-90% of calories are distributed between carbohydrate and fat. Saturated fat, because of its atherogenic risk, and polyunsaturated fat, because of its adverse impact on high-density lipoprotein (HDL) cholesterol, should each be limited to <10% of total daily calories. In addition, cholesterol should be limited to ≤300 mg daily. The

distribution of the remaining 60%-70% of calories, composed of monounsaturated fat and carbohydrate, may be tailored to individual needs, although it does remain in dispute whether saturated fat calories should be replaced by fat, carbohydrate, or both. Potential problems with a high-carbohydrate (60% of total calories) and low-fat (20%-25% of total calories) diet, at least short-term, include elevation of triglycerides and very low-density lipoprotein (VLDL) cholesterol and postprandial hyperglycemia, as reported in NIDDM subjects[28,29]. In contrast, a diet higher in monounsaturated fat, comprising up to 20% of total calories, with a more moderate carbohydrate intake of 50%-60% of calories may offer advantages to the individual with elevated blood triglycerides and VLDL. However, this diet may be counterproductive in the obese diabetic patient.

Despite prior dogma that sweets and refined sugars be replaced with complex carbohydrates, contending that they incur greater immediate postprandial hyperglycemia, a large body of literature shows no significant difference in glycemic control from sucrose or complex carbohydrate forms[30-41] (Table 25.6). What is important, however, is the total number of calories. Sucrose may replace other carbohydrates, but the diet should remain isocaloric. Also, other nutrients often consumed with sucrose, such as fat, must be considered.

Dietary fructose, as found in fruits, vegetables, and honey, produces less postprandial hyperglycemia than either sucrose or most starches[32,42,43] and is an excellent caloric sweetener except in large quantities, when it may adversely affect serum low-density lipoprotein (LDL) and total cholesterol[44-46].

Table 25.6
Studies Comparing Glycemic Effects of Isocaloric Amounts of Sucrose and Starch in Diabetic Subjects

Ref.	No. of diabetic subjects	Duration	Calories from sucrose (%)	Adverse effects of sucrose on glycemia
32	22	Single meal	25	No
33	18	Single meal	14	No
34	21	Single meal	15	No
35	6	Single meal	15	No
36	18	Single meal	14	No
37	24	8 days	23	No
38	16	5 days	7	No
39	10	2 days	10	No
40	18	4 weeks	38	No
41	12	4 weeks	19	No

Meals were provided to subjects by the investigators.

Source: References are listed within the table

Dietary fiber, both soluble and insoluble, is healthy for all individuals, including people with diabetes; the recommended daily consumption is 20-35 g[47,48], which is two to three times the average daily consumption. Insoluble fiber prolongs gastric emptying and intestinal transit time and increases stool volume[49,50]. Its effects on bowel health include beneficial effects on diverticulitis, hemorrhoids, constipation, and possibly cancer[51]. Soluble fiber, on the other hand, increases gastric emptying and intestinal transit time, and with intake >20 g daily, may lower triglycerides (fasting and postprandial) and LDL and total cholesterol without adversely affecting HDL cholesterol[52,53]. Interestingly, soluble fiber intake has been reported to be inversely proportional to cardiovascular disease[54]. In addition, by increasing intestinal transit time and reducing absorption time, it has been suggested[55,56], although with dubious significance, to improve glycemic control. Contrary to popular belief, high dietary fiber does not predispose to bezoar formation in diabetic patients[57].

Although salt-sensitive hypertension does occur more frequently in certain population groups such as blacks and diabetic patients[58,59], these individuals are not easily identified. Therefore, it is suggested that the general population restrict sodium intake to ≤3 g daily[60] (~50% the average daily intake of 4-6 g) and, for mild to moderately hypertensive individuals, to 2.4 g daily.

Moderate alcohol consumption, defined as one 5-ounce drink for women and two 5-ounce drinks for men, may be advocated to decrease cardiovascular risk in the diabetic population as in the general population. However, alcohol may produce either postprandial hyperglycemia due to enhanced glycogenolysis and peripheral insulin resistance[61], or fasting hypoglycemia by indirectly interfering with gluconeogenesis and by its association with depleted glycogen stores[62]. Therefore, reducing alcohol intake is necessary in certain diabetic patients and other individuals, including those with uncontrolled diabetes, those treated with both insulin and sulfonylureas, and those with conditions such as pancreatitis, hypertriglyceridemia, and neuropathy[63]. Other more common-sense indications for alcohol restriction include pregnancy, a history of alcohol abuse, alcoholic cardiomyopathy or liver disease, and concomitant use of certain medications including tranquilizers and barbiturates.

There is little rationale for micronutrient (vitamins and minerals) supplementation in diabetes or in the general population when a nutritionally adequate diet is maintained[64,65]. The few particular circumstances include chromium and magnesium for poorly controlled hyperglycemia[66-70] and zinc for improved venous stasis ulcer healing[71,72]. However, chromium deficiency is unlikely in most diabetic individuals, and although serum zinc levels are generally lower in the diabetic population, it is unclear that supplementation is beneficial in all such cases of venous stasis ulcers. Finally, magnesium replacement is only recommended in documented deficiency.

Current guidelines for daily caloric intake for pregnant women are unclear and range from 70-240 kcal[73,74] to 300 kcal during the second and third trimesters to ensure optimal birth weight. Therefore, pregnant women with either preexisting or gestational diabetes should be monitored for urine ketones, blood glucose, weight gain, and appetite with any nutritional prescription. Table 25.7 shows recommendations for weight gain for pregnant women.

ORAL HYPOGLYCEMIC AGENTS

The first-line therapy modality for NIDDM includes an optimal diet with appropriate weight reduction and exercise accompanied by patient education and self-management. Only when these measures fail to restore adequate glycemic control should pharmacologic treatment be considered.

The sulfonylureas are the major group of oral hypoglycemic agents used in the United States, although the biguanide drug metformin has recently been approved for use. The second-generation drugs glipizide and glyburide are unique for their more potent equivalent therapeutic dose than the first-generation agents and for their nonpolar anionic properties. The mechanism of action of sulfonylureas is not fully understood. They enhance β-cell insulin secretion, directly via high-affinity receptors and indirectly by promoting sensitivity to glucose, and they may inhibit

Table 25.7
Recommended Total Weight Gain Ranges for Pregnant Women

Weight-for-height category	Recommended total weight gain
Low (BMI <19.8)	12.5-18 kg (28-40 lb.)
Normal (BMI 19.8-<26)	11.5-16 kg (25-35 lb.)
High (BMI 26-29)	7-11.5 kg (15-25 lb.)
Obese (BMI >29)	<6 kg (15 lb.)

BMI, body mass index.

Source: National Academy of Sciences recommendations

glucagon secretion[75]. Extrapancreatic effects include increased insulin receptor binding and postreceptor activity involving the liver, decreased glucose production and increased glucose utilization, and increased glucose and fatty acid uptake in muscle and adipose cells[76]. Because sulfonylurea receptors have not been identified and because these agents are ineffective for IDDM, it appears that their predominant hypoglycemic action is on the β-cell[77]. Approximately one-third of NIDDM subjects do not adequately respond to sulfonylureas[78,79], most often because of dietary noncompliance or markedly impaired β-cell function. Of those who do initially respond, 5%-10% develop secondary failure annually, related to noncompliance to diet, progressive β-cell impairment, drug interactions, or stressful events such as pregnancy and infections. After 10 years, only ~50% of initial responders have adequately controlled blood glucose[80]. Optimal patient selection includes those with onset of diabetes at age >40 years, duration of disease <5 years, normal or increased body weight, no history of prior insulin therapy, good glycemic control with <40 units of insulin daily, and fasting plasma glucose <180 mg/dl[81,82].

INTENSIVE INSULIN THERAPY— THE DCCT AND ITS IMPLICATIONS

By definition, IDDM with onset in lean individuals at age <30 years requires insulin therapy to avoid diabetic ketoacidosis, diabetic coma, and death. NIDDM typically affects middle-aged obese individuals and is characterized by insulin resistance and often requires insulin therapy for optimal metabolic control. Both forms of diabetes share the complications of microvascular retinopathy, nephropathy, and neuropathy, as well as vascular disease and consequent tissue and organ damage.

The DCCT[17] was designed to evaluate the influence of tight metabolic control (maintaining mean blood glucose and glycohemoglobin values close to the normal range) on both delaying the onset and slowing the progression of vascular complications in IDDM. The study was primarily designed to evaluate retinopathy and examined 1,441 patients, half of whom were each designated as primary or secondary intervention cohorts. The primary prevention cohort was selected to have a disease duration of 1-5 years and the absence of hypertension, retinopathy, and microalbuminuria. The secondary prevention cohort was required to have 1-15 years disease duration, mild to moderate nonproliferative retinopathy, microalbuminuria but no frank proteinuria, and absence of hypertension. The patients were assigned randomly to intensive insulin

therapy using either the external insulin pump or ≥3 insulin injections daily with frequent blood glucose monitoring, or to more conventional therapy using one to two daily insulin injections. The patients were followed for a mean of 6.5 years with regular assessment of the onset or progression of retinopathy as well as nephropathy and neuropathy.

Although normalization of blood glucose values was not achieved, with a mean blood glucose in the intensively treated group of ~40% above normal values, there was ~40%-70% risk reduction in retinopathy, nephropathy, and neuropathy, compared with conventionally treated subjects (Figures 25.4 and 25.5). This benefit of intensive therapy applied to both the delay in onset and progression of the complications. These results, moreover, were seen regardless of the patients' age, sex, or duration of disease within the parameters of the study. This trial has been the longest and largest prospective study to show that improved glycemic control directly correlates with reduction in incidence and progression of diabetic microvascular complications. It complements two other recent studies[83,84] and seems to answer the longstanding controversy of whether there is additional benefit of further glycemic control beyond that required to allay the symptoms of uncontrolled diabetes[85,86].

Interestingly, in both the primary and secondary intervention cohorts, the presence and degree of urinary albumin excretion correlated positively with both gly-

Figure 25.4

Rates of Development of Retinopathy, Nephropathy, and Neuropathy in IDDM Patients in the DCCT Primary Prevention Cohort
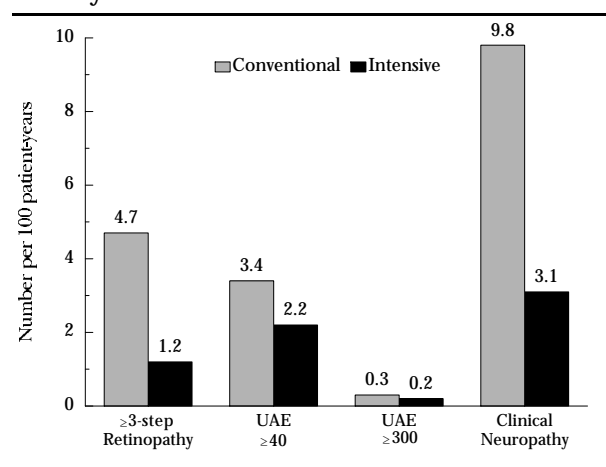
DCCT, Diabetes Control and Complications Trial; UAE, urinary albumin excretion. Change in the severity of retinopathy was defined as a change observed by fundus photography of ≥3 steps from baseline that was sustained for ≥6 months; clinical neuropathy was measured at 5 years after baseline.

Source: Reference 17

Figure 25.5

Rates of Development and Progression of Retinopathy, Nephropathy, and Neuropathy in IDDM Patients in the DCCT Secondary Intervention Cohort
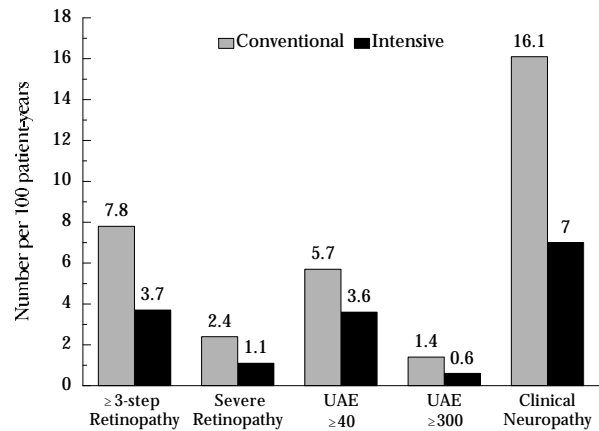

DCCT, Diabetes Control and Complications Trial; UAE, urinary albumin excretion. Change in the severity of retinopathy was defined as a change observed by fundus photography of ≥3 steps from baseline that was sustained for ≥6 months; severe retinopathy defined as severe nonproliferative or proliferative retinopathy; clinical neuropathy was measured at 5 years after baseline.

Source: Reference 17

cohemoglobin and creatinine clearance[17]. This has been attributed to increased hydrostatic pressure and/or disrupted vascular permeability[87,88]. Urinary albumin excretion also correlated closely with the presence and extent of retinopathy[89], as shown by previous cross-sectional studies[90]. These findings suggest common factors in the pathogenesis of early retinopathy and nephropathy. Because microalbuminuria is highly correlated with coronary artery disease[91], it may serve as a marker for widespread vascular damage[92], all of which may be prevented or delayed by vigilant diabetic glycemic control.

Despite our broadened understanding of the goals in diabetes management provided by the DCCT results, many questions remain unanswered. One such question focuses on the threefold greater risk of hypoglycemia in the intensively treated DCCT patients versus the conventionally treated control group. Clearly, hypoglycemia is the major risk of vigorous glycemic control, the consequences ranging from subclinical effects of neuroglycopenia to symptoms and signs of impaired motor coordination, cognitive dysfunction, seizures, and coma[93,94]. Contraindications to tight glucose control includes patients' unwillingness to actively participate in self-management[85]. It is also contraindicated in children age <2 years, and because normal brain development is not complete until age 7 years, glucose control should be managed with extreme caution in these patients. Tight glycemic control in young children is especially difficult because of relatively unpredictable food intake, activity level, and adherence to treatment regimens, compared with adults. Because preadolescents rarely develop microvascular complications, intensive insulin management might be avoided in this patient group[85]. However, in elderly diabetic patients with a higher prevalence of coronary and cerebrovascular atherosclerosis, the attendant counterregulatory hyperadrenergic response to hypoglycemia exposes a higher risk of permanent vital tissue damage. Therefore, such elderly individuals and others with advanced macrovascular disease are relatively contraindicated for tight control[85,93]. The DCCT Research Group cautions that intensive treatment may cause even more frequent severe hypoglycemic episodes in less motivated individuals than those studied in the DCCT[93]. Further, their data should be generalized with due caution to groups such as insulin-requiring NIDDM patients, preadolescents, the elderly, those with diabetic complications, and patients who are less than highly motivated.

The DCCT did not specifically study patients with NIDDM. However, the pathophysiology of microvascular disease is considered to be the same as in IDDM, and thus tight metabolic control is generally recommended in both diabetic groups. Because NIDDM usually affects older individuals with a greater prevalence of macrovascular disease and a tendency for severe consequences of hyperglycemia, such as stroke, heart attack, and sudden death, recommendations for tight control in this group must be made selectively and judiciously. In addition, NIDDM is associated with a constellation of comorbid clinical features, including obesity, hypertension, and dyslipidemia, and requires separate management for these conditions. Importantly, there is some concern[95,96] that exogenous insulin may itself propagate macrovascular atherogenesis, but a number of studies disagree with this (see Tables 19.11-19.13). Furthermore, insulin can promote weight gain that may result in increased insulin resistance and further insulin requirements. Hence, although it seems logical that tight metabolic control has beneficial consequences on microvascular complications in NIDDM, as has been demonstrated by the DCCT in IDDM, this goal needs to be pursued with caution for undue risk of hypoglycemia and by using strategies that improve insulin sensitivity, such as diet, exercise, and oral sulfonylureas. The difficulty with this approach, however, is noncompliance to diet and exercise and disease progression. It remains unclear whether early intervention may delay the onset or progression of diet-resistant hyperglycemia.

PATIENT EDUCATION

Patient education can translate to increased self-management skills, including self-glucose monitoring, compliance with overall management, improved glycemia for insulin-treated diabetes, and a reduction in complication incidence[2,97-99]. In two studies based on diabetic subjects in the 1989 NHIS, self-blood glucose monitoring at least once per day and having a dilated eye examination at least once in the past year were substantially more frequent for NIDDM patients who had received patient education compared with those who had not (Table 25.8). In the Michigan study of diabetes in communities[14], mean glycosylated hemoglobin was lower for IDDM patients who had prior education (Table 25.9).

Despite these favorable effects, only a minority of people with diabetes in the United States (35%) have taken an educational class or program[100]. Certain subgroups of diabetic patients are particularly less likely to have had diabetes education. These findings were based on a probability sample of 2,405 people with diabetes in the 1989 NHIS. In this study, subjects were asked whether they had ever attended a course or class in how to manage diabetes themselves and the contents of this course. Forty-six percent of IDDM subjects, 41% of those with insulin-treated NIDDM, and 18% of NIDDM subjects not treated with insulin had attended a self-management course[100]. The average number of instruction hours reported was 11.8. As shown in Table 25.10, meal planning, blood and urine glucose testing, foot care, diabetes management when sick, and insulin injection and dose adjustment were reported by the majority of individuals to be covered in the courses.

Table 25.8

Effect of Diabetes Patient Education on Self-Blood Glucose Monitoring and Dilated Eye Examinations, Age ≥18 Years, U.S., 1989

	IDDM	NIDDM, insulin-treated	NIDDM, not insulin-treated
Self-blood glucose monitoring ≥ once per day			
Yes	39.9	33.9*	11.4*
No	39.3	18.6	3.5
Dilated eye examination in the past 12 months			
Yes	57.4	58.2*	52.0*
No	55.5	51.7	41.7

*Significantly different (yes versus no) at p<0.05.

Source: References 2 and 99, 1989 National Health Interview Survey

Table 25.9

Mean Glycosylated Hemoglobin Values (%), According to Diabetes Education History, Michigan, 1991

Type of diabetes	Had education at some time in the past				Did not have prior education
	<3 years	3-5 years	>5 years	All	
All diabetic patients	10.2	10.7	10.6	10.5	9.9
IDDM	11.2	12.0	11.0	11.3	12.0
NIDDM					
Insulin-treated	10.9	11.2	10.9	10.9	11.3
Not insulin-treated	9.4	9.4	9.9	9.5	9.3

Source: Reference 14

Diabetic subjects in the 1989 NHIS were also asked whether they had attended any other education program or class about their diabetes, in addition to being asked specifically about a diabetes management course. Table 25.11 combines these responses and shows the proportion of individuals who had had any diabetes education course or class, according to their sociodemographic and clinical factors[100]. Insulin use appears to be an independent predictor for diabetes education in these data. Those with IDDM had the highest proportion (58.6%) who had received patient education, compared with 48.9% of people with insulin-treated NIDDM and 23.7% of those with NIDDM not treated with insulin. Another predictive factor was age, which was inversely associated with patient education. For individuals with NIDDM, blacks were more likely and Mexican Americans were less likely than whites to have prior patient education. Residence in the Midwest (for all diabetic subjects) and within or near a metropolitan statistical area (for insulin-treated NIDDM subjects) were also associated

Table 25.10

Contents of Diabetes Management Course or Class Taken by Diabetic Individuals, Age ≥18 Years, U.S., 1989

Topic	Courses addressing topic (%)
Meal planning	97.2
Blood and urine glucose testing	91.6
Foot care	89.8
Sick day management	83.4
Injecting insulin	78.1
Insulin dose adjustment	68.7

46% of IDDM subjects, 41% of those with insulin-treated NIDDM, and 18% of NIDDM subjects not treated with insulin had attended a course in diabetes self-management.

Source: Reference 100, 1989 National Health Interview Survey

Table 25.11
Percent of Individuals Who Attended a Patient Education Class or Course on Diabetes, by Type of Diabetes and Selected Characteristics, Age ≥18 Years, U.S., 1989

Characteristics	IDDM	NIDDM, insulin-treated	NIDDM, not insulin-treated
All individuals	58.6	48.9*	23.7*
Age (years)			
18-39	62.3	58.5	34.6
40-64	46.1	53.7*	25.1*
≥65		41.2*	21.3*
Sex			
Male	62.1	48.9	23.5
Female	54.7	48.8	23.9
Race			
Non-Hispanic white	59.1	47.2	22.7
Non-Hispanic black		56.4	28.8*
Mexican American		35.8*	17.2
Residential location			
Within MSA	64.6	50.9	24.2
Outside MSA	40.4	43.2*	22.4
Region			
Northeast	42.2	41.4	19.4
South	49.3	43.0	20.9
West	65.3	47.5	27.4*
Midwest	71.0	65.3*	29.9*
Income ($)			
<10,000	65.4	43.7	19.4
10-19,999	60.2	47.2	24.5*
20-39,999	61.3	52.8	28.1*
≥40,000	57.2	59.3	25.3
Health insurance			
Yes	58.2	49.1	23.5
No	55.4	40.9	27.4
Education (years)			
<9		37.6	18.2
9-12	56.8	49.8*	23.6
>12	63.0	59.9*	31.9*
Marital status			
Married	53.6	50.2	23.6
Widowed		39.1	20.7
Divorced/separated	59.4	53.3	27.3
Never married	73.8	58.6	29.5
Household composition			
Living with spouse	53.9	50.5	23.4
Living with other relative	68.8	48.1	21.9
Living with non-relative			21.0
Living alone	57.7	46.3	25.7*
Has regular diabetes physician			
Yes	59.3	48.2	22.7
No	53.8	55.9	33.9

Table 25.11—Continued next column

Table 25.11—Continued

| Characteristics	IDDM	NIDDM, insulin-treated	NIDDM, not insulin-treated
Frequency of visits to diabetes physician per year			
0	57.4	57.3	37.3*
1-3	69.8	49.8	20.4
≥4	44.8	47.5	23.2
Number of diabetes-related complications			
0	64.3	51.2	15.3
1	58.4	43.5	26.4*
≥2	54.2	50.7*	24.2*

MSA, metropolitan statistical area. *Statistically significant in multiple logistic regression relative to other levels of the variable; see Figures 25.6 and 25.7. Cells with no data have unreliable estimates due to small sample size; diabetes patient education was based on responses to questions about whether information about diabetes had been obtained from a diabetes education class, whether the subject had ever taken a course or class in how to manage diabetes, and whether the subject had attended any other education program or class about diabetes; health insurance includes Medicare, private health insurance, military health coverage, Medicaid, and coverage through any public assistance program; having a regular diabetes physician was based on responses to the question, "Is there one doctor you usually see for your diabetes?"; complications of diabetes include self-reported retinopathy, neuropathy (symptoms of pain, tingling, numbness, decreased hot/cold sensation), proteinuria, kidney disease, amputation, sores on feet that do not heal, angina, hypertension, stroke, glaucoma, and cataracts.

Source: Reference 100, 1989 National Health Interview Survey

with patient education. Increasing income was associated with a greater likelihood of patient education, and education level appeared to be a stepwise, positive predictor for prior patient education in both IDDM and NIDDM patients. Interestingly, NIDDM subjects not treated with insulin who either lived alone, had no regular diabetes physician, or had not visited a diabetes physician within the past year were markedly more likely to have had patient education. Possibly, those individuals felt a stronger need to be informed about their diabetes. A greater number of complications was correlated with patient education in NIDDM subjects. Figures 25.6 and 25.7 show odds ratios for predictors of patient education based on multiple logistic regression analysis for NIDDM individuals treated and not treated with insulin, respectively[100]. The figures show the variables that were significant independent predictors after controlling for the other variables in Table 25.11.

Diabetic subjects in the 1989 NHIS were also questioned about where they had obtained any information about diabetes (Table 25.12). Almost all had obtained information from some source, with a physician being the most likely source.

Figure 25.6

Odds Ratios for the Effect of Independent Variables on Whether Insulin-Treated NIDDM Subjects Had Patient Education, Age ≥18 Years, U.S., 1989
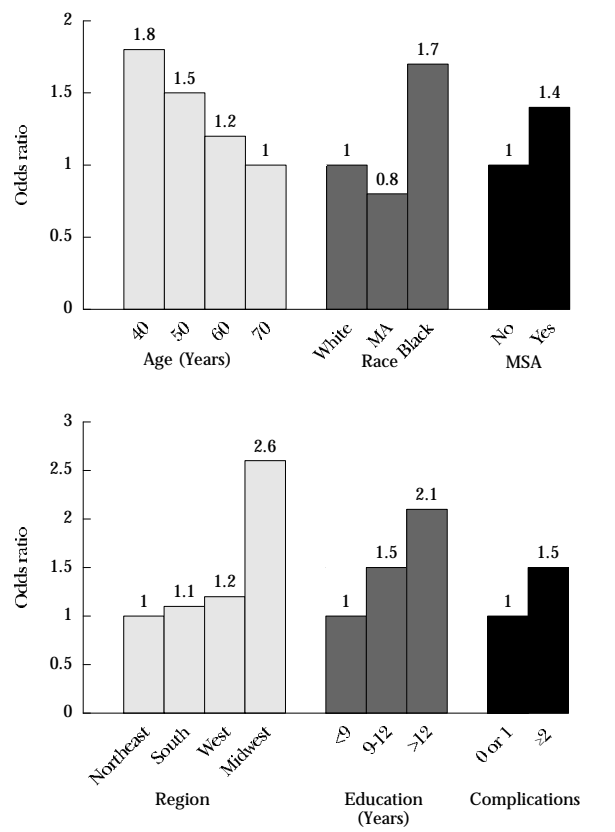
MA, Mexican American; MSA, metropolitan statistical area. Odds ratios are from multiple logistic regression equations that included the variables in Table 25.11; variables with a value of unity are the reference groups.

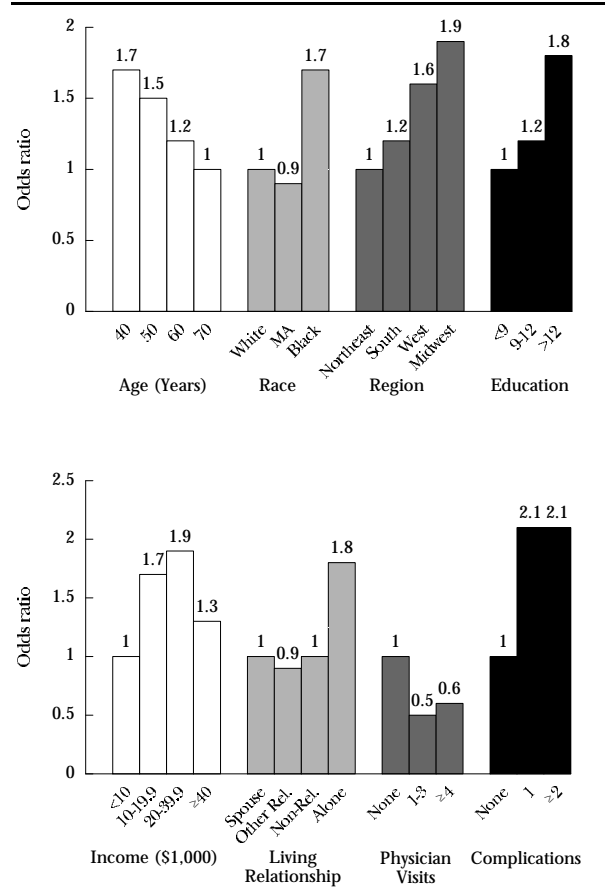*Source*: Reference 100, 1989 National Health Interview Survey

Table 25.12

Sources of Information About Diabetes Reported by Diabetic Individuals, Age ≥18 Years, U.S., 1989

Source	Percent of subjects
Any source	97.1
Physician in physician's office	86.3
Nurse in physician's office	17.8
Dietitian or nutritionist	28.0
Physician or nurse in a hospital	25.2
Relative or friend	14.0
Another person with diabetes	10.1
Diabetes education class	12.2
Diabetes organization	12.2
Newspaper	11.6
Library	5.3
Diabetes support group	4.4
Health department	2.9
Other	15.1

Sources were options listed for the question, "Where have you obtained information about diabetes?"

Source: Reference 100, 1989 National Health Interview Survey

Figure 25.7

Odds Ratios for the Effect of Independent Variables on Whether NIDDM Subjects Not Treated with Insulin Had Patient Education, Age ≥18 Years, U.S., 1989

MA, Mexican American. Odds ratios are from multiple logistic regression equations that included the variables in Table 25.11; variables with a value of unity are the reference groups.
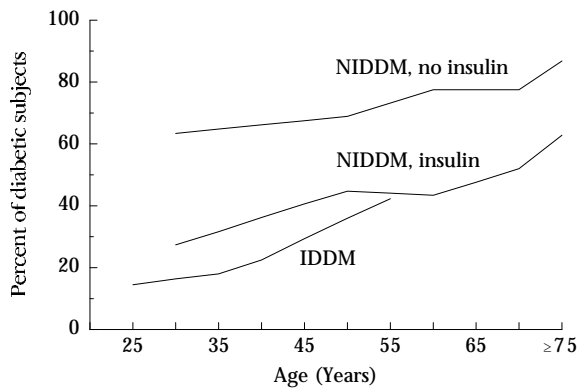
Source: Reference 100, 1989 National Health Interview Survey

SELF-BLOOD GLUCOSE MONITORING

Based on the 1989 NHIS, it appears that the majority of people with diabetes in the United States have never self-tested their blood glucose[2] (Figure 25.8). Moreover, only a small proportion monitored their blood glucose at least once daily: 39.6% of IDDM subjects, 25.8% of insulin-treated NIDDM subjects, and 5.3% of NIDDM subjects not treated with insulin (Figure 25.9). The proportion who self-monitored at least once per day declined markedly with increasing age (Figure 25.10).

Table 25.13 shows the percent of diabetic subjects in the 1989 NHIS who self-monitor at least once per day[2]. Insulin use is a strong marker for self-monitor-

Figure 25.8
Percent of Diabetic Subjects Who Have Never Monitored Their Blood Glucose, U.S., 1989

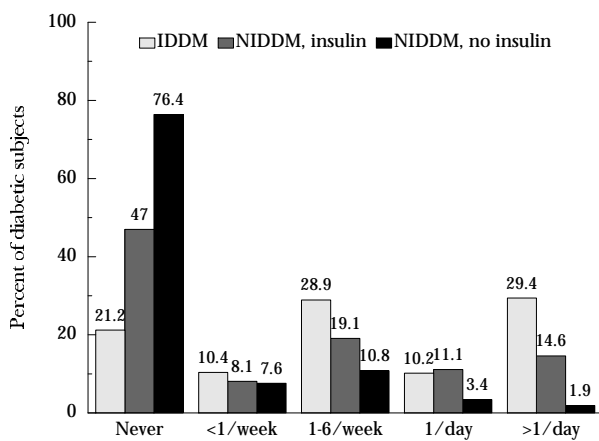*Source*: Reference 2, 1989 National Health Interview Survey

Figure 25.10
Percent of Diabetic Subjects Who Monitor Their Blood Glucose at Least Once per Day, Age ≥18 Years, U.S., 1989
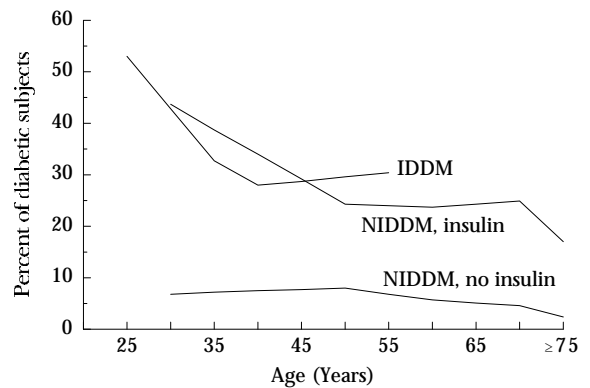
Source: Reference 2, 1989 National Health Interview Survey

ing, with a fivefold greater chance for an insulin-treated NIDDM subject to self-test at least once per day than an NIDDM individual not treated with insulin. With an increasing number of insulin injections daily, there is a stepwise increase in the frequency of self-monitoring. White and Mexican-American adults with diabetes are more likely to self-test than blacks. Both increasing income and having health insurance were associated with self-testing, although in logistic regression these were not independent predictors[2]. Twelve or more years of education was associated with an 80% increased probability of self-testing, and diabetic patient education and more frequent physician visits were also positive predictors.

Figure 25.9
Percent Distribution of Diabetic Subjects, by Frequency of Self-Monitoring of Blood Glucose, Age ≥18 Years, U.S., 1989

Source: Reference 2, 1989 National Health Interview Survey

Although cost has been considered a barrier to self-monitoring, this study failed to show that economic factors, including health insurance and income, were statistically significant determinants of self-testing in multivariate logistic regression analysis[2]. Furthermore, only a small minority of diabetic individuals (2% of those age ≥65 years and 14% of those age 18-65 years) do not have health insurance[101], and blood glucometers and strips can be covered by Medicare and commercial health insurance[102]. For IDDM patients in an independent study, a correlation between self-testing and presence of health insurance was not found[103]. The only subset of patients in the 1989 NHIS that had an independent correlation of self-glucose monitoring with level of income were those of Mexican ethnicity; however, the true effect of income in Hispanics remains unclear, as this finding was based on only a small population sample[2].

Self-blood glucose monitoring can be valuable for patients in the armamentarium of their diabetes management. It enables the motivated patient to make day-to-day decisions in adjusting hypoglycemic medication to fluctuations in diet and physical activity. It allows the managing clinician important data for optimal evaluation of diabetic control[104,105], and it may alert the patient to ensuing ketoacidosis or hypoglycemic emergency. It now seems clear that chronic hyperglycemia is the single most significant determinant of the occurrence of renal and retinal microvascular disease, in both IDDM and NIDDM subjects[17,106-110]. Therefore, the most useful advantage of self-blood glucose monitoring is its role in achieving consistent control of hyperglycemia. It can reduce both the incidence and magnitude of hyperglycemic events. The literature supports the notion that self-blood glucose

Table 25.13
Percent of IDDM and NIDDM Patients Who Perform Self-Blood Glucose Testing at Least Once per Day, Age ≥18 Years, U.S., 1989

Characteristic	IDDM	NIDDM, treated with insulin	NIDDM, not treated with insulin
All patients	39.5	25.8*	5.3*
Insulin injections per day			
1	26.5	15.1	NA
2	43.2	35.8*	NA
≥3 or insulin pump	60.9	54.6*	NA
Insulin dose (units/day)			
<30	29.0	27.2	NA
30-60	43.4	24.5	NA
>60	36.0	29.0	NA
Age			
18-39	42.7	48.5	8.7
40-64	29.9	24.7*	6.5*
≥65		22.7*	3.8*
Sex			
Men	36.8	24.6	3.9
Women	42.8	26.7	6.3
Race			
Non-Hispanic white	40.6	29.8	5.1
Non-Hispanic black	23.1	14.0*	4.0*
Mexican American		29.0	6.6
Income			
<$10,000	29.1	19.9	5.7
$10-20,000	42.2	23.9	4.7
$20-40,000	39.9	30.5	4.7
>$40,000	35.9	39.0	8.2
Health insurance			
Yes	40.0	26.7	5.0
No	34.6	15.6	6.4
Education (years)			
<9		17.6	4.6
9-12	36.7	24.8	4.4
>12	40.7	37.9*	8.1*
Duration of diabetes (years)			
<10	54.7	25.5	5.4
≥10	34.8	26.9	5.4
Visits to doctor for diabetes in past year			
<4	38.2	24.9	3.4
≥4	40.6	26.2*	6.7*
Diabetes patient education			
Yes	39.9	33.9	11.4
No	39.3	18.6*	3.5*
Number of complications of diabetes			
0	39.0	24.3	3.7
1	38.4	26.4	4.5
≥2	41.8	25.8	6.0
Obesity			
Yes	NA	24.2	6.0
No	39.5	29.2	4.2

*Statistically significant in multiple logistic regression relative to other levels of the variable. Cells with no data have unreliable estimates due to small sample size; NA, data category not applicable to this group; health insurance includes Medicare, private health insurance, military health coverage, Medicaid, and coverage through any public assistance programs; complications of diabetes include self-reported retinopathy, neuropathy (symptoms of pain, tingling, numbness, decreased hot/cold sensation), proteinuria, kidney disease, amputation, sores on feet that do not heal, angina, hypertension, stroke, glaucoma, cataract; obesity defined as body mass index ≥27 (men) and ≥25 (women), based on self-reported height and weight.

Source: Reference 2, 1989 National Health Interview Survey

monitoring results in improved glycemic control[111,112] and a reduced incidence of progression to retinopathic disease[17,113]. In addition, home glucose monitoring is cost-effective by reducing other patient expenses[114]. Blood glucose measurements obtained during physician office visits are too infrequent to allow satisfactory consistent glycemic control that would permit a reduction in microvascular complications. Self-monitoring is an important tool that needs to be integrated into a diversified combined approach in the overall management of the diabetic patient, including instructions on hypoglycemic therapy and insulin dose adjustment, nutrition instruction, patient education, optimal physical activity, smoking cessation, monitoring other blood and urine biochemistries, and proper evaluation and management of diabetic complications[115-117].

Glucometers are based on a simple oxidase colorimetric reaction of glucose following the addition of a drop of blood to a reagent strip. The color change is either visually apparent or determined by a reflectance meter. These instruments, when properly used, are reliable and accurate[118-121], with the meter-read strip perhaps more accurate and more suitable for visually impaired individuals. Optimal use of a home monitoring device is contingent on sufficient frequency of testing, accurate recording and reporting of results, and proper technique in using the device. The latter includes timing of the test, adequate volume and placement of blood on the test strip, and removal of blood from the strip prior to reading[122,123]. New patients[124] and individuals requested to test >4 times daily[123] may be particularly prone to inaccurate reporting of results and improper use of the device. Motivated IDDM patients accurately report their testing frequency[112]; however, NIDDM patients who newly self-test and have relatively infrequent contact with health care professionals tend to overestimate testing frequency[124]. Individuals for whom recording errors are problematic, however, do not seem to have compromised glycemic control using glycosylated hemoglobin as an index[112]. Improper testing technique may be corrected by properly training the individual[125,126].

In summary, many diabetic patients in the United States do not use self-glucose monitoring devices. This proportion is particularly high in various subgroups of the diabetic population for which self-testing should be targeted. Although it appears that self-glucose monitoring improves glycemic control and metabolic status of the diabetic individual[2,111-113], further investigation is needed to establish the benefits and effectiveness of this procedure as judged by the overall outcome of the patients.

PANCREATIC TRANSPLANTATION

Pancreatic transplantation in the United States is being performed with increasing frequency. By November 1992, >2,700 cases had been reported to the International Pancreas Transplant Registry (IPTR), with >75% of such cases reported since October 1987[127,128] and 549 reported in 1990 (Table 25.14). Pancreatic transplant is the only treatment for IDDM capable of establishing an insulin-independent state with euglycemia and normal glycosylated hemoglobin. Pancreatic β-cell replacement may be accomplished by either whole pancreatic transplantation or selective islet cell transplantation, with the former procedure currently more likely to succeed[129,130]. The primary value of simultaneous pancreas and kidney transplantation is improved quality of life associated with insulin and dialysis independence. The indication for pancreas transplant alone is limited by the cost of potential immunosuppressive toxicity until less toxic antirejection strategies are developed. The principal role for pancreas transplant alone is improved day-to-day quality of life in diabetic patients with severely labile glucose control, in whom insulin therapy is not only difficult but perhaps dangerous. Evidence for a favorable influence of pancreas transplant alone on the progression of secondary complications of diabetes has not been uniform, hence pancreas transplant alone, solely for this potential benefit, cannot be advocated.

Pancreas transplantation, with associated euglycemia, may retard or prevent the development of early diabetic nephropathy in IDDM patients with renal allografts[131-134]. In patients with pancreas transplant alone, renal function initially decreases, presumably due to cyclosporine nephrotoxicity[135]. However, long-term renal function is usually[131], but not consistently[134,136], stable. Pancreas transplantation after kidney transplantation does appear to halt progression and pre-

vent recurrence of glomerular lesions in recipients[134,137]. The influence of pancreas transplantation on established renal lesions in IDDM is not completely understood. In human studies, the scarce available data suggest a favorable impact of pancreas transplantation on regression of diabetic glomerular lesions based on either glomerular basement membrane width or mesangial volume[133,134]. In animal studies, however, using streptozotocin-induced diabetic rats, both functional and morphologic parameters reversed to the normal range only if pancreatic transplants were performed within 4 months of induction of diabetes. This evidence indicates there is a critical threshold for irreversible diabetic nephropathy[137-141].

Successful pancreatic transplantation has been demonstrated to at least stabilize, if not improve, sensory, motor, and autonomic indices in subjects, in contrast to patients who either failed or did not undergo transplantation[134,142,143]. In addition, diabetic autonomic neuropathy predicts higher mortality, which has been shown to improve in successfully transplanted individuals, compared with those who had either failed or did not undergo pancreas transplantation[134,142,144].

Although retinopathy may be stabilized long term after pancreas transplantation[130], advanced retinopathy does not appear to either reverse or stabilize following successful pancreas transplantation and consequent euglycemia[134,145].

ADVANCES IN DIABETES INTERVENTION

Advances in the therapy of diabetes include new oral medications such as thiazolidinedione; troglitazone, a disaccharidase inhibitor; acarbose; and metformin, a biguanide used in Europe that is now available in the United States. New insulin preparations to modify the current insulin regimens will soon be marketed. Finally, advances with islet cell transplantation and modulation therapies to render them less immunogenic should contribute to our growing armamentarium of treatment resources for the diabetic patient.

ADJUVANT THERAPY FOR PREVENTION AND TREATMENT OF CHRONIC DIABETIC COMPLICATIONS

A number of treatments for chronic diabetic complications are available. Vigilant blood pressure control can slow the progression or delay the onset of neph-

Table 25.14
Number of Transplants Performed in 1990

Organ	No. performed	1-year graft survival (%)
Kidney	9,560	81*
Liver	2,656	69
Heart	2,085	82
Pancreas	549	71
Heart-lung	50	57
Lung	262	48

*Represents cadaveric donor, 91% if donor is living-related.

Source: References 127 and 128

ropathy[146,147]. Nondihydropyridine calcium slow-channel inhibitors and angiotension-converting enzyme inhibitors delay progression of microproteinuria and macroproteinuria[148,149]. In addition, because of a positive metabolic profile and enhancement of insulin sensitivity, they serve as first-line antihypertensive agents along with alpha-antagonists[150]. Thiazide diuretics may be used at low doses to reduce total exchangeable sodium[150]. Photocoagulation is useful for treating proliferative retinopathy[151], and vitrectomy is used when proliferative retinopathy[152] becomes advanced. As mentioned above, a protein-restricted diet is recommended when microalbuminuria is present. Minimizing nephrotoxic agents is imperative, as the kidneys are susceptible to acute injury. Finally, the presence of autonomic neuropathy with orthostatic hypotension makes the management of hypertension difficult. A high-sodium diet or mineralocorticoids may worsen supine hypertension and trigger congestive heart failure. Conservative management should include wearing stockings and elevating the head of the bed during sleep, using gravity as a method of antihypertension.

Dr. Brian J. Fertig is Fellow in Endocrinology, Tulane University Medical Center, New Orleans, LA; Dr. David A. Simmons is Associate Professor of Medicine and Dr. Donald B. Martin is Professor of Medicine, Rodebaugh Diabetes Center, University of Pennsylvania Medical Center, Philadelphia, PA. Dr. Fertig was formerly Fellow in Endocrinology and Diabetes at the University of Pennsylvania Medical Center.

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Appendix 25.1

Percent of Adults with Diabetes Who Report Using Diabetes Therapies, by Duration of Diabetes, U.S., 1989

Duration of diabetes (years)	Use insulin (%)	Use oral agents (%)	Follow a diabetes diet (%)
All diabetic subjects age ≥18 years			
0-4	23.5	63.2	64.5
5-9	41.1	51.4	63.6
10-14	46.8	47.0	61.3
15-19	61.3	36.1	62.6
≥20	64.3	31.8	66.7
IDDM, age ≥18 years			
0-14	100.0	2.3	70.0
≥15	100.0	1.2	73.7
NIDDM, age ≥18 years			
0-4	22.2	64.2	64.0
5-9	38.5	53.5	62.9
10-14	44.3	49.2	62.0
15-19	57.7	39.5	62.2
≥20	58.3	36.9	64.9
NIDDM, age 18-44 years			
<5	24.7	44.9	57.6
5-9	64.7	29.2	56.1
≥10	65.9	14.7	59.2
NIDDM, age 45-64 years			
<5	24.2	62.8	66.3
5-9	41.4	56.9	61.2
10-14	47.8	46.4	62.7
15-19	63.5	32.2	59.2
≥20	64.0	30.1	55.3
NIDDM, age ≥65 years			
<5	18.5	75.1	64.3
5-9	27.5	57.6	66.7
10-14	39.7	55.2	62.8
15-19	50.6	51.2	65.8
≥20	53.8	42.1	69.4

Data on following a diet are the percent of persons who answered that they had been given a diet for their diabetes and that they were now following this diet all or most of the time.

Source: 1989 National Health Interview Survey

Appendix 25.3

Percent of Diabetic Subjects Using Insulin and Oral Hypoglycemic Agents, U.S., 1964-89

Date and age (years)	Insulin	Oral agents	Diet
1964-65			
Age 25-44	30	31	
45-54	25	49	
55-64	21	56	
65-74	23	53	
≥75	21	55	
All ages	28	48	
1976			
Age 20-39	31	15	
40-59	23	36	
≥60	18	50	
All ages	22	40	
1978-79			
Age <30	51	11	
31-40	36	20	
41-50	23	28	
51-60	25	39	
61-70	21	44	
>70	22	47	
1976-80			
Age 12-34	46	7	35
35-44	47	15	46
45-54	22	34	48
55-64	21	39	53
65-74	24	47	48
All ages	26	35	48
1989			
Age ≥18	43	49	64
18-34	75	6	66
35-44	54	37	59
45-54	42	48	57
55-64	44	51	66
65-74	37	57	65
≥75	33	56	68

Source: Data for 1964-65, 1976, and 1989 are from the National Health Interview Surveys; for 1976-80 are from the Second National Health and Nutrition Examination Survey; and for 1978-79 are from U.S. Public Health Service outpatient clinics (Reference 11)

Appendix 25.2

Number of Diabetic Subjects and Percent Using Diabetes Therapies, U.S., 1960-91

Year:	1960-62	1964-65	1970	1976	1976-80	1978-79	1980	1979-81	1989	1991
Ref.:	6	7	10	8	9	11	12	13	2	14
No. with diabetes (millions)	1.9	2.3	3.6	5.0	5.2	5.1	5.5	5.4	6.5	7.2
Percent using										
Insulin	33	28	24	22	26	26	26	37	43	45
Oral agents	43	48	24	40	35	35	27	40	49	40
Diet				53	48		51		64	

Data for prevalence of diabetes for all years and for diabetes therapy for 1960-62, 1964-65, 1976, and 1989 are from the National Health Interview Surveys; 1970 data are from the Rochester, MN population of diabetic patients; 1976-80 data are based on the Second National Health and Nutrition Examination Survey; 1978-79 data are based on pharmaceutical information from the outpatient population of U.S. Public Health Service clinics; 1980 data are from a survey of diabetic patients conducted by the Michigan State Health Department; 1979-81 data are from the southern Wisconsin population of diabetic patients; and 1991 data are from a study of diabetic patients in eight Michigan communities.

Source: References are listed within the table