

NHLBI Working Group

Interdisciplinary Approaches to Diabetic Heart Disease: Mechanisms, Prevention, Early Detection and Therapeutic Targets

Executive Summary

The National Heart, Lung, and Blood Institute (NHLBI) convened a Working Group of experts in diabetic heart and vascular disease, cardiac progenitor/stem cells, angiogenesis, large animal models, mitochondrial dysfunction, myocardial substrate metabolism, and cardiovascular imaging on July 27-28, 2009 in Bethesda, Maryland, to advise the Institute on: 1) promising research strategies to find new diagnostic tools, disease risk stratification, and identify novel therapeutic targets for diabetic heart disease; 2) opportunities for fundamental and translational research to address the genetic, molecular and environmental underpinnings of the cardiovascular complications of diabetes, and 3) improved understanding of disease pathophysiology which will ultimately lead to more effective therapeutic interventions and diagnostic approaches to this serious health problem. This Working Group is responsive to [NHLBI Strategic Plan Goals 1 & 2](#) and the [Division of Cardiovascular Diseases Strategic Plan Goals 2, 2, 4c, d](#)

Discussion - The nature and scope of the problem:

In 2008, 12 percent of US adults age 20 and older have diabetes. The American Diabetes Association estimates there will be nearly 50.2 million people with diabetes by 2025 due to the growing epidemic of obesity. According to estimates of the World Health Organization, the number of people with diabetes will double worldwide to 366 million by 2030, a problem of pandemic proportions. These numbers have grave implications for the public health of the US, which already struggles to provide care for millions of patients with diabetes, many of whom belong to vulnerable groups, such as the elderly or minorities. Cardiovascular disease is the leading cause of death of individuals with Type 1 and Type 2 diabetes. In addition to increased atherosclerotic vascular disease leading to myocardial ischemia/infarction and stroke, diabetes also increases the incidence of heart failure, even in the absence of ischemic insult or hypertension. The term ‘diabetic cardiomyopathy’ has been used to describe heart failure that is associated with diabetes and which is not obviously attributable to other etiologies. Diabetic cardiomyopathy may present as solely diastolic dysfunction or combined diastolic and systolic dysfunction via mechanisms that are likely distinct from myocardial ischemia. The unique pathogenesis of diabetic cardiomyopathy likely accounts for the observation that traditional cardiologic therapies are less effective in the diabetic population.

Given the dismal prognosis of diabetic heart failure and lack of highly effective therapy, particularly for diastolic dysfunction, the working group focused their effort on the review of the state of knowledge regarding the molecular pathogenesis of diabetic cardiomyopathy, screening for diabetic cardiac dysfunction, identification of new biomarkers, identification and validation of therapeutic targets, the development of clinically relevant models and technology platforms, and the testing of metabolic modulator therapies aimed at this important problem.

Recommendations:

Diabetes-associated cardiac dysfunction is associated with mitochondrial dysfunction, derangements in fuel utilization, and altered cellular signaling. In particular, increased lipid uptake and incomplete oxidation lead to the accumulation of triglyceride and other lipids that may act as direct toxins or signaling mediators and may lead to remodeling of organellar membrane composition. This complex process has been termed ‘lipotoxicity’. Impaired glucose oxidation in the myocyte might also lead to “glucotoxicity” including increased O-GlcNAC modifications of mitochondrial and sarcoplasmic reticulum (SR) proteins leading to alterations in excitation-contraction coupling and contractile dysfunction. Diabetes adversely influences multiple cell types within the heart (cardiomyocytes, endothelial cells, stem cells). Paracrine interactions between these cells are incompletely understood, such as the contribution of microvascular dysfunction or potentially the loss of the progenitor stem cells to myocyte dysfunction or cell death.

Many patients with diabetes have other co-morbidities such as hypertension, myocardial ischemia and obesity. The interactions between these co-morbidities and diabetes need to be elucidated. Moreover, similarities and differences between the cardiac phenotypes of type 1 and type 2 diabetes need to be understood. Current imaging modalities have described altered substrate metabolic fluxes and triglyceride accumulation in diabetic hearts and have identified subtle changes in cardiac diastolic relaxation and changes in cardiac structure such as cardiac fibrosis and defects in microvascular perfusion. However questions remain including the role of such imaging approaches in early disease detection and in predicting long-term prognosis, outcomes and responses to therapy. In particular, more information is needed on how metabolic modulator therapies, if proven efficacious, impact on cardiac metabolism and function. Based upon this review of the state of the field, the working group identified the following key areas as targets for future research:

1. Mechanisms and Pathophysiology:

- Define the mechanisms responsible for mitochondrial dysfunction by identifying transcriptional mechanisms and post-translational modifications of the mitochondrial proteome. Consideration should be given to defining the role of changes in mitochondrial dynamics, membrane remodeling, metal homeostasis and autophagy and how they impact on traditional functional physiologic endpoints of mitochondrial bioenergetics.
- Elucidate mechanisms for and consequences of derangements in fuel utilization, lipotoxicity (e.g. membrane remodeling, lipid-mediated signaling, endoplasmic

reticulum (ER) stress, and oxidative stress), and glucotoxicity (O-GlcNAC modification).

- Characterize the contribution of gene – environment interactions in the pathophysiology of diabetic cardiomyopathy.

2. Biomarker Discovery:

Exploit therapeutic target discovery platforms such as metabolomics and proteomics to identify molecular signatures in tissue samples, body fluids and easily accessible membranes such as from circulating blood cells. Ideally, biomarkers should be relatively non-invasive, specific, and predictive of outcomes and response to therapy. The long-term goal is to identify the relative contribution of the diabetic state versus other co-morbidities (e.g. hypertension, ischemic damage) to cardiac dysfunction at a very early stage to provide a more personalized therapeutic approach aimed at the relevant pathogenic pathways in a given individual.

3. Refine and Validate Therapeutic Targets and Diagnostic Markers:

Current imaging modalities need to be refined to increase the power of these approaches to predict subclinical disease, stratify risk, and predict response to therapy at early stages of disease. As biomarkers and potential targets are identified, there is a strong need to validate these targets as prognostic indicators and predictors of therapeutic responses and outcomes.

4. Development of Clinically Relevant Experimental Models and Paradigms:

To accelerate translation of mechanistic insights into clinically efficacious paradigms, additional preclinical models are needed. These include large animal models or “humanized” rodent models that more closely mimic the human condition. Such models could be used to clarify the natural history, pathophysiology and response to therapeutic strategies and serve as platforms with which to validate biomarkers. In order to move efficiently across experimental models, multi-disciplinary groups should be established. For example, the power of screening in genetically tractable lower organisms could serve as a discovery pipeline that leads to new mechanistic studies, additional screening in the chemical biology realm, and testing of new “probes” of disease pathways and potential therapeutic targets in larger animal models that more closely reflect human disease. Ideally, more effective in vivo gene targeting of somatic cells in large animal models could provide both mechanistic insights and better translation to human disease. Consideration should also be given to primary adult human cell culture systems and induced pluripotent stem cell platforms that are “coaxed” to relevant lineages to validate mechanism and new small molecule probes.

5. Testing of Novel Therapies for Diabetic Cardiomyopathy in Large Animals and/or Humans:

Given that there are no therapies currently available that are specifically indicated for diabetic cardiomyopathy, and given that there is no therapy that improves survival for diabetic patients with diastolic heart failure, there is a definite need for testing of new potential therapies. For example, the results from studies performed in rodent and canine models that demonstrate the efficacy of novel metabolic modulator therapies may be translated into humans. Other studies demonstrate that nonpharmacologic therapies (such

as weight loss) improve diastolic dysfunction in patients without heart failure. Whether such therapy is beneficial in patients with diabetic cardiomyopathy and heart failure is not clear and is currently not recommended.

Publication Plans:

The Working Group report is planned for publication in a peer-reviewed journal.

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