Jeanette A. Zavala
L2
LSU Health Sciences Center, New Orleans, LA

Patricia E. Molina, MD, PhD
LSUHSC New Orleans, LA, Department of Physiology; Comprehensive Alcohol-HIV/AIDS Research Center; Alcohol and Drug Abuse Center of Excellence

At-Risk Alcohol Use and Impaired Glucose Tolerance Decrease Skeletal Muscle Mitochondrial Turnover in People Living with HIV

At-risk alcohol use is nearly twice as prevalent among people living with human immunodeficiency virus (PLWH). Chronic at-risk alcohol use and HIV are independently associated with skeletal muscle (SKM) dysfunction. Skeletal muscle is a key determinant of energy homeostasis and resting metabolism and SKM mitochondrial dysfunction is associated with metabolic dysregulation. Mitochondrial homeostasis depends on continuous biogenesis, fusion, fission, and mitophagy resulting in a highly dynamic network. These processes are regulated by several mitochondrial-related genes and proteins. Previous preclinical studies from our laboratory have demonstrated that chronic binge alcohol (CBA) administration alters mitochondrial gene expression in simian immunodeficiency virus (SIV) infected macaques. These SKM alterations are associated with impaired glucose metabolic homeostasis as demonstrated by intravenous glucose tolerance test in both male and female macaques. Because mitochondrial homeostasis is critical in the maintenance of functional metabolic SKM mass, and PLWH are at increased risk for at-risk alcohol use and metabolic dysregulation, we hypothesized that at-risk alcohol consumption and dysglycemia alter SKM expression of genes involved in mitochondrial biogenesis and function in PLWH. Studies were conducted in PLWH recruited as part of the Aging in Louisiana: Immunosenescence, HIV, and Socioenvironmental Factors-Exercise (ALIVE-Ex) study. All participants (N=35, 24 males, 11 females, age: 53±9, BMI: 29.0±6.6 kg/m^2) underwent an oral glucose tolerance test and completed the Alcohol Use Disorder Identification Test (AUDIT) to asses at-risk alcohol use. Muscle biopsies were collected from the vastus lateralis muscle. qPCR was used to determine skeletal muscle expression of genes implicated in regulating mitochondrial biogenesis and dynamics. Impaired glucose tolerance significantly decreased expression of PGC1A ($p<0.01$), PGC1B ($p<0.01$), and PPARA ($p<0.01$); at-risk alcohol use increased expression of PPARA ($p<0.05$) and decreased expression of DRP1($p<0.01$) and MFF ($p<0.01$); and at-risk alcohol use decreased expression of PPARG ($p<0.01$) only in participants with impaired glucose tolerance. Altogether, results indicated decreased expression of fission-related genes with at-risk alcohol use, decreased expression of master regulators of mitochondrial biogenesis with impaired glucose tolerance, and decreased expression of lipid handling-related genes with both factors. The independent and synergistic dysglycemia- and alcohol-mediated changes in mitochondrial gene expression may be indicative of altered bioenergetic function and impaired mitochondrial turnover, functions which are essential for mitochondrial health. Future work will build on these findings to include assessments of mitochondrial function and mitophagy. This work was funded by grants from the NIH/NIAAA: P60AA009803 (PEM), UH2AA026198 (PEM), F32AA027982 (DEL).