Unraveling the Mechanisms of Increased Cardiovascular Disease in HIV-infected Patients

Steven Grinspoon, MD, Massachusetts General Hospital

Worldwide, over 35 million people are infected with the HIV virus, including approximately 1 million people in the U.S. Because of the increasing success of antiretroviral therapy (ART) to improve immune function, HIV-infected patients are living longer. However, recent trends suggest an increase in the number of chronic non-AIDS related complications among HIV patients, including those with well suppressed viremia (a condition where viruses enter the bloodstream) on ART. Among the most common complications is cardiovascular disease (CVD). Studies I’ve conducted with colleagues at MGH, including Jeanne Triant, MD, Janet Lo, MD, and Markella Zanni, MD, have been instrumental in highlighting the increasing prevalence and mechanisms of CVD in HIV-infected patients. Studies from the Research Patient Data Registry at Partners Health Care demonstrate a 50 to 75 percent increased relative risk of myocardial infarction in HIV-infected patients relative to non-HIV-infected control subjects. Recently published data from the Veterans Administration cohort confirm this trend in excess CVD among HIV-infected patients.

Studies performed at the HCCRC at MGH have advanced the understanding of the mechanisms of increased CVD in HIV-infected patients. These studies suggest that traditional risk factors, including increased lipid and glucose levels, which can result from HIV infection and specific types of antiretroviral therapy, do contribute to increased CVD rates. However, these traditional risk factors, including excess smoking rates in HIV-infected patients, account for only a portion of the excess cardiovascular risk in the HIV population. Using newer techniques of virtual CT angiography, the MGH studies have shown increased rates of atypical coronary plaque lesions which are non-calcified and demonstrate high risk morphology and are potentially more likely to rupture. Of note, these lesions are not associated with traditional risk factors, but rather with increased immune activation indices, particularly those of monocyte activation.

Taken together, these studies suggest an emerging hypothesis that increased inflammation, driven in part by immune activation, contributes to excessive CVD rates in the HIV population. Increased immune activation is seen even among viremically well controlled patients on ART, and may relate to HIV-infection of gut-associated lymphoid tissue, resulting in “leaky gut” and increased microbial translocation across the gut.

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Nutrition Interns Rotate Through Three CRCs

Each year the Metabolism and Nutrition Research groups at HCCRCs dedicate a period to educate dietetic students enrolled in post-baccalaureate study accredited by the Accreditation Council for Education in Nutrition and Dietetics (ACEND). This year, three of the sites collaborated for a combined internship rotation to highlight the varied nutrition resources that Harvard Catalyst offers.

At BCH students are introduced to pediatric nutrition research, including food intake collection methods, and to the Bodpod machine technology. The primary focus of MGH rotation is the evaluation of energy expenditure (both by indirect calorimetry and common predictive equations), body composition (by DXA), and bioelectrical impedance analysis and physical activity assessment. At BWH, the interns learn how to calculate and prepare a controlled nutrient research diet and the role of the metabolic kitchen in clinical research trials. In addition to the research diet methodology, they are also introduced to the science of sleep medicine and the intricacies of implementing circadian research.

Scheduler Update

The roll-out of HCCRC Scheduler is under way at BCH, and is expected to be complete in April. The HCCRC Implementation Team is meeting with the operation team at BCH weekly to ensure that the project moves forward smoothly. Version 2.8 is currently being rolled out across four HCCRC sites. This new version includes improvements to performance and stability of the system, as well as bug fixes and several new features. Release notes with these changes will be sent to staff the week the software goes live at that site.
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epithelial surface. In addition, co-infections such as CMV and hepatitis may contribute.

In a recent paper published in *JAMA*, the MGH group used a novel imaging technique, FDG-PET, to investigate inflammation at the endothelial surface of the arterial wall among HIV-infected patients compared to non-HIV-infected patients carefully matched on traditional risk factors. The study was performed in collaboration with Ahmed Tawakol, MD, and Udo Hoffmann, MD, from the MGH Cardiovascular Imaging. Arterial inflammation was significantly increased among the HIV-infected patients compared to the non-HIV-infected patients. The increased arterial inflammation was not related to traditional risk factors, but to indices of increased monocyte activation. This study, funded by the NIH, is among the first pieces of direct evidence of the hypothesis that

CRC updates

HCCRC @ BCH

Construction Update on the CTSU/Pavilion 6

Plans to build a research pharmacy on the CTSU in the current office space are in the final stages, as well as moving stadiometer/scales and creating more storage capacity. Stay tuned for signs/new access over the next couple of months.

Staffing Updates – Stop by and say “Hi”

Stephanie Patriarcha, part-time lab technician, joined us in early November.

BodPod Service

The BodPod service is now available. This system uses air displacement plethysmography (ADP) to measure body mass and body volume, with a calculation of body density, percent fat, and percent fat-free mass using age and sex-specific equations. ADP is an easy, safe, and quick (approximately five minutes total test time) procedure. The machine is located on Pavilion 5 in the GPU clinic and is available on Mondays, Tuesdays, Thursdays, and Fridays. To schedule a research BodPod appointment, please contact Nicolle Quinn, CTSU Nutrition Manager.

Questions? Please email:
Chris Duggan: christopher.duggan@childrens.harvard.edu
Nicolle Quinn: nicolle.quinn@childrens.harvard.edu
or Lori Bechard: lori.bechard@childrens.harvard.edu

Psychometrician Services

The Clinical Behavioral Science Core, housed within the Department of Psychiatry Program in Behavioral Science, co-directed by Deborah Waber, PhD, and Michelle Bosquet Enlow, PhD, provides consultation services and psychometrician services. To access these services, go to: www.childrenshospital.org/crc. For questions, please call Deborah Waber at 617-355-6523 or Michelle Bosquet Enlow at 617-919-4680.

immune-mediated inflammation at the endothelial surface may drive accelerated atherogenesis in the HIV population and serves as an investigative model for other disease states in which inflammation contributes to atherogenesis.

Further studies are now underway by the MGH group to assess the specific mechanisms of increased arterial inflammation in HIV and to prevent CVD in the HIV population. These studies are investigating strategies to reduce immune activation with the use of HMG coA-reductase inhibitors and of strategies to potentially reduce harmful microbial translocation across the gut surface to decrease immune-mediated atherogenesis. This work has been supported in part by The KL2/Catalyst Medical Research Investigator Training funding to MGH HCCRC investigators.

HCCRC @ BIDMC

Research Coordination/Nursing Project Management Support

The Harvard Catalyst Clinical Research Center staff at BIDMC actively works with investigators to provide research support for projects. The Clinical Research Center has expanded our joint Research Coordination/Nursing Project management services to better support research activities within the dedicated CRC at other locations in the hospital or in the community.

This service provides research nursing care, sample processing, research coordination, adverse event and clinical monitoring, guided by expert research nurses, and research project management. It is designed to provide investigators with administrative, regulatory, and clinical support for projects. The program is subsidized by Harvard Catalyst for junior faculty, and investigators are eligible for limited pro bono support.

Experienced research nurses and coordinators from the CRC work closely with study team members to develop tools to conduct the study, facilitate the participant activity on other clinical units, and closely monitor study milestones and clinical data to ensure that projects are completed accurately and in a timely way. CRC staff work collaboratively with investigators to set up the support they need for their projects from a menu of possible options.

For more information, contact Linda Godfrey-Bailey, Site Nurse Director (lgodfrey@bidmc.harvard.edu) or Michelle Beck, Site Administrative Director (mbeck1@bidmc.harvard.edu)
**HCCRC @ MGH**

**Metabolism and Nutrition Research (MNR) Services: CPN & DXA Scan Analysis**

The MNR service at MGH has the expertise of a certified pediatric nutritionist (CPN) and specialty DXA scan analyses. Hip structural analysis (HSA), trabecular bone score (TBS), and visceral adipose/subcutaneous adipose tissue (VAT/SAT) measurement can be applied to Hologic DXA images done concurrently and previously.

TBS is a technique that uses variations in gray level distribution from lumbar DXA images to derive information about bone microarchitecture. It correlates significantly with three-dimensional parameters of bone microarchitecture independently of areal bone mineral density (BMD) in human cadavers. It is a useful strategy to predict bone structure and strength without the higher radiation associated with quantitative CT scans of the spine. HSA calculates the structural geometry of the hip, providing a better predictor of biomechanical strength than using bone mineral density alone. This feature helps determine whether the hip is reduced in strength to the point that treatment is required. The measurement of visceral fat using a DXA whole body scan is highly correlated to visceral fat measurements by CT. VAT software identifies anatomical features at the level of the fourth lumbar vertebrae. SAT is estimated from the subcutaneous fat on each side of the abdominal cavity.

For more information about these specialty services, please contact Ellen Anderson, MNR Director at MGH eanderson1@partners.org

**Congratulations!**

Congratulations to Tara M. Holmes, RD, LDN, CBDT, CPN, metabolism & nutrition research dietitian at MGH, who recently achieved board certification from the Academy of Nutrition and Dietetics as a certified pediatric nutritionist (CPN). Her nutrition expertise in pediatrics will enhance the implementation of our expanding pediatric research protocols.

**HCCRC @ BWH**

**BWH CRC Celebrates Distinguished Nurse Scientists**

Nurses trained as clinical scientists conduct research that guides a commitment to excellence in nursing practice, investigate the biological underpinnings of complex disease, and translate improved clinical interventions based on this knowledge. Today, these professionals are uniquely positioned at the center of patient care as they interact with patients, families, and the entire healthcare team. In these roles, they have an opportunity to question their practice and to conduct research aimed at answering important questions.

The National Institute of Nursing Research (NINR) at the National Institutes of Health (NIH) support much of the work conducted by nurse scientists and focuses on projects that build the scientific foundation for nursing practice, prevention of disease and disability, management and elimination of symptoms caused by illness, and enhancement of end-of-life and palliative care. BWH is home to many nurse scientists who contribute to this work and utilize the rich clinical and scientific resources. Working with multi-disciplinary scientific teams to implement methods to improve nursing practice, the end result is better outcomes for complex patient care. In recognition of the important role that nurse scientists play in leading and conducting patient-centered research at BWH, the HCCRC and the Center for Clinical Investigation recently celebrated the extraordinary contributions of nurse scientists.

**Patricia Dykes, RN, PhD,** is a Haley Nurse Scientist in the Center for Nursing Excellence and an assistant professor of medicine in the Division of General Internal Medicine and Primary Care at BWH. In this role she collaborates with patients, clinicians, and scientists from across disciplines to conduct patient safety and informatics research.

Other recognized research nurses include:

**Katherine Gregory, RN, PhD,** The overall aim of her research is to identify early predictors of disease in premature infants, and specifically, patterns of early intestinal colonization and gastrointestinal (GI) disease that commonly affects the immature bowel.

**Patricia Underwood, RN, FNP-BC, PhD,** Her work focuses on understanding the genomic and physiologic underpinnings of vascular complications of diabetes mellitus in humans.

**Lichuan Ye, RN, PhD,** Her program of research is to promote health through improving sleep and the management of sleep disorders.

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