Growth Hormone Antagonism Provides Metabolic and Joint Protection Against Aging Associated OA

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INTRODUCTION: Aging is one of the major risk factors for osteoarthritis (OA). Emerging evidence indicates that altered metabolism is a key factor underlying aging-associated OA. Growth hormone (GH) is a central regulator of metabolism, bone, and cartilage physiology. Excess GH, as in acromegaly or as we reported previously in GH transgenic mice, predisposes to joint degeneration, accelerated aging, and metabolic stress. Conversely, loss of GH signaling protects against age-related pathologies including OA and extends lifespan. The G119R GH receptor antagonist (GHa) blocks GH receptor activity. We hypothesized that combining GH excess with antagonism (bGH-GHa mice) would yield intermediate systemic phenotypes, attenuating GH-driven metabolic stress and thereby delaying knee OA.

METHODS: Male and female mice (ages 3 and 6 months; genotypes: wt, bGH, GHa, bGH-GHa; n = 8–23) were studied. Body composition was assessed by NMR. Metabolic phenotyping (120 hours) was performed in indirect calorimetry cages (Oxymax/CLAMS) to measure O_2 consumption (VO_2), CO_2 production (VCO_2), total energy expenditure (EE), respiratory exchange ratio (RER), food and water intake, locomotor activity, and energy balance. Glucose tolerance was assessed by intraperitoneal glucose tolerance test (ipGTT), and insulin tolerance by intraperitoneal insulin tolerance test (ipITT). Knee hyperalgesia was measured by Pressure Application Measurement (PAM) applied to the medial joint lines bilaterally. Data were analyzed by two-way ANOVA; significance was set at $p<0.05$. All procedures were approved by the Ohio University IACUC.

RESULTS SECTION: At 3 months, NMR analysis revealed apparent genotype-specific differences in body composition. bGH mice had the lowest fat mass (~10–12% of body weight), compared with wt (~12–14%), while GHa mice had the highest fat mass (~18–19%), and bGH-GHa combo mice were intermediate but closer to GHa (~16–17%). Lean mass followed the inverse pattern, with bGH highest and GHa lowest. By 6 months, these differences were accentuated: bGH mice remained the leanest (~12–13% fat), GHa mice became markedly fattest (~20–30%), and combo mice were intermediate (~18–22%), while wt averaged ~14–15%. Free body fluid differences were smaller but trended higher in combo mice and lower in GHa in males, and opposite in females. During ipGTT, bGH mice-maintained glucose clearance better than wt, with AUC values lower than controls; in contrast, GHa mice exhibited impaired tolerance with ~20–25% higher AUC than wt ($p<0.05$), most pronounced in females which showed delayed return to baseline. bGH-GHa mice again displayed intermediate excursions and AUC values. Indirect calorimetry over 120 h confirmed that bGH mice had the highest total energy expenditure (EE; ~25–30% above wt), whereas GHa mice had the lowest EE (~10–15% below wt). Combo mice consistently tracked between bGH and GHa. PAM thresholds, normalized to body weight, showed statistically significant pairwise differences: at 3 months, wt mice had higher thresholds than bGH ($p<0.01$), while both GHa ($p<0.001$) and Combo ($p<0.05$) exhibited higher thresholds than bGH; in females, Combo mice showed markedly higher thresholds than both wt and bGH ($p<0.0001$), and GHa were also higher than bGH ($p<0.001$). By 6 months, males displayed higher thresholds in GHa compared to bGH ($p<0.001$), whereas females showed no significant differences across groups. These results indicate that systemic metabolic changes are robust and appear early, while nociceptive alterations measured by PAM are more variable and influenced by age and sex.

DISCUSSION: These results demonstrate that GH action produces opposing systemic phenotypes detectable by 3 months and accentuated at 6 months. bGH mice are lean and hypermetabolic, burning more energy and relying more on lipid oxidation, yet they preserve or slightly improve glucose clearance. In contrast, GHa mice are fatter and expend less energy, and despite reduced GH drive, they exhibit impaired glucose tolerance, particularly in females. bGH-GHa mice show intermediate phenotypes across fat mass, glucose handling, and EE, indicating that antagonism partially offsets the extremes of GH excess. Importantly, PAM revealed age- and sex-dependent nociceptive changes, with GHa and combo effects emerging early but diminishing by 6 months. Ongoing studies of the joint structural changes will be further linked these systemic and knee outcomes directly.

SIGNIFICANCE/CLINICAL RELEVANCE: This study demonstrates that GH receptor antagonism mitigates early aging-related metabolic stress, providing a protective trajectory against knee vulnerability.

IMAGES: