We Know More Than We Can Tell About Diabetes and Vascular Disease: The 2016 Edwin Bierman Award Lecture

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Diabetes 2017;66:1735–1741 | https://doi.org/10.2337/db17-0093

The Edwin Bierman Award Lecture is presented in honor of the memory of Edwin L. Bierman, MD, an exemplary scientist, mentor, and leader in the field of diabetes, obesity, hyperlipidemia, and atherosclerosis. The award and lecture recognizes a leading scientist in the field of macrovascular complications and contributing risk factors in diabetes. Clay F. Semenkovich, MD, the Irene E. and Michael M. Karl Professor and Chief of the Division of Endocrinology, Metabolism and Lipid Research at Washington University School of Medicine in St. Louis, St. Louis, MO, received the prestigious award at the American Diabetes Association's 76th Scientific Sessions, 10–14 June 2016, in New Orleans, LA. He presented the Edwin Bierman Award Lecture, "We Know More Than We Can Tell About Diabetes and Vascular Disease," on Sunday, 12 June 2016.

Diabetes is a disorder of abnormal lipid metabolism, a notion strongly supported by the work of Edwin Bierman, for whom this eponymous lecture is named. This abnormal lipid environment continues to be associated with devastating vascular complications in diabetes despite current therapies, suggesting that our understanding of the pathophysiology of blood vessel disease in diabetes is limited. In this review, potential new insights into the nature of diabetic vasculopathy will be discussed. Recent observations suggest that while the concept of distinct macrovascular and microvascular complications of diabetes has been useful, vascular diseases in diabetes may be more interrelated than previously appreciated. Moreover, the intermediary metabolic pathway of de novo lipogenesis, which synthesizes lipids from simple precursors, is robustly sensitive to insulin and may contribute to these complications. De novo lipogenesis requires fatty acid synthase, and recent studies of this enzyme suggest that endogenously produced lipids are channeled to specific intracellular sites to affect physiology. These findings raise the possibility that novel approaches to treating diabetes and its complications could be based on altering the intracellular lipid milieu.

As a scientist who also provides medical care for people with diabetes, I am honored to deliver the Edwin Bierman Award lecture. Dr. Bierman was an eminent physician-scientist, and it is likely that he would have agreed with the statement that nothing drives the search for novel mechanisms that might lead to new therapies like managing a patient with the chronic complications of diabetes.

PROGRESS IN VASCULAR COMPLICATIONS

Dr. Bierman helped define the role of abnormal lipid metabolism in the pathogenesis of vascular disease, the most common cause of death in people with diabetes. Since the time of his contributions, authentic progress has been made to decrease the incidence of diabetes-related complications involving both macrovascular and microvascular disease (1). Relative risks for acute myocardial infarction, stroke, amputations, and end-stage renal disease associated with diabetes decreased between 1990 and 2010. How this happened is probably multifactorial, including the use of statins and inhibitors of the renin-angiotensin system, more options for glucose lowering, and less tobacco use. Despite this progress in relative risk, the overall burden of vascular complications continues to increase for at least two reasons. First, despite currently available therapies, people with diabetes remain much more likely that those

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Received 19 January 2017 and accepted 31 March 2017.

without diabetes to have heart attacks, strokes, limb loss, and renal failure (1). And second, the incidence of both type 1 and type 2 diabetes has increased (2,3).

The considerable residual risk of complications despite modern treatment often prompts clinicians to rely on tacit knowledge that is not easily explained. The title of this lecture, "We Know More Than We Can Tell About Diabetes and Vascular Disease," paraphrases a concept known as Polanyi's Paradox for diabetes care. Michael Polanyi (1891–1976) was an accomplished physical chemist who subsequently became a social scientist and philosopher, developing the premise that human tacit knowledge is critical for the scientific process (4). His paradox deals with the idea that certain tasks require intuitive knowledge that is experiential and cultural and that is distinct from detailed technical knowledge. For example, driving a car requires more than knowing how an engine interacts with a transmission to transmit force to wheels. Likewise, anticipating hypoglycemic events and altering treatment in the context of complicated medical regimens and psychosocial conditions requires more than knowing how insulin suppresses gluconeogenesis and promotes glucose disposal. Tacit knowledge is not evidence-based medicine but is almost certainly required for designing clinical trials that produce robust results destined to alter practice patterns. And in the absence of relevant trial data for an individual patient, skilled providers use tacit knowledge to care for people with diabetes.

RELATIONSHIPS BETWEEN VASCULAR DISEASES IN DIABETES

Tacit knowledge implies that some of the distinctions between macrovascular (larger vessel disease leading to heart attacks, strokes, and limb loss) and microvascular (smaller vessel disease leading to retinopathy, nephropathy, and neuropathy) disease are artificial. Recent studies support this concept. In a very large (more than 49,000 subjects) population-based cohort of people with type 2 diabetes, the cumulative burden of microvascular disease was associated with major adverse cardiovascular events (MACE) (5). This study also reported a dose-response relationship between the number of microvascular disease states and MACE hazard ratio as well as death from cardiovascular disease. Although these data are based on static measures of disease, other work suggests that dynamic changes in a microvascular target tissue may predict macrovascular events. In a discovery cohort as well as a replication cohort of individuals with type 2 diabetes representing a broad spectrum of ethnicity, subtle decrements in renal function over time were associated with a greater risk of MACE (6). These findings, generated in patients free of chronic kidney disease based on prevailing concepts of this disorder, suggest that changes in the renal vasculature mirror progression of macrovascular disease.

There is also evidence that specific vascular complications in diabetes may be interactive, i.e., the pathophysiology of one complication may modulate progression of another. We recently reported retinal microvascular disease in the setting of high-fat diet–induced obesity in mice without the administration of streptozotocin, a potential neurotoxin. Over the course of a year, mice with insulin resistance and glucose intolerance developed vascular lesions characteristic of diabetic retinopathy, but this was preceded by electroretinographic defects, suggesting that vascular disease in the eye may be modulated by neuropathy (7). Serial studies of humans with diabetes also suggest that neurodegeneration in the retina precedes classic findings of retinopathy (8). Hyperglycemia was present in both studies (7,8), clinical diabetic retinopathy is rarely observed in the absence of hyperglycemia, and glycemic control is important for the treatment and prevention of diabetic retinopathy, which may be driven in part by abnormalities in retinal nerve function.

CONUNDRUMS IN DIABETIC VASCULAR DISEASE

In addition to the possibility that various vascular complications may be more interrelated than appreciated, other unexplained vascular conundrums (Table 1) offer opportunities to develop new paradigms for treatment. Despite striking differences in pathophysiology, type 1 and type 2 diabetes are associated with generally similar types of atherosclerotic lesions. Glycemia contributes to most diabetic vascular complications, but lowering blood pressure using drugs with divergent mechanisms of action decreases some of these complications, suggesting that events beyond hyperglycemia impact blood vessel disease. Statin drugs decrease macrovascular events in people with diabetes but also increase the risk of diabetes, especially in the setting of metabolic syndrome. Statin drugs have transformed the landscape of coronary disease and stroke, but they are not effective for lower-extremity peripheral vascular disease. Curiously, they are also not effective for coronary disease in people with end-stage renal disease. Circulating triglycerides predict macrovascular disease and specific genetic variants responsible for this effect have been identified (9,10), but triglycerides are not major components of vascular lesions.

These conundrums are in part the product of studying clinical end points from the perspective of circulating biomarkers. Biomarkers may be associated with vascular

Table 1—Vascular conundrums in diabetes

Atherosclerotic lesions are generally similar in type 1 and type 2 diabetes.
Lowering blood pressure may improve vascular complications driven by hyperglycemia.
Statins that decrease the risk of coronary vascular events and stroke increase the risk of diabetes.
Statins do not improve lower-extremity peripheral vascular disease.
Statins are not beneficial in end-stage renal disease.
Triglycerides predict vascular disease but are not major components of atherosclerotic lesions.

disease as in the case of HDL particles, which are strongly inversely related to disease in multiple populations. But this association does not ensure a direct role in disease, as for HDL, since elevating levels of HDL independent of assessing its function by administering niacin or cholesteryl ester transfer protein inhibitors does not improve vascular event rates (11,12). Polanyi's tacit knowledge suggests that intracellular lipid metabolism contributes to vascular disease in diabetes. De novo lipogenesis, the production of fats from simple precursors, is altered in diabetes, and this process requires fatty acid synthase (FAS).

FAS AND INTRACELLULAR LIPID METABOLISM

FAS is large, consisting of two identical ~270 kD subunits that contain multiple distinct catalytic activities necessary for the synthesis of fatty acids. After being primed with acetyl-CoA, the enzyme successively adds two carbon fragments to an acyl chain in the form of malonyl-CoA (with the loss of carbon dioxide at each addition) to yield a long-chain fatty acid that is cleaved from the enzyme by a thioesterase activity in FAS. FAS produces mostly palmitate (16:0) (as well as smaller amounts of myristate [14:0] and stearate [18:0]), which requires eight moles of ATP. De novo lipogenesis is stimulated by insulin signaling, in part through transcriptional events. The FAS message is strongly increased by insulin, and SREBP-1c is involved in this induction, although other transcription factors also stimulate FAS expression.

FAS expression is decreased in many tissues of diabetes models, and its tissue-specific inactivation in mice has revealed phenotypes relevant to the complications of diabetes. Mice with liver-specific inactivation of FAS develop fatty liver, hypoglycemia, and enhanced insulin sensitivity (13). Liver FAS knockout animals phenocopy mice with genetic deficiency of the nuclear receptor PPARα (14); their metabolic abnormalities are rescued by administration of pharmacological activators of PPARα, such as fibrates; and subsequent studies of these liver-specific mice identified a specific phosphatidylcholine species as one of the endogenous ligands of PPARα (15). Knockout of FAS in the hypothalamus (16,17) decreases body weight through bioenergetic effects that include altered food intake and physical activity, a phenotype that is rescued by central nervous system infusion of a PPARα agonist. Knockout of FAS in macrophages results in PPARα-associated changes in genes involved in atherosclerosis (18) and protects mice from experimental atherosclerosis. Collectively, these findings suggest that FAS is involved in channeling phospholipids to modulate PPARα activity in a manner that could impact vascular disease in diabetes.

Consistent with the idea that macrovascular and microvascular complications may be more related than appreciated, the PPARα agonist fenofibrate appears to decrease the risk of both cardiovascular events (in selected subgroups) and retinopathy in diabetes. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid trial did not demonstrate cardiovascular benefit for the addition of fenofibrate to a statin (19), but long-term follow-up of the participants in this study suggests that fenofibrate is beneficial in a subgroup of people with diabetes, triglycerides >204 mg/dL, and HDL cholesterol <34 mg/dL (20), consistent with subset analyses from other fibrate trials. Fenofibrate, which can rescue some cellular effects induced by FAS deficiency, decreased diabetic retinopathy progression in the ACCORD trial (21). The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, another fibrate trial, showed that fenofibrate did not reduce the coronary event primary outcome (22) but did demonstrate decreased need for laser treatment of diabetic retinopathy (23), an effect independent of circulating lipids. The underlying mechanism is unknown, and it is possible that benefits of fenofibrate in the eye are due to effects on circulating lipids not generally measured in clinical trials, such as phospholipids, or related to potential antioxidant actions of this drug. However, one plausible interpretation of these results is that intracellular lipid metabolism, perhaps driven by insulin effects on FAS, can impact vascular disease in diabetes.

In normal mice, the induction of hind limb ischemia results in an angiogenic response that preserves blood flow to the extremity. In mice with FAS deficiency in endothelial cells, this response is impaired and causes limb loss, an effect associated with deficient palmitoylation of endothelial nitric oxide synthase (eNOS) (24). Palmitoylation of cysteine residues is required for normal localization of eNOS to the plasma membrane, where it carries out several functions relevant to vascular health. As FAS is insulin responsive in human vascular endothelial cells and eNOS palmitoylation is decreased in animal models of insulin deficiency and insulin resistance (24), it is plausible that effects on endothelial FAS could be involved in peripheral vascular disease and the risk for amputation in people with diabetes. Although FAS is necessary for endothelial integrity, it also appears to maintain epithelial integrity in the gut. When intestinal FAS is inactivated using an inducible Cre, mice develop systemic inflammation due to disruption of the mucinous barrier that limits the access of the microbiota to the vasculature (25). This effect is associated with deficient palmitoylation and secretion of mucin 2, a critical component of the gel-like mucinous barrier in the gut. As FAS deficiency in the intestine characterizes mouse models of diabetes (25) and colonic lymph drains to pancreatic lymph nodes (26), it is possible that deficient FAS in the gut could be responsible for the observation that subclinical endotoxemia in humans appears to promote the development of diabetes independent of BMI, glucose, and metabolic syndrome (27).

In adipose tissue, another site where FAS is strongly induced by insulin, FAS knockout promotes the formation of beige fat and decreases insulin resistance (28). Beiging is associated with the loss of an interaction of alkyl ether lipids with the nuclear receptor PPARγ. Adipose knockout of the terminal peroxisomal enzyme required for ether lipid synthesis, PexRAP (peroxisomal reductase activating

PPARγ), causes the same phenotype as FAS adipose knockout mice (28), suggesting FAS and PexRAP share a lipogenic pathway contributing to insulin resistance in diabetes. Insulin resistance and diabetes commonly contribute to heart failure. FAS expression is increased the hearts of humans with end-stage cardiomyopathy as well as mouse models of heart failure (29), an unexpected finding as energy depletion characterizes heart failure and FAS requires abundant ATP to synthesize lipids. Mice with FAS deficiency in the heart die soon after the experimental stress of transaortic constriction and die prematurely with age, both likely due to abnormal calcium handling (29).

COMPLEX EFFECTS OF ALTERING DE NOVO LIPOGENESIS

Given the striking effects of FAS modulation on diabetes phenotypes mediated by the mechanisms shown in Fig. 1, it is not surprising that several companies have pursued pharmacological inhibition of FAS. Platensimycin, a reversible small molecule inhibitor of FAS, improves insulin resistance in mouse models of diabetes (30) and nonhuman primates (31), but this compound is no longer being developed for human applications. A summary of the tissue-specific effects of FAS inhibition is presented in Table 2. FAS inhibition in liver, macrophages, hypothalamus, and adipose tissue would be beneficial through decreased hepatic glucose production, less atherosclerosis, less adiposity caused by decreased appetite and increased physical activity, and less adiposity due to beiging of white fat. But FAS inhibition in skeletal muscle, heart, endothelium, and intestine would be detrimental because of weakness despite improved glucose control, arrhythmias caused by aberrant calcium handling, hypertension and defective angiogenesis due to endothelial dysfunction, and endotoxemia due to loss of the normal gut barrier. As FAS is ubiquitous, its inhibition would be problematic unless specific sites were targeted. Notably, FAS is increased in many cancers and an FAS inhibitor, TVB-2640, is in clinical trials for the treatment of advanced stage solid malignancies (NCT02223247).

Palmitate is the dominant direct product of the FAS reaction, but the effects of FAS deficiency in mice are not rescued by addition of exogenous palmitate. Cells can distinguish between endogenous palmitate from FAS and exogenous palmitate from other sources. FAS-derived fatty acids appear to be channeled to specific sites, and these lipid channeling pathways and their targets could be modified to alter the course of vascular disease in diabetes. Translational studies of skeletal muscle provide support for this strategy.

In skeletal muscle, high-fat feeding and insulin resistance in normal mice are associated with an increase in FAS message, protein, and enzyme activity (32), effects opposite to those in most other tissues. This unexpected induction represents a stress response in the setting of high-fat feeding to specifically remodel the sarcoplasmic reticulum (SR) membrane to preserve muscle contractile function. Chow-fed mice with skeletal muscle–specific inactivation of FAS are phenotypically normal in terms of metabolic variables and muscle strength. However, when these mice are fed a high-fat diet, they are protected from obesity-associated insulin resistance but become weak without changes in expression of PPARα-dependent genes or palmitoylation. Instead, the muscle findings are due to a reduction in the activity of sarco/endoplasmic reticulum calcium ATPase (SERCA), which normally sequesters calcium from the

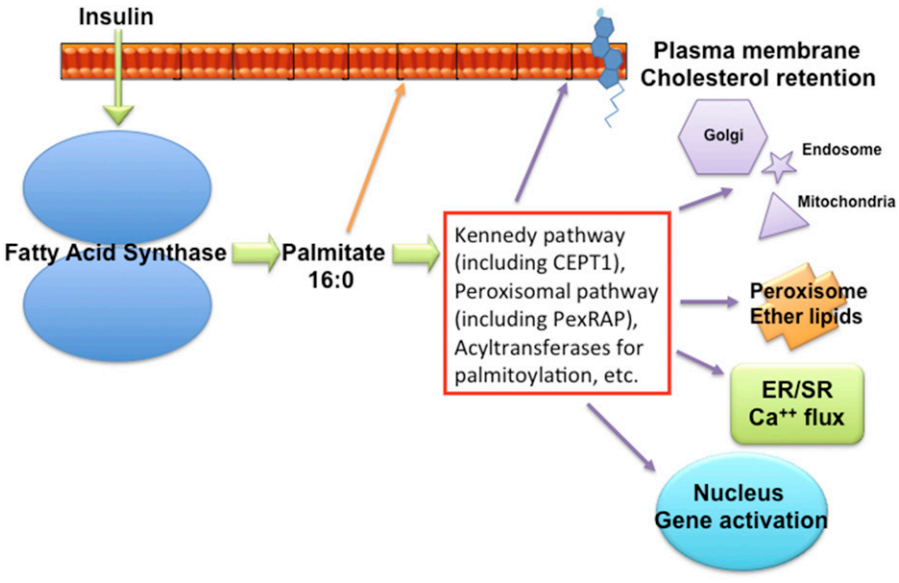

Figure 1—De novo lipogenesis driven by the insulin-responsive enzyme FAS channels lipids to specific intracellular sites relevant to the vascular complications of diabetes. Depending on the tissue being targeted, inactivating FAS can impact inflammation, insulin sensitivity, atherosclerosis, vascular function, muscle function, and intestinal barrier function, among other effects. ER, endoplasmic reticulum.

Table 2—Tissue-specific effects of FAS

Site of FAS inhibition	Effects
Liver	Lower blood glucose
Macrophage	Less atherosclerosis and decreased inflammation
Hypothalamus	Less adiposity due to decreased appetite and increased activity
Adipose tissue	Less adiposity and lower blood glucose due to beiging
Skeletal muscle	Lower blood glucose but decreased muscle strength
Heart	Decompensation with pressure overload
Endothelium	Hypertension and decreased angiogenesis
Intestine	Endotoxemia and systemic inflammation

cytoplasm. Elevated cytosolic calcium promotes glucose uptake but decreases muscle contraction. The decrease in SERCA activity is caused by altered phospholipid composition of the SR, specifically an increase in the ratio of phosphatidylcholine (PC) to phosphatidylethanolamine (PE) species (32) due mostly to decreased abundance of PE. Decreased PE in model membranes is known to impair SERCA activity (33), and our findings of an increased PC-to-PE ratio leading to decreased calcium uptake confirms the work of others studying endoplasmic reticulum (the homolog of SR in nonmuscle tissue) stress in liver (34).

FAS channels lipids to phospholipid synthesis mediated by the Kennedy pathway (35). The terminal enzyme in this pathway is choline/ethanolamine phosphotransferase 1 (CEPT1), and as seen with FAS, high-fat feeding to normal mice induces CEPT1 (36). Mice with skeletal muscle–specific inactivation of CEPT1 have the same phenotype as mice with FAS deficiency in muscle: normal strength and glucose metabolism with chow feeding, protection from insulin resistance with high-fat feeding at the expense of muscle weakness, and decreased SERCA activity due to altered phospholipid composition of the SR. This pathway appears to be relevant to metabolic disease in humans. Human skeletal muscle CEPT1 mRNA is inversely correlated with insulin sensitivity determined by hyperinsulinemic-euglycemic clamp, and bariatric surgery–induced weight loss in obese humans is associated with decreased skeletal muscle CEPT1 protein that is correlated with glucose disposal (36). Others also recently reported that phospholipid composition in human skeletal muscle affects metabolism (37). These findings raise the possibility that pharmacologically altering the phospholipid composition of skeletal muscle, perhaps by repurposing available agents with favorable safety profiles that were not useful for their original indication, could improve skeletal muscle function, facilitating exercise to decrease the risk of cardiovascular events in part by decreasing chronic inflammation (38).

Studies in other tissues also show that cells can distinguish FAS-derived fatty acids from exogenous fatty acids. Exogenous palmitate does not reverse FAS-deficient phenotypes in endothelial cells (24), heart (29), liver (39), or macrophages (40). FAS biology in macrophages may be particularly important as the relationship between diabetes and chronic inflammation is axiomatic (41).

FAS AND INFLAMMATION

Macrophages are involved in diabetic vascular complications such as atherosclerosis (42). Recent findings further support the notion that FAS channels phospholipids to specific sites in the macrophage to impact the chronic inflammatory state in diabetes. When normal macrophages are exposed to palmitate or lipopolysaccharide, inflammatory stimuli common in diabetes, FAS is induced, suggesting that activation of innate immunity is associated with increased synthesis of saturated fatty acids (40). In mice with macrophage-specific FAS deficiency, high-fat feeding results in the same degree of adiposity as compared with control mice, but the animals are protected from insulin resistance and there are fewer macrophages in target tissues. Using multiple Cre models as well as chemical and short hairpin RNA approaches in multiple cell culture systems, we demonstrated that FAS deficiency decreases macrophage activation (40). FAS deficiency disrupted membrane organization, specifically altering the phospholipid and protein composition of detergent-resistant microdomains responsible for inflammatory signaling coordinated by Rho GTPases. Exogenous palmitate did not rescue the phenotype, but inflammatory signaling and membrane order were rescued by exogenous cholesterol, a known component of membrane signaling complexes.

These observations have several potentially important implications for the chronic inflammation that promotes vascular disease in diabetes. FAS appears to drive the phospholipid composition of the plasma membrane so that it promotes the assembly of cholesterol-dependent signaling complexes that engage the cytoskeleton. Cholesterol is known to promote inflammation. Cholesterol is also the major lipid component of atherosclerotic lesions, but the relationships between intracellular cholesterol trafficking and cell function are still poorly understood. In one of his most cited articles, Dr. Bierman reported that disruption of sphingomyelin, a component of signaling microdomains that requires FAS for assembly in macrophages, alters the distribution of cholesterol between the plasma membrane and intracellular pools (43), a finding conceptually similar to our studies of FAS in macrophages (40). Our work confirms that cells can distinguish between chemically identical lipids, such as palmitate produced by de novo lipogenesis as opposed to palmitate from exogenous sources, likely because synthesized lipids are channeled through organelles that respond to lipid flux, a finding reported by other investigators studying viral infections in macrophages (44). Others have also recently shown that membrane phospholipids control clustering of domains required for signaling (45). Dendritic cell activation (46), T-helper 17 cell differentiation (47), and UCP2-induced activation of the inflammasome in macrophages (48) appear to require de novo

lipogenesis, suggesting that FAS-mediated membrane effects may have broad relevance to inflammation biology. Consistent with this concept, a newly discovered protein named FAMIN forms a complex with FAS at the peroxisome to promote de novo lipogenesis and modulate risk for juvenile rheumatoid arthritis, leprosy, and Crohn disease (49). Collectively, multiple lines of evidence support the notion that pathways involving FAS and directing newly synthesized lipids to specific intracellular sites could be targeted to treat the vascular complications of diabetes, perhaps by repurposing drugs that modulate phospholipid metabolism.

A PRACTICAL APPROACH TO VASCULAR DISEASE IN DIABETES

Although our evolving understanding of the potential role of FAS in diabetes complications may lead to new therapies, many patients are not deriving maximal benefit from currently available therapies. In more than 2,000 adults with diabetes but no cardiovascular disease followed for 11 years, achieving blood pressure, LDL cholesterol, and HbA_{1c} goals was associated with substantially lower risk of heart disease (50). Unfortunately, only about 7% of patients reached these relatively modest targets for blood pressure (130/80 mmHg), LDL cholesterol (100 mg/dL), and HbA_{1c} (7% [53 mmol/mol]).

So how should we manage a typical patient with type 2 diabetes at risk for vascular disease? One approach is presented in Table 3. Appropriate glycemic control should be achieved using metformin often in combination with either a sodium–glucose cotransporter 2 inhibitor (51) or GLP-1 receptor agonist (52) shown to provide mortality benefits. Context-specific counseling should be provided about diet, exercise, and smoking cessation, and blood pressure should be controlled, which usually requires more than one agent. In the absence of a contraindication, every person with diabetes should be treated with a high-intensity statin. Fenofibrate can be considered in certain clinical situations, especially in males with elevated triglycerides and low HDL cholesterol who have suffered cardiovascular events in the setting of statin therapy, as it may decrease cardiovascular event rates and prevent progression of retinopathy. PCSK9 inhibitors, despite their cost, might be shown to be beneficial and could be especially useful in statin-intolerant patients.

Table 3—One approach to decrease vascular risk in type 2 diabetes

Glycemic control, such as metformin with SGLT2 inhibitor or GLP-1 receptor agonist
Exercise, diet, and smoking cessation counseling
Blood pressure control, often with more than one agent
High-intensity statin, as tolerated
Fenofibrate, especially in males with elevated triglycerides and low HDL cholesterol
Consideration of PCSK9 inhibition based on clinical circumstance

SGLT2, sodium–glucose cotransporter 2.

An aphorism attributed to both Hippocrates and William Osler holds that it is more important to know what sort of patient has a disease than what sort of disease a patient has. Knowing what sort of patient has diabetes requires intuitive skills represented by Polanyi's statement that "we know more than we can tell." FAS-mediated intracellular lipid flux channels lipids to specific sites. Most scientists focus on altering the function of proteins to affect end points, but protein function is frequently dependent on the lipid environment. The intracellular phospholipid environment could be amenable to modifications appropriate for treating vascular disease in diabetes. But it may take knowing more than we can tell to convince our patients that doing the hard work of diabetes care using currently available therapies often prevents serious complications.

Acknowledgments. The author is thankful for the help of dedicated colleagues and deeply appreciative of the support of the American people through the National Institutes of Health.

Funding. This work has been funded most recently by National Institute of Diabetes and Digestive and Kidney Diseases grants DK101392, DK076729, DK020579, DK056341, and T32 DK07120.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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