Epidemiology of Diabetes

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The incidence of diabetes mellitus, particularly type 2 diabetes, is increasing dramatically in the United States and in other Westernized, industrialized societies because of increasing obesity, sedentary lifestyle, and population aging. There are currently 20 million persons with diabetes in the United States, of whom more than 5 million remain undiagnosed. The diabetic population consumes a disproportionate share of health care resources because of both microvascular and macrovascular complications. Diabetes is a major cause of new-onset blindness, end-stage renal disease, and nontraumatic amputation in the United States. Cardiovascular disease accounts for up to 80% of premature excess mortality in diabetic patients. Strategies to lessen the disease burden in these patients include hygienic measures (diet and exercise) as well as rigorous treatment of hypertension, dyslipidemia, and hyperglycemia.

Keywords: *Type 2 diabetes; cardiovascular disease; health care; obesity; morbidity; mortality*

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Diabetes, a serious and economically devastating illness that is reaching epidemic proportions in both industrialized and developing countries, poses a major threat to public health in the 21st century. Diabetes was the fifth leading cause of death in the United States in the year 2000.[1] Of the more than 200,000 Americans with diabetes who succumb annually to diabetes-related complications, most die of coronary heart disease (CHD) or other cardiovascular disease (CVD) conditions.[2] Compared to nondiabetic persons younger than 45 years of age, those with diabetes are more than tenfold as likely to have CVD and are at significantly greater risk for peripheral vascular, ophthalmic, and renal disease and other chronic conditions. Diabetes is associated with an increased incidence of stroke, heart failure, new-onset blindness, limb amputations, end-stage renal disease (ESRD), birth complications, and sexual dysfunction. Persons with diabetes often have associated CVD risk factors, including hypertension, dyslipidemia, and obesity.[3]

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Diabetes occurs more frequently in older persons and in certain racial groups, such as Hispanics, African Americans, American Indians, and Alaskan Natives. The shift in population demographics, which includes a rise in the proportion of these ethnic minorities, has contributed to the increasing prevalence of diabetes. In 1998, the estimated total direct cost for diabetes health care in the United States, including caring for diabetes complications and hospitalization, was more than $60 billion. In addition, indirect costs, such as productivity losses due to illness, work absence, disability, premature retirement from the workforce, and premature death, may exceed direct costs. The estimated average cost for care of a person with diabetes in 1997 was $10,071, compared to $2699 for a person without diabetes.[4]

PREVALENCE OF DIABETES

The prevalence of diagnosed diabetes has increased dramatically over the past 40 years both in the United States and worldwide. In 1985, there were approximately 30 million people with diabetes worldwide[4]; by 1995, this number had escalated to 135 million (4% of the world population), and by 2025, it is projected that the incidence of diabetes will increase by 42%, affecting 300 million people (5.4% of the world population). Most of the expected increase will be in type 2 diabetes, which accounts for > 90% of cases of diabetes, while the incidence of type 1 diabetes is anticipated to remain stable. By 2025, the countries with the largest

number of people with diabetes will be India (> 57 million; prevalence 6%), China (> 37 million; prevalence 3.4%), and the United States (> 21 million; prevalence 8.9%).[5] Currently, more than 17 million Americans have diagnosed diabetes, and 5.9 million are unaware that they have the disease. Based on prevalence rates predicted from 1980-1998 trends, the number with diagnosed diabetes in the United States will swell to 29 million by 2050 (Figure 1).[6] In industrialized countries, diabetes will be prevalent in persons older than age 65, whereas in industrializing countries, the majority of persons with diabetes will be 45 to 65 years old, which could negatively affect the economic productivity, fertility, and reproduction of these disadvantaged communities.

A substantial proportion of the U.S. population has diabetes that remains undiagnosed. About 5.4 million persons (2.7%) have fasting plasma glucose ≥ 126 mg/dL, and 13.4 million (6.9%) have impaired fasting glucose (110 to 125 mg/dL).[7] Efforts to screen individuals at risk for the development of diabetes are important because the risk of progression from impaired glucose tolerance to type 2 diabetes may be reduced by lifestyle changes, including weight loss[8-10] and/or pharmacotherapy.[10] Moreover, early diagnosis becomes even more critical in light of data indicating that the clock starts ticking for CVD complications of diabetes many years before the diagnosis of clinical type 2 diabetes.[11]

The terms describing diabetes as *juvenile onset* and *adult onset* have become misnomers since 7.4% of patients ages 30 to 74 with diabetes in the United States have type 1 diabetes,[12] while the increasing cases of children and adolescents with type 2 diabetes will likely outnumber those with type 1 diabetes within 10 to 20 years.[13] Over a 10-year period, the incidence of type 2 diabetes among adolescents in Cincinnati, Ohio, climbed 10-fold,[14] while in Japanese schoolchildren, the incidence of type 2 diabetes increased 1.5-fold annually between 1975 and 1990.[15] Minority children and adolescents of Native American,[16] African American,[17] and Mexican American[18] parentage are disproportionately affected by type 2 diabetes.

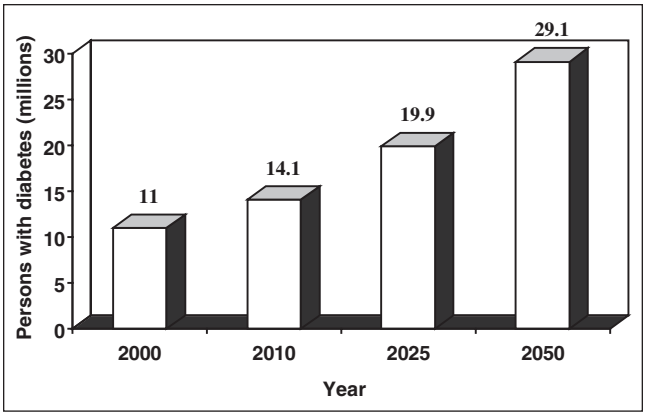

Figure 1. Projected changes in the number of people with diabetes in the United States in 2010, 2025, and 2050. The changes assume a steady increase in the prevalence of diabetes from 3.99% in 2000 to 7.21% in 2050, continuing population growth from 275 million in 2000 to 404 million in 2050, and demographic changes, with the largest increases in the older age group and in blacks. Changing demography is expected to account for the largest proportion of the increase. Data are adapted from Boyle et al.[6]

ETIOLOGIC FACTORS IN THE INCREASED INCIDENCE OF DIABETES

The worldwide increase in the incidence of diabetes over the past one to two decades has been fueled by globalization, which has led to changes in lifestyle in both industrialized and developing nations. Ironically, advances in public health that have increased longevity by eliminating many infectious diseases have added to the global burden of diabetes.[19] The abundance of overly rich nutrients, the availability of "fast food," modern mass-media advertising and the marketing of food products, changes from labor-intense to sedentary occupations, mechanization, and easily available transportation have contributed to a striking increase in the prevalence of overweight U.S. children and adults in the past decade. Comparing the years 1988-1994 with 1999-2000, the prevalence of overweight in the age groups of 2 to 5, 6 to 11, and 12 to 19 years increased from 7.2%, 11.3%, and 10.5% to 10.4%, 15.3%, and 15.5%, respectively.[20] Among adults during the same period, the prevalence of overweight (body mass index [BMI] = 25-30 kg/m^2) increased from 55.9% to 64.5%, obesity (BMI = ≥ 30 kg/m^2) from 22.9% to 30.5%, and extreme obesity (BMI ≥ 40 kg/m^2) from 2.9% to 4.7%.[21] The parallel rise in the incidence of both obesity and diabetes has been aptly labeled as the "diabesity" epidemic.[22]

Studies of ethnic populations such as the Pima Indians show that obesity combined with increased genetic susceptibility can lead to type 2 diabetes. The "thrifty genotype" hypothesis holds that the expression of ancestral genes, which evolved in response to the need to store energy as fat, provided a powerful survival advantage during periods of famine or natural disaster; in today's environment of caloric abundance and sedentary lifestyle, such genes are maladaptive and promote obesity and diabetes.[23] Low birth weight secondary to intrauterine malnutrition has been postulated to lead to obesity and diabetes in adult life. The survival of in-

Table I Cardiovascular Disease Risk Factors Associated with Metabolic Syndrome

- Hypertension
- Central obesity, especially increased mesenteric adiposity
- Hyperinsulinemia and insulin resistance
- Endothelial dysfunction
- Microalbuminuria
- Dyslipidemia (low HDL cholesterol, elevated triglycerides, and small, dense LDL cholesterol particles)
- Increased Apo-lipoprotein B levels
- Increased fibrinogen levels
- Increased plasminogen activator inhibitor–1, decreased plasminogen activator levels
- Increased C-reactive protein and other inflammatory markers
- Blunted nocturnal dipping of blood pressure and heart rate
- Increased salt sensitivity
- Left ventricular hypertrophy
- Premature/excess CHD, stroke, and peripheral vascular disease

HDL, high-density lipoprotein; LDL, low-density lipoprotein; CHD, coronary heart disease.

fants with low birth weight might also reflect expression of a thrifty genotype in an environment of intrauterine malnutrition.[24]

Many studies confirm the relationship of the 2-hour oral glucose tolerance test,[25] hemoglobin A_{1c},[26,27] fasting insulin levels,[28-30] and serum lipids[31] as predictors of subsequent CVD morbidity and mortality. The close linkage of type 2 diabetes with micro- and macrovascular disease suggests a common physiologic pathway that involves insulin resistance as well as conventional risk factors (i.e., hypertension and dyslipidemia). Tissue resistance to the action of insulin is associated with a cluster of CVD risk factors, termed the *metabolic syndrome*.[32,33] The major features of this clinical complex include central obesity; dyslipidemia, characterized by hypertriglyceridemia, reduced high-density lipoprotein cholesterol levels, and atherogenic small, dense low-density lipoprotein cholesterol particles; hyperglycemia; and hypertension. Additional risk factors are salt sensitivity, elevated levels of C-reactive protein and other inflammatory markers, absence of the nocturnal fall in blood pressure and heart rate, increased cardiovascular (CV) oxidative stress, impaired endothelial function, an abnormal coagulation/fibrinolytic profile, left ventricular hypertrophy, hyperuricemia, and microalbuminuria (Table I).[33]

National survey data from a representative sample of adult Americans indicate that the metabolic syndrome is common, affecting approximately 24% of the U.S. population (47 million people), with a higher prevalence in older persons (43.5% in the 60- to 69-year age range and 6.7% in the 20- to 29-year-old group) and in Mexican-Americans.[34] The Botnia study evaluated the risk of CV events associated with the metabolic syndrome in 3306 subjects, ages 35 to 70 years, who had type 2 diabetes, impaired fasting glucose, or insulin resistance and two of the following: obesity, hypertension, dyslipidemia, or micro- albuminuria. During a median 6.9-year follow-up period, patients with the metabolic syndrome had a threefold greater risk for CHD and stroke and a nearly sixfold increased risk for CVD mortality.[35]

PATHOGENESIS OF ATHEROSCLEROSIS IN TYPE 2 DIABETES

Hyperglycemia results from both insulin resistance and insulin deficiency secondary to pancreatic beta-cell failure. Resistance to the action of insulin is directly proportional to the extent of visceral fat accumulation.[36] In patients with type 2 diabetes, enlarged, fat-engorged omental adipose cells, unrestrained by the inhibitory influence of insulin, release free fatty acids or other mediators, such as leptin and resistin. These substances may affect insulin action and pancreatic β-cell function[37] and lead to increased hepatic gluconeogenesis[38] and decreased peripheral glucose uptake.[39] Central adipose tissue is also a rich source of cytokine production (i.e., tumor necrosis factor-α [TNF-α] and interleukin-6 [IL-6]), which, in turn, stimulates production of inflammatory substances, such as C-reactive protein (CRP). Also, in omental fat, increased expression of the type 1 isoform of 11β-hydroxysteroid dehydrogenase, which converts cortisone to cortisol, may promote adipocyte differentiation, reflecting "Cushing's disease of the omentum."[40]

Hyperglycemia may increase protein glycation in the setting of oxygen-free radicals with the production

of advanced glycation end products. Increased lipid and lipoprotein peroxidation may contribute to arterial wall foam cell formation. Recent studies suggest that chronic inflammation may play a role in the development of diabetes. Baseline levels of IL-6 and CRP, sensitive markers of subclinical inflammation, were elevated in participants in the Women's Health Study who later developed diabetes. IL-6 and CRP were associated with increased BMI, hyperglycemia, insulin resistance, and diabetes.[41] A similar relationship of CRP to the risk of developing type 2 diabetes in older persons was found in the Cardiovascular Health Study.[42] In the Mexico City Diabetes Study, women with CRP in the highest tertile at baseline had an increased risk for developing the metabolic syndrome and diabetes after 6 years, whereas CRP was not a significant predictor in men.[43] In the Insulin Resistance Atherosclerosis Study, CRP was also increased in persons with diabetes, as well as in overweight and obese adults, and correlated with BMI, serum triglycerides, blood pressure, and insulin resistance.[44] The renin-angiotensin system (RAS) may play a role in the inflammatory process by activating various nuclear transcription factors, including NFκB, which may be important in regulating production of proinflammatory cytokines and adhesion molecules. Fosinopril, an angiotensin-converting enzyme (ACE) inhibitor, reduced levels of the soluble adhesion molecule, VCAM-1, in patients with type 2 diabetes and microalbuminuria.[45] Several clinical trials, including the Heart Outcomes Prevention Evaluation (HOPE)[46] and the Losartan Intervention for Endpoint (LIFE) reduction in hypertension[47] trials, have shown that RAS inhibition significantly reduces the risk of new-onset diabetes, raising the question as to whether inflammation contributes to this preventative effect.

IMPACT OF DIABETES ON CVD MORBIDITY AND MORTALITY

Diabetes markedly reduces life span; for example, a 50-year-old man with diabetes may have a life expectancy 10 years less than that of a person without diabetes, although it is possible that his prognosis may be improved with tighter glycemic control and treatment of comorbid conditions.[48] Many observational studies show that CVD is a major factor in reducing longevity in persons with diabetes. The Multiple Risk Factor Intervention Trial (MRFIT) found that the risk of death from CVD in men ages 35 to 57, followed over 12 years, was significantly greater for those with diabetes compared to those without diabetes, regardless of age, ethnic background, or CVD–risk factor level. Increased serum cholesterol level, higher systolic blood pressure, and cigarette smoking progressively amplified the adverse effect of diabetes on CVD mortality.[49] Also, in an 8-year follow-up of a cohort of more than 116,000 women ages 30 to 55 years, diabetes was associated with a markedly increased risk of fatal and nonfatal myocardial infarction, stroke, and all-cause mortality that was increased by cigarette smoking, hypertension, and obesity.[50]

DIABETES AND CORONARY HEART DISEASE (CHD)

The Minnesota Heart Survey reported a nearly twofold increase in the prevalence of diabetes among men and women who sustained a myocardial infarction (MI) between 1970 and 1985. The likelihood of in-hospital mortality was 1.5 times greater in patients with diabetes than in those without diabetes, and the risk of death after 6 years of follow-up was 40% higher in diabetic persons, an outcome that was worse in women than in men.[51] Both men and women with diabetes who suffered their first MI were found to have mortality rates that were significantly greater at 28 days and 1 year post-MI than in those without diabetes.[52] In a 7-year study of populations from eastern and western Finland, the 7-year incidence rates for MI in nondiabetic subjects with and without previous MI at baseline were 19% and 4%, respectively. For diabetic subjects with and without previous MI at baseline, the 7-year incidence rates for MI were 45% and 20%, respectively. Also, fatal or nonfatal strokes in patients with diabetes without prior MI and nondiabetic subjects with a prior MI were 10.3 and 7.2 per 100 person-years, respectively (Figure 2). These data indicate that the risk of MI and stroke is similar in patients with diabetes with no previous MI and persons without diabetes who have had an MI; thus, diabetes should be considered a "coronary equivalent" and treated aggressively.[53] Similarly, in patients with diabetes admitted to coronary care units with unstable angina or non-Q-wave MI, the 2-year mortality rate for patients with diabetes and no history of CVD was identical to that of nondiabetic subjects with no history of CVD. These findings confirm that a previously healthy patient with diabetes has the same long-term prognosis as a patient with established CVD but without diabetes.[54]

A recent autopsy study from the Rochester Epidemiology Project found a higher prevalence of atherosclerosis among diabetic decedents without a history of clinical manifestations of coronary artery disease (CAD) than in age-matched subjects without diabetes; nearly 75% of the diabetic decedents without CAD had high-grade coronary atherosclerosis, and more than

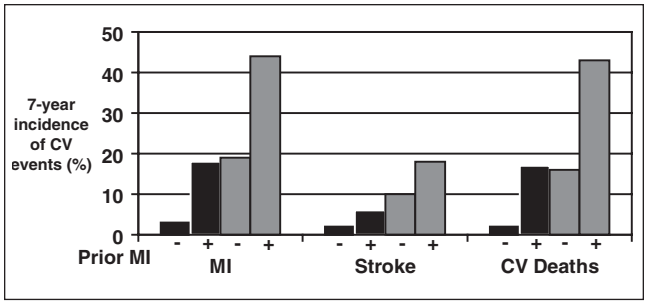

Figure 2. Seven-year incidence of cardiovascular events in Finland among diabetics and nondiabetics. The combination of diabetes (crosshatched bars) and a history of prior myocardial infarction (MI) was associated with an increased incidence of cardiovascular (CV) events. Nondiabetics (solid bars) with a history of MI also have an increased incidence of CV events. The incidence of MI was similar in diabetics with no prior MI (–) and nondiabetics who have had an MI (+). Similar trends were seen in stroke and CV death. Data are adapted from Haffner et al.[53]

50% had multivessel disease. The global CAD burden and high-grade atherosclerosis in diabetic decedents were similar to that in nondiabetic subjects with clinical CAD, providing mechanistic insight into the excessive risk of clinical CAD among individuals with diabetes.[55] Findings from a 10-year follow-up from the Health Professionals Study indicate that men with either diabetes or prior MI have increased CAD mortality and that having both conditions escalates the risk of fatal MI. The duration of diabetes independently predicted the likelihood of fatal MI.[56]

CORONARY ARTERY BYPASS GRAFT AND PERCUTANEOUS INTERVENTION IN DIABETES

Among patients with CAD undergoing percutaneous coronary catheter intervention, in-hospital mortality did not differ in patients with and without diabetes, but after 1 year, the risk of mortality and the need for revascularization were significantly higher in the diabetic group.[57] Likewise, diabetic patients undergoing coronary artery bypass grafting had in-hospital mortality rates comparable to those without diabetes but had longer hospitalization; an increased incidence of postoperative renal failure, stroke, mediastinitis, and wound infection; and a higher 30-day mortality.[58]

CONGESTIVE HEART FAILURE IN DIABETES

The prevalence of diabetes as a risk factor for the development of congestive heart failure (CHF) has been reported to range from 10% to more than 30%.[59] Among high-risk patients in a community-based population, the prevalence of left ventricular systolic dysfunction attributed to diabetes was 5.8%.[60] Although diabetes was found to be an independent risk factor for morbidity and mortality in symptomatic congestive heart failure and asymptomatic left ventricular dysfunction,[61] the pathophysiology of heart failure in diabetes is not completely clear. Left ventricular diastolic dysfunction was found in 60% of normotensive patients (ages 38-67 years) with uncomplicated type 2 diabetes without CAD or signs and symptoms of CHF; however, the age-related increase in stiffness of the left ventricle confounds the findings.[62] The increased prevalence of CHF in diabetes is likely attributable to ischemic, hypertensive, and diabetic cardiomyopathy.[61]

DIABETES AND STROKE

Stroke is the third leading cause of death in the United States, affecting more than 700,000 Americans.[63] In the decade prior to 1998, the mortality from stroke rose by 5.3%.[63] Patients with diabetes have up to three times as many strokes as those in the general population, with especially high rates in Sweden[64] and in the southeastern United States.[65] In the Honolulu Heart Program, Hawaiian-Japanese men with diabetes had double the risk of thromboembolic stroke as nondiabetic men, an increase in incidence that was independent of other factors known to predispose to stroke.[66] In the Framingham Heart Study, subjects with glucose intolerance were twice as likely to suffer brain infarction as those without diabetes, with the relative risk being greater in women than in men.[67] African American[63] and Caribbean[68] men with diabetes have more than a twofold increased incidence of stroke than their nondiabetic counterparts, reflecting the greater propensity for hypertension and diabetes in these groups.

Patients presenting with stroke are more likely to have undiagnosed type 2 diabetes. In the prospective Honolulu Heart Study, the prevalence of thromboembolic, but not hemorrhagic, stroke was increased in those whose serum glucose exceeded 120 mg/dL at 1 hour after a 50-g glucose load.[69]

Patients with diabetes are less likely than nondiabetics to survive a stroke and more likely to have persistent disability should they survive. In a Finnish study, only 20% of diabetic persons were alive 5 years after a stroke compared to 40% of an age- and sex-matched control group. Furthermore, 20% of the diabetic patients were first diagnosed when they presented with their stroke.[70] An English study showed

that in the first month, complete recovery from hemiparesis occurred only in those with persistent blood glucose < 120 mg/dL.[71]

Because the incidence of stroke is greater and prognosis worse in persons with diabetes, attempts to prevent stroke in this population are extraordinarily important. Hypertension, cardiac disease (including atrial fibrillation [AF]), heart failure, and cigarette and alcohol use are modifiable risk factors both in those with and without diabetes. In the United Kingdom Prospective Diabetes Study (UKPDS), stroke incidence over 8 years was strongly associated with hypertension, especially systolic blood pressure elevation. Even persons with diabetes whose systolic blood pressure ranged from 125 to 142 mmHg had a twofold higher risk than those with lower systolic blood pressure.[72] In an 8-year population-based study of persons ages 35 to 74 years, 15.1% of diabetic patients with stroke had previously documented AF compared with 10.7% of those without diabetes.[73] Since anticoagulation therapy with warfarin in patients with AF reduces the risk of stroke by two-thirds,[74] and the risk of cerebral hemorrhage is less in diabetic patients than in nondiabetics,[75] warfarin therapy is clearly indicated in diabetic patients with AF.

Blood pressure control is critical in preventing stroke in patients with diabetes. The UKPDS trial showed that in the "tight" blood pressure control group (mean achieved blood pressure 142/82 mmHg), the risk of fatal and nonfatal stroke was reduced by a persuasive 44% compared with less aggressive control (mean achieved blood pressure 154/87 mmHg).[76] In contrast, improved glycemic control in the UKPDS failed to produce a significant reduction in stroke incidence during 9 years of follow-up. Among diabetic patients in the Systolic Hypertension in the Elderly Program (SHEP) trial, antihypertensive treatment also reduced stroke risk but by only 20%.[77] Data from the Systolic Hypertension in Europe trial demonstrated that in older patients with diabetes and isolated systolic hypertension, the excess risk of stroke associated with diabetes was abolished by a calcium channel blocker–based antihypertensive treatment regimen.[78] In the Micro-HOPE subanalysis of the HOPE trial, 3577 diabetic patients showed a combined reduction of the primary endpoints of myocardial infarction, stroke, and CVD by 25% and in stroke alone of 33%.[79] Recent studies have shown the beneficial effects of ACE inhibition in the reduction of secondary endpoints in high-risk patients, including diabetics. These data support recent guidelines[80] of a goal blood pressure < 130/80 mmHg in diabetics in conjunction with lifestyle changes, including exercise, cessation of smoking, and avoidance of excessive alcohol consumption.

MICROALBUMINURIA AND CARDIOVASCULAR EVENTS

The presence of proteinuria predicts cardiovascular events. Among 1056 patients with type 2 diabetes, 36% developed an atherosclerotic vascular disease event over a 7-year follow-up period. Thromboembolic or hemorrhagic stroke occurred in 23% of diabetic subjects with clinical proteinuria, 11.1% with borderline proteinuria, and 7.2% without proteinuria. Lower limb amputations were performed in 10% of the diabetic subjects. Nondiabetic subjects with proteinuria also developed cardiovascular events but to a lesser extent. The findings suggest that proteinuria may reflect a generalized vasculopathy.[81] That microalbuminuria may be a harbinger of cardiovascular events in subjects without diabetes was shown in a 10-year prospective study of 2085 participants initially free of cardiac or renal disease; microalbuminuria independently predicted the development of ischemic heart disease and increased the adverse effect associated with other risk factors.[82] In high-risk participants in the HOPE study, microalbuminuria, which was detected in 36.2% of those with diabetes and 14.6% of those without diabetes at baseline, was associated with an increased relative risk of MI, stroke, or CV death; all-cause mortality; and CHF hospitalization.[83]

CONCLUSIONS

Changes in lifestyle and increased food intake, combined with genetic susceptibility, have led to a worldwide epidemic in obesity and type 2 diabetes, which disproportionately affects ethnic minorities. Patients with diabetes are at a greatly increased risk for morbidity and mortality from myocardial infarction, stroke, congestive heart failure, renal failure, and other cardiovascular diseases. Obesity, particularly the accumulation of mesenteric fat, may lead to insulin resistance and the metabolic syndrome. Endothelial dysfunction lipid peroxidation, production of advanced glycation end products, and subclinical inflammation may play a role in the atherogenesis of type 2 diabetes. Efforts to screen individuals at risk for the development of diabetes are important since clinical trials employing lifestyle changes and/or medication may prevent the development of new-onset diabetes and the complications of diabetes.

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