ATVB In Focus

Diabetic Vascular Disease: Pathophysiological Mechanisms in the Diabetic Milieu and Therapeutic Implications

Richard A. Cohen

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology begins a series of review articles on recent research advances into the mechanisms of diabetic vascular complications. The goal of this series is to review basic mechanisms by which diabetes accelerates vascular disease, an intense area of current interest. Research into diabetic vascular complications has received increased attention over the last 10 years as indicated by the number of articles published annually in ATVB that featured the term “diabetes” in the title, abstract, or text (Figure). Looking at the Figure, you might wonder what accounts both for the increase, and for the apparent lack of interest before this. This burst of activity was preceded by a greater realization that both type I and type II diabetes dramatically increase the risk for the development of macrovascular disease and its complications. The increase in published articles is also undoubtedly caused by many interdependent factors. First, it is now generally accepted that risk factors such as diabetes, hypertension, and hyperlipidemia have relatively acute effects on vascular cells to which their chronic adverse effects on vascular structure and function can be ascribed. For instance, in the case of diabetes, this principle is based on results from short-term cellular and physiological models in which vascular or blood cells in both animal models and in vitro are exposed to elevated concentrations of glucose for relatively brief periods of time. These are reasonably easy experiments to do, and bolstered by the fact that elevated glucose rapidly causes endothelial cell dysfunction in humans, they have provided a gristmill for many novel experimental observations. Second, with the growth of knowledge regarding molecular and cellular function of vascular cells, a more thorough understanding is evolving regarding the mechanisms by which elevated glucose causes cellular dysfunction. The period of increased publications on diabetes in ATVB coincides with the emerging importance of oxidant stress in the pathophysiological effects of cardiovascular risk factors, particularly diabetes. For example, there is an increasing understanding of how altered cellular metabolism in cells exposed to elevated glucose concentrations results in altered cellular function.

Third, important external factors have undoubtedly influenced the increased number of articles. One is the encouragement provided by increased funding from the National Institutes of Health whose budget has doubled over this time, and which has developed several programs that have targeted diabetic vascular disease. In addition, the Juvenile Diabetes Foundation International and the American Diabetes Association provide a unique resource to encourage research on diabetic vascular complications, perhaps most importantly to young and developing investigators. Other potential factors are changes to the Journal itself, which added the term “Vascular Biology” to its title in 1995, and the changes in the composition of the Editorial staff that ensued.

See page 1342

This series, which will include 10 reviews, begins with the article by Nada et al in this issue, which focuses on receptors for advanced glycation endproducts (RAGE). It is the first of several in the series that will address inflammatory pathways and mediators that are important in inducing a change in phenotype of diabetic vascular cells. It is interesting that this first review concerns a mechanism that was proposed to cause diabetic cellular dysfunction more than 2 decades ago. AGEs had a checkered history for years, which may have risen and fallen on the fortunes of one drug, sorbinil. The discovery of RAGE and its ability to stimulate inflammation brought fundamental understanding, renewed interest, and potential new avenues of therapy to the AGE area. Other reviews will focus on inflammatory mediators, including the role of arachidonic acid metabolites, which will be covered in next month’s issue. Abnormalities in prostacyclin, thromboxane, and endoperoxides were also noted to cause altered vascular cell signaling in diabetes more than a decade ago, and the

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authors of next month’s review, Rama Natarajan and Jerry Nadler, update this area and add to it their intriguing work on lipoxygenases. Several reviews in this series will address additional cell signaling pathways including those involved in insulin resistance in vascular cells, an important feature of Type II diabetes. This area, and related treatments with PPAR α and γ agonists, has been a particularly active one, and has provided understanding of a unified theory of obesity, hyperlipidemia, and accelerated diabetic vascular disease, which has spurred the development of multiple new clinical drug treatments. Protein kinase C activity was also identified years ago to be involved in diabetic cellular and animal models. The study of protein kinase C in diabetes has stimulated not only many fundamental research advances, including the growing number and functions of PKC isoforms, but has also resulted in clinical drug development.

One of the richest and most rapidly expanding areas of research in the pathogenesis of vascular disease over the last 10 years, particularly in diabetes, is oxidant stress. “Oxidant stress” is one of those “grab-bag” terms to which the vascular field had been attempting to provide understanding and specificity for some time now. Accordingly, several reviews will be devoted to summarizing progress in understanding the enzymatic sources of the generation of oxidants within diabetic cells, eg, NADPH oxidase, mitochondrial electron transport, and xanthine oxidase, as well as the disposition of oxidants by scavenging enzymes. In addition, the effects of oxidants on cellular proteins will be addressed. Recent research has identified the fact that many key vascular proteins, including prostacyclin synthase and endothelial nitric oxide synthase, are the targets of oxidants that alter their enzymatic activity in diabetes. Identifying the proteins that are affected by oxidants and the types of chemical changes occurring in the proteins may help to identify the oxidants involved and their enzymatic sources. Such studies may lead to the development of more sophisticated diagnostic tests to monitor the severity of the diabetic metabolic state and its vascular consequences.

Finally, at least two reviews will address abnormal metabolism of cells in the diabetic milieu. In endothelial cells, intracellular glucose levels are not limited by glucose transporters, so that levels rise and the flux through metabolic pathways is increased and altered during hyperglycemic states. This result has many implications, not the least of which is that the redox state of the cell is affected. However, possibly because flux measurements are so complex and rarely done, the pathways involved, their interrelationships, and their individual importance are incompletely understood and hotly debated. In addition, it is being increasingly recognized that elevated glucose is not the only challenge to be met by a diabetic cell, and that other important blood constituents, fatty acids and triglycerides, affect their function. Exciting new discoveries are being made related to cellular fuel sensing enzymes and their effects on cell glucose and lipid metabolism, insulin sensitivity, and function. For instance, one of these, AMP kinase, a stress kinase that responds to alterations in metabolism, appears to be able to both respond to and ameliorate the affects of the diabetic milieu on vascular cell function, including oxidant stress. This growing area has already contributed to a better understanding of the connection between metabolism of cells in the diabetic milieu and abnormal cell function. Short of perfect metabolic control of diabetes, areas such as this are likely to lead to new adjunctive treatments to lessen the effects of diabetes on vascular cells and limit disease progression.
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