Chapter 1

Summary

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DESCRIPTIVE EPIDEMIOLOGY

CLASSIFICATION AND DIAGNOSTIC CRITERIA

Diabetes mellitus comprises a heterogeneous group of disorders characterized by high blood glucose levels. Four major types of diabetes have been defined: insulin-dependent diabetes mellitus (IDDM), non-insulin-dependent diabetes mellitus (NIDDM), gestational diabetes mellitus (GDM), and diabetes secondary to other conditions. IDDM characteristically presents with prominent diabetes symptoms and extreme hyperglycemia. NIDDM can be diagnosed by the presence of the classical signs and symptoms of diabetes together with unequivocally elevated blood glucose levels; by fasting plasma glucose (FPG) ≥140 mg/dl; or by venous plasma glucose ≥200 mg/dl at 2 hours after a 75-g oral glucose challenge. Criteria for GDM vary but require an oral glucose challenge and measurement of post-load plasma glucose.

PREVALENCE AND INCIDENCE

Based on the National Health Interview Survey (NHIS), there were ~7.8 million diagnosed cases of diabetes in the United States in 1993. The rate for all ages of 3.1% in 1993 was more than three times the prevalence of 0.93% in 1958. The number of people with diagnosed diabetes increased fivefold between 1958 and 1993. In the 1989 NHIS diabetes supplement, ~43% of people with diagnosed diabetes were treated with insulin. IDDM with onset at age <30 years comprised ~7% of all diagnosed cases. Most of the remainder can be considered to be NIDDM, although some studies indicate that ~7% of insulin-treated cases with onset at age ≥30 years may be IDDM. Diabetes associated with or secondary to other conditions occurs in ~1%-2% of all disorders comprising the syndrome of diabetes. In addition to the diagnosed cases, there are probably ~7 million undiagnosed cases of NIDDM in the United States, based on oral glucose tolerance tests (OGTTs) in representative samples of people without diagnosed diabetes. GDM occurs in ~3%-5% of all pregnancies. Impaired glucose tolerance (IGT) is a class that encompasses people whose OGTT values are intermediate between normal and diabetic; ~11% of adults had IGT when tested by oral glucose challenge in the 1976-80 Second National Health and Nutrition Examination Survey (NHANES II).

Insulin-Dependent Diabetes

The prevalence of IDDM with onset at age <30 years in the United States is estimated to be ~120,000 individuals age <20 years and ~300,000-500,000 individuals of all ages. There may also be ~500,000 adults who have adult-onset IDDM (onset at age ≥30 years). The incidence of IDDM is ~30,000 new cases each year. There are considerable racial and ethnic differences in IDDM incidence in children. For example, the annual incidence per 100,000 was 8.8 for Hispanics in Colorado, 12.1 for African Americans in Alabama, and 17.3 for whites in Pennsylvania. Some countries in Europe show an increasing IDDM incidence over time. In the United States, incidence has been stable over the past several decades, except for rapid rises during certain years which may be suggestive of epidemics.

Non-Insulin-Dependent Diabetes

Of the ~7.8 million people in the United States who had diagnosed diabetes in 1993, ~90%-95% appeared to have NIDDM. Prevalence rates were 1.3% at age 18-44 years, 6.2% at age 45-64 years, and 10.4% at age ≥65 years. In addition to the known cases of diagnosed NIDDM, there is about one undiagnosed case of NIDDM for every diagnosed case, based on oral glucose tolerance testing in NHANES II. Thus, the total prevalence of NIDDM is estimated to be twice that of diagnosed diabetes. When IGT is also considered, rates of total glucose intolerance may range from ~9% at age 20-44 years to ~42% at age 65-74 years. NIDDM prevalence rates are similar for men and women in the United States, but diabetes is more common in blacks, Mexican Americans, Japanese Americans, and Native Americans than in non-Hispanic whites. From the NHIS, it is estimated that ~625,000 new cases of diabetes are diagnosed annually in the United States.

Secondary and Other Types of Diabetes

These conditions include diabetes and glucose intolerance that develop in association with disorders or factors such as pancreatic diseases, endocrinopathies, many genetic syndromes, and the diabetogenic effects of drugs, chemical agents, and toxins. The prevalence is ~1%-2% of all diabetes. Studies on the genetics of diabetes have defined a specific genetic basis for diabetes in some families. Although all mutations identified thus far account for only a small fraction of the diabetic population, further genetic studies should provide an increasingly scientific basis for the heterogeneity of diabetes.

SCREENING FOR NIDDM

Based on the National Ambulatory Medical Care Survey (NAMCS), blood glucose tests were ordered or performed in 23.5 million visits of patients without diabetes to office-based physicians in 1985, and urine glucose tests in 55.3 million visits. These tests were presumably used in screening for hyperglycemia and glycosuria. NAMCS data from 1989-90 indicate that ~3.2 million OGTTs were performed annually during patient visits to office-based physicians. Virtually all people with NIDDM in the 1989 NHIS stated that they had a blood test at diagnosis of diabetes, with 38% indicating an OGTT had been performed.

About 31% of adults without diagnosed diabetes in the 1989 NHIS reported they had been screened for diabetes in the previous year. Screening is most appropriately carried out in groups at high risk for NIDDM. Major risk factors for NIDDM include older age; obesity; family history of diabetes; race/ethnicity of black, Hispanic, and American Indian; and presence of complications related to diabetes. In the 1989 NHIS, 78% of nondiabetic adults in the United States had at least one of these risk factors and 23% had three or more; 39% of people with three risk factors or complications, and 57% of people with four or more, reported being screened for diabetes in the previous year.

Detection of undiagnosed NIDDM can be conducted by an oral glucose challenge or by measurement of FPG, although only ~25% of adults with undiagnosed NIDDM in NHANES II had fasting hyperglycemia (≥140 mg/dl). Based on NHANES II, if a 75-g oral glucose challenge were used to screen for undiagnosed NIDDM in the U.S. population, the yield of positive screenees (2-hour glucose ≥200 mg/dl) would be 9% when people age ≥40 years who have a percent desirable weight (PDW) ≥120 are screened. This would detect 67% of all U.S. adults with undiagnosed NIDDM. The yield could be increased to 25% if people age ≥40 years with PDW ≥140 and a family history of diabetes were screened. This would detect only 25% of all cases of undiagnosed NIDDM, but only 6% of adults in the United States would have to be administered the oral glucose challenge. The cost effectiveness and long-range benefit to the patient of such screening strategies remain to be defined.

CHARACTERISTICS OF PERSONS WITH NIDDM

Sociodemographic Characteristics

Based on the 1989 NHIS, 58% of people with NIDDM are women, 70% are non-Hispanic white, 20% are black, 5% are Mexican American, and 5% are of other race/ethnicity. Median age is 64 years, and 58% are age ≥60 years. Mean age at diagnosis of NIDDM is 51 years, and 27% have duration of diabetes ≥15 years. Mean age at diagnosis is oldest in whites (52 years), intermediate in blacks (49 years), and youngest in Mexican Americans (45 years). Mean age at diagnosis does not differ by sex.

Persons with NIDDM most frequently (72%) live in or just outside a city. Most (61%) persons with NIDDM are married. About 24%, including 35% of those age ≥65 years, live alone. Even after accounting for their older age, persons with NIDDM have less education and lower income levels than nondiabetic adults. The proportion of adults who have completed at least some college education is 21% for NIDDM and 40% for nondiabetic persons. The proportion in 1989 with family income ≥$40,000 was 16% for NIDDM and 33% for nondiabetic persons; the proportion with family income <$10,000 was 28% and 13%, respectively. Likewise, at every age, persons with NIDDM are less likely to be employed. For example, at age 45-64 years, whereas 68% of nondiabetic adults were employed in 1989, 51% of persons with NIDDM were not in the labor force.

Physical and Metabolic Characteristics

Mean FPG values in patients with diagnosed NIDDM vary widely in community-based studies. Mean FPG was 141 mg/dl for an upper middle-class group of white diabetic patients in Rancho Bernardo, CA, 182-198 mg/dl in Hispanics in San Luis Valley, CO and San Antonio, TX, and 197-243 mg/dl in three groups of Native Americans, whereas mean FPG was only 91 mg/dl in persons with normal glucose tolerance in a U.S. population sample in NHANES II. Large differences also occurred for 2-hour post-challenge plasma

glucose levels in diagnosed NIDDM, ranging from 235 mg/dl in Rancho Bernardo to 336-360 mg/dl in Japanese Americans in Seattle, WA, and 247-356 mg/dl in the three Native American groups. These values were substantially greater than the mean post-challenge value of 97 mg/dl for adults with normal glucose tolerance in NHANES II.

In NHANES II, the frequency of obesity (body mass index (BMI) ≥30) for those age 40-64 years with NIDDM was higher in white women (53%) than white or black men (21%) and was markedly high in black women (65%). The proportion of NIDDM subjects with BMI ≥30 was also high in most community-based studies, ranging from 19%-53% for white women, 19%-36% for white men, 47%-59% for Mexican-American women, 32%-42% for Mexican-American men, 61%-71% for Native American women, and 48%-65% for Native American men. Obesity was lower only in Japanese American NIDDM subjects; BMI ≥30 was found in only 18% of women and 6% of men. Central obesity was more evident in persons with NIDDM compared with nondiabetic persons, as measured by subscapular-to-triceps skinfold ratios of 1.7 versus 1.5 for men and 1.0 versus 0.8 for women in NHANES II.

The prevalence of hypertension (≥160/95 mmHg or using antihypertensive medication) in persons age 45-64 years in NHANES II was 50% for diagnosed NIDDM versus 23% for those with normal glucose tolerance. Only ~12% of the hypertension in NIDDM was undiagnosed, but 37% of the known hypertension was uncontrolled. Among persons with NIDDM who had physician-diagnosed hypertension in the 1989 NHIS, 76% said they were taking antihypertensive medication, 87% were restricting salt intake, 58% were engaging in physical exercise, and 70% were trying to lose weight or control their weight. Dyslipidemia was common in persons with NIDDM in NHANES II: 41% had total cholesterol ≥240 mg/dl, 74% had total cholesterol ≥200 mg/dl, 39% had low-density lipoprotein (LDL) cholesterol ≥160 mg/dl, 18% had high-density lipoprotein (HDL) cholesterol <35 mg/dl, and 19% had fasting triglycerides ≥250 mg/dl.

The proportion of subjects in the 1989 NHIS who reported they smoke cigarettes was similar for those with and without diagnosed diabetes (20% and 26%). Based on NHANES II, the proportion who stated they drank any alcohol in the past 3 months was lower for diabetic (47%) than nondiabetic (67%) adults. Participating in regular exercise was reported by 28% of diabetic and 34% of nondiabetic adults in the 1990 NHIS. Among those age 45-64 years in the 1989 NHIS, excellent or very good health status was reported by 58% of nondiabetic adults but by only 18% of subjects with NIDDM.

RISK FACTORS FOR DEVELOPMENT OF DIABETES

Insulin-Dependent Diabetes

Epidemiologic patterns for IDDM suggest that both environmental and genetic factors are involved in its etiology. Concordance for IDDM among identical twins is only ~30%-50%, much less than would be expected for a disease with a strictly genetic basis. More than 80% of IDDM occurs in children with no family history of the disease. However, in families that have a person with IDDM, the risk of IDDM in relatives is much greater than in the general population. For example, the prevalence of IDDM by age 30 years in siblings of IDDM patients is about 3%-6%, whereas IDDM prevalence in the general population is <0.2% at age 20 years. Prevalence in parents of IDDM patients is also about 3%-6%.

The genes that confer susceptibility to IDDM are located in the HLA region of chromosome 6, which contains genes that control immune response. Individuals who have autoantibodies to islet cell antigens (ICA), to insulin, or to glutamic acid decarboxylase (GAD) are at greatest risk for developing IDDM. An increased risk of IDDM occurs in children who are breast fed for a shorter time or are introduced to cow's milk at a younger age; an autoimmune response to cow's milk proteins may mediate the increased risk of IDDM. Viruses have long been invoked as etiologic agents for IDDM, but a mechanism for the association between IDDM and viral infections has not been substantiated. Older age of the mother is a risk factor for IDDM in the child, but children with an IDDM father are more likely to have the disease than children with a IDDM mother (4%-9% versus 1%-4%). Further studies of host and environmental risk factors and their interactions are needed to provide information about the causes of IDDM and approaches to disease prevention.

Non-Insulin-Dependent Diabetes

NIDDM is heterogeneous in its etiology and clinical course, and there is no single cause of the disease. A large number of rare genetic syndromes are associated with development of NIDDM, but these currently account for <1% of all cases. The majority of NIDDM cases are believed to result from a combination of hyperinsulinemia/insulin resistance and β-cell failure, but this major type of diabetes may also be composed

of several distinct etiologic entities. Given the high prevalence of NIDDM and IGT (~45% of those age 65-74 years), it is likely that a large proportion of the U.S. population is at risk for NIDDM.

Risk markers for NIDDM include older age, positive family history of diabetes, minority ethnicity, and lower socioeconomic status. Each of these is probably a reflection of underlying causal factors. Genetic factors play a major causal role in the etiology of NIDDM. The concordance for NIDDM in monozygous twins, although only ~60% in unbiased studies, is still twice the rate for dizygous twins. Numerous studies have investigated the association of NIDDM with specific candidate genes, but the genes that determine NIDDM are yet to be identified.

Many studies support the role of physiologic and lifestyle factors in NIDDM etiology. Such factors include greater total obesity, longer duration of obesity, intraabdominal location of body fat, and physical inactivity. There is little evidence that any specific component of the diet, other than caloric intake, influences susceptibility to NIDDM. The risk for developing NIDDM increases with higher blood glucose values, and the pathogenesis of NIDDM seems to proceed through a stage of abnormal glucose tolerance such as IGT. Metabolic challenges such as gestational diabetes may unmask a prediabetic state.

Even though a number of risk markers and risk factors for NIDDM are known, it remains unknown whether interventions focused on such components as weight loss and increased physical activity can prevent diabetes or reverse the pathology in those already diagnosed with diabetes.

MORTALITY

Insulin-Dependent Diabetes

Mortality rates for IDDM patients are ~5-7 times that of the general U.S. population for males and ~9-12 times for females. In the Pittsburgh, PA Children's Hospital IDDM cohort age 30-34 years, the annual mortality rate was 14.6 per 1,000 for females and 29.6 per 1,000 for males. Life expectancy for patients with IDDM is reduced by ~15 years; >15% of IDDM patients will die by age 40 years. The majority of deaths of people with IDDM occur in middle and late adulthood.

There are marked changes in the cause of death with longer duration of IDDM. In the early years after diagnosis, acute coma is the leading cause of death, while renal disease predominates in the middle years. After 30 years of IDDM, two-thirds of deaths result from cardiovascular disease. In IDDM, as in the general U.S. population, African Americans have a higher mortality rate than whites. Cigarette smoking and hypertension are important predictors of mortality. Metabolic control of diabetes is the strongest predictor of survival in patients with IDDM.

Non-Insulin-Dependent Diabetes

Based on a 1986 study, it is estimated that deaths of persons with NIDDM account for 17.2% of all deaths in the United States for those age ≥25 years. Death rates for people with diabetes in 1986 were 1.0% for those age 25-44 years, 2.8% for age 45-64 years, 5.8% for age 65-74 years, 13.6% for age ≥75 years, and 5.5% for all diabetic persons age ≥25 years. The 1982-84 followup of the 1971-75 NHANES I and a community-based study in southern Wisconsin in 1980-88 also found that ~5%-6% of adults with NIDDM die each year. This rate is twice the rate for adults in the general U.S. population.

In the 1986 study, diabetes was listed on the death certificate in only 38% of deaths of persons with diabetes and was listed as the underlying cause in <10%. Thus the mortality impact of diabetes is greatly underestimated by death certificate data.

The four leading causes of death in persons with NIDDM are diseases of the heart (~50% of deaths), diabetes (13%), malignant neoplasms (13%), and cerebrovascular disease (10%). The risk of heart disease mortality is ~2-4 times higher for NIDDM than for nondiabetic persons. Although persons with NIDDM possess more and higher levels of known risk factors for mortality, this does not fully explain their excess mortality. Among middle-aged populations with NIDDM, life expectancy is reduced by ~5-10 years. Reduction in life expectancy is greater for diabetic women than men and for those with complications, and decreases with increasing age at diagnosis of diabetes.

COMPLICATIONS OF DIABETES

DISABILITY

Disability affects large numbers of people with diabetes in the United States. In the 1989 NHIS, the proportions of diabetic subjects who reported any activity limitation related to an impairment or health problem (50%), being unable to carry on their major activity

(20%), and restricted activity days in the past 2 weeks (22%) were two to three times higher than reported by persons without diabetes.

The largest impact of disability appears to be for the most severe forms of disability, including being unable to work. At every age, persons with NIDDM are less likely to be employed than those without diabetes. For example, at age 45-64 years, whereas 68% of nondiabetic adults were employed in 1989, 51% of persons with NIDDM were not in the labor force. Of those age 45-64 years who were employed in 1989, 10% of NIDDM reported workloss days in the past 2 weeks compared with 5% of nondiabetic subjects.

The consequences of disability are also extensive for IDDM. In the Children's Hospital of Pittsburgh IDDM registry, the proportion of IDDM subjects who had experienced work limitations by age 45 years was 48%. IDDM subjects with disability had higher rates of unemployment than those not disabled (49% versus 12%) and higher rates of absenteeism for those who did work (13.8 days per year versus 3.0 days per year). Persons with IDDM were seven times more likely to report work disability as their nondiabetic siblings (32% versus 5%).

Diabetic persons with disabilities use health care services more frequently than those not limited in activity. In the 1989 NHIS, 32% were hospitalized in the past year versus 13% of those not limited and the length of stay (LOS) in the hospital was longer (14 days versus 9 days). The average number of physician visits was 13.9 per year for persons limited in activity, compared with 6.5 visits per year for those not limited. Limitations in the personal care activities of daily living (ADL) were also more common among diabetic (5%) than nondiabetic (2%) individuals in the 1989 NHIS. Self-reported health status is lower in subjects with diabetes. Among those age 45-64 years in 1989, excellent or very good health status was reported by 58% of nondiabetic adults but by only 18% of subjects with NIDDM.

ACUTE METABOLIC COMPLICATIONS

The acute metabolic complications of diabetes include diabetic ketoacidosis (DKA), hyperosmolar nonketotic coma (HNC), lactic acidosis (LA), and hypoglycemia. The incidence rate for DKA in population-based studies is ~5-8 per 1,000 diabetic persons per year. DKA is more common in young diabetic people, who had rates of 54 per 1,000 persons age <15 years per year in one study and 13 per 1,000 in another study. In contrast, rates at age >30 years were ~2-3 per 1,000 persons per year. About 100,000 hospital discharges were coded to DKA annually in 1989-91, based on the NHDS. The average annual number of hospital discharges listing the other conditions were 10,800 (HNC), 18,800 (acidosis), 4,500 (coma), 13,000 (hypoglycemic coma), and 48,500 (hypoglycemia). Mortality rates in past studies were ~9%-14% for DKA and ~10%-50% for HNC.

VISION DISORDERS

Diabetic retinopathy is the leading cause of new cases of blindness in adults in the United States. Among all new cases of legal blindness in adults, 11% are due to diabetic retinopathy including 12% at age 20-44 years, 19% at age 45-64 years, and 8% at age ≥65 years. Of people who are legally blind, 9% have diabetes as the cause.

In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), about 97% of IDDM, 80% of insulin-treated NIDDM, and 55% of NIDDM not treated with insulin had evidence of retinopathy by 15 years of diabetes. The most severe stage, proliferative diabetic retinopathy, was present in 30% of IDDM, 10%-15% of insulin-treated NIDDM, and 5% of NIDDM not treated with insulin after 15 years of diabetes. The incidence of retinopathy during 4 years in WESDR among those with no retinopathy at baseline was 20%, 15%, and 10%, respectively.

The major risk factor for incidence and progression of diabetic retinopathy is hyperglycemia. Indeed, differences among the three types of diabetes in WESDR were minimal when their level of glycemia was taken into account. For example, the 10-year incidence of proliferative retinopathy was similar (~7%-15%) for those with baseline glycosylated hemoglobin of ~9% and increased linearly for all three types of diabetes to a 10-year incidence of ~35%-45% for those with baseline glycosylated hemoglobin of ~12%.

About 20% of patients with NIDDM have evidence of diabetic retinopathy at diagnosis of diabetes. This is believed to be due to a long (~10 years) preclinical period between onset of NIDDM and its diagnosis, during which time the untreated hyperglycemia is causing retinopathy.

Clinical trials in persons with severe proliferative retinopathy have shown the efficacy of panretinal photocoagulation in reducing the incidence of serious loss of vision by ~50%. In addition, focal photocoagulation can reduce the incidence of doubling of the visual angle by ~50%. The Diabetes Control and Complica-

tions Trial (DCCT) demonstrated that persons with IDDM who had no retinopathy at baseline had a 60% reduction in the progression of retinopathy with intensive insulin treatment compared with conventional insulin treatment. For those who had retinopathy at baseline, intensive insulin treatment was associated with a 54% reduction in progression of retinopathy, a 47% reduction in the incidence of preproliferative or proliferative retinopathy, and a 54% reduction in laser treatment, compared with those with conventional insulin treatment.

Two other complications of diabetes, cataracts and glaucoma, can lead to visual loss. Senile lens changes measured by ophthalmic examination were found in 63% of NIDDM age 50-64 years and 78% of those age 65-74 years in the Framingham Eye Study. Rates of cataract are often ~50% higher in NIDDM than in nondiabetic persons. Prevalence of clinically-determined glaucoma in the Beaver Dam, WI Eye Study increased from 2% of NIDDM age 43-54 years to 13% of those age ≥75 years. After adjusting for age and sex, the risk of glaucoma was 70% higher in people with NIDDM.

Ophthalmic care for people with diabetes may not be adequate to detect vision problems and institute treatment to prevent blindness. Of adults with diabetes in the 1989 NHIS, only 45% had seen an ophthalmologist in the past year and only 49% had had a dilated eye examination within the past year.

NEUROPATHY

Neuropathy is a common complication of IDDM and NIDDM. In population-based studies, 30%-70% of patients were affected, depending on neuropathy criteria. In the Rochester, MN Diabetic Neuropathy Study, the prevalence was 60% for any neuropathy, 47% for distal polyneuropathy, 34% for carpal tunnel syndrome, and 5% for autonomic neuropathy. Most cases of distal polyneuropathy and carpal tunnel syndrome were subclinical or asymptomatic. In the San Luis Valley, CO Diabetes Study, definite neuropathy was found in 28% of Hispanic and Anglo patients with NIDDM, based on history and absent/decreased reflexes and altered vibration perception threshold. The prevalence of distal symmetrical neuropathy increased from 17% at 0-4 years duration of NIDDM to 50% at ≥15 years duration. Neuropathy rates were ~5 times greater in those with NIDDM compared with nondiabetic subjects. Prevalence of symptoms of sensory neuropathy was 38% in NIDDM subjects in the 1989 NHIS versus 10% in those without diabetes. Absent knee/ankle reflexes were found in 13% of subjects with previously diagnosed NIDDM in NHANES II. This was substantially higher than the rate of 5% in subjects with normal glucose tolerance.

In the DCCT, intensive treatment of diabetes with near-normalization of glycemia reduced the 5-year prevalence of neuropathy by 60%-70%, compared with the conventional treatment group.

KIDNEY DISEASES

Diabetes accounts for ~35% of all new cases of end-stage renal disease (ESRD) in the United States and is the leading cause of new ESRD. Persons with diabetes comprise the fastest growing group of renal dialysis and transplant recipients. In 1991, 48,274 persons with diabetes were receiving renal replacement therapy and there were 17,888 new cases of diabetic ESRD. There were also 11,361 deaths among diabetic ESRD patients in that year. The annual cost for treatment of diabetic ESRD exceeds $2 billion, not including the costs associated with reduced productivity and unemployment.

A large proportion of persons with diabetes have elevated urinary albumin excretion, with ~20%-30% having microalbuminuria and ~20%-30% having macroalbuminuria. In IDDM, the incidence of persistent proteinuria rises during the first 10 years of diabetes and reaches ~25% after ~15 years of diabetes. In NIDDM, ~10% have macroalbuminuria within 5 years of diagnosis and prevalence reaches 25% at 20 years after diagnosis. Clinical proteinuria in IDDM heralds a relentless decline of renal function that often leads to ESRD. Of IDDM patients at the Joslin Clinic in Boston, MA, 50% developed chronic renal failure after 10 years of persistant proteinuria. In NIDDM subjects in Rochester, MN, the proportion was 11%. There has been a secular decline since ~1960 in the incidence of proteinuria in IDDM, possibly due to improved control of hyperglycemia, but a similar decline in NIDDM has not been reported. The presence of microalbuminuria in IDDM is associated with a nearly threefold increased risk of death from cardiovascular disease, and survival in patients with NIDDM and microalbuminuria is also substantially reduced. In Pima Indians with NIDDM, an excess risk of death was found in diabetic patients with proteinuria but not in those without proteinuria.

Diabetic ESRD is four times more common in blacks than in whites among patients with NIDDM, but the risk in IDDM is the same for blacks and whites. Hyperglycemia is the major risk factor for proteinuria. Other factors associated with development of diabetic

nephropathy include longer diabetes duration, hypertension, and cigarette smoking. Diabetic renal disease is more common in some families than in others, suggesting that there is a genetic component to renal disease. Increased plasma prorenin activity, lipoprotein abnormalities, autonomic neuropathy, pregnancy, a high-protein diet, and drug nephrotoxicity have been implicated as risk factors in some studies.

Control of blood glucose can reduce the rate of progression of renal disease in diabetes. In the DCCT, intensive insulin therapy was associated with a 39% reduced risk of microalbuminuria and a 54% reduced risk of macroalbuminuria. Control of blood pressure also decreases the rate of progression of renal disease, and angiotensin converting enzyme (ACE) inhibitors may be renoprotective independent of their effects on blood pressure. Several studies suggest that reduction of dietary protein may lower the rate of progression of renal disease. Most studies of risk factors have been conducted in IDDM, and little is known about the effectiveness of these treatment modalities in NIDDM.

Other renal diseases that occur with greater frequency in diabetic patients include asymptomatic bacteriuria, pyelonephritis, papillary necrosis, and radiocontrast-induced renal failure.

PERIPHERAL VASCULAR DISEASE

Lower extremity arterial disease (LEAD) is identified clinically by intermittent claudication and/or absence of peripheral pulses in the lower legs and feet, representing decreased arterial perfusion of the extremity. In population-based studies, pulse deficits were found in ~10% of diabetic subjects, absent foot pulses in ~20%-30%, and intermittent claudication in ~9%. Prevalence of pulse deficits in subjects with NIDDM in NHANES II was about twice that of subjects with normal glucose tolerance.

The incidence of LEAD in diabetic subjects without LEAD at baseline in the Rochester, MN population was ~10 times that of nondiabetic subjects (25.1 per 1,000 person-years versus 2.6 per 1,000). The incidence increases with older age, longer duration of diabetes, and the presence of hypertension, cigarette smoking, and dyslipidemia. LEAD in diabetes is also compounded by the presence of peripheral neuropathy and susceptibility to infection. These factors contribute to progression of LEAD to ulcerations of the feet, gangrene, and ultimately to amputation of the extremity.

Mortality is increased in patients with LEAD. In the Rochester, MN and Framingham, MA studies, mortality rates for diabetic patients with LEAD were two to three times greater than mortality in the general population.

LOWER EXTREMITY FOOT ULCERS AND AMPUTATIONS

Lower extremity ulcers and amputations are an increasing problem among individuals with diabetes. The annual incidence of foot ulcers in community-based studies was 2%-3%, and prevalence was 4%-10%. In the 1983-90 NHDS, 6% of hospital discharge records that listed diabetes also listed a lower extremity ulcer condition, and chronic ulcers were present on 2.7%. The average length of stay for diabetes discharges with ulcer conditions was 59% longer than for diabetes discharges without them. Clinical epidemiologic studies suggest that foot ulcers precede ~85% of nontraumatic lower extremity amputations in individuals with diabetes.

The incidence of amputation in patients with diabetes is ~0.4%-0.8% per year. About half of amputations in the United States occur in people with diabetes. NHDS data indicate there were an annual average of ~54,000 hospital discharges listing diabetes and a nontraumatic lower extremity amputation in 1989-92. Lower level amputations (toe, foot, and ankle) comprised 55%. Hospital discharge data indicate that 9%-20% of amputees experienced a second amputation within 12 months. By 5 years after an initial amputation, 28%-51% had undergone a second amputation. Perioperative mortality among diabetic amputees averaged 5.8% in the 1989-92 NHDS. Five-year mortality following amputation was 39%-68% in other studies.

Risk factors for amputation include hyperglycemia, longer duration of diabetes, older age, and the presence of neuropathy, peripheral vascular disease, and foot ulcers. Several studies have demonstrated the beneficial effect of patient education on reducing the rate of lower extremity amputations. A randomized trial showed that interventions at the patient and health care provider levels were effective in preventing serious foot lesions. Several amputation prevention programs have reported striking differences in amputation frequency after instituting comprehensive foot care programs.

HEART DISEASE

In contrast to nondiabetic subjects, heart disease in

diabetes appears earlier in life, affects women almost as often as men, and is more often fatal. The most common cause of death in adults with diabetes is coronary heart disease, and ~50% of deaths of people with diabetes are due to ischemic heart disease.

In community-based studies in which both history and electrocardiograph (ECG) evidence were used to measure heart disease in subjects with diabetes, prevalence of coronary heart disease was 42% in white men and women in Rancho Bernardo, CA; 37% in men and 51% in women among non-Hispanic whites and 30% in men and 45% in women among Hispanics in San Luis Valley, CO; and 41% in men and 37% in women among Japanese Americans in Seattle, WA. These rates were substantially greater than in persons with normal glucose tolerance.

The excess risk of heart disease in diabetic versus nondiabetic subjects has been found in numerous community-based studies. The risk ratio for incident coronary heart disease in diabetic versus nondiabetic subjects was 2.3 for men and 2.9 for women in the Framingham Study; 1.7 for men in the Honolulu Heart Study; 3.1 for women in the Nurses' Health Study; and 1.8 for men and 3.2 for women in a New Haven, CT study. Elevated mortality from coronary heart disease has also been found for diabetic versus nondiabetic subjects. Mortality risk ratios for men varied from 1.5 to 3.8 in community studies; for women the ratios varied from 2.6 to 4.7. The only data based on a U.S. population sample come from a 9-year mortality study of the 1971-75 NHANES I, in which the age-adjusted death rate per 1,000 person-years was 28.4 for diabetic men and 10.2 for nondiabetic men age 40-77 years at baseline, and 10.5 and 4.1 for diabetic and nondiabetic women, respectively. Diabetic subjects have a poorer prognosis after a myocardial infarction than subjects without diabetes. The risk ratios for reinfarction in community studies were 1.4-3.1; risk ratios for death were often 1.5-3.0.

The excess risk of heart disease may be greater for IDDM than NIDDM. For example, in the Nurses Health Study the age-adjusted risk ratio for mortality from coronary heart disease in diabetic versus nondiabetic women was 6.7 for NIDDM but was 12.2 for IDDM.

Adults with diabetes are more likely than those without diabetes to have hypertension and dyslipidemia, but some of the increased risk of heart disease associated with diabetes appears to be independent of these factors. Endogenous and exogenous insulin and lack of glycemic control may act as cardiovascular disease risk factors, but the data are inconsistent.

STROKE

In the 1989 NHIS, 9% of adults with diabetes reported that they had had a stroke. Rates increased from 2% at age 18-44 years to 13% at age ≥65 years. In the 1989-91 NHDS, 11% of all diabetes hospital discharges listed stroke, and 20% of all stroke discharges listed diabetes. In the 10-year followup of the 1971-75 NHANES I, there was a 2.5-fold higher risk of stroke in diabetic versus nondiabetic subjects; this risk ratio was similar for blacks and whites. The risk of fatal and nonfatal stroke was also higher for diabetic subjects in Rancho Bernardo, CA than for nondiabetic subjects, with risk ratios of ~1.5 for men and ~2.0 for women. The relative risk of stroke for women in the Nurses Health Study was 4.1 and for men in the Honolulu Heart Program was 1.9.

Elevated blood pressure is the major risk factor for stroke; other risk factors include cigarette smoking and high LDL cholesterol. Prevention of stroke is feasible by identification and treatment of these risk factors, but it is unknown whether reduction of blood glucose levels will reduce the risk of stroke in persons with diabetes.

DIGESTIVE DISEASES

Based on 1989 NHIS and 1976-80 NHANES II data on self-reported diabetes and digestive diseases, diabetic subjects are more likely than the general U.S. population to report a number of digestive conditions, including ulcers, diverticulitis, symptoms of irritable bowel syndrome, abdominal pain, constipation, diarrhea, and gallstones. NHDS data from 1987-91 suggest that diabetic patients may also be more prone than the general population to hospitalizations for gastrointestinal infections, cancers of the liver and pancreas, gastritis and other stomach disorders, intestinal impaction, liver disease, pancreatitis, and hematemesis. Based on the 1987-91 NHDS, there were an annual average of ~2.5 million hospital discharge records that listed diabetes, and 32% of those also listed at least one digestive diagnosis.

In studies based on clinic and community populations, it is difficult to demonstrate that people with diabetes are at much higher risk of digestive conditions than the general population, despite well-characterized syndromes such as diabetic gastropathy and diabetic diarrhea. These studies suggest that diabetic subjects are more likely than the general population to have constipation and increased risk of liver disease and gallstones. Patients with IDDM have an increased risk of celiac disease, and those with NIDDM have an

increased risk of pancreatic cancer. The risk of developing diabetes is markedly increased by diseases of the exocrine pancreas, particularly pancreatic cancer and chronic pancreatitis, and may also be increased by chronic liver disease.

INFECTIONS

Studies in clinic, community, and hospital populations indicate that diabetic subjects probably have a higher risk of some infections, including asymptomatic bacteriuria, lower extremity infections, reactivation tuberculosis in American Indians, infections in surgical wounds after sternotomy and total hip replacement, and group B streptococcal infection. Population-based data support a probable higher mortality from influenza and pneumonia. There is a possible association of diabetes with other infections, but appropriate studies have not been conducted.

In 12 studies of outpatients, prevalence of bacteriuria was 9%-27% in diabetic women versus 3%-19% in nondiabetic women; prevalence was 1%-11% in diabetic men versus 0%-4% in nondiabetic men. Nine of the 12 studies reported a two- to fourfold higher bacteriuria prevalence in diabetic subjects. In the 1989 NHIS, 23% of diabetic women reported having ≥1 urinary tract infections in the past year versus 13% of women without diabetes; this differential occurred for all age groups ≥18 years. At least 60% of diabetic amputations are preceded by an infected foot ulcer. Osteomyelitis of the ankle or foot is listed on hospital discharge records with diabetes 12 times as frequently as on records without diabetes, and cellulitis of the toe is listed 14 times as frequently. Local and systemic immunologic defects and autonomic and sensory neuropathy probably contribute to the increased propensity to infections.

ORAL COMPLICATIONS

Studies during the past 40 years have found that periodontal disease is more severe and occurs with higher frequency in diabetic patients. In one study, the prevalence of periodontal disease in IDDM patients was 9.8% compared with 1.7% in people without diabetes. The rate in the IDDM patients increased from 0% at age ≤10 years to 30% at age ≥19 years. Prevalence of gingivitis was ~70% of those age <19 years and ~98% of those age ≥19 years. Periodontal attachment loss was ~50% greater in IDDM patients with retinopathy compared with nondiabetic patients, but was not elevated in IDDM patients without retinopathy. These and other data indicate that poor glycemic control increases the extent and severity of periodontal disease in IDDM.

Few studies have dealt with NIDDM. In Pima Indians, attachment loss and alveolar bone loss was more extensive than in nondiabetic Pimas. Toothlessness was 15 times more frequent in the diabetic than the nondiabetic group, and the incidence of periodontal disease was 2.6 times higher. Reasons for the greater occurrence of periodontal destruction in diabetes are not clear. Studies of the periodontal flora find similar microorganisms in diabetic and nondiabetic individuals, suggesting that alteration in the patient's responses to periodontal pathogens may account for the differences in periodontal destruction.

PSYCHOSOCIAL ASPECTS OF DIABETES

In studies that used structured diagnostic interviews, the mean prevalence of current depression in diabetic adults was ~14%. In investigations that used depression symptom scales, the mean prevalence of clinically significant depression symptomatology in diabetic subjects was ~32%. These rates are substantially greater than prevalence in the general U.S. population. However, whether depression is more common in diabetes than in other chronic diseases is less clear.

Significant associations between depression and severity of diabetes were found in a minority of measurements. The presence of diabetes complications alone may not result in depression unless severe functional limitations such as blindness, impotence, and cognitive impairment are also present. Depression was found to be highly correlated with reported diabetes symptoms, but both physiological and psychological factors may contribute to diabetes symptoms. Findings on the relationship between stress and glucose regulation in diabetes have been inconsistent.

The efficacy of psychotropic medication for psychiatric disorders in diabetic populations is largely unknown. These agents may have side effects that can limit their use in persons with diabetes, and psychotherapy may have a prominent place in the diabetes treatment armamentarium.

MEDICAL CARE FOR DIABETES

THERAPY

The most recent information about therapy used by adults with diabetes in the United States is available

from the 1989 NHIS diabetes supplement. For all adults, ~43% were treated with insulin and ~49% were treated with oral agents. About 2% of IDDM and 10% of insulin-treated NIDDM reported they were using oral agents in addition to insulin. The proportion of NIDDM treated with insulin increased from 22% at 0-4 years duration of diabetes to 58% at ≥20 years duration. Concomitantly, the proportion treated with oral agents declined from 64% at 0-4 years duration to 37% at ≥20 years duration. For both IDDM and insulin-treated NIDDM, the average insulin dose was ~50 units per day. Two or more insulin injections daily were taken by 61% of IDDM and 48% of insulin-treated NIDDM; use of an insulin pump was rare.

About 64% of subjects in the 1989 NHIS reported they were following a diet for their diabetes, but 90% believed that diet is important in control of their diabetes. A variety of situations were problematic in maintaining their diet, most notably the desire to eat foods that are not on the diabetes diet. Two important situations were not issues: lack of support from family and friends, and being unsure about what foods they should eat.

Patient education can translate to increased self-management skills, but only 35% of people with diabetes in the 1989 NHIS had ever attended a diabetes educational class or course. About 40% of IDDM and 26% of insulin-treated NIDDM reported they self-test their blood glucose at least once per day, but this proportion was only 5% for NIDDM not treated with insulin.

AMBULATORY MEDICAL CARE

Based on the 1990 NHIS, persons with diabetes in the United States had ~96 million outpatient medical care contacts, including 53 million visits to physician's offices, 14 million visits to outpatient clinics, 1.6 million visits to emergency rooms, 11 million telephone contacts, and 16 million visits to other ambulatory care settings. For all ages, there was an average of 15.5 contacts with physicians for ambulatory care per person with diabetes in 1990, compared with 5.5 contacts per person in the general U.S. population. Rates were two to three times higher for diabetic subjects in all age groups. The number of physician contacts for ambulatory care per person with diabetes was 22.6 at age <25 years, 10.9 at age 25-44 years, 16.2 at age 45-64 years, and 16.1 at age ≥65 years. The annual number of physician contacts was higher for diabetic females (17.6) than for diabetic males (12.8).

In the 1989 NHIS, 91% of persons with diabetes stated they have one physician whom they see for regular care of their diabetes; of these, 65% saw this physician four or more times each year. In the 1990-91 NAMCS, most visits for diabetes to office-based physicians were made to general and family practitioners (34%) and internists (37%). Only 8% of visits were made to diabetologists or endocrinologists; the remaining 21% were visits to a variety of other surgical and medical specialists. Diabetic subjects in the 1989 NHIS were asked about visits to certain physician specialists in the previous year: 23% had seen a cardiologist, 45% had seen an ophthalmologist, and 15% of women had seen an obstetrician/gynecologist. In addition, 17% had seen a podiatrist and 20% had seen a dietitian or nutritionist.

Based on the 1990 NAMCS, the mean duration of an office visit for diabetes was 17.4 minutes, and 68% of visits were ≤15 minutes. Medicare was a source of payment for 46% of office visits, Medicaid for 10%, commercial insurance for 26%, and in 30% the patient had out-of-pocket expenses.

HOSPITALIZATIONS

Based on the NHDS, there were ~2.8 million hospitalizations in 1990 that listed diabetes as one of the discharge diagnoses. However, in only ~60% of hospitalizations of people with diabetes is diabetes listed on the hospital discharge record. Of discharges in which diabetes was listed in 1990, diabetes was the primary diagnosis in only 15%. Thus NHDS data can seriously underestimate the extent of hospitalizations of people with diabetes.

In the 1989 NHIS, 24% of adults with diabetes reported they were hospitalized at least once in the previous year; 8% reported two or more hospitalizations. Hospitalization rates were three times higher than persons without diabetes. There were few differences by gender or by race in the proportion hospitalized. Having complications of diabetes was clearly associated with hospitalization. The proportion of diabetic adults who were hospitalized at least once in the past year increased from 12% for persons reporting no complications to 34% for persons reporting ≥3 complications. Average length of stay per hospitalization was ~8 days in both NHIS and NHDS data.

LONG-TERM CARE

Based on the 1987 National Medical Expenditure Survey (NMES), ~18% of all nursing home residents age ≥55 years were known to have diabetes (389,000 persons), compared with 13% of the general population.

Persons age ≥55 years with diabetes were twice as likely as nondiabetic persons to reside in a nursing facility (6.1% versus 3.9%). The proportion of nursing facility residents who were known to have diabetes doubled between 1964 and 1987.

About 70% of diabetic nursing home residents in 1987 were women, 32% were age ≥85 years, and 79% had incomes <$10,000. More than 80% had cardiovascular disease, 56% had hypertension, 39% had senile dementia, and 69% had two or more chronic conditions in addition to their diabetes. About 24% had impaired hearing, 33% had impaired vision, and 6% were blind. Almost all were limited in their ability to perform the activities of daily living (ADL). Diabetic residents of nursing facilities in 1987 were in the facility for a median of 243 days; only 8% were discharged back into the community. Of expenditures for care of diabetic residents in 1987, 54% was covered by Medicaid and 40% by the residents or their families; <4% of residents had any care covered by private health insurance.

Home health care agencies serve as an increasingly important source of formal long-term care. In a 1992 survey, ~1.2 million persons were enrolled in home health care programs, of whom >8% were believed to have diabetes. The number of Americans who will need long-term care is increasing due to an increase in life expectancy and the large number of Americans who are moving into older age groups. When this demographic shift is coupled with the increasing prevalence rates for diabetes in older persons, nursing facility care will be required for an even greater number of people with diabetes.

ECONOMIC ASPECTS OF DIABETES

HEALTH INSURANCE

Among all adults with diabetes, 92% have some form of health insurance, including 87% of those age 18-64 years and 99% of those age ≥65 years, according to data from the 1989 NHIS. Based on 1993 prevalence of diabetes, ~640,000 people with diabetes do not have any form of health care coverage. Among diabetic persons age 18-64 years, 10% were covered by Medicare, 69% by private health insurance, 6% through military benefits, and 14% through Medicaid or other public assistance programs in 1989. Among those age ≥65 years, 95% were covered by Medicare, 69% by private health insurance, 5% through military benefits, and 15% through Medicaid or other public assistance programs. Government-funded programs were responsible for health care coverage for 57% of adults with diabetes, including 26% of those age 18-64 years and 96% of those age ≥65 years.

Virtually all diabetic patients covered by Medicare or private health insurance had coverage for hospital care and physician/surgeon bills in 1989. Coverage for prescription medicines occurred for 62.9% of adults with diabetes. There were only small differences between people with diabetes and those without diabetes in the proportion covered and the types of health care coverage. The costs of private health insurance were also similar for people with and without diabetes in studies in 1977 and 1987.

ECONOMIC IMPACT

Substantial costs to society and its citizens are incurred for direct costs of medical care for diabetes and for indirect costs including lost productivity resulting from diabetes-related morbidity and premature mortality. Economic analyses performed in the 1980s suggested that the economic costs associated with diabetes in the United States were between $14 and $20 billion in 1980s-era dollars, including an estimated $7.4-$11.6 billion for direct medical care expenditures and another $6.3-$10.8 billion for lost productivity. A more recent study estimated $91.8 billion for the cost of diabetes in 1992, including $45.2 billion direct costs and $46.4 billion indirect costs. Another study found that the direct costs of all medical care for people with diabetes was $85.7 billion in 1992.

Medical costs for persons with diabetes are higher because they visit physician's offices, hospital outpatient departments, and emergency rooms more frequently than their nondiabetic counterparts and are more likely to be admitted to the hospital and to nursing homes. Americans with diabetes have two to five times higher per capita total medical expenditures and per capita out-of-pocket expenses than people without diabetes. These expenses and their associated loss of productivity impact not only diabetic patients and their families, but federal and state governments and society as a whole.

DIABETES IN SPECIAL POPULATIONS

AFRICAN AMERICANS

Among U.S. black children age <15 years, estimates of IDDM incidence from population registries range from 3.3 to 11.8 per 100,000 per year. Rates for white

children are nearly twice as high, ranging from 13.8 to 16.9 per 100,000 per year. In contrast, prevalence of diabetes in adults is 1.4 to 2.3 times more frequent in blacks than whites. Based on the 1993 NHIS, the prevalence of known, physician-diagnosed diabetes among African Americans is 3.7%, rising from 1.3% at age 0-45 years to 17.4% at age 65-74 years. The rate of diagnosed diabetes in blacks has tripled during the past 30 years, and ~1.3 million African Americans have been diagnosed as having diabetes. In addition, approximately half of black adults who meet diagnostic criteria for NIDDM are undiagnosed. Data on the frequency of diabetes complications in African Americans are limited but suggest that this population experiences considerable morbidity and excess frequency of many diabetic complications.

HISPANIC AMERICANS

Most of the information on diabetes in Hispanic Americans comes from community studies in Texas and Colorado and the 1982-84 Hispanic Health and Nutrition Examination Survey (HHANES). These studies have clearly established that the prevalence of NIDDM is two to three times higher in Mexican Americans than in non-Hispanic whites. In the HHANES, diabetes prevalence in persons age 45-74 years was 24% in Mexican Americans; 26% in Puerto Ricans in the Miami, FL area; and 16% in Cuban Americans in the New York City area. In all groups, much of NIDDM was undiagnosed.

Risk factors for NIDDM in Hispanic Americans are similar to those in non-Hispanics and include obesity, unfavorable distribution of body fat, physical inactivity, and hyperinsulinemia. These abnormalities are more common in Hispanics. NIDDM prevalence in Mexican Americans in San Antonio, TX tended to be inversely related to socioeconomic status and degree of acculturation to mainstream U.S. society. For example, diabetes rates at age 25-64 years were 6.5% for those in the suburbs, 12.6% in the transitional neighborhood, and 14% in the barrio. There is a strong association between the percentage of Native American genetic admixture and the prevalence of diabetes in Hispanic populations, and this may explain some of the differences in diabetes rates.

In contrast to NIDDM, registry data indicate that the incidence of IDDM is lower in Hispanics than non-Hispanic whites. In Colorado, annual incidence in 1978-88 was 7-10 per 100,000 children age <18 years in Hispanics versus 15-16 per 100,000 in non-Hispanic whites.

In the San Antonio Heart Study and the 1988-91 NHANES III, there was a higher rate of microvascular complications in diabetic Mexican Americans than in non-Hispanic whites. This is partly related to differing levels of hyperglycemia; in San Antonio, diabetic Mexican Americans were substantially more hyperglycemic than non-Hispanics, with mean FPG of 185 mg/dl versus 165 mg/dl. Prevalence of retinopathy was 85% after 10 years of diabetes in San Antonio and 56% after 15 years in NHANES III. Clinical proteinuria was found in 19% of Mexican Americans with diabetes in San Antonio versus 10% of non-Hispanic whites. State-wide surveillance in Texas and Colorado indicates that rates of diabetic ESRD are markedly higher in Hispanics than in non-Hispanics. However, data from Texas indicate that the survival of Mexican Americans on dialysis is longer than for non-Hispanic whites.

In contrast to microvascular disease, rates of coronary heart disease are lower in Hispanics than in non-Hispanic whites. The prevalence of previous myocardial infarction and coronary heart disease was lower in diabetic Mexican American men in Colorado and Texas than in diabetic non-Hispanic white men. Mortality from coronary heart disease in diabetes was lower in Hispanics than non-Hispanics in Texas. However, there is evidence that diabetic Mexican Americans have a higher prevalence of peripheral vascular disease as assessed by ankle-arm blood pressure ratios than non-Hispanic whites with diabetes.

ASIAN AND PACIFIC ISLANDER AMERICANS

There are ~7.3 million Asian and Pacific Islander Americans, and they comprise more than 20 different population groups. The majority are Asian (95%). IDDM is relatively rare, and diabetes in Asian and Pacific Islanders is predominantly NIDDM; much of the NIDDM is undiagnosed. A study in Japanese-American men and women in Seattle, WA in 1983-88 found that prevalence of NIDDM was 20% and 16%, respectively, which was substantially higher than in U.S. whites in NHANES II (12% and 14%) and in Japanese in Japan (5% and 4%). Studies show that prevalence of NIDDM is generally higher in Asian groups in the United States than in their native countries. For Pacific Islanders, the limited data available indicate that prevalence rates for NIDDM are high in Hawaiians and Samoans.

NIDDM is considered to be one of the diseases whose development is associated with lifestyle changes that occur with westernization. Indeed, diabetes in Japa-

nese Americans in Seattle is associated with obesity, particularly central obesity, a high saturated fat diet, reduced physical activity, and insulin resistance with hyperinsulinemia, as in other populations.

NORTH AMERICAN INDIANS AND ALASKA NATIVES

An epidemic of NIDDM in Native American communities of the United States has occurred during the second half of the twentieth century. Prevalence of the disease has increased dramatically as traditional lifestyles have been abandoned in favor of westernization, with accompanying increased body weight and lower physical activity. There are >500 tribal organizations in North America. Prevalence of NIDDM ranges widely, from rates from ~3% among Native Americans in Alaska to 50% among the Pima Indians in Arizona, the population with the highest recorded prevalence of NIDDM in the world.

Much of our understanding of the natural history of NIDDM is derived from studies of the Pima Indians. The relationship of diabetes to total obesity, duration of obesity, body fat distribution, hyperinsulinemia and insulin resistance, sedentary lifestyle, and genetics have been delineated in studies of the Pima Indians. Diabetes was once described as benign in Native Americans; now, complications of diabetes are major causes of morbidity and mortality in all Native American populations except the isolated Arctic groups whose lifestyles remain relatively unchanged. In studies of three Native American tribes, hyperglycemia was more severe than in non-Indian populations. Native American communities experience high rates of retinopathy, ESRD, and lower extremity amputation. However, rates of cardiovascular disease appear to be lower than found in studies of Caucasians.

GESTATIONAL DIABETES

GDM complicates between 1% and 14% of pregnancies in the United States, depending on the screening method and diagnostic criteria used and the population tested. Most studies report prevalence rates of 2%-5%. Prevalence is higher in population groups with higher risk of NIDDM, i.e., blacks, Hispanics, and Native Americans.

Perinatal mortality rates in GDM pregnancies are proportional to the level of maternal hyperglycemia. However, most studies in the past 15 years find no increase in the perinatal mortality rate in pregnancies that included treatment for GDM. The major morbidity in GDM is macrosomia, and this is also related to the degree of metabolic control. Maternal hyperglycemia appears to be a risk factor for both obesity and development of NIDDM in the offspring. For the mother, GDM is a strong risk factor for her own subsequent development of NIDDM.

PREGNANCY IN PREEXISTING DIABETES

Two major forms of maternal diabetes occur during pregnancy, preexisting diabetes and gestational-onset diabetes. The former constitutes ~10% of maternal diabetes, and prevalence rates for preexisting diabetes are in the range of 0.1%-0.3% of all pregnancies. Preterm delivery occurs in ~25% of IDDM pregnancies and cesarean delivery in ~24%-66%; these rates are three to five times higher than rates in the general population. In the absence of special preconceptional diabetes management, spontaneous abortions occur in 7%-17% of pregnancies with preexisting diabetes and major malformations occur in 7%-13%. Rates of these complications are highest in women with marked hyperglycemia during the first trimester, but are lower when maternal blood glucose is controlled prior to and during early pregnancy. Macrosomia is the most frequent fetal complication, affecting 10%-33% of infants depending on the definition used for macrosomia. Stillbirths are uncommon in diabetic pregnancies; congenital malformations and complications of maternal hypertensive disorders account for most of the 1.5- to twofold higher perinatal mortality, compared with nondiabetic pregnancies. The perinatal mortality rate in diabetic pregnancies is ~30-50 per 1,000 births.

Maternal risks in diabetic pregnancies are greatest in the presence of retinopathy and nephropathy. Diabetic retinopathy is present in 15%-66% of women with IDDM early in pregnancy, and the retinopathy frequently worsens during gestation. Overt diabetic nephropathy is present before pregnancy in ~5%-10% of IDDM women; many of these manifest hypertensive disorders during pregnancy. Nephropathy increases the prevalence of intrauterine growth retardation, prematurity, fetal morbidity, and fetal mortality. Maternal mortality during diabetic pregnancy is ~3-7 per 100,000, which is similar to the rate in nondiabetic pregnancies.

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