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Forum Editorial

Redox Imbalance in Diabetes

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Diabetes has become pandemic in recent years (1, 14) and parallels the pandemic of obesity, which has even resulted in the new descriptive term "diabesity." Even though the topic of diabetes has been given priority in this guest-edited edition of *Antioxidants and Redox Signaling,* the following articles can only scratch the surface of this complicated disease with its multiple metabolic toxicities, resultant oxidative-redox stress, and end-organ involvement. The importance of excessive reactive oxygen species and the resultant antioxidant imbalance within the β-cells, islets, and the end-organ tissues affected by this imbalance should not be underestimated (8).

This particular field of study is ripe for expanding knowledge and breakthroughs to delay its development and prevent or delay the multiple diabetopathies, which result in increased morbidity and premature mortality. This current pandemic extends beyond the normal population and importantly involves our adolescent youth; this results in diabetopathies with retinopathy, nephropathy, and cardiovascular-peripheral vascular disease at rates similar to those of their adult counterparts. Alarmingly, at the time of diagnosis, more that half of these youths will have one or more cardiovascular risk factors (including hypertension or increased lipid values), placing them at high risk for early metabolic syndrome and cardiovascular events (2). These findings may result in a dramatic increase in end-organ involvement with end-stage disease occurring at a much younger age as compared with the general population. Delaying the onset of type 2 diabetes mellitus and its complications could result in not only a significant reduction in morbidity and mortality but also a reduction of the high cost to the existing social structure related to this pandemic.

Type 2 diabetes mellitus is a heterogeneous, multifactorial, polygenic disease, which results in the dysfunction and ultimate failure of the pancreatic islet β-cells to produce the required amount of the hormone insulin to meet the needs of the body resulting in hyperglycemia (5). In type 1 diabetes mellitus (T1DM), this loss of β-cell function is due to a complex autoimmune process. In type 2 diabetes mellitus (T2DM), accounting for ≥90% of all types of diabetes, a combined interaction of preceding insulin resistance occurs, which places and undue burden on the islet β-cell to overcome and compensate for this insulin-resistant state so closely associated with the obesity epidemic and β-cell dysfunction and failure. Approximately 80% of these insulin-resistant patients are able to compensate, at least for a time, and do not develop insulin deficiency to control glucose levels; remaining normogylcemic. This endogenous compensatory hyperinsulinemia does not come without a price and has long been known to be associated with accelerated cardiovascular disease and end-organ impairment.

The requirement for β-cell dysfunction or failure is becoming increasingly important to better understand the development of impaired glucose tolerance—prediabetes and overt T2DM. Additionally, the importance of the progressive nature of T2DM, resulting in complete loss of β-cell function primarily through apoptosis, is resulting in new findings that help both the clinician and the researcher to understand better the role of oxidative-redox stress and the coexisting imbalance of the antioxidant defense mechanisms within the islet and β-cell (7).

The article by Ido (9) introduces the concept of redox reactions (allowing the production of unpaired electrons by either reduction or oxidation), which results in tissue injury in diabetes. His in-depth discussion of reductive stress in diabetes begins this forum and reflects on the early work done in this field by Williamson and Kilo in the 1970s; they first demonstrated the importance of reductive stress regarding the increased ratio of NADH/NAD+ in diabetes. Further, this article provides an excellent up-to-date review of redox imbalance in diabetes and suggests that we have come a long way in this exciting field of mitochondrial and cytosolic knowledge, but that a great deal still remains to be understood about redox imbalance, regarding the combined roles of oxidative and reductive stress.

In T1DM, the interaction between autoimmune mechanisms and NAD(P)H oxidase enzymes generating ROS, in the

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article by Flores and Nicolls (4), suggests that the immune system may be capable of transferring impaired endothelial function and impaired vascular reactivity, even before the development of hyperglycemia. Their findings suggest that immune dysregulation and alterations in redox homeostasis may be the initiating mechanisms and that these same mechanisms may be in play against the background of controlled Hb_{A1c} levels in diabetic patients. Further, their article provides us with an improved understanding of the phenomena that may link autoimmunity, oxidative stress, and vascular injury, which may culminate in new therapeutic modalities in those patients with T1DM in whom progressive vascular disease develops, even when glucose levels are properly controlled.

The article by Lastra and Manrique (10) discusses the expanding role of oxidative stress, the renin-angiotensin system, and β-cell dysfunction, including apoptosis in the cardiometabolic syndrome and T2DM more from a clinical perspective, while including many relevant signaling mechanisms and pertainent mechanistic explanations throughout. This article introduces many new concepts and presents an organized up-to-date view of the development and natural progressive history of T2DM.

A more in-depth examination of T2DM using the C57BL/KSJ obese +db/+db mouse model of T2DM and obesity by Chu and Leung (3) demonstrates that islet AT1R activation in young diabetic obese mice can generate progressive islet β-cell failure through NADPH oxidase-driven UCP2 activation (a negative regulator of islet function). Further, they were able to demonstrate that angiotensin II type 1-receptor antagonism with an angiotensin-receptor blocker abrogated this oxidative stress-driven activation of uncoupling protein 2 while improving pancreatic islet β-cell function.

The role of homocysteine and it mechanisms in producing an uncoupling of the endothelium-myocyte interactions through increased extracellular matrix accumulation, resulting in a dys-synchronous myocardium and diastolic dysfunction, is presented by Sen *et al.* (12). This article additionally supports a role for the competitive inhibition of PPAR gamma agonists by homocysteine, resulting in decreased activities of PPAR gamma. This concept may have important clinical implications, in that controlling hyperhomocysteinemia, when present, could possibly improve the effects of PPAR gamma agonists and their effects on diabetes.

Pennathur and Heinecke (11) discuss diabetic cardiovascular disease, and studies from their laboratory support the hypothesis that unique reactive intermediates generated by myeloperoxidase generating hypochlorous acid, glycoxidation-lipoxidation, and reactive carbonyls in localized microenvironments of vulnerable tissues (micro- and macrovasculature) promote diabetic damage. They further propose that interrupting these reactive pathways in vascular tissue might help prevent cardiovascular disease in this high-risk patient population. They discuss in detail the multiple pathways responsible for the generation of reactive oxygen species. This is an excellent and timely review of this exciting area of research.

Shah *et al*. (13) present a comprehensive review highlighting the role of oxidative stress in the pathogenesis of diabetes and further discuss the major clinical trials conducted on the prevention of type 2 diabetes mellitus. This topical review discusses and reviews current literature regarding oxidative stress, free radical cell injury, and their relation to the metabolic syndrome. Further, they discuss hyperglycemia and its relation to diabetic complications of cardiovascular disease, nephropathy, neuropathy, and retinopathy, and present exciting recent information on the prevention of type 2 diabetes, including findings from the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial and previous studies. This group believes that oxidative stress may serve as a common-soil hypothesis for the various interventional trials involving the prevention of type 2 diabetes.

Finally, Hayden and Sowers (6) present information from human and animal studies, more from the microscopic and ultrastructural point of view. They have included multiple images with bright-field and polarizing light microscopy and used different staining techniques, as well as the transmission electron microscopic imaging to enhance the cellular and extracellular remodeling changes in the islet associated with type 2 diabetes. These images and discussions meld function and structure and additionally incorporate the process of redox imbalance within the endocrine pancreas regarding the development of type 2 diabetes mellitus. They introduce the concept of the islet itself being an end organ regarding the multiple diabetopathies and even suggest that the term *isletopathy* be used to describe the structural changes associated with islet remodeling, including islet amyloid and fibrosis, as well as the remodeling cellular changes within the islet and specifically β-cell apoptosis involvement as a result of redox imbalance within the islet and the peri-islet areas of the pancreas.

Overall, this forum focusing on diabetes has been an exciting way to gather information and ideas regarding the role of antioxidants and redox signaling from various laboratories, with the intent to review the current state of diabetes, as it is related to the oxidant-antioxidant imbalance within the islet and myriad tissues of the diabetic end organs.

We are indeed grateful to the Editor of *Antioxidants and Redox Signaling*, Chandan Sen, for allowing us the opportunity and experience to gather the information from various laboratories to provide this forum for others to enjoy.

FUTURE DIRECTIONS

Our hopes are that the ideas and concepts expressed in this forum will stimulate others to delve deeper and to search for more new ideas and findings that may lead to newer therapies for this pandemic disease of type 2 diabetes mellitus and help us further to understand the role of redox imbalance in diabetes.

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