

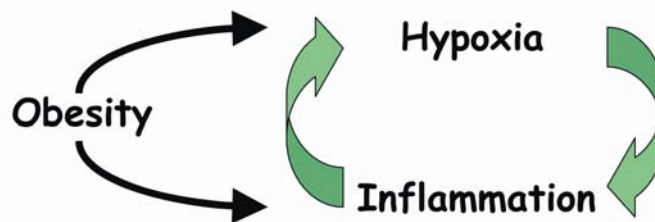
Cardiovascular Consequences of Metabolic Disease

Affinity Research Collaborative
Kenneth Walsh, pre ARC Director

Background: Currently 71% of men, 61% of women and 33% of children are overweight in USA. It has been estimated that obesity will increase the risk of disease as much as 20 years. Excessive body mass promotes the risk of coronary artery disease, hypertension, heart failure, stroke and myocardial infarction. Due in part to the increased prevalence of obesity-linked cardiovascular diseases, it has been proposed that the longevity of the American populace will be shortened by as much as 5 years.

Goals: This ARC is intended to promote translational research by bringing basic and clinical research laboratories at Boston University together to study the cardiovascular consequences of obesity and diabetes. ARC support will be used to sponsor monthly meetings between participants with the purpose of fostering collaborations. The ARC will promote research projects involving 2 or more participating laboratories for the purpose of developing a new research area and for generating pilot data for new PPG applications.

Currently we envision the focus to be on the analysis of how metabolic dysfunction impacts the function of vascular and inflammatory cells. It is becoming increasingly appreciated that macrophages play key roles in the development of chronic inflammation and metabolic dysfunction associated with obesity. Obesity leads to macrophage accumulation in the adipose tissue, and this accumulation correlates with the development of insulin resistance. The status of the vascular cells in adipose tissue has received recent attention because it can also contribute to fat pad dysfunction. Obesity is associated with capillary rarefaction and systemic vascular dysfunction. Adipose tissue hypoxia will favor adipocyte necrosis, leading to macrophage recruitment. In turn, the fat pad milieu of an obese organism will favor an activated macrophage phenotype and lead to further degradation of the vascular bed. Although unproven at this stage, it is reasonable to speculate that obesity favors a vicious cycle of fat pad hypoxia and inflammation. This cycle will stimulate the release of pro-inflammatory adipocytokines that promote systemic endothelial cell dysfunction and ultimately lead to cardiovascular disease. This cycle will also attenuate the production of anti-inflammatory adipocytokines that protect against vascular dysfunction.



Therefore the ARC intends to integrate clinical and basic science labs to translate findings from murine genetic models. For example, the consequences of obesity will be examined in mouse models that are genetically engineered to over- and under-express the anti-inflammatory adipocytokine adiponectin to study the functional interrelationships between fat pad capillarization and macrophage phenotype. Related studies will examine vascular function and macrophage phenotype in fat tissue biopsy specimens from morbidly obese individuals before and after bariatric surgery. Other members of this ARC have developed expertise in the

molecular analysis of polyphenols in rodent models of metabolic disease. This work dovetails with studies that examine the effects of resveratrol, a polyphenol, on monocyte and endothelial cell function in patients with type 2 diabetes mellitus. Finally, newly identified cytokines in mouse models can be evaluated in patient populations through collaborations with clinical labs within the ARC.

The proposed studies within this ARC will be facilitated by the Gene Expression Core located in the Whitaker Cardiovascular Institute. This core is run by Jane Freedman and Karhaman Tanriverdi, and it is equipped for high throughput studies for DNA and RNA isolations, DNA and RNA quality controls, reverse transcription reactions, PCR, and Real-Time PCR analysis for gene expression, Single Nucleotide Polymorphisms (SNPS), and Copy Number Analysis. This core has an extremely high throughput capacity and the analysis platform works with nano volumes diminishing the consumption of reagents and samples.

In summary, using interdisciplinary approaches, this ARC will elucidate the mechanism of causal link of adipose hypoxia and inflammation with the development of obesity-related cardiovascular disease. Specifically, this ARC will identify the adipocytokines that affect macrophage phenotype and vascularization in fat pad with anti- or pro-inflammatory properties, thereby contributing to modulation of vascular function. These factors will be evaluated in a mouse model of loss-of- and gain-of function genetic manipulations. This ARC will also dissect the molecular mechanism of how these hormonal factors regulate macrophage activation and capillarization in adipose tissues. Finally, this ARC will assess the relationship of these adipocytokines, macrophage and vascular function with clinical manifestation in patients with obesity and diabetes.

Key Participants/Project Expertise:

Kenneth Walsh PhD, Professor, CVI, BUSM, ARC Co-Director. Cardiovascular consequences of adiponectin-mediated regulation of macrophage phenotype.

Noriyuki Ouchi MD PhD, Assistant Professor, BUSM, ARC Co-Director. Characterization of cardiovascular-regulatory properties of adipocyte-derived cytokines.

Noyan Gokce MD, Associate Professor, Medicine. Associations between macrophage phenotype and vascular function in obese patients before and after bariatric surgery.

Joseph Vita, MD, Professor, Medicine. Associations between vascular reactivity and mitochondrial function in monocytes and endothelial cells isolated from diabetic and non-diabetic patients.

Richard Cohen MD, Professor, Medicine. Mechanisms of impaired angiogenesis due to metabolic dysfunction and oxidant stress.

Jane Freedman MD, Professor, CVI, Medicine. Robotic high-throughput PCR analysis of vascular cell phenotype to define the metabolic, inflammatory and angiogenic status of tissues and cells.

If you are interested in joining this ARC please contact kxwalsh@bu.edu.