We have recently demonstrated that dietary nitrate, a source of nitric oxide via the enterosalivary pathway, can improve muscle contractile function in healthy older men and women. Nitrate ingestion has also been shown to reduce blood pressure in older individuals. However, the optimal dose for eliciting these beneficial effects is unknown. We therefore performed a randomized, double-blind, crossover study to determine the effects of ingesting 3.3 mL/kg of beetroot juice (BRJ) containing 0, 212, or 425 µmol/kg of nitrate in six healthy older (age 69±3 y) subjects. Maximal knee extensor speed (Vmax) and power (Pmax) were measured 2 h after BRJ ingestion using isokinetic dynamometry; blood pressure was monitored periodically throughout each study. Mean arterial pressure (in mmHg) was lower ($P<0.05$) after the high (80±4) vs. the low (84±3) or placebo (88±2) doses. Vmax (in rad/s), however, was higher ($P<0.05$) after the low dose (11.7±0.8), but not the high dose (10.8±1.0), compared to the placebo (10.5±1.0). Pmax (in W/kg) also tended to be higher ($P=0.11$) in the low (3.9±0.5) compared to the placebo (3.7±0.5) or high (3.7±0.5) trials. Five out of six subjects achieved a higher Vmax and Pmax after the low vs. the high dose. We conclude that dietary nitrate has differential effects on muscle function and blood pressure in older individuals. A high dose of nitrate intake further lowers blood pressure but does not enhance muscle contractility as much as a lower dose. Supported by Indiana University Purdue University Indianapolis and by the NIA (R21 AG053606)

AGE-RELATED CHANGES TO MACROPHAGES AFFECT FRACTURE HEALING

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Fracture healing follows a strict temporal sequence characterized by an initial inflammatory phase. Perturbation of the inflammatory phase may be responsible for the poorer fracture healing outcomes in older adults. Herein, we examine age-related changes to the macrophage during fracture healing. Macrophages regulate inflammation through pro-inflammatory (M1) and anti-inflammatory (M2) phenotypes. Anti-inflammatory activity is promoted via activation of triggering receptor expressed on myeloid cells 2 (TREM2). Tibia fractures were made in old (24 months) and young (3 months) mice. Immune cells from the fracture callus were analyzed via RNAseq and FACS, and fracture healing was evaluated histologically. Old mice demonstrated significantly delayed fracture healing compared to young ($p<0.05$). The quantity of infiltrating macrophages into the fracture callus was similar in young and old mice. However, 1222 genes were significantly differentially regulated (FDR<0.1) in callus macrophages from old mice compared to young, and old macrophages demonstrated a more pro-inflammatory phenotype. TREM2 expression was increased in macrophages after fracture in both groups but was significantly less in old mice compared to young via RNAseq and FACS (FDR<0.1, $p<0.05$). TREM2-/- mice demonstrated increased pro-inflammatory cytokine expression within the callus with resulting significant delays in fracture healing compared to age-matched controls ($p<0.05$). Inhibition of macrophage infiltration into the fracture callus significantly improved fracture healing in old mice compared to age-matched controls. Age-related changes to macrophages, including increased pro-inflammatory cytokine expression and dysregulated TREM2 expression, may explain fracture healing deficits observed in older adults. Therapeutically targeting macrophages may improve management of fractures in older adults.

THE ROLE OF PERCEIVED SOCIAL SUPPORT AND PRUDENT DIET INTAKE ON ALLOSTATIC LOAD AMONG OLDER ADULTS

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Allostatic load (AL), an index of multisystem physiological dysregulation due to chronic stress, has been identified as a predictor of poor health outcomes in late life. Research suggests that perceived social support (PSS) improves health outcomes by buffering the negative effects of stress on wellbeing and increasing health promoting behaviours including consumption of a healthy prudent diet (i.e., fruits, vegetables, lean meats, nuts, and seeds). Research to date has independently demonstrated that higher PSS and prudent diet intake have an effect on AL. A paucity of research, however, has examined how dietary consumption and PSS interact to effect AL in older adults. The objective of this study was to examine the interaction between PSS and prudent diet pattern on AL in 164 non-demented, community-dwelling older adults (Mage= 68.5(.52), 64% female). PSS and diet intake were measured using the Perceived Social Support Scale and the EPIC-Norfolk Food Frequency Questionnaire, respectively. AL was composed of 16 biomarkers stemming from neuroendocrine, metabolic, inflammatory, and cardiovascular systems, stratified by sex. Controlling for age and usual daily energy intake, higher prudent diet consumption (B=-2.04, p=.001), but not PSS, was associated with lower AL. Moderation analysis revealed that higher prudent diet intake was associated with lower AL only for those with low PSS (B=-.83, p=.0006) and mean level of PSS (B=-.43, p=.02). These findings suggest that chronic biological stress may be mitigated by consuming a healthy diet specifically for older adults with lower social support and may further inform intervention strategies to promote healthy aging.

METABOLOMICS IN MEN WITH DISTINCT INFLAMMATION TRAJECTORIES FOLLOWING HIP FRACTURE REVEAL RESPONSE MECHANISMS

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Introduction: Following hip fracture, men exhibit different trajectories of inflammation: high (HiInf) vs. low (LoInf). The purpose of this analyses was to compare metabolomics Between these groups. Methods: Seven men with HiInf and 7 with LoInf were randomly selected to quantify serum metabolites at baseline, 2, and 6 months following hip fracture in Baltimore Hip Study-7. We performed analysis of variance and mixed effects models. A p <0.05 was considered significant. Results: At baseline, men with HiInf had higher oxidative stress, lipid-related inflammatory markers, and antioxidant compounds compared to

LoInf group. These markers were reduced in both groups at follow-up, consistent with reduced stress. However, the attenuation level was significantly different between the two groups. Kynurenate, that indicates activation of the immune system, was higher in HiInf group and remained elevated over 6 months follow-up. Polyamines with anti-oxidant activity and boosting autophagy activities were declined more significantly in the LoInf group presumably indicating more response to bodily anti-oxidant activity compared to the HiInf group. Arachidonic acid-derived eicosanoids, mediators of the immune response, were significantly elevated at baseline in the LoInf while oxidative stress markers were increased more in HiInf group. Branched-chain amino acids (BCAAs), the essential amino acids abundant in muscle, were elevated at baseline in the LoInf compared to HiInf group. Conclusion: Both groups showed an increase in anti-oxidative stress while LoInf group showed more reduction in oxidative stress and immune cell activity. Reduced intermediate compounds of BCCA suggest that their catabolism was attenuated following hip fracture in LoInf.

THE ASSOCIATION BETWEEN D3CR MUSCLE MASS AND MORTALITY IN COMMUNITY-DWELLING OLDER MEN

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We have shown that men with low muscle mass assessed by D3Cr (deuterated creatine) dilution are more likely to have worse physical performance and incident fractures, injurious falls and disability. However, the relation between D3Cr muscle mass and mortality is unknown. With data from Year 14 Visit of the MrOS study (N=1400, mean age 84.2 yrs), proportional hazards models estimated the risk of mortality (hazard ratio and 95% CI) by quartiles of D3Cr muscle mass (standardized to body mass); we calculated p for trend across quartiles. Models were adjusted for age, race, clinical center, alcohol use, smoking status, comorbidities, activity, percent fat, exhaustion, and cognitive function. Cause of death was centrally adjudicated. Over 3.3±0.8 years of follow-up, 197 (14.1%) men died. Men in the lowest quartile of D3Cr muscle mass/wgt were 2.8-fold more likely to die than men in the highest quartile (HR: 2.8, 95% CI: 1.6, 4.9; p for trend<.001). The HRs for each cause-specific mortality outcome were of similar magnitude to the HR for overall mortality: cancer death (HR, Q1 vs Q4: 2.2, 95% CI: 0.7, 7.1; p trend =0.140); CVD death (HR, Q1 vs Q4: 3.7, 95% CI: 1.3, 10.5; p trend =0.008); or non-cancer non-CVD death (HR, Q1 vs Q4: 2.4, 95% CI: 1.0, 5.6; p trend=0.019). We conclude that low muscle mass assessed by D3Cr dilution is a strong risk factor for mortality in older men, providing additional evidence that low muscle mass is an important risk factor for adverse health outcomes.

THE PROBLEM OF INTEGRATING OF BIOLOGICAL AND CLINICAL MARKERS OF AGEING

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The number of potential biological markers of ageing increases dramatically especially with the development omics technologies. These biomarkers are not generally independent from each other and also related to clinical markers of aging that also could be markers of some illnesses. We discuss three ways of integrating biological and clinical markers of ageing: a frailty index (FI), indices of biological age, and a statistical distance as a measure of physiological dysregulation. We shows that FI has a strong theoretical support in the complex dynamical network model of the ageing process. The theory allows to explain why the interdependence of variables (representing the attributes of health) is essential for understanding of the basic properties both of the FI and of ageing such as a Gompertz law of mortality. Further progress in the field will go hand-in-hand with the development of new technologies that allow more data to be collected and interpreted.

THE ASSOCIATION BETWEEN MODERATE-TO-VIGOROUS PHYSICAL ACTIVITY AND MUSCLE OXIDATIVE CAPACITY IN OLDER ADULTS

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Age-related decline in muscle oxidative capacity negatively affects muscle function and mobility, which may lead to disability and frailty. Whether exercise and other life-style practices reduce age-related decline in muscle oxidative capacity is unclear. We assessed whether, after accounting for age, higher daily physical activity levels are associated with greater muscle oxidative capacity. Participants included 384 adults (54.7% women) aged 22 to 92 years from the Baltimore Longitudinal Study of Aging. Muscle oxidative capacity was measured in vivo using phosphorous magnetic resonance spectroscopy. We determined the time constant for phosphocreatine recovery (τPCr, in seconds) after exercise, with lower values of τPCr reflecting greater oxidative capacity. Time spent in moderate-to-vigorous physical activity (MVPA) was assessed using accelerometers that participants wore for 5.9 ± 0.9 consecutive days in the free-living environment. In linear regression models, older age was associated