



Ethnic, Racial and Hereditary Influences in Diabetes

Is it nature, nurture, or both?

BY KENNETH B. REHM, DPM

Having practiced all my life in various urban and rural areas with ethnically and racially diverse demographics, I have repeatedly observed in my practice unambiguous patterns in the clinical presentation of diabetes, demonstrating distinctly different phenotypes, which are replicated consistently within each of my different patient population groups.

I always wanted to know why these stark differences occur. Was it

the individual's culture and/or cuisine that each was immersed in, i.e., the typical Mexican diet, or the soul food that was central to the southern African-American culture? Or was it merely biology or genetics, or a combination of nature and nurture?

Why did I observe certain groups of Hispanic men to be generally thin and on dialysis, and African Americans as more obese?³¹ Women of Mexican descent having more visceral fat around the belly? Caucasian women being more Rubenesque? The

motivation to seek out answers came from the nagging desire to develop efficient, targeted and optimized preventive strategies. To try to seek out answers, this article attempts to:

- 1) Identify population groups that are at high risk for diabetes mellitus and its complications
- 2) Extract meaning from the trends seen with different clinical presentations, always keeping in mind how foot pathology is related
- 3) Allow the reader to appreciate

Continued on page 126

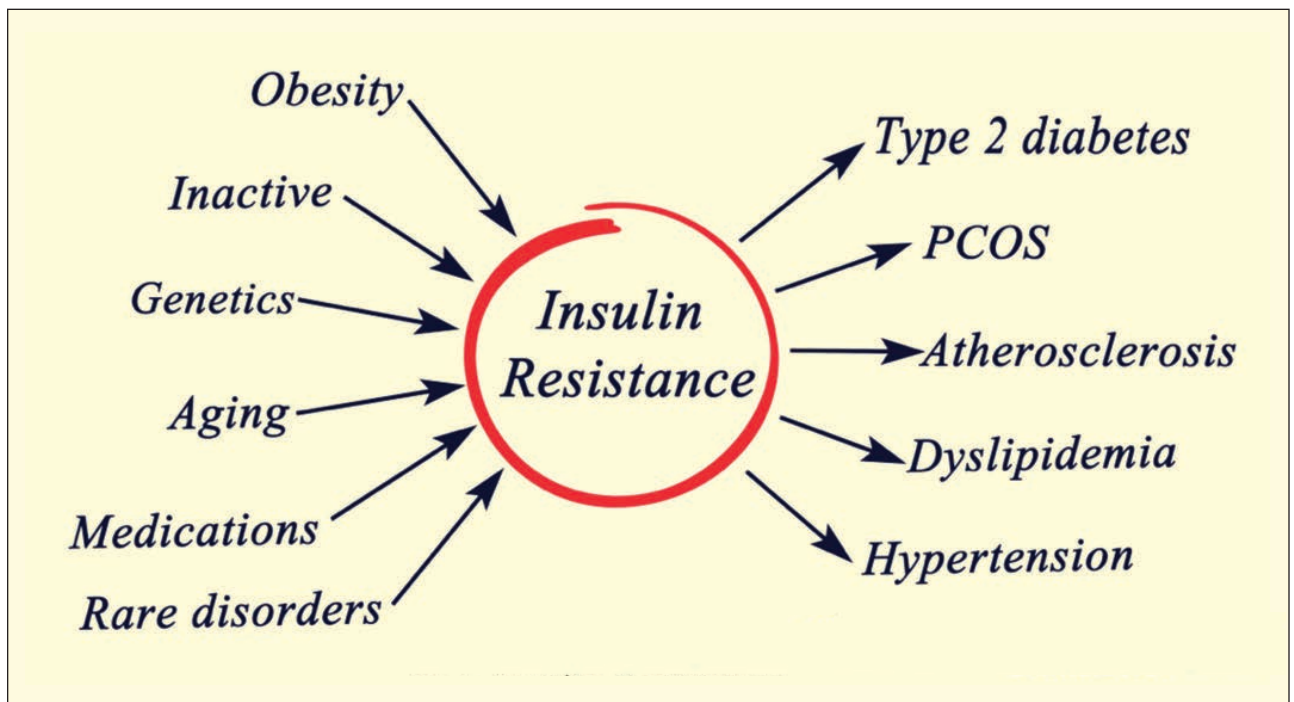


Figure 1: Insulin Resistance



Ethnic (from page 125)

the most effective approaches that would, if possible, prevent these complications of diabetes. This effort must incorporate any ethnic and/or racial influences.

Many factors contribute to the mosaic pattern of the clinical presentation and complications seen in diabetes. To begin the process of exploring the mystery of what's behind these myriad variations—and the role that ethnicity and race might play—it is important to elucidate the definitions of ethnicity and racial categories. This lends clarity to our conversation regarding the clinical patterns of diabetes being passed on from generation to generation.



Figure 2: Risk Factors of Diabetes

Two Categories of Ethnicity

Primarily, there are two categories of ethnicity typically used as the benchmarks when discussing this subject:

- Non-Hispanic or Non-Latino.
- Hispanic or Latino

Ethnic groups included with those of Hispanic origin are the following: Mexican, Puerto Rican, Cuban, Central American, South American, others of Spanish origin regardless of race. It is interesting to note that nearly all Americans of Hispanic origin are racially classified as White.

Race, on the other hand, is a social construct and not a consistent biologic one and may change over time. This presents a challenge in reconciling classifications representing diversity of populations. However, traditionally, there are five basic race categories:

- Black or African American
 - Asian
 - Pacific Islander, which includes those from Guam, native Hawaiians, Samoans, natives or descendants from other Pacific Islands.
 - American Indian, including Alaskan native
 - Caucasian or White
- Of course, deciding which factors

are inherited and which are not is a daunting task for epidemiologists.

Factors that Come into Play

There are *genetic as well as pure biologic factors*. For instance, the more fatty tissue one has, the more resistant cells are to insulin. (Figure 1) Are

migration status all play a vital and distinct role in the development of diabetic complications.

Risk factors for type 1 diabetes include family history, race (with whites at higher risk than other racial or ethnic groups), and certain viral infections during childhood, suscepti-

Religion, belief systems, cultural differences, cuisine and immigration status all play a role in the development of diabetic complications.

there groups of people that tend to have more body fat than another? Men vs. women? The more active you are, the less risk there is for diabetes. Are there inherited factors that would predispose someone to different activity levels?

There are *social as well as environmental factors* that play into various health behaviors. These are influenced by economic factors, level of education as well as health care access and health insurance considerations. Religion, belief systems, cultural differences, cuisine and im-

bility to which may be sometimes biologically or genetically established.

Risk factors for type 2 diabetes are more diverse; some are modifiable, and others are not. Non-modifiable risk factors for type 2 diabetes include age, race, ethnicity, family history and genetic predisposition, history of gestational diabetes, and low birth weight (Figure 2).

One illustration of how race and ethnicity become risk factors for development of diabetes is that African Americans are more likely to devel-

Continued on page 127



Ethnic (from page 126)

op diabetes type 2 than Caucasians.¹ Moreover, the disease is often pre-determined to show up in adulthood because of deficient prenatal care and low-birth-

as diet and physical activity) appear also to be significant culprits.¹

**Major Diabetic Complications:
Their Racial and Ethnic Influences**
Diabetic complications affecting

ly that multiple genes influence disease expression, making it difficult to isolate and characterize the effects of each disease-determining locus. Genes may interact (epistasis) or induce susceptibility independently (heterogeneity). And of course the idea of pinpointing causation is made even more difficult because of social and environmental factors.

While macrovascular complications affect the coronary, cerebral and peripheral arteries, microvascular complications cause diabetic kidney disease (DKD), which can lead to renal failure, diabetic retinopathy (DR) that often leads to loss of sight, as well as peripheral and autonomic neuropathy. Pathologically elevated blood glucose levels, measured as glycated hemoglobin, are a major risk factor for both micro and macrovascular disease. In addition to clinical risk factors, it is important to discuss how genetic factors affect the risk as well.

Continued on page 128

D2T is often pre-determined to show up in adulthood because of deficient prenatal care and low-birth-weight, which is commonplace with babies in the black communities.

weight, which is commonplace with babies in the black communities.

Another illustration: in Native Americans, the rates of diagnosed diabetes range from 5% to 50% in different tribes and population groups. Little difference exists in terms of sex. Besides genetic factors, non-genetic or lifestyle risk factors (such

the kidneys, retina, nerves, and the cardiovascular system are the major causes of morbidity and mortality in diabetes; and based upon recent findings, especially from genome-wide association studies², there appears to be a certain amount of genetic ethnic basis for these complications. For most complex diseases, it is like-



Ethnic (from page 127)

Diabetic Retinopathy

Diabetic retinopathy (DR) is the most common microvascular complication of diabetes. Visual loss from diabetic retinopathy results primarily from two complications: 1) new vessels grow on the retina; this is known as proliferative retinopathy and accounts for the majority of severe visual loss; and 2) retinal blood vessels can become permeable and cause swelling of the center of the

retina—this is called diabetic macular edema. Clinically significant macular edema is a leading cause of moderate visual loss in diabetes. Proliferative retinopathy, severe non-proliferative retinopathy and clinically significant macular edema can be considered as sight-threatening retinopathy. The established risk factors of DR include prolonged exposure to hyperglycemia and hypertension. However, DR can progress despite optimal control of these risk factors. It is thought that genetics play a central role here.⁹

DR is one of the leading causes of blindness worldwide⁹ affecting 30% of subjects with T2D (type 2 diabetes) and 50–80% of subjects with T1D (type 1 diabetes).^{14,15} In addition to partially shared pathophysiological mechanisms, there is evidence of a shared genetic background between DR and DKD.²⁷ In one study, among the T1D subjects with severe renal complications, nearly all have at least some level of diabetic retinal changes.¹

Interestingly, DR has the high-

Continued on page 129

DIABETIC NEPHROPATHY KIDNEY DISEASE

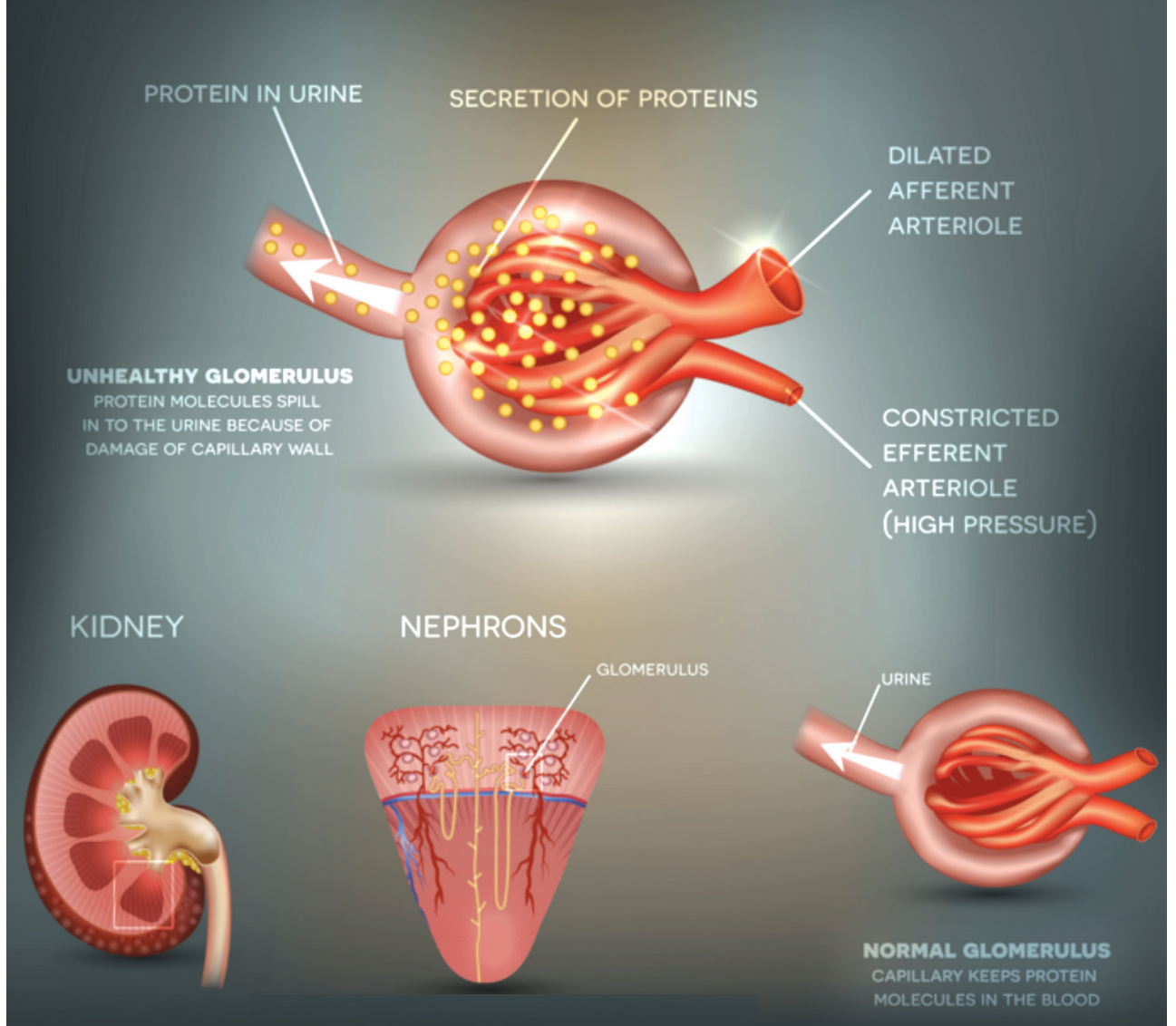


Figure 3: Diabetic Kidney Disease



Ethnic (from page 128)

est sibling recurrence risk of the microvascular diabetic complications¹⁶ and the heritability estimates for DR range from 25 to 52%.^{17,21}

One study¹ reports that in type 2 diabetes, the prevalence of any DR was highest in African/Afro-Caribbeans; and was higher than South Asians with European Caucasians the lowest. Similarly, sight-threatening DR was also significantly more prevalent in Afro-Caribbeans and South Asians compared to White Europeans. Differences observed in Type 1 diabetes did not achieve levels of statistical significance.

Recent studies showed that the prevalence of any diabetic retinopathy and macular edema was significantly higher in Blacks and Hispanics than in Caucasians or Chinese.²⁸ Mexican-Americans were found to have significantly higher prevalence of DR than Non-Hispanic Blacks. Native Americans have one of the highest prevalence rates of DR when compared with all Non-Native American populations. Significant independent predictors of any retinopathy were found to be: longer duration of diabe-

Renal Complications in Diabetes

Diabetic kidney disease (DKD) (Figure 3) is a devastating sequela of both T1D and T2D. This progressive disease classically commences with microalbuminuria (urinary excretion of low concentrations of albumin)

interesting to note that according to one major study³⁸ there is a two-fold risk of women developing ESRD over men. Also, there is a strong genetic susceptibility seen in African Americans for many non-diabetic renal diseases. This study also indicates

In other studies Asians had significantly higher rates of End-Stage Renal Disease as compared to all Non-Hispanic Whites.

and progresses to macroalbuminuria (urinary excretion of high amounts of albumin); it then leads to a decreased estimated glomerular filtration rate (eGFR), heralding a loss of renal function. This loss can also occur without albuminuria. Despite advances in medical care, from 2-20% of those with T1D develop end-stage renal disease (ESRD) requiring dialysis or renal transplant, which poses a 14-fold risk of mortality compared with diabetic subjects without renal complications.⁹

The way that DKD presents clinically is termed the phenotype, and

that end stage renal disease attributable to diabetes is greatest among black men and women and lowest among white women. The appreciation of these inheritance patterns in subjects with T2D is then likely due to unrecognized non-diabetic renal disease co-occurring with T2D. This highlights the challenge of phenotypic heterogeneity, particularly in subjects with T2D: while most subjects with T1D and albuminuria have pathological renal lesions characteristic of diabetic nephropathy, there is a spectrum of renal pathologies in subjects with T2D where only a third of the patients with albuminuria have typical diabetic nephropathy.³³

Furthermore, genetic variants of T2D suggest an increased susceptibility to DKD with increasing BMI, suggesting that BMI and metabolic changes behind T2D also play the same role in the development of DKD and T1D. There is also genetic evidence that supports epidemiological findings that smoking cessation is beneficial for avoiding DKD. In addition to proposing novel genes for the pathology of DR, some authors² suggest that DNA patterns could be used as biomarkers to predict

DR, a step in the right direction for employment of our available genetic technology to potentially prevent this devastating complication.

Interestingly, various other clinical studies show that African-American and Hispanic Americans have higher prevalence rates of end-stage renal disease (ESRD) but with lower mortality rates as compared with Non-Hispanic Whites. In other stud-

Continued on page 130

Recent studies showed that the prevalence of any diabetic retinopathy and macular edema was significantly higher in Blacks and Hispanics than in Caucasians or Chinese.²⁸

tes, higher fasting serum glucose, use of diabetic oral medication or insulin and greater waist to hip ratio. In these studies, race, in and of itself, however, was not considered an independent predictor of any retinopathy.

In other research⁵ on DR, genetic markers were found in Mexican Americans, Taiwanese, Chinese, Japanese and White Australian subjects with T2D and in

European subjects with T1D. Minority ethnic communities with type 2 diabetes in the UK were found to be more prone to diabetic retinopathy, including sight-threatening retinopathy and maculopathy, compared to White Europeans.

various specific phenotypes and their associated genetic markers show up in different ethnic and racial groups. In the population of European Americans who have T1D, there have been genetic loci isolated for DKD by itself. In those who claim European ancestry outside of the United States who have T1D, genetic loci have been isolated for both phenotypes; one that presents with both DKD and ESRD together; and another that presents with just ESRD. In Finnish subjects there are genetic markers for just albuminuria. With T2D, there are genetic loci isolated for the phenotype DKD in both the Japanese and the African American population. It is



Ethnic (from page 129)

ies Asians had significant higher rates of ESRD as compared to all Non-Hispanic Whites.

Diabetic Neuropathy

Diabetic neuropathy is the most common complication of diabetes mellitus (DM), affecting as many as 50% of those afflicted with either Type 1 or Type 2 diabetes. This condition is thought to result from a microvascular injury to the small blood vessels, the vasa nervorum, which delivers blood and nutrition to the interior parts of peripheral nerves and their coverings (Figure 4). It is also one of the most common complications seen affecting the feet, showing up as a spectrum of clinical manifestations. This clinically manifests in myriad expressions, including sensory neuropathy, autonomic neuropathy and/or motor neuropathy. Moreover, each of these types of neuropathy has its own varietal expression. Sensory neuropathy can be revealed through a host of symptoms such as severe pain, loss of sensation, burning and itching. Motor neuropathy presents as atrophy and weakness. Autonomic neuropathy is expressed as dryness and/or atrophy of the skin, as well as the dysfunction of the autonomic physiology of the body, most commonly affecting urologic, cardiac and gastrointestinal function. Distinct distribution patterns such as mononeuropathy, cranial nerve palsy, and polyneuropathy are also characteristic of different forms of neuropathy.

It therefore becomes apparent, as evidenced by the many clinical

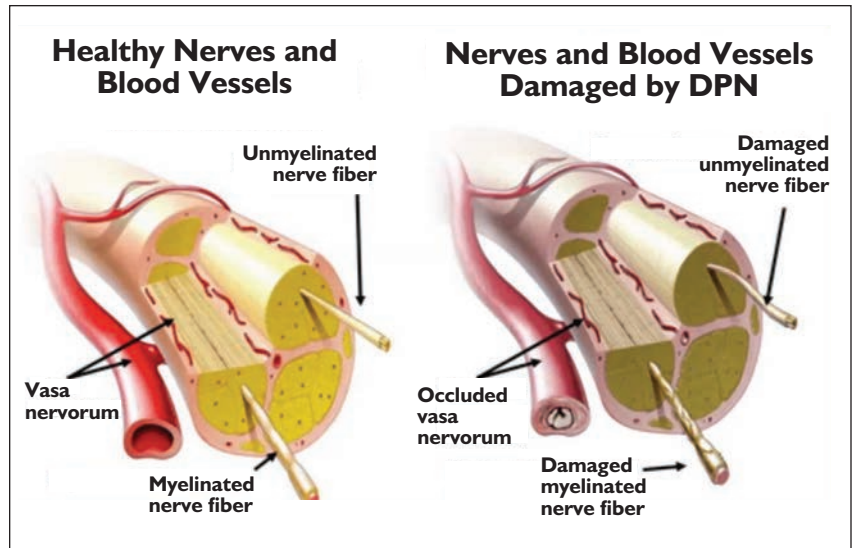


Figure 4: Nerves and Blood Vessels: Healthy vs Damaged by DPN

variations possible, that defining a specific phenotype that encapsulates peripheral neuropathy is virtually unattainable. Because of these challenges, only a few studies focusing on inheritance patterns in diabetic neuropathy have been performed. There have been, however, a few studies² on individual genes, deletions and insertions that show some evidence of inheritance patterns that could potentially be aligned with diabetic neuropathy. In addition, familial clustering has been documented,³³ but the numbers are more modest than for other microvascular complications. One recent study³⁴ demonstrates an inheritance pattern for diabetic neuropathic pain; and when stratified by gender the heritability was higher in males (30%) than in females (15%).

In other literature, a comprehensive review¹ of the available studies found no statistically significant

variance among different ethnic or racial groups. However, these results should be interpreted with caution, as there was variability in the definition of diabetic neuropathy, consistency of methodology, as well as cultural and language barriers that could have impacted the results.

Cardiovascular Complications in Diabetes

Cardiovascular disease (CVD) is a major cause of morbidity and the most common cause of death in those afflicted with either T1D or T2D. Here, genetic background acts in concert with lifestyle factors to determine the rate at which risk factors degenerate into the three main avenues by which CVD manifests itself: coronary artery disease (CAD), cerebrovascular disease and peripheral arterial disease (PAD). Research-

Continued on page 131

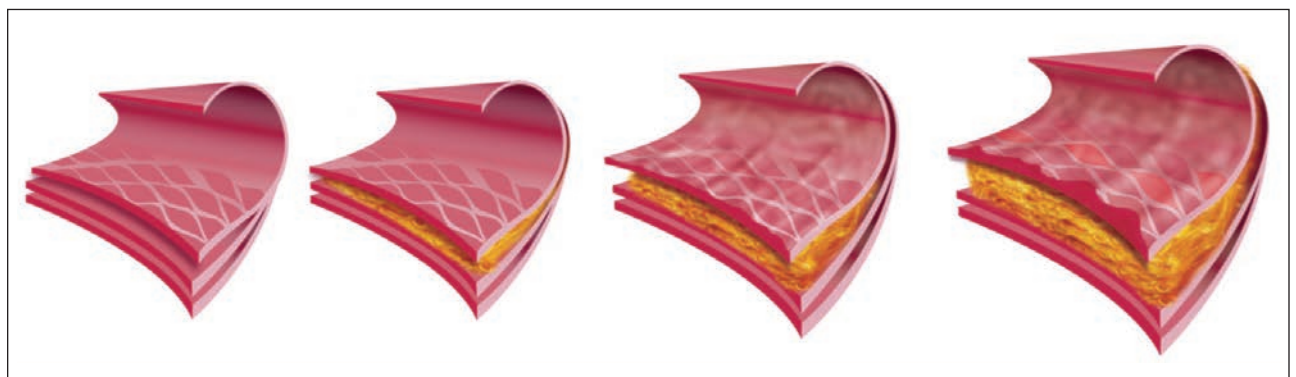


Figure 5: Stages of Atherosclerosis



Ethnic (from page 130)

ers have discovered how diabetes and insulin resistance, by driving inflammation and therefore slowing blood flow, dramatically accelerates atherosclerosis, or hardening of the arteries (Figure 5), which is essential to the development of CVD. Experts once believed that atherosclerosis developed solely when too much cholesterol clogged arteries with fatty deposits called plaques; and when blood vessels became completely blocked, heart attacks and strokes occurred. Today most agree, however, that the reaction of the body's immune system to fatty build-up, more than the build-up itself, creates cardiovascular risk.² This inflammatory

and with women and men equally affected.^{35,36} It is worth mentioning that among subjects with T2D, an adverse cardiovascular risk profile can be observed, even before diabetes diagnosis,³⁷ whereas CVD occurs much quicker in the disease process and is a long-term complication, in T1D.

One has to consider the inheritance patterns unique to each clinical pathway displayed in CVD.² In CAD specifically, family history is an important risk factor in both the general population and among insulin-treated subjects with diabetes, suggesting a genetic influence. In family studies in T2D, a heritability of 41% was attained for intima media thickness, a marker of subclinical atherosclerosis that would eventually lead to frank

In Coronary Artery Disease, family history is an important risk factor in both the general population and among insulin-treated subjects with diabetes.

condition is the main contributor to narrowing of the arteries; and the resulting compromised blood flow to organs such as the heart muscle, the brain and the extremities is what causes the devastating sequelae of cardiovascular disease. Herein lies the vital impact that an inflammatory lifestyle has on the complicated etiology of cardiovascular disease. Still, genetics also play a key role in the development of this morbidity.

It is interesting to note that diabetes has been considered a "CVD equivalent," i.e., subjects with diabetes have the same risk of a cardiovascular event as subjects with pre-existing CVD, shedding uncertainty on the role of diabetic-related pathology in the development of CVD, and the relative significance of the associated inheritance patterns.

What do we know? One thing is that the connection between DKD and CVD is particularly strong in T1D: 40% of patients with DKD develop CVD by the age of 40, as compared to 7% in patients without DKD.³⁵ CVD also occurs much earlier in life in T1D than in T2D, with a more rapid disease progression,

coronary artery disease. Also, there are markers that were identified on certain genes associated with the development of CAD in persons with both types of diabetes, but in non-diabetic participants, no association of this same marker was identified.² To complicate the picture even more, genetic patterns have been studied that proposed that the degree of morbidity and also the degree of mortality are individually inherited traits. Further, there are genes present in those with diabetes as well as those without that represent equal cardiovascular risks in the face of normoglycemia. However, with poor glycemic control in T2D these same genes magnify the risk of CAD considerably, leading to the postulation that these genes are only triggered by hyperglycemia.

Concerning the genetic basis of *cerebrovascular disease, or stroke*, in T1D as well as T2D, we do know that the incidence is elevated, particularly in the presence of other complications. Genetic studies on stroke in diabetes are currently lacking; some of the genetic studies on cardiovascular complications in diabetes have in-

Continued on page 132



Ethnic (from page 131)

cluded stroke in the composite CVD phenotype, but have not separately considered stroke or its subtypes.

In the general population, however, we do know that there are genetic factors involved in the different subtypes of strokes, namely ischemic strokes stemming from large vessel disease, cardioembolic phenomena causing stroke, and those which are caused by small vessel disease.²

Peripheral arterial disease, clinically, is seen rather uniformly in persons with diabetes across the ethnic and racial divides.² In so keeping, relatively few genetic risk loci have been identified that affect the development of this complication. There is, however, a gene identified associated with PAD in both the general population as well as in diabetes; but there exist polymorphisms of this gene that are only associated with PAD in diabetes.

In Summary

We have seen that there *are* racial and ethnic influences that play a role in the clinical landscape of diabetes mellitus. Nonetheless, the pathways of inheritance, posing so many variables, present a complicated maze of diverse algorithms, each of which offers an unpredictable outcome. What we do know, undeniably, is that genetics are not solely and purely formative, but rather they interplay

with the subtle influences of economics, access to care, environment, attitude, behavior, lifestyle, social support, quality of life, personal responsibility and self-care. A clear-cut demonstration of inheritance patterns is therefore indeterminable because the missing link in the equation is the patient himself, who still has control over his life and has a major impact on the severity of his own disease.

In conclusion, there is a lot more that needs to be dis-

We have seen that there *are* racial and ethnic influences that play a role in the clinical landscape of diabetes mellitus.

cussed to fully appreciate racial and ethnic influences in the development of diabetes and its complications. Further discussions should focus not only on the biologic sciences but also on the social, political and economic issues that impact care for those with diabetes, a life or death condition for those that we see as patients, and those we probably wouldn't. **PM**

References

- ¹ Elias K. Spanakin, MD and Sherita Hill Golden, MD, MHS Race/Ethnic Difference in Diab. *Curr Diab Rep.* Author manuscript; available in PMC 2014 Dec 1. Published in final edited form as: *Curr Diab Rep.* 2013 Dec; 13(6): 10.1007/s11892-013-0421-9.
- ² Emma Dahlström & Niina Sandholm, Progress in Defining the Genetic Basis of Diabetic Complications. *Curr Diab Rep* (2017) 17: 80
- ³ Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA.* 2002;287(19):2570–81.
- ⁴ Groop PH, Thomas MC, Moran JL, Wadèn J, Thorn LM, Mäkinen VP, et al. The presence and severity of chronic kidney disease predicts all-cause mortality in type 1 diabetes. *Diabetes.* 2009;58(7):1651–8.
- ⁵ Forbes JM, Cooper ME. Mechanisms of diabetic complications. *Physiol Rev.* 2013;93(1):137–88.
- ⁶ University of Rochester Medical Center. "How Diabetes Drives Atherosclerosis." *ScienceDaily*, 17 March 2008. www.sciencedaily.com/releases/2008/03/080313124430.htm
- ⁷ Ahlqvist E, van Zuydam NR., Groop LC, McCarthy MI, The genetics of diabetic complications. *Nat Rev Nephrol.* 2015 May;11(5):277–87.
- ⁸ Anjali D Deshpande, Marcie Harris-Hayes, Mario Schootman Epidemiology of Diabetes and Diabetes-Related Complications. *Phys Ther.* 2008 Nov; 88(11): 1254–1264.
- ⁹ Cowie CC1, Port FK, Wolfe RA, Savage PJ, Moll PP, Hawthorne VM. Disparities in incidence of diabetic end-stage renal disease according to race and type of diabetes. *N Engl J Med.* 1989 Oct 19;321(16):1074–9.
- ¹⁰ Andrew J. Karter, PhD; Assiamira Ferrara, MD, PhD; Jennifer Y. Liu, MPH; et al Howard H. Moffet, MPH; Lynn M. Ackerson, PhD; Joe V. Selby, MD, MPH Ethnic Disparities in Diabetic Complications in an Insured Population *JAMA.* 2002;287(19):2519–2527. doi:10.1001/jama.287.19.2519
- ¹¹ Jung-Ah Lee, MN, RN, Chuan-Fen Liu, PhD, MPH, Research Assistant Professor, and Anne E Sales, PhD, RN, Asso-

Continued on page 133



Ethnic (from page 132)

ciate Professor, Racial and Ethnic Differences in Diabetes Care and Health Care Use and Costs. *Prev Chronic Dis.* 2006 Jul; 3(3): A85.

¹² Ira J. Goldberg, Why does diabetes increase atherosclerosis? I don't know! *J Clin Invest.* 2004 Sep 1; 114(5): 613–615.

¹³ Lin JI, Marcum CS1, Myers MF2, Koehly LM1 Racial differences in family health history knowledge of type 2 diabetes: exploring the role of interpersonal mechanisms. *Transl Behav Med.* 2018 Jul 17;8(4):540-549. doi: 10.1093/tbm/ibx062.

¹⁴ Yeh HC, et al. Smoking, smoking cessation, and risk for type 2 diabetes mellitus: a cohort study. *Ann Intern Med.* 2010;152(1):10–7.

¹⁵ Kurian AK, Cardarelli KM. Racial and ethnic differences in cardiovascular disease risk factors: a systematic review. *Ethn Dis.* 2007;17(1):143–52.

¹⁶ American Diabetes, A. Standards of medical care in diabetes—2013. *Diabetes Care.* 2013;36(Suppl 1):S11–66.

¹⁷ Kirk JK, et al. Racial and ethnic disparities in self-monitoring of blood glucose among US adults: a qualitative review. *Ethn Dis.* 2007;17(1):135–42.

¹⁸ Gonzalez JS, et al. Depression and diabetes treatment non-adherence: a meta-analysis. *Diabetes Care.* 2008;31(12):2398–403.

¹⁹ Li C, et al. Prevalence of depression among U.S. adults with diabetes: findings from the 2006 behavioral risk factor surveillance system. *Diabetes Care.* 2008;31(1):105–7

²⁰ Wagner J, et al. Racial and ethnic differences in diabetic patient-reported depression symptoms, diagnosis, and treatment. *Diabetes Res Clin Pract.* 2007;75(1):119–22.

²¹ Heisler M, et al. Mechanisms for racial and ethnic disparities in glycemic control in middle-aged and older Americans in the health and retirement study. *Arch Intern Med.* 2007;167(17):1853–60

²² Karter AJ, et al. Educational disparities in health behaviors among patients with diabetes: the Translating Research Into Action for Diabetes (TRIAD) Study. *BMC Public Health.* 2007;7:308.

²³ Casagrande SS, et al. Built environment and health behaviors among African Americans: a systematic review. *Am J Prev Med.* 2009;36(2):174–81.

²⁴ Lovasi GS, et al. Built environments and obesity in disadvantaged populations. *Epidemiol Rev.* 2009; 31:7–20.

²⁵ Black JL, Macinko J. Neighborhoods and obesity. *Nutr Rev.* 2008;66(1):2–20.

²⁶ Papas MA, et al. The built environment and obesity. *Epidemiol Rev.* 2007;29:129–43

²⁷ Auchincloss AH, et al. Neighborhood resources for physical activity and healthy foods and incidence of type 2 diabetes mellitus: the Multi-Ethnic study of Atherosclerosis. *Arch Intern Med.* 2009;169(18):1698–704.

²⁸ Golden SH, et al. Health disparities in endocrine disorders: biological, clinical, and nonclinical factors—an Endocrine Society scientific statement. *J Clin Endocrinol Metab.* 2012;97(9):E1579–639.

²⁹ Centers for Disease Control and Prevention: Diabetes Complications. Available from: http://www.cdc.gov/diabetes/statistics/complications_national.htm.

³⁰ Karter AJ, et al. Ethnic disparities in diabetic complications in an insured population. *JAMA.* 2002;287(19):2519–27.

³¹ Albu JB, et al. Independent association of insulin resistance with larger amounts of intermuscular adipose tissue and a greater acute insulin response to glucose in African American than in white nondiabetic women. *Am J Clin Nutr.* 2005;82(6):1210–7.

³² Fioretto P, Mauer M. Histopathology of diabetic nephropathy. *Semin Nephrol.* 2007;27(2):195–207.

³³ Monti MC, Lonsdale JT, Montomoli C, Montross R, Schlag

E, Greenberg DA. Familial risk factors for microvascular complications and differential male-female risk in a large cohort of American families with type 1 diabetes. *J Clin Endocrinol Metab.* 2007;92(12):4650–5.

³⁴ Meng W, Deshmukh HA, van Zuydam NR, Liu Y, Donnelly LA, Zhou K, et al. A genome-wide association study suggests an association of Chr8p21.3 (GFRA2) with diabetic neuropathic pain. *Eur J Pain.* 2015;19(3):392–9.

³⁵ Tuomilehto J, Borch-Johnsen K, Molarius A, Forsen T, Rastenyte D, Sarti C, et al. Incidence of cardiovascular disease in type 1 (insulin-dependent) diabetic subjects with and without diabetic nephropathy in Finland. *Diabetologia.* 1998;41(7):784–90.

³⁶ de Ferranti SD, de Boer IH, Fonseca V, Fox CS, Golden SH, Lavie CJ, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. *Circulation.* 2014;130(13): 1110–30.

³⁷ Hu FB, Stampfer MJ, Haffner SM, Solomon CG, Willett WC, Manson JE. Elevated risk of cardiovascular disease prior to clinical diagnosis of type 2 diabetes. *Diabetes Care.* 2002;25(7):1129–34.

³⁸ The Genetics of Nephropathy—an International Effort (The Genie Study).



Dr. Rehm is Medical Director, The Diabetic Foot & Wound Treatment Centers San Marcos, California. He is board certified by the American Board of Multiple Specialties in Podiatry.