ETHNIC DISPARITIES IN TYPE 2 DIABETES: PATHOPHYSIOLOGY AND IMPLICATIONS FOR PREVENTION AND MANAGEMENT

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Based on 2000 census data, ethnic minorities constitute approximately 25% of the overall population of the United States, and the population of minority groups has been increasing at a faster rate than the general U.S. population. Compared with caucasians, persons from minority ethnic groups suffer disproportionately from type 2 diabetes and its long-term complications. Acute complications of diabetes occur with varying frequencies in the different demographic groups, but there are indications that the rate of hospitalization for diabetic ketoacidosis and nonketotic coma may be higher among certain minority populations. Genetic and lifestyle factors likely account for the increased prevalence of type 2 diabetes among ethnic minorities. However, the increase in morbidity and mortality from diabetes may be the result, in part, of socioeconomic factors. Pathophysiologically, several studies have documented a higher prevalence of insulin resistance in minority groups, even after correction for obesity and lifestyle factors. These findings underscore the need for a more aggressive approach to diabetes management in high-risk populations. Behavioral and pharmacologic interventions that reduce insulin resistance have profound beneficial effects in African-American patients and subjects with diabetes from other ethnic groups. Indeed, much of the ethnic difference in morbidity from diabetic complications disappears when caucasians and non-caucasians are treated to identical degrees of glycemic control. (*J Natl Med Assoc.* 2003;95:774–789.)

Key words: ethnic minorities ♦ diabetes ♦ insulin resistance

INTRODUCTION

Recent epidemiologic studies indicate that diabetes is being diagnosed at alarming rates in the United States. Between 1958 and 1994, the prevalence of diagnosed cases of diabetes increased by 500%[1,2], and more recent surveys show no abatement in the diabetes epidemic[3]. Although prevalence of type 1 diabetes has increased, the vast majority of the surge in diabetes has been type 2 diabetes.

In 1990, ethnic minorities constituted approximately 25% of the overall population of the United States. The population of these minority groups has been increasing at a faster rate than the general U.S. population. When the pattern of increased prevalence of type 2 diabetes is analyzed demographically, a marked disparity becomes immediately obvious: ethnic minority populations in the United States carry a disproportionately heavier disease burden compared with whites[4-6]. This review discusses the etiology of the ethnic disparities in diabetes from the pragmatic perspective of modifiable determinants. The roles of nature and

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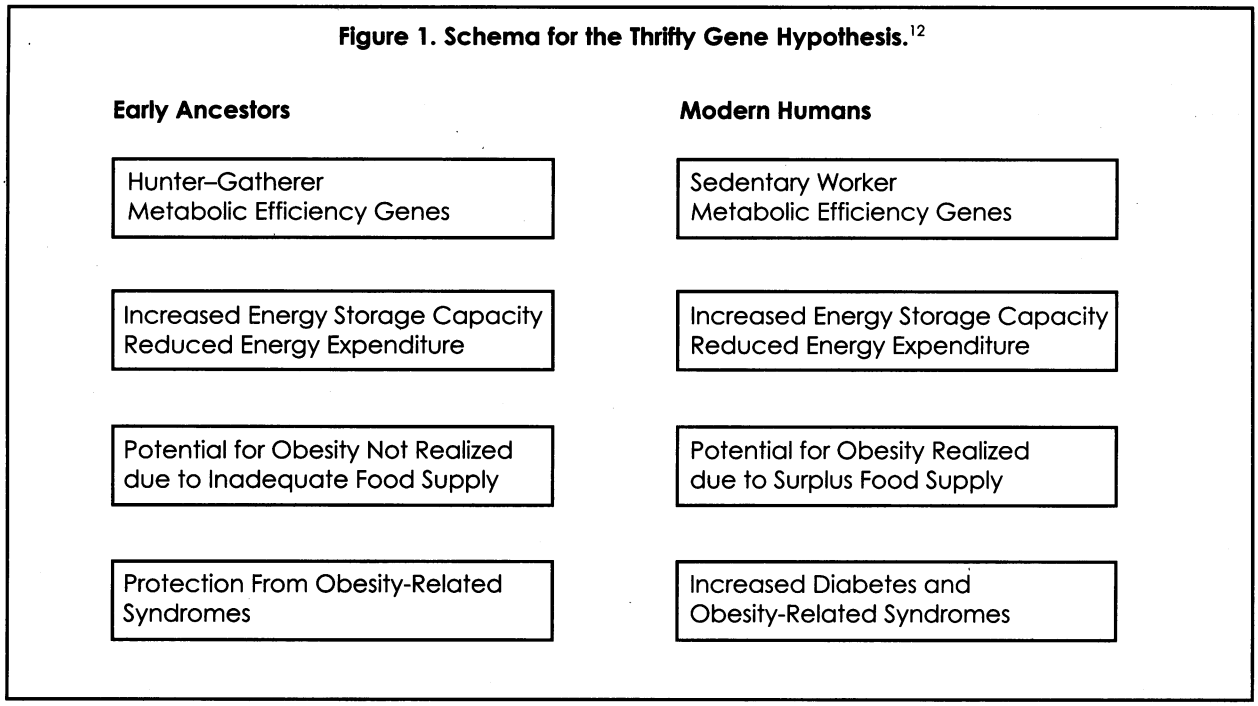
Figure 1. Schema for the Thrifty Gene Hypothesis.[12]



nurture are evaluated in a balanced context that highlights the prominent contribution of socioeconomic factors to the apparent ethnic disparities in the prevalence and ferocity of diabetes. Finally, interventions for the prevention and management of type 2 diabetes are discussed in a paradigm that advocates appropriate matching of pathophysiologic targets with effective remedies. The consistent efficacy of lifestyle and pharmacologic interventions for diabetes across all ethnic groups constitutes a compelling rationale for aggressive therapy to mitigate consequences of the disproportionate burden of diabetes in minorities.

ETIOLOGY OF ETHNIC DISPARITY

Compared with the prevalence rate of diabetes in white Americans, the relative increase in the prevalence of type 2 diabetes is approximately one-and-a-half-fold in African Americans, two-and-a-half-fold in Hispanic-Americans, three- to four-fold in Asian-Americans and Pacific Islanders, and ten-fold or greater in certain Native American ethnic groups[4-9]. The exact reasons for the ethnic and racial differences in the incidence and prevalence of type 2 diabetes are not known with certainty. A collusion of genetic predisposition and environmental triggers likely accounts for the development of type 2 diabetes in any population. The nature and identity of the diabetogenes are still being actively investigated[10,11].

Genetic Factors

The thrifty gene hypothesis[12] posits that millions of years ago, the ancestors of modern humans might have been selected for survival based on certain genetically driven metabolic traits. In those primeval times, when food availability was insecure and natural disasters (i.e., floods, fires, famine) were rampant, people who were metabolically efficient or "thrifty" survived better than others. When food was available, metabolic thriftiness ensured efficient storage of energy as fat for use during famine. Ancient man also was a hunter-gatherer for whom daily physical activity was mandatory. Over time, these "thrifty" genes have been transmitted to progeny right down to the present era, when famine is no longer rampant and modern exercise-sparing inventions are in universal use. The result of guaranteed food surplus and markedly reduced physical activity, superimposed on a background of ancestral thrifty genes, is the epidemic of obesity in affluent countries and among the elite in developing countries[13,14]. Genes that once predicted survival in an era of starvation have now become a handicap in a time of plenty (Fig. 1). The thrifty gene hypothesis is generally

accepted as a possible explanation for obesity, but its extension to explain type 2 diabetes has been challenged[15]. Indeed, as argued by Lev-Ran[15], the teleological reasons for conservation of genes that would lead to diabetes are unclear, whereas the connection between thrifty genes and obesity is much clearer. Obesity ensured survival by making available stored energy during starvation; diabetes, on the other hand, reduces survival by a full decade and compromises quality of life through its numerous complications. Thus, the application of the thrifty gene hypothesis to type 2 diabetes appears not to be as convincing as its link to obesity.

Other Hypotheses

Based on the foregoing premise, alternative hypotheses—one of which is called "antagonistic pleiotropy"[16]—have been proposed. This concept suggests that there might be a trade-off between fitness components in earlier and later stages of life. As proposed under this scheme, thriftiness at a younger age ensured survival and reproductive viability, but, after middle age, these thrifty genes predispose to diabetes. The major weakness of antagonistic pleiotropy is that it lacks empirical examples in nature. The second alternative is the "genetic trash can" hypothesis: the conservation of multiple, individually neutral gene mutations that confer aggregate risks for type 2 diabetes when accumulated and concentrated in a given population[15,17]. Because diabetogenes are generally recessive, such a hypothesis would be consistent with the increased prevalence of type 2 diabetes in ethnic populations that have been less exogamous than European populations[15]. Exogamy, migrations, conquests, invasions, interbreeding, and admixtures exert a dilutional effect on mutant genes, and many aboriginal societies have experienced fewer of these diluting events than have caucasians[15,18,19].

Environmental Triggers

The role of the environment in uncovering latent genetic predispositions is well known[20]. This was clearly demonstrated in the studies that showed a three-fold increase in the rate of type 2 diabetes in Japanese immigrants to the United States compared with native Japanese[21]. Such a dramatic increase in disease prevalence in humans cannot be attributed to sudden new genetic mutations. Environmental and cultural factors, including change in diet and lifestyle, most probably account for the expression of the innate genetic predisposition to type 2 diabetes in the Japanese immigrants. The exact mechanisms whereby environmental triggers induce diabetes in genetically predisposed persons are not known with certainty. However, the traditional environmental factors associated with increased occurrence of type 2 diabetes—often referred to as risk factors—include obesity, physical inactivity, history of gestational diabetes, hypertension, and dyslipidemia, among others.

The distribution of these individual risk factors varies across the different ethnic groups, but the aggregate risk factor burden in various populations must overlap considerably. Therefore, ethnic differences in conventional risk factors alone cannot account for the marked disparities in diabetes prevalence. For example, although obesity is the single most compelling (and most predictable) of the traditional risk factors for type 2 diabetes[22] in the general population, the incidence of diabetes among even massively obese persons is far from being 100%. Indeed, obesity triggers diabetes only in a susceptible minority, the majority of obese persons being capable of escaping diabetes as a metabolic consequence of their obesity. Obesity is more prevalent among African-American and Hispanic subjects compared with caucasians at the time of diagnosis of type 2 diabetes[23,24]. However, as already noted, obesity does not lead to diabetes in most subjects. Part of the disparity between measures of global obesity and the risk of diabetes may be due to the confounding effect of differences in regional fat distribution and pancreatic β-cell response. Visceral obesity is well-known to correlate with increased insulin resistance, which together with impaired β-cell function greatly increases the risk for type 2 diabetes[25,26].

In the Atherosclerosis Risk in Communities (ARIC) study, weight gain emerged as a strong predictor of incident diabetes in African Americans[9]. The incidence of diabetes per 1,000 person-years was ~ 2.4-fold greater in African-American women and ~ 1.5-fold greater in men than in their white counterparts[9]. Notably, the waist-to-hip ratio (a measure of visceral adiposity) was greater in African-American women compared with caucasian women[9]. Similarly, weight gain predicted progression from normal glucose tolerance (NGT) to impaired glucose tolerance and diabetes in a longitudinal study of Pima Indians[27]. Individuals who progressed from NGT to diabetes gained an average of 13 kg over a five-year follow-up period, as compared with 6 kg in

Table 1. Major Criteria for Dysmetabolic Syndrome X* (ICD-9 277.7)
(reproduced from reference 32, with permission)

- Insulin resistance (hyperinsulinemia relative to glucose levels), or
- Acanthosis nigricans
- Central obesity (waist circumference >102 cm in men or >88 cm in women)
- Dyslipidemia: HDL cholesterol <45 mg/dL in women or <35 mg/dL in men or triglyceride levels >150 mg/dL
- Hypertension (blood pressure ≥130/≥85 mm Hg)
- Impaired fasting glucose (>110 mg/dL) or type 2 diabetes
- Hyperuricemia

HDL = high-density lipoprotein
* Diagnostic criteria and operational definition developed by American Association of Clinical Endocrinologists.

nonprogressors[27]. However, changes in percent body fat and waist-to-hip ratio (WHR) were not different between groups[27]. Thus, the absolute amount of weight gain, rather than changes in body composition or fat distribution, appears to predict diabetes risk in the Pima Indian population, a finding that is in discord with findings in other populations[9,28]. It remains to be established, however, whether individuals from different ethnic backgrounds exhibit differential susceptibility to the individual risk factors for diabetes.

Cultural factors are an important consideration in the etiology of ethnic disparity in type 2 diabetes. Ingrained attitudes toward physical activity, obesity, and diet composition may all bear on the expression of a metabolic disorder. Thus, cultural practices that promote corpulence or express approval for large physique[14] may inadvertently increase the risk for diabetes.

Psychodynamic factors manifesting as stress, depression, or neuropsychiatric illness may alter glucoregulation. These factors have been associated with new-onset diabetes or a worsening of preexisting diabetes[29,30]. It is thus possible that differential susceptibility to environmental stress may also contribute to the ethnic disparity in the prevalence of diabetes.

Underlying Pathophysiology

In the final analysis, type 2 diabetes develops because of a combination of insulin resistance and impaired insulin secretion by the pancreatic β cells[25,26]. The concurrent roles of insulin resistance and β-cell dysfunction in predicting the development of type 2 diabetes were confirmed in a longitudinal study of Pima Indians[27], and may represent a general model in other ethnic groups. Studies that compared various populations of West African descendants (including African Americans and native Ghanaians) and caucasians have reported higher degrees of insulin resistance among West African descendants[31,32]. These studies have also suggested alterations in hepatic insulin clearance in African populations compared with caucasians[31]. The Insulin Resistance Atherosclerosis Study (IRAS) also showed higher degrees of insulin resistance among African Americans and Latinos than among caucasians[30]. The ethnic differences in insulin sensitivity persisted after adjusting for age, gender, clinic site, body mass index, waist-to-hip ratio, and physical activity score[33]. These studies provide evidence for genetically driven insulin resistance as an underlying factor for the ethnic disparities in the prevalence of type 2 diabetes.

Recent findings from the Diabetes Prevention Program (DPP) offer interesting new perspectives: the incidence of type 2 diabetes was found to be similar (~11%) among African Americans, Asian-Americans and Pacific Islanders, caucasian Americans, Hispanic-Americans, and Native Americans[34]. The well-known ethnic disparity in the risk of type 2 diabetes was surprisingly not evident among the DPP cohort of approximately 3,000 subjects, with impaired glucose tolerance (IGT), who were followed for two to four years. By definition, persons with IGT have normal fasting plasma glucose levels and two-hour levels of 140–199 mg/dL during a 75-g oral glucose tolerance test. The finding of similar transethnic diabetes rates in the DPP suggests that once individuals have progressed from normal glucose tolerance to IGT, the risk of further progression to diabetes is the same across ethnic

Table 2. Minor Features of Dysmetabolic Syndrome X (ICD-9 277.7) (reproduced from reference 32, with permission)

- Hypercoagulability
- Polycystic ovary syndrome
- Vascular endothelial dysfunction
- Microalbuminuria
- Coronary heart disease

groups. Thus, the ethnic/genetic factors that predispose to diabetes must have exerted their maximal effects during the transition from normal metabolism to IGT. This intriguing and novel notion has obvious implications for the design and translation of primary prevention strategies.

The Metabolic Syndrome

The risk factors for IGT and type 2 diabetes overlap considerably, with insulin resistance as a common underlying thread. Many patients with IGT have features of the insulin resistance (metabolic) syndrome, including decreased high-density lipoprotein (HDL) cholesterol levels, increased low-density lipoprotein (LDL) cholesterol levels (particularly small, dense LDL particles), hypertriglyceridemia, upper-body obesity, hyperinsulinemia, hypertension, and abnormal fibrinolysis, among others. The metabolic syndrome affects millions of prediabetic persons in the United States, is associated with a two-fold increased risk of cardiovascular disease, and has recently been allocated the International Classification of Diseases (ICD)-9 code of 277.7[35]. Major and minor criteria to assist in recognition of this syndrome have been developed by the American Association of Clinical Endocrinologists (Tables 1 and 2),[35] and the National Cholesterol Education Program has put forth a simplified diagnostic tool (Table 3)[36].

At present, no drug therapy has been approved for treatment of prediabetic persons with the metabolic syndrome. However, lifestyle modifications (caloric restriction, reduction in saturated fats, increased physical activity) are remarkably effective in preventing progression to diabetes and improving cardiovascular risk markers[34].

ETHNIC DISPARITY IN DIABETES COMPLICATIONS

Do the differences in the prevalence of type 2 diabetes predict increased burden from diabetes

Table 3. Adult Treatment Panel III (ATP III): Criteria for Diagnosis of the Metabolic Syndrome* (ICD-9 277.7) (reproduced from reference 33, with permission)

Abdominal obesity (waist circumference)	
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	≥150 mg/dL
HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/≥85 mm Hg
Fasting glucose	≥110 mg/dL

HDL = high-density lipoprotein
* Diagnosis is established when >3 of these risk factors are present.

complications in patients from ethnic minority populations? This is not a rhetorical question, or one whose answer is designed to be automatically in the affirmative. Examples abound where there is dissociation between prevalence and outcome of a disease condition. For instance, African Americans develop end-stage renal disease (ESRD) requiring dialysis at a disproportionately higher rate than caucasians, but have a lower mortality rate on dialysis than caucasians[37]. Another example relates to obesity and the risk of dyslipidemia. African-American women have a higher prevalence of obesity than caucasian women but do not show the expected pattern of obesity-related dyslipidemia[38]. Acute diabetic complications occur with varying frequencies in the different ethnic groups, but there are suggestions that the rate of hospitalization for diabetic ketoacidosis and nonketotic coma may be higher among certain minority groups, such as African Americans[7]. Ethnic disparities in chronic diabetes complications are discussed in the sections that follow.

Microvascular Complications

Diabetes-specific microvascular complications include retinopathy, nephropathy, and neuropathy. These complications do not occur in persons with impaired glucose tolerance, but require hyperglycemia as an initiating factor. The pathogenesis of microvascular complications is not fully understood. Suggested mechanisms include genetic predisposition, hyperglycemia-induced abnormalities in the polyol pathway, toxic effects of advanced

glycated end products, glomerular hyperfiltration, aberrant growth factor expression, and abnormal endothelial, pericyte, and mesangial structure and/or function[26,39]. The development of microvascular complications is a function of both the duration of the diabetes and state of metabolic control; nearly 25% of patients with type 2 diabetes have already developed one or more microvascular complications by the time of diagnosis[40]. The single most modifiable factor underlying microvascular complications is hyperglycemia, and intensive glycemic control is the only strategy known to prevent the development and slow the progression of microvascular complications[41,42].

In the Third National Health And Nutrition Examination Survey (NHANES III), a fundus photograph of a single eye was taken with a nonmydriatic camera, and a standardized protocol was used to grade diabetic retinopathy in subjects from a cross-section of the U.S. population. The prevalence of any lesions of diabetic retinopathy in persons with diagnosed diabetes was 46% higher in African Americans and 84% higher in Mexican-Americans compared with non-Hispanic whites. African Americans and Mexican-Americans also had higher rates of moderate and severe retinopathy and higher levels of many putative risk factors for retinopathy[43]. Similarly, the rates of ESRD are approximately three-fold or more higher in African Americans, latinos, and Native Americans compared with caucasians[44]. Diabetic nephropathy is the leading cause of ESRD, although there is substantial contribution from hypertension. Microalbuminuria (~30 mg to 300 mg albumin/24 h), a potentially reversible stage of incipient nephropathy, precedes overt proteinuria (>500 mg protein/L or >300 mg albumin/day) by several years in patients with diabetes. After gross proteinuria has developed, progression to nephrotic syndrome and ESRD occurs over a shorter time frame. The mean duration from diagnosis of diabetes to development of overt proteinuria is approximately 17 years, and the time from occurrence of gross proteinuria to ESRD averages five years[45]. Thus, a wide window of opportunity exists for nephroprotection in patients with diabetes. The proven methods for providing nephroprotection include intensive glycemic control[41,42], aggressive blood pressure control, appropriate use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) in microalbuminuric patients, and modification of other risk factors[46].

The third microvascular complication, diabetic neuropathy, encompasses a wide variety of focal as well as diffuse neurological syndromes, the most well-recognized example of which is peripheral neuropathy. Paresthesias, numbness, tingling, and burning sensation in a glove-and-stocking distribution are typical symptoms of peripheral neuropathy. Physical examination typically shows diminished perception of light touch, vibration, and painful stimuli in the lower extremities. The loss of protective pain sensation predisposes the diabetic limb to trauma, injuries, polymicrobial infections, gangrene formation, and lower-extremity amputation. The rates of hospitalization for lower-extremity ulcers are similar across all ethnic groups, but lower-extremity amputation rates are two to three times higher in Mexican-American and African-American patients compared with caucasians[47]. Diabetic neuropathy can be prevented by a policy of tight glycemic control (glycosylated hemoglobin [HbA_{1c}] levels <7%)[41,42]. Furthermore, the downstream consequences of established diabetic neuropathy are not inevitable. Screening for foot sensation using the 5.07 monofilament identifies patients at high risk, who can then be triaged to intensive limb-preservation practices[46].

Macrovascular Complications

Diabetes mellitus leads to accelerated atherosclerosis. Consequently, there is a two- to four-fold increase in the prevalence of coronary artery disease (CAD), stroke, and peripheral vascular diseases (collectively referred to as macrovascular complications) in patients with diabetes, compared with subjects who do not have diabetes. The risk of first myocardial infarction in patients with diabetes is similar to that of recurrent myocardial infarction in persons without diabetes who have had a previous heart attack[48]. Thus, diabetes is not merely a risk factor but a CAD risk-equivalent. Patients with diabetes present with atypical manifestations of CAD (including painless myocardial infarction), which could delay timely diagnosis and intervention. Moreover, myocardial infarction carries a worse prognosis, and angioplasty gives less satisfactory results in patients with diabetes than in those without. These tragic features of macrovascular disease in diabetes operate across all ethnic lines.

Unlike microvascular complications, the rela-

Table 4. Diabetes Management: Patient Compliance and Practices by Ethnicity* (adapted from reference 49, with permission)

	Hispanic (%)	African-American (%)	Caucasian (%)
Missed clinic	1.4	1.9	1.5
Noncompliance	34	27	26
Alcoholism	3.4	2.2	2.5
Missed foot clinic	0	2.7	5.6
Missed weight visit	17	15	9
Missed eye clinic	0	2	7

* There were no significant radical/ethnic differences in compliance behavior.

tive risks of macrovascular complications have not been shown consistently to be higher among ethnic minorities with diabetes. In fact, the collective data indicate similar or lower rates of myocardial infarction and stroke in African-American, Asian, and Hispanic populations compared with white Americans[49,50]. Given the higher prevalence of hypertension and diabetes in African Americans compared with whites, the findings of reduced relative risks for myocardial infarction and stroke suggest the presence of possible mitigating factors, among which may be a less atherogenic lipoprotein profile[38]. In contrast to the similar or reduced rates of macrovascular disease, mortality from CAD is disproportionately higher in minority populations (especially African-American women) than in caucasians[51]. Thus, the finding of somewhat better macrovascular risk profile in patients with diabetes from minority populations is no reason for complacency. The usual primary and secondary prevention practices (e.g., smoking cessation, aspirin prophylaxis, judicious use of ACE inhibitors and (β-blockers, and aggressive control of blood glucose, blood pressure, and lipids) should be enthusiastically implemented in patients with diabetes from all ethnic backgrounds.

MECHANISMS AND MEDIATORS

Theoretically, the increased microvascular complications of diabetes among ethnic minorities may be caused by genetic susceptibility or acquired environmental (including cultural, behavioral and socioeconomic) factors.

Genetic Susceptibility

There is some evidence for familial clustering of microvascular complications—especially diabetic nephropathy—in certain ethnic minority populations[38]. This suggests a role for hereditary factors in the pathogenesis of microvascular complications. Data from landmark studies offer an expanded perspective in this area. In the Diabetes Control and Complications Trial[41], intensive glycemic control resulted in a 50% to 70% reduction in the risk of development of retinopathy, neuropathy, or nephropathy. In the United Kingdom Prospective Diabetes Study (UKPDS), intensive glucose control reduced the risk of a doubling of serum creatinine by 74%, among other benefits[42]. These rather large effects of glycemic control on target organ end points indicate that genetic factors are permissive rather than obligate determinants of risk. In the NHANES III retinopathy data, the black/white disparity no longer was significant after adjusting for known risk factors for retinopathy, such as chronicity of diabetes, HbA_{1c} level, and blood pressure[43].

Acquired Factors

Nongenetic factors that could promote the development of complications from a chronic disease include patient practices, suboptimal care, and socioeconomic factors. What follows is a discussion of the role of these factors in determining increased morbidity from diabetes in ethnic minorities.

Patient Compliance. Physicians and other healthcare providers often explain away suboptimal outcome on the basis of possible noncompliance with therapeutic recommendations. Such sentiments are frequently expressed in clinical settings around the world. Yet careful studies have revealed no evidence of significant ethnic or racial differences in global compliance with diabetes-related tasks (Table 4)[52]. A notable exception is self-monitoring of blood glucose (SMBG); approximately

Table 5. Medical Care for Black Adults and White Adults with type 2 Diabetes*
(adapted from reference 7, with permission)

	Black (%)	White (%)
≥4 physician visits/y	62.4	58.9
Insulin	51.9	35.9
Oral agents	50.1	39.9
Following diet	88.9	88.2
SMBG	18	35
Visit dietitian	28	19
Diabetes education	43	32
Eye examination	64	60
Visit podiatrist	19	16

SMBG = self-monitoring blood glucose
* National Diabetes Data Group. Analysis based on 1989 clinical data.

18% of African-American patients were testing at the minimum recommended frequency compared with approximately 30% of Latino and caucasian patients[7]. It must be noted, however, that the frequency of self-monitoring is suboptimal even among Latinos and caucasians.

An unsubstantiated impression of general noncompliance tends to undermine further aggressive therapeutic action by the physician. This could be tragic for the effective management of diabetes, an undertaking that draws sustenance from positive interactions between patient and physician. It is therefore imperative that the label of noncompliance be avoided, unless admitted to by patients or proven by objective criteria. Even after a patient has been found to be noncompliant, it behooves the caring physician to understand and attempt to correct the barriers or misguided premise that led to such behavior.

Physician Practices. Another theoretical explanation for the increased morbidity from diabetes in ethnic minorities is systematic delivery of suboptimal care. Indeed, reduced HbA_{1c} testing frequency and poorer results have been reported in African Americans compared with caucasians[53]. Such reports indicate that there are disparities in the quality of care rendered to persons with diabetes. However, national surveys do not support the notion of widespread, systematic undertreatment of minority patients as an explanation for the increased morbidity from diabetes (Table 5)[54]. There is no evidence of discrimination in referral patterns or use of insulin or oral agents for correction of hyperglycemia[54]. What is evident is a poor overall state of diabetes control in the nation at large[55-57].

Socioeconomic Factors. There is abundant literature on the contributions of low socioeconomic status, limitations in access to care, lack of health insurance or underinsurance, and other socioeconomic barriers to increased burden of diabetes and its complications[53,58]. One glaring example is diabetic ketoacidosis (DKA): in one study of African Americans, cessation of insulin was the major precipitating cause of DKA[59]. It was further documented in that study that 43% of patients stopped taking insulin, because they had no means of replenishing their spent stock of insulin, and 25% stopped because of a fundamental misunderstanding of the role of insulin therapy during sick days[60]. Thus, nearly two-thirds of the cases of DKA among African Americans in that study were preventable, either through renewal of insulin supplies or education to improve self-management skills.

Indeed, much of what passes as ethnic disparities in clinical outcomes may be mediated to a large extent by socioeconomic factors. For example, the marked ethnic disparity in lower-extremity amputation rates observed in the general diabetic population is not evident in an ethnically diverse population with uniform healthcare coverage[50]. Even the low frequency of SMBG has socioeconomic underpinnings: with identical health insurance coverage, the frequency of SMBG among African Americans increased to match or exceed that of Asian, Latino, or caucasian patients[50].

IMPLICATIONS FOR DIABETES PREVENTION AND MANAGEMENT

Studies have shown that when blood glucose levels are controlled to a similar degree, the rates of diabetic nephropathy, neuropathy, and retinopathy are similar in white and non-white patients. Also, in the recently concluded Diabetes Prevention Study, the response rates to intensive lifestyle or pharmacologic intervention were identical in African Americans, Asian Americans and Pacific Islanders, Latinos, Native Americans, and white Americans[34]. These findings, demonstrating lack of ethnic disparity in the responsiveness to antidiabetic regimens, are indeed heartening. The targets for glycemic control for persons with diabetes, as recommended by the American Diabetes Association, are: average preprandial blood glucose values of

80–120 mg/dL; bedtime blood glucose of 100–140 mg/dL; and HbA_{1c} of 7% or lower[61]. The American College of Endocrinology Diabetes Mellitus Consensus Conference recommends a fasting glucose target of less than 110 mg/dL and an HbA_{1c} of less than 6.5%. All recommendations are in general agreement that the goals of diabetes management are normalization or near-normalization of fasting and postprandial blood glucose levels and prevention of acute and long-term complications.

Nonpharmacologic Approaches

Self-monitored blood glucose is an important (but underutilized) tool of diabetes management and education. Performance of SMBG is associated with superior glycemic control[62]. The recommended frequency of SMBG is two to four times or more daily for insulin-treated patients. The optimal frequency has not been established for patients with type 2 diabetes treated with oral agents, but regular SMBG (at least once daily) is recommended. The results of SMBG should be reviewed by the physician, and appropriate feedback should be given.

Diabetes education, and dietary and exercise counseling are effective in minority populations, as was demonstrated clearly in a study at Grady Memorial Hospital in Atlanta, GA[63]. These approaches should be promoted as important adjuncts to pharmacotherapy of type 2 diabetes—best accomplished through referral to certified diabetes educators and dietitians. Regular physical activity enhances insulin sensitivity, decreases abdominal obesity, and improves blood pressure and lipid levels. Exercise programs should be tailored to the individual patient's physical condition and should always include warm-up and cool-down periods. To be effective, programs should use aerobic exercise (e.g., walking, cycling, swimming) at approximately 60% of maximum oxygen utilization (VO_2 max) for 30 minutes, three or more times per week. Cardiac screening with stress electrocardiogram (ECG) is recommended for patients aged 35 years or older, especially those who have been sedentary.

Medications

The ideal treatment for type 2 diabetes should reverse insulin resistance (and the associated metabolic syndrome), normalize hepatic glucose production, improve β-cell function, and prevent the development of long-term complications[26,46]. Medications used for treating diabetes include insulin and oral agents. The oral agents include insulin secretagogues (sulfonylureas, repaglinide, nateglinide); metformin, which is a biguanide; a-glucosidase inhibitors (acarbose and miglitol); and insulin sensitizers or thiazolidinediones (rosiglitazone and pioglitazone).

Pharmacotherapy for diabetes is most effective if initiated as part of a comprehensive management plan that includes SMBG, patient education, and dietary and exercise counseling. The mnemonic MEDEM (**m**onitoring, **e**ducation, **d**iet, **e**xercise, **m**edications) can be used to recall the key modalities of diabetes management[60]. Long-term therapy for type 2 diabetes requires the use of multiple agents in combination because of progressive β-cell failure and insulin resistance. Based on data from the UKPDS, approximately 60% of patients responding initially to treatment with sulfonylurea or metformin will require a second agent within three years, to maintain HbA_{1c} at 7% or below[64]. This loss of glycemic control is attributable to the fact that the traditional antidiabetic agents (sulfonylureas, metformin, insulin) do not preserve β-cell function or directly impact insulin resistance, two core defects underlying type 2 diabetes. Medications for combination therapy should be selected from drug classes that lower blood glucose by different mechanisms, to ensure additive or synergistic effects and to maximize nonglycemic benefits.

Matching Pathophysiology with Treatment

Genetically driven insulin resistance is an underlying feature of type 2 diabetes in minority populations. Given this backdrop, it can be predicted that interventions that improve insulin sensitivity will be particularly effective in these populations. Indeed, experience with dietary and pharmacologic interventions support such a notion. Restriction of total and saturated fat intake, with augmentation of complex carbohydrates and dietary fiber, enhance insulin sensitivity[65]. Using a dietary approach based broadly on these principles, Ziemer and colleagues demonstrated excellent response rates among African-American patients with type 2 diabetes[63]. Within six to twelve months of initiation of the program, HbA_{1c} levels decreased by nearly 2%, and the need for insulin secretagogues and exogenous insulin was substantially reduced[63]. Thus, the basis for the improved glycemic control is most consistent with amelioration of insulin resistance. Regular

exercise, caloric restriction, and weight loss have profound insulin-sensitizing effects that constitute a prophylaxis against the development of diabetes in high-risk patients, as was shown in the Diabetes Prevention Program[34].

Thiazolidinediones

Of the numerous classes of medication available for treatment of type 2 diabetes, only the thiazolidinediones (TZDs) exploit tissue sensitization to insulin as their dominant mechanism of action (66). Rosiglitazone and pioglitazone are the two TZDs in current clinical use. The TZDs enhance insulin sensitivity via mechanisms that involve binding to a nuclear receptor (called peroxisome proliferator-activated receptor γ or PPARγ). Interaction between TZDs and PPARg receptors influences the transcription of genes that regulate carbohydrate and lipid metabolism.

The TZDs have beneficial effects on many components of the metabolic syndrome, thereby improving risk markers for cardiovascular disease[67]. There is also evidence that the TZDs exert a favorable effect on pancreatic β-cell function [68,69]. A dual effect on insulin resistance and β-cell function by the TZDs can be expected to result in improved glycemic control that is sustained over long periods[70], thereby reducing the risk of diabetic complications. As predicted, exquisite sensitivity to the metabolic effects of rosiglitazone has been reported in ethnic minority populations with type 2 diabetes, including African Americans, Mexican-Americans, and Chinese patients[69,71,72].

Aggressive glycemic control is needed to maintain HbA_{1c} levels below 6.5% and to prevent the development of diabetic complications (61,73). Consequently, combination therapy with oral antidiabetic agents with complementary mechanisms of action—such as a TZD and a biguanide or an insulin secretagogue—is often needed to reach and maintain target HbA_{1c} levels.

CONCLUSION

There are many reasons why attention should be focused on minority issues in relation to diabetes. First, minorities suffer disproportionately from type 2 diabetes, the subtype that accounts for 95% of all cases of diabetes. Second, many of the long-term complications of diabetes, including premature death[74], occur more frequently among minorities compared with non-Hispanic whites, thus compromising quality and quantity of life. Third, there are indications of disparities in access to care and socioeconomic factors that aggravate the unequal burden of diabetes among minority populations. The ethnic disparities in diabetes complications are largely erased by equalization of glycemic control across ethnic groups. Indeed, all interventions tested to date (lifestyle and pharmacologic) have been effective in controlling diabetes and preventing complications in all populations. Thus, there is no ethnic disparity in the responsiveness to antidiabetic interventions. This realization should trigger a policy of aggressive diabetes management in patients from ethnic minority backgrounds, in an effort to minimize the ravages of diabetes in these populations. Ultimately, a well-articulated public health approach focusing on primary prevention would be an even more compelling endeavor.

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