MUSCLE MITOCHONDRIAL DNA COPY NUMBER, DELETION MUTATION FREQUENCY, AND PHYSICAL PERFORMANCE IN OLDER ADULTS

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Mitochondrial DNA (mtDNA) quantity and quality influence hallmarks of aging – mitochondrial dysfunction and genomic instability. The interactions between mtDNA quantity and quality and physical performance have not been extensively examined in humans. The aim of this study was to test the interactions between skeletal muscle mtDNA copy number, mtDNA deletion mutation frequency, and physical performance measures in older adults. Total DNA was isolated from muscle biopsies and used for quantitation of mtDNA copy number and mutation frequency by digital PCR. The biopsies were obtained from a cross-sectional cohort of 53 adults aged 50 to 86 years. Before the biopsy, physical performance measures were collected. MtDNA deletions increased exponentially with advancing age. On average, mtDNA deletion frequency increased 18-fold between 50 and 80, with a trend toward lower deletion frequency in females. MtDNA deletion frequency predicted declines in VO2 max, where 4.7% of the variation in VO2 max was explained by mtDNA deletion frequency. MtDNA copy number was negatively correlated with age and mtDNA deletion frequency, but positively correlated with lean mass. There was a trend to lower mtDNA deletion frequency in females, consistent with increased longevity in females. Larger studies may better delineate sex effects. These data are consistent with a role for mitochondrial function and genome integrity in the maintenance of physical performance with age. Analyses of mtDNA quality and quantity in longitudinal studies could extend our understanding of the importance of mitochondria in human aging and longevity.

PICK YOUR POISON CAREFULLY: HOW ALCOHOL CONSUMPTION AND SERUM BIOMARKERS INFLUENCE BODY FAT – A UK BIOBANK STUDY

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Aging is characterized by physiological alterations in body composition, such as increased visceral adiposity accumulation and bone loss. Alcohol consumption is thought to partially drive these associations, but findings have been mixed. To clarify inconsistent findings, different types of alcohol--beer, liquor, and wine--may show different association patterns with body composition. Our longitudinal U.K. Biobank study leveraged 1,874 White British participants (aged 40-79 years; 58.9% male). Participants self-reported demographic, alcohol and dietary consumption patterns, and lifestyle factors using a touchscreen questionnaire. Anthropometrics and serum for proteomics were collected and body composition was obtained via dual-energy X-ray absorptiometry (DEXA). Structural equation modeling was used to probe direct and indirect associations between adiposity and bone, alcohol types, and cardiometabolic biomarkers. Over a mean duration of four years, greater consumption of beer and liquor were significantly associated with more visceral adiposity (β=.069, p<.001 and β=.014, p<.001, respectively); these associations were driven by dyslipidemia and insulin resistance. In contrast, greater red wine consumption predicted less adipose mass (β=-.023, p<.001), and this association was mediated by reduced inflammation and higher high-density lipoproteins (HDL) cholesterol. White wine consumption did not influence visceral adiposity but did predict greater bone mineral density (BMD) (β=.051, p=.003). Taken together, these data suggest that beer and liquor may drive the "empty calorie" hypothesis related to adipogenesis, while red wine may be protective due to anti-inflammatory and eulipidemic effects. Furthermore, white wine may benefit bone mineral density in older adults.

PROTEIN KINASE C DOWNREGULATION UPON RAPAMYCIN TREATMENT ATTENUATES NEUROINFLAMMATION AND MITOCHONDRIAL DISEASE

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Mitochondrial dysfunction causes many poorly understood diseases, such as Leigh Syndrome, that are often caused by dysfunctions in proteins involved in the electron transport chain. My lab previously reported mTOR is pathologically involved in the neurodegenerative phenotype and premature death of mice missing the Complex I subunit Ndufs4 (Ndufs4-/- mice). We discovered treatment with rapamycin extends lifespan, reduces neuroinflammation, and attenuates the neurodegenerative phenotype in these mice, although the mechanisms remain unclear. Rapamycin-treated Ndufs4-/- mice exhibited decreased activation of the mTORC1 pathway. It also deactivated the mTORC2 pathway. We observed that phosphorylation of the canonical protein kinase C (PKC) isoforms (PKC-α, -β, and -γ) decreased more than any other kinases, leading us to hypothesize its deactivation contributes to the observed lifespan extension. To test this, we treated Ndufs4-/- mice with three different PKC inhibitors: the pan-PKC inhibitors GO6983 and GF109203X, and the PKC-β specific inhibitor ruboxistaurin. Similar to rapamycin, all three drugs were able to significantly delay the onset of neurological symptoms (i.e. clasping) and increase survival. We also observed that PKC-β inhibition reduced skin inflammation to suppress the hair loss phenotype displayed by Ndufs4-/- mice at weaning. We further discovered PKC-β inhibition reduces neuroinflammation by deactivating the NF-kB inflammatory pathway. These results suggest that mTORC2 may play a critical role in the etiology of mitochondrial diseases such as Leigh Syndrome.