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Weightlifting outperforms voluntary wheel running for improving adiposity and insulin sensitivity in obese mice

Robert J. Shute [a,†], Ryan N. Montalvo [b], Wenqing Shen [a], Yuntian Guan [a], Qing Yu [a], Mei Zhang [a,b], Zhen Yan [a,b,c,d,*]

[a] *Center for Skeletal Muscle Research, Robert M Berne Cardiovascular Research Center, School of Medicine, University of Virginia, Charlottesville, VA 22903, USA*

[b] *Center for Exercise Medicine Research, Fralin Biomedical Research Institute, Virginia Tech Carilion, Roanoke, VA 24016, USA*

[c] *Department of Human Nutrition, Foods, and Exercise, College of Agriculture and Life Sciences, Virginia Tech, Blacksburg, VA 24061, USA*

[d] *Division of Cardiovascular Medicine, Departments of Medicine, School of Medicine, University of Virginia, Charlottesville, VA 22903, USA*

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Abstract

Background: Exercise is an effective intervention for obesity and type 2 diabetes, with significant physiological benefits over pharmacological interventions. However, there is limited preclinical data available comparing endurance and resistance exercise for the impacts on obesogenic pathology and glycemic control.

Methods: Male mice were subjected to 8 weeks of diet-induced obesity (DIO) by high-fat diet (HFD) feeding concurrent with voluntary wheel running (endurance exercise (E_{EX})) or weightlifting (resistance exercise (R_{EX})). Sedentary (SED) mice fed on normal chow (NC) or HFD were used as controls.

Results: E_{EX} and R_{EX} interventions significantly attenuated weight gain *vs*. HFD-SED due to reduction of fat mass, not changes in lean mass, as assessed by EchoMRI. While R_{EX} suppressed visceral and subcutaneous fat accumulation significantly, only E_{EX} enlarged brown fat mass. Exercise tolerance testing (i.e., run-to-fatigue) revealed significantly improved exercise capacity in E_{EX} group *vs*. NC-SED. Interestingly, although HFD led to trends of increased skeletal muscle mass, only E_{EX} with HFD led to significant muscle weight gain. Neither exercise modality resulted in significant changes of hindlimb skeletal muscle contractile properties and cardiac function compared to SED mice on HFD. Importantly, R_{EX} showed significantly enhanced benefits over E_{EX} in improving homeostatic model assessment of insulin resistance (HOMA-IR), glucose tolerance, and insulin tolerance.

Conclusion: These results provide a direct and translatable comparison of endurance and resistance exercise training in a preclinical context of obesity and hyperglycemia. The current data set demonstrates an advantage of resistance exercise over endurance exercise in improving glucose and insulin tolerance under the condition of obesity, and that these improvements are independent of significant alterations of muscle weight gain and exercise performance.

Keywords: Diabetes; High-fat diet; Hyperglycemia; Obesity; Skeletal muscle

1. Introduction

Insulin serves as an anabolic stimulus for skeletal muscle and functions to promote glucose uptake, glycogen storage, protein synthesis, and to limit muscle protein breakdown.[1–5] The widely beneficial effects of insulin signaling on skeletal muscle homeostasis are diminished in obesogenic diseases, such as type 2 diabetes (T2D), where insulin resistance in skeletal muscle is central to the pathology. Indeed, diet-induced obesity (DIO) progresses from simple hyperglycemia to T2D via the central etiology of insulin resistance. Pharmacological interventions are the primary treatments utilized to combat DIO and T2D through improved glycemic control. Although first- and second-line sodium glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor

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* Corresponding author.
E-mail address: zhenyan1@vtc.vt.edu (Z. Yan).
† Current address: Department of Health and Human Sciences, Bridgewater College, Bridgewater, VA 22812, USA

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agonists have proven effective in management of DIO and T2D,[6] pharmacological intervention is limiting due to comorbidities, prescription cost, and an overall reliance on the drug for prospective hyperglycemic management. Most importantly, drug treatments only manage the symptoms of T2D and do not address the underlying physiology of insulin resistance, and patients that discontinue treatment (and often begin again) may have refractory weight gain and associated pathology and/or may become subsequently non-respondent to therapies.[6–8] On the contrary, exercise has been proven to be particularly effective for the prevention and treatment of obesity and T2D.[9] In this regard, a considerable amount of work has characterized the effects of exercise on glucose uptake, insulin sensitivity, and mitigation/reversal of obesogenic pathology.

Four years after the discovery of insulin, Hetzel[10] observed that exercise amplified metabolic processes in skeletal muscle in diabetic patients, experimentally demonstrated as increased insulin-stimulated glucose uptake. Several classical and recent experiments have confirmed that even a singular bout of endurance exercise (also known as aerobic exercise) increases glucose transport into skeletal muscle and has sustained effects on insulin sensitivity for 24–48 h.[11–13] Presently, the molecular mechanisms of exercise-induced glycemic control have been well-articulated in a litany of primary investigations and reviews.[9,14–17] The predominant modality of physical activity utilized in these studies has been based in endurance exercise with sustained cardiovascular efforts. Indeed, endurance exercise is a common intervention for clinical populations and has a low barrier to entry to be adopted in pre-clinical contexts. Separately, resistance exercise involves repeated contraction against a mechanical load and may serve to activate glucose uptake more robustly, but the pre-clinical models of resistance training have methodological and translational limitations (e.g., ladder climbing).[18] Our lab has developed a high throughput squat-like exercise (weightlifting (resistance exercise (R_{EX})) that has been validated to yield hindlimb muscle hypertrophy and insulin sensitivity in young healthy mice.[19] Importantly, this training approach overcomes described limitations of other resistance exercise models, such as decreased food consumption or weight loss during training, and most importantly closely mimics the voluntary aspect of voluntary wheel running.[18,20]

Assessment of exercise modalities has been performed in preclinical models of heart failure,[21] obesity,[22] sarcopenia,[23] cachexia,[24] and others, but there has yet to be a description of the comparative benefits of endurance and resistance training to combat the effects of high-fat diet (HFD) on body composition, exercise capacity, skeletal muscle mass and contractility, and whole-body insulin sensitivity, which carry significant translatability in the clinical setting. In this regard, the purpose of this study was to determine the efficacy of endurance exercise (E_{EX}) as compared to R_{EX} in mitigating obesity and hyperglycemia in a model of DIO. Herein, we present data that support the benefits of E_{EX} and R_{EX} in mitigating fat mass gain, while R_{EX} demonstrates superior benefits in improving glycemic control in the context of HFD feeding. The results of the current report may help to inform exercise prescriptions for individuals with obesity, type 2 diabetes, and other disease conditions to mitigate the harmful impact of impaired glycemic control.

2. Methods

2.1. Animals, diet, and exercise interventions

Male C57BL/6J mice (8–10 weeks) were purchased from the Jackson Lab (Bar Harbor, ME, USA) and housed in the animal care facility under 12-h light and dark cycle standard conditions. All experiments were approved by the Institutional Animal Care and Use Committee at the University of Virginia (#3762).

Mice were separated into 4 groups (Fig. 1A): (a) normal chow sedentary (NC-SED; *n*: 8–18), (b) high-fat diet sedentary (HFD-SED; *n*: 8–18), (c) high-fat diet voluntary wheel running/endurance (HFD-E_{EX}; *n*: 10–16), and (d) high-fat diet voluntary weightlifting/resistance (HFD-R_{EX}; *n*: 8–15). HFD food consisted of 60% kcal fat (#D12492; Research Diets, New Brunswick, NJ, USA). The resistance weightlifting protocol (R_{EX}) was followed as previously described.[19] A normal housing cage was modified to have a weightlifting cage top that holds food in a specialized container that could be reached by a mouse through a hole in a plate lever with a hinge (Fig. 1B). The cage required a small ramp for the mouse to reach the cage top and food. To access food, mice were fit with a small collar around the shoulders that required them to lift and set down the cage lid in a squat-like motion, which activates concentric and eccentric muscle contraction. Following 2 days of acclimatization, the mouse started to push 100% bodyweight load to access food, followed by incremental increasing load by 20% each day until achieving a 240% bodyweight load (Fig. 1C). The training started with a weightlifting cage top placed at the beginning of the dark cycle (7:00 p.m.), which was switched back to a regular cage top at 7:00 a.m. to minimize the potential impact of limited food intake during the dark cycle. Mice were single-housed, and recordings were collected daily. Voluntary wheel running (E_{EX}) was conducted as previously described in single-housed mice with access to voluntary running wheels and food and water ad-libitum, with daily running distance recorded via computer system.[25] NC-SED mice were housed in standard conditions with standard cage enrichment and food and water provided ad-libitum. Mice remained in their respective groups throughout 8 weeks of the intervention period and were weighed weekly. Outcome measures were collected at the beginning of the light cycle (7:00 a.m.–12:00 p.m.).

2.2. Body composition

At the end of 8 weeks, body composition was assessed using nuclear magnetic resonance (NMR) EchoMRI (Echo Medical Systems, Houston, TX, USA). Lean mass, fat mass, and total body water were measured. Lean mass (g) was normalized to tibia length (mm) and fat mass (g) was normalized to bodyweight (g).

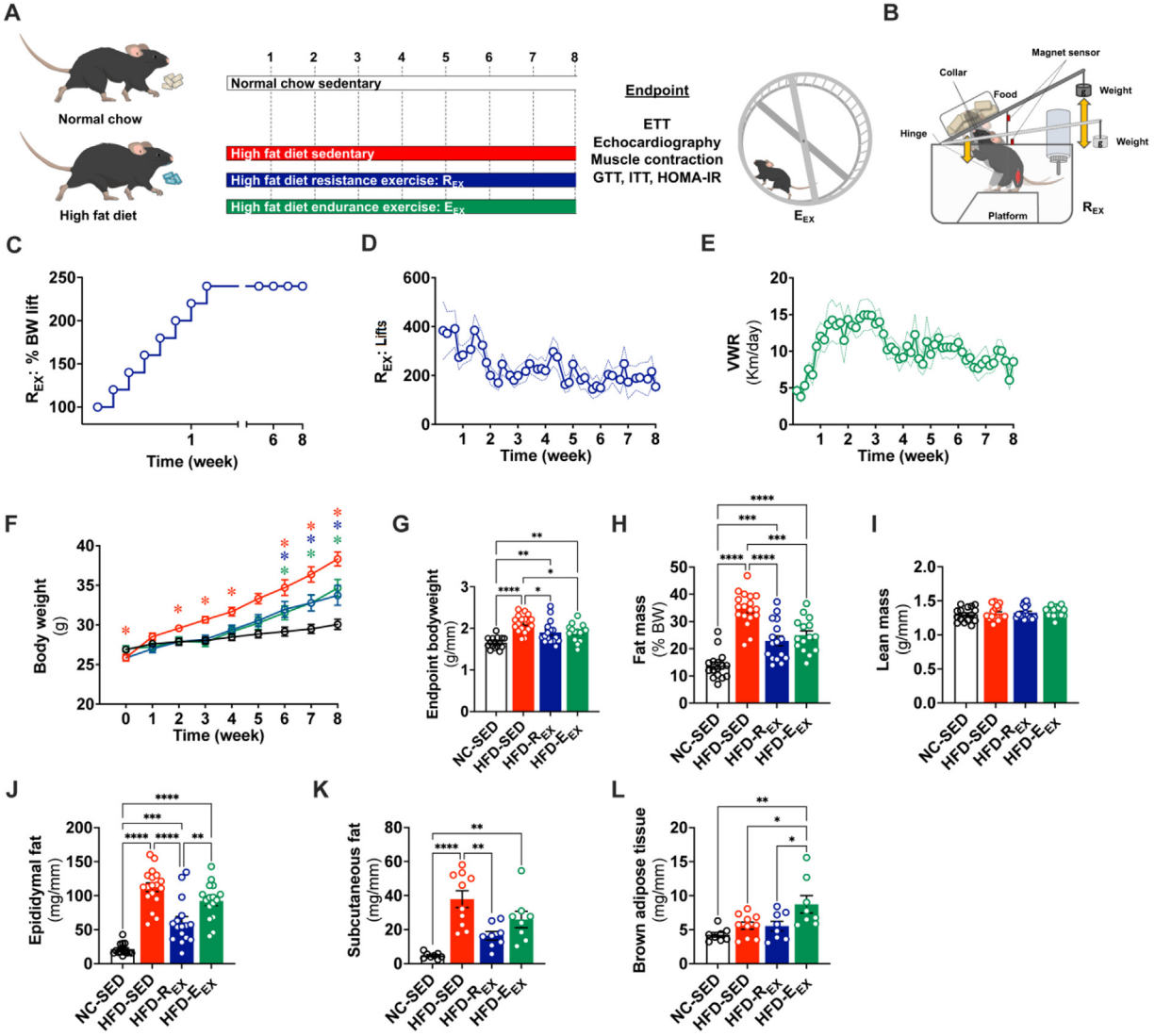

Fig. 1. Endurance and resistance exercise training differentially impact endurance exercise capacity and fat accumulation in response to HFD feeding. (A) Male C57BL/6J mice (8−10 weeks) were separated into 4 groups differentiated by diet (normal chow *vs*. HFD) and exercise (sedentary *vs*. weightlifting (R_{EX}) or voluntary wheel running (E_{EX})) with endpoint measures made after 8 weeks of treatment. Body weight was measured weekly, and body composition was determined at the end of the study. (B) Weightlifting model and cage for R_{EX}. (C) R_{EX} began with 100% body weight load and increased by 20% daily until achieving 240% body weight load (8 days) where it remained for the entirety of the study. (D) Average daily lifts (repetitions) for R_{EX} and (E) average daily kilometers for E_{EX}. (F) Body weight gain over study period. Colored * indicates significant difference from NC-SED. (G) Body weight at endpoint. (H and I) Body composition measurements by EchoMRI for fat mass (% BW) and lean mass (g/mm tibia length). (J−L) Weight of epididymal fat, inguinal fat, and brown fat (mg) normalized by tibia length (mm). Data presented as mean ± standard error of the mean. Statistical analysis performed by analysis of variance among groups: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, and **** $p < 0.0001$. NC-SED *n*: 8−16 (white); HFD-SED *n*: 8−18 (red); HFD-R_{EX} *n*: 10−16 (blue); HFD-E_{EX} *n*: 8−15 (green). BW = body weight; E_{EX} = endurance exercise; ETT = exercise tolerance test; GTT = glucose tolerance test; HFD = high-fat diet; HOMA-IR = homeostatic model assessment for insulin resistance; ITT = insulin tolerance test; NC = normal chow; R_{EX} = resistance exercise; SED = sedentary; VWR = voluntary weightlifting.

2.3. Treadmill exercise test

A treadmill endurance exercise test was conducted as depicted in Fig. 2 and performed as previously described.[25,26] Briefly, all mice were familiarized with the treadmill through daily running sessions at 0% incline and 13.41 m/min speed for 10 min (Days 1−3). On Day 4, mice underwent a graded exercise test on a fixed 5% incline, starting at 0.5 miles per hour (mph; 13.41 m/min) with incremental increases of speed by 0.1 mph every 30 min until exhaustion. Exhaustion was defined as the time when the mice remained on the shock grid for 5 s continuously. Complete exhaustion was confirmed by pre- and post-running tail vein blood lactate measurements.

2.4. Muscle function

Muscle contractile function of hindlimb plantar flexor muscles was measured *in vivo* under anesthesia using the Aurora Dual-Mode Lever System (Model 300C-LR; Aurora Scientific, Aurora, Canada) at least 24 h after a bout of exercise depicted in Fig. 3 and performed as previously described in detail.[19,27]

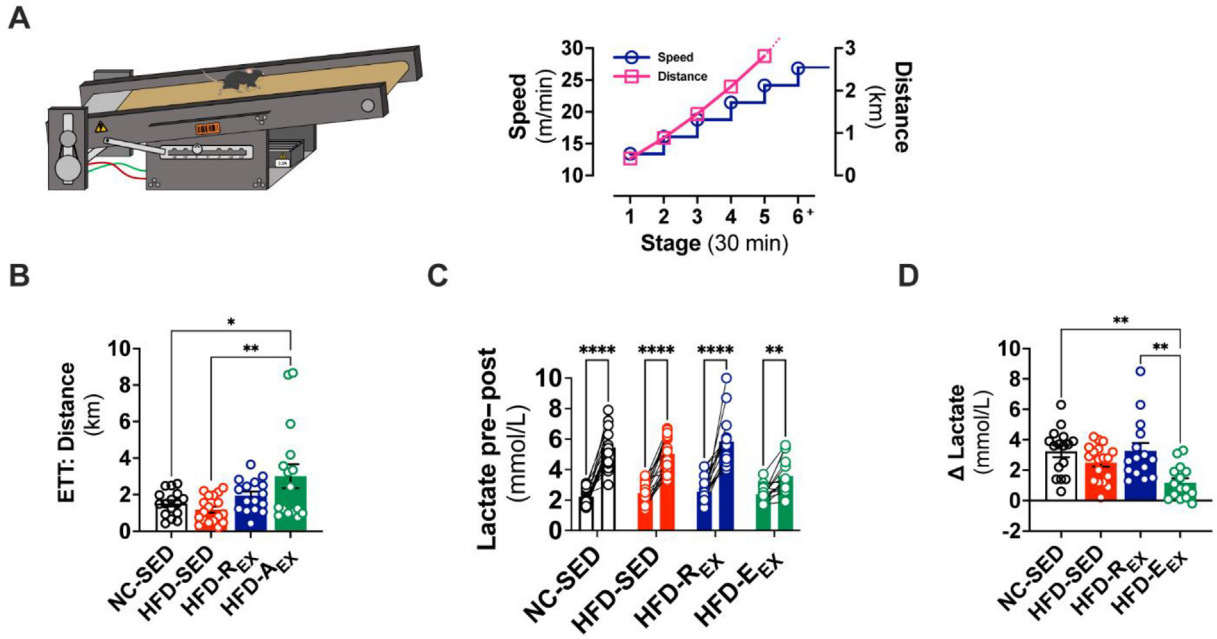

Fig. 2. Endurance exercise specifically improves exercise capacity under the condition of HFD feeding. All mice were tested by a treadmill running test following 8 weeks of diet and exercise interventions. (A) Depiction of a standardized ETT on an inclined treadmill (5%) that progresses through 30-min stages at 13.41, 16.09, 18.78, 21.46, and 24.14 and then remains at 26.82 m/min till exhaustion. (B) ETT performance is determined by total distance (km). (C and D) Exhaustion as confirmed by pre- and post-exercise blood lactate tests from the tail vein. Data presented as mean ± standard error of the mean. Statistical analysis performed by analysis of variance between groups: * $p < 0.05$, ** $p < 0.01$, and **** $p < 0.0001$. NC-SED $n = 16$ (white); HFD-SED $n = 18$ (red); HFD-R_{EX} n: 15−16 (blue); HFD-E_{EX} n: 14−15 (green). E_{EX} = endurance exercise; ETT = exercise tolerance test; HFD = high fat diet; NC = normal chow; R_{EX} = resistance exercise; SED = sedentary.

2.5. Echocardiography (ECG)

Mice were anesthetized via nasal inhalation of 2.5% isoflurane (No. 66749-017-10; Piramal Critical Care, Bethlehem, PA, USA) mixed with O_2 at a flow rate of 200 mL/min and then positioned supine on a 37°C heated platform; this was followed by hair removal from the chest with Nair™ (Church and Dwight, Ewing, NJ, USA) and ocular lubrication. Hind and forelimb pads were attached to ECG lead platform by tape, with readings facilitated by Spectra® 360 electrode gel (12-08; Parker Labs, Fairfield, NJ, USA). Aquasonic® 100 ultrasound gel (01-08; Parker Labs) was applied to the mid-chest and 13 MHz linear transducer probe. Two-dimensional imaging was used to locate the parasternal short-axis view at the level of the papillary muscles to obtain M-mode tracings of the left ventricle contractile function, chamber diameters during contraction (systole (s)) and relaxation (diastole (d)), and diameter of the posterior and anterior walls. Fractional shortening % was calculated by dividing the left ventricle internal diameter (LVID) during diastole and systole: $\frac{\text{LVIDd} - \text{LVIDs}}{\text{LVIDd}} \times 100\%$.

Cardiomyocyte hypertrophy of the posterior and anterior wall thickness (WT; mm) was assessed by calculation of $\frac{\text{WTs} - \text{WTd}}{\text{WTd}} \times 100\%$.

Images were analyzed using FIJI software (Version 1.53f; National Institutes of Health, Bethesda, MD, USA) and by a blinded co-author in accordance with defined protocols.[28]

2.6. Metabolic testing

Two days after the final exercise bout, all mice underwent a 6-h fast lasting from 9:00 a.m.−3:00 p.m. Glucose tolerance testing (GTT) was performed with a sterilized D-glucose solution (MP Biomedicals, Irvine, CA, USA; 200 mg/mL) in normal saline administered via intraperitoneal (IP) injection at 2 mg/kg body weight. Blood glucose levels were measured via tail vein before injection (0 min) and at 30-, 60-, and 120-min post-injection. Two-day following the GTT, mice underwent another 6-h fast from 9:00 a.m.−3:00 p.m. for the insulin tolerance test (ITT). Mice were IP injected with 0.1 U/kg sterile insulin (Cat. No. HI-213; Eli Lilly, Indianapolis, IN, USA) in normal saline. Blood glucose was measured via tail vein blood before (0 min) and at 15-, 30-, and 60-min post-insulin injection. The homeostatic model assessment of insulin resistance (HOMA-IR) testing was evaluated 2 days following the ITT, after mice were subjected to an overnight fast (5:00 p.m.−9:00 a.m.). Blood glucose was measured via tail vein by glucometer. After blood glucose measurement, ~100 μL of blood was collected, allowed to settle at room temperature for 4 h, then centrifuged for 15 min at 1500*g* at 4°C (Centrifuge 5417R; Eppendorf, Framingham, MA, USA). Serum was collected and stored at −80°C until insulin measurement was performed via enzyme-linked immunosorbent assay (ELISA) according to manufacturer's instructions (#90080; Crystal Chem, Elk Grove Village, IL, USA). HOMA-IR was calculated from glucose and insulin measurements according to standardized methods.[29]

2.7. Western blot analysis

At endpoint, mice were kept under anesthesia (2.5% oxygenated isoflurane (Piramal Critical Care)), and following an assessment of the negative pedal reflex, the plantaris was

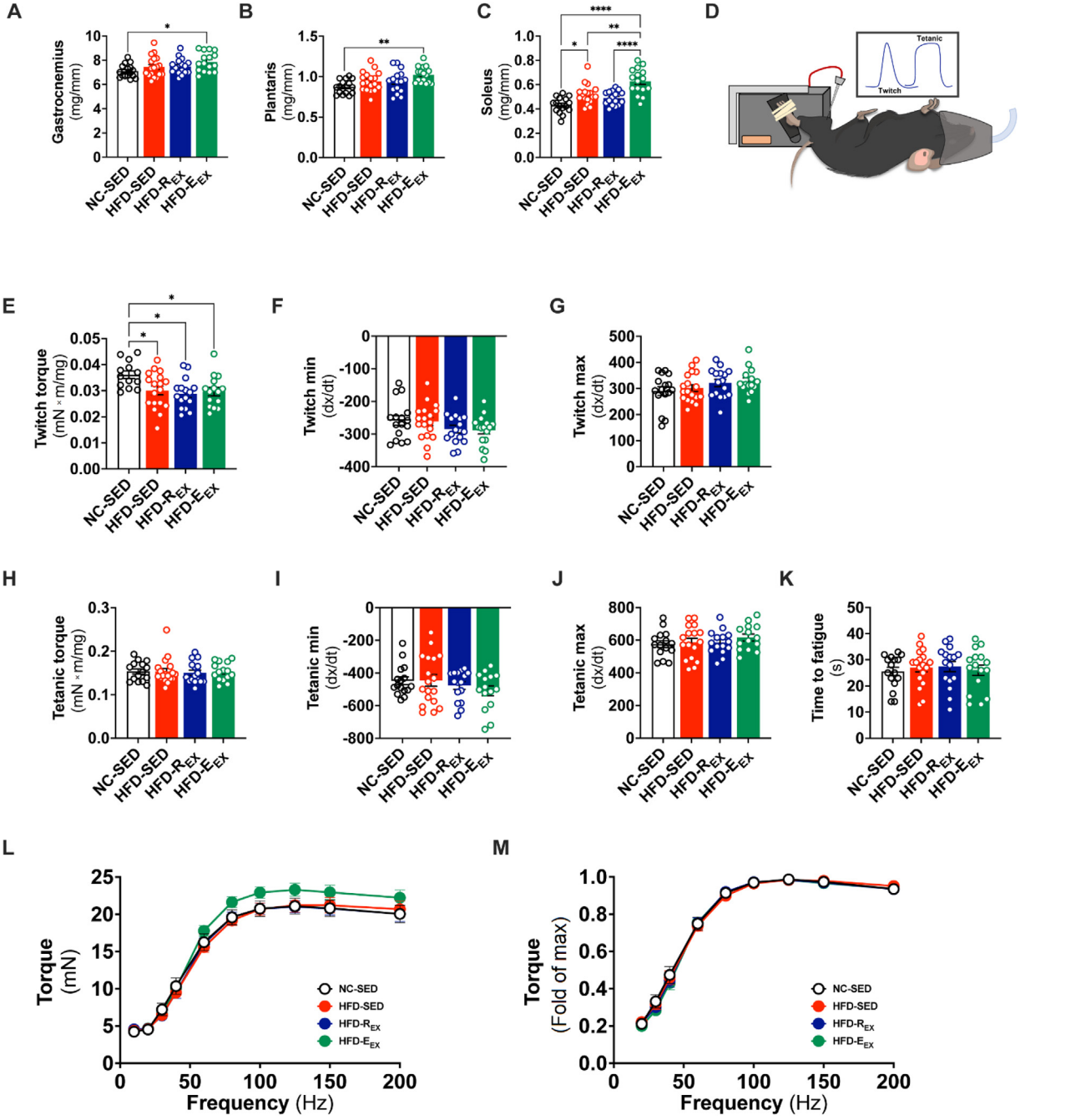

Fig. 3. Limited impacts of HFD and exercise interventions on muscle mass and *in vivo* contractile properties in young mice. Following 8 weeks of diet and exercise interventions, all mice were assessed for their hindlimb plantarflexor muscle contractile function by using the Aurora 2-mode muscle contraction system. (A−C) Hindlimb muscle weights (mg) for gastrocnemius, plantaris, and soleus normalized to tibia length (mm). (D) Depiction of plantarflexion muscle contractile apparatus. (E−J) Contractile twitch and tetanic torque (mN × m/mg) minimum and maximum (dx/dt). (K) Time to fatigue (s) from 100% max torque to 50% at 60 Hz repeated contractions. (L) Force−frequency curves were produced by stimulations at 10 Hz, 20 Hz, 30 Hz, 40 Hz, 60 Hz, 80 Hz, 100 Hz, 125 Hz, 150 Hz, and 200 Hz with 45 s of rest in between contractions. (M) Torque calculated in relationship to maximal capacity. Data presented as mean ± standard error of the mean. Statistical analysis performed by analysis of variance between groups: * $p < 0.05$, ** $p < 0.01$, and **** $p < 0.0001$. NC-SED *n*: 13−16 (white); HFD-SED *n*: 17−18 (red); HFD-R_{EX} *n*: 15−16 (blue); HFD-E_{EX} *n*: 14−15 (green). E_{EX} = endurance exercise; HFD = high fat diet; max = maximal; min = minimal; NC = normal chow; R_{EX} = resistance exercise; SED = sedentary.

isolated from the left leg and homogenized in 2× Laemmli sample buffer containing protease and phosphatase inhibitors (Sigma-Aldrich, Burlington, MA, USA). The left leg was then clamped to prevent blood loss, mice were injected with 5 U/kg of insulin (Eli Lilly), and the contralateral plantaris was harvested after 10 min and processed in the same manner. Muscle homogenate was heated at 97°C for 5 min and stored at −80°C for Western blot. Standard insulin treatment and immunoblotting procedures were performed as previously described.[26,30] The plantaris was chosen based on previous

studies showing efficacious response to exercise training as well as insulin response.[30] Primary antibodies used for analysis were from Cell Signaling Technologies (Danvers, MA, USA) and diluted 1:1000 unless otherwise stated as follows: protein kinase B (Akt; 1:500; #4691; Cell Signaling Technologies), phospho-Akt (pAkt) S473 (1:500; #9271; Cell Signaling Technologies), Ubiquitin (#3933; Cell Signaling Technologies), microtubule-associated protein light chain 3 (LC3 II/I; #4018; Cell Signaling Technologies), cytochrome c oxidase subunit 4(COX4; #11967; Cell Signaling Technologies), Akt substrate 160 (AS160 S318; #8619; Cell Signaling Technologies), AS160 T642 (#8881; Cell Signaling Technologies), eukaryotic translation initiation factor 4E binding protein (4E-BP1; #9452; Cell Signaling Technologies), and glyceraldehyde 3 phosphate dehydrogenase (GAPDH; #2118; Cell Signaling Technologies). Secondary antibodies were goat anti-rabbit IR800 and anti-mouse IR680 (# 926-32211 and 926-32222 respectively; LiCor Biosciences; Lincoln, NE, USA).

2.8. Statistical analysis

Data are presented as mean ± standard error of the mean. One-way analysis of variance was used for comparison among the 4 groups. When a statistical significance was observed, a Tukey's *post hoc* analysis was used to determine where differences existed among groups. *A priori* statistical significance was set at $p < 0.05$ and indicated in figures according to * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, and **** $p < 0.0001$.

3. Results

3.1. Endurance and resistance exercise training differentially impact fat accumulation and endurance exercise capacity in response to HFD feeding

Classically, the efficacy of exercise intervention is assessed by alteration in insulin sensitivity and glycemic control. To address this question, we designed an 8-week exercise study using a DIO model in mice that compared endurance (HFD-E_{EX}) and resistance (HFD-R_{EX}) exercise training in four groups (Fig. 1A and 1B). Voluntary weightlifting involved a progressive increase of load from ~100% body weight to a maximum of 240% body weight over 8 days, remaining at this steady load over the study period.[19] Mice in the R_{EX} group had an average of 231.0 ± 10.7 lifts/day (Fig. 1C and 1D) and the E_{EX} group ran 10.5 ± 0.4 km/day (Fig. 1E). These outcomes confirmed the voluntary exercise volume in the context of HFD. The DIO model was confirmed by the weight gain in the HFD groups compared to the normal chow sedentary group (NC-SED) (Fig. 1F and 1G). The HFD-SED group gained significant body weight by the second week, which was delayed in both exercise modalities. The body weight gain in the exercise groups did not reach statistical significance from NC-SED until Week 6. Both E_{EX} and R_{EX} resulted in significantly reduced body weight gain at endpoint compared to HFD-SED. Body composition analysis demonstrated that R_{EX} and E_{EX} attenuated fat mass increase at endpoint, without any differences in lean mass (Fig. 1H and 1I). Interestingly, R_{EX} resulted in greater reductions in visceral (epididymal) and subcutaneous (inguinal) fat enlargement compared to HFD-SED (Fig. 1J and 1K). Contrastingly, E_{EX} led to a significant increase of brown fat mass compared with any other conditions, which is consistent with endurance exercise training (Fig. 1L).

To evaluate the impacts of HFD and exercise on exercise capacity, we performed a treadmill exercise test (depicted in Fig. 2A). All groups significantly increased blood lactate in pre-post measurements, confirming anaerobic crossover, but only the E_{EX} group had improved total distance compared to the sedentary groups (Fig. 2B and 2C). Interestingly, the pre−post (Δ) blood lactate change was lower in the E_{EX} compared to NC-SED and R_{EX} groups, again consistent with expected endurance exercise training response as training has been demonstrated to cause reduced lactate production and increased lactate clearance[31,32] (Fig. 2D). Taken together, E_{EX} holds an advantage under the condition of HFD feeding in improving exercise performance, but R_{EX} exerts a superior benefit over E_{EX} in mitigating subcutaneous and visceral fat accumulation under the condition of DIO.

3.2. Concurrent exercise and HFD feeding displays minimal effects on muscle contractile function

Conditions of severe obesity and HFD have been shown to impair skeletal muscle protein synthesis and/or activate protein degradation in preclinical and clinical contexts.[33−39] Several studies have demonstrated obesogenic metabolic dysfunction in the absence of impaired muscle function,[36−39] warranting further investigation in the exercise models. Here, we show that in young mice, relatively short-term HFD (8 weeks) caused no significant reduction in hindlimb muscle mass (normalized by tibia length to control for growth), suggesting that this duration is not long enough to induce sarcopenia. In fact, HFD led to a trend of increased muscle mass of all 3 hindlimb plantar flexor muscles (gastrocnemius, plantaris, and soleus), and E_{EX} caused significant growth of these muscles over the study period, but R_{EX} did not (Fig. 3A−3C).

To ascertain the impacts of HFD and endurance and resistance exercise training on muscle contractile function, we performed *in vivo* muscle contractile function assay using the Aurora Dual-Mode system via stimulation of the sciatic nerve (Fig. 3D). All HFD groups had diminished twitch torque compared to NC-SED mice, while tetanic torque was not significantly altered. Null results were also observed for contraction and relaxation speed measured as twitch max and min (dx/dt) and tetanic max and min (dx/dt) (Fig. 3E−3J). Lastly, we performed muscle fatiguability test with repeated tetanic contractions at 60 Hz by measuring the time (s) to reach 50% of maximal contractile force. We did not observe significant alterations by diet or training modalities (Fig. 3K). When we performed stimulations with increasing frequencies (0, 20 Hz, 30 Hz, 40 Hz, 60 Hz, 80 Hz, 100 Hz, 125 Hz, 150 Hz, and 200 Hz), we did not observe significant differences in force-frequency curve among any of the groups (Fig. 3L and 3M). These results indicate that under the

condition of HFD neither exercise modality affected significant changes of contractile properties in young mice, other than E_{EX} resulting in significant but moderate weight gain of weight-bearing muscles. Although our results are generally in line with current literature, there is high variability in study design and implementation.[36−39] Nevertheless, this is the only study with the current weightlifting model in DIO mice, which clearly warrants further investigation.

3.3. Endurance exercise induces physiological cardiac hypertrophy under HFD condition but neither endurance exercise nor resistance exercise significantly affects cardiac function

Standard echocardiography measures were taken at endpoint to evaluate impacts of HFD feeding with/without exercise interventions on cardiac function[21,22] (Fig. 4A). Heart weight was moderately but significantly increased in E_{EX} groups compared with NC-SED and HFD-SED groups (Fig. 4B). Heart rate under inhaled isoflurane did not differ between groups (Fig. 4C). Functionally, the contractile capacity of the left ventricle was also unaltered at endpoint (Fig. 4D−4F). HFD-SED, HFD-E_{EX}, and HFD-R_{EX} groups did not show increased or decreased posterior cardiac wall thickness (PWTs/d) or anterior cardiac wall thickness (AWTs/d) (Fig. 4G−4L). In previous preclinical models, HFD feeding has been demonstrated to not cause cardiac dysfunction after 6−12 weeks,[40] 5 weeks,[41] and 4−16 weeks[42] but to cause dysfunction after 18 weeks,[40] 20 weeks,[41] and 24 weeks,[42] respectively. In line with these reports, our data show that 8 weeks of HFD is insufficient to cause cardiomyopathy, and that endurance exercise training—but not resistance exercise training—resulted in a moderate physiological cardiac hypertrophy.

3.4. Resistance exercise exceeds the benefits of endurance exercise in ameliorating metabolic dysfunction

Glycemic control is paramount to the efficacy of exercise in mitigating obesogenic pathology.[43] In the present study, HFD resulted in elevated fasting blood glucose and insulin (Fig. 5A and 5B) without significant increase in HOMA-IR (Fig. 5C). R_{EX} mice demonstrated diminished HOMA-IR compared with the HFD-SED group, indicating an improvement in whole-body insulin sensitivity despite no changes from the NC-SED group (Fig. 5C). We performed metabolic testing through a bolus IP injection of glucose or insulin to evaluate the impact of exercise training on whole-body glucose clearance and insulin sensitivity during obesogenic hyperglycemia. During the GTT, HFD-SED mice demonstrated significant increases in blood glucose above NC-SED at 0, 30 min, 60 min, and 120 min compared with NC-SED mice, indicating severely impaired glucose tolerance. Further, these results indicate hyperglycemia during the 6-h fast, complimenting the overnight fast for HOMA-IR. While R_{EX} completely mitigated this defect, E_{EX} only showed partial improvement (Fig. 5D). These findings are also reflected by the integrated area under the curve of the GTT (Fig. 5E). Similarly, an ITT demonstrated a more robust benefit of R_{EX} in whole-body insulin sensitivity over E_{EX}, although no differences were observed from NC-SED groups (Fig. 5F and 5G).

To further dissect this mechanism, we utilized an *in vivo* protocol of contralateral hindlimbs to evaluate Akt phosphorylation in response to insulin injection.[30] All HFD feeding groups had diminished response of Akt phosphorylation in skeletal muscle, while the impacts of exercise interventions did not reach statistical significance for improvement (Fig. 5H−5J). We further measured intramuscular glucose handling regulation through phosphorylation of AS160 at S318 and T642, as these sites have been implicated in regulating glucose uptake through GLUT4.[44,45] NC-SED showed a significant increase in insulin-stimulated S318, which was blunted in the HFD mice, and AS160 T642 showed increased response in all groups except R_{EX} (Fig. 5K−5N). However, neither phosphorylation site demonstrated significant changes from pre-post insulin stimulation. Mammalian target of rapamycin (mTOR) signaling has been demonstrated to be aberrantly impacted by HFD feeding but is sensitive to exercise, implicated by its role in canonical muscle protein synthesis pathways.[46,47] In this regard, phosphorylation of 4E-BP1 was increased with HFD feeding alone and was mitigated in the E_{EX} but not R_{EX} mice (Fig. 5O and 5P). Raptor was not significantly altered in any of our treatment groups (Fig. 5Q). Additional mechanisms of HFD pathology, such as decrements to mitochondrial volume (COX4; Fig. 5R) and increased protein breakdown mechanisms through the autophagy (LC3 II/I; Fig. 5S) and ubiquitin-proteosome (ubiquitin; Fig. 5T) pathways, were also evaluated without observed differences.

4. Discussion

Despite the recent advent of pharmacological intervention (i.e., semaglutide inhibitors or GLP1 agonists), regular exercise remains the most effective intervention for the management and prevention of obesity and T2D. Indeed, numerous randomized control trials (RCTs) have been conducted over the past several decades that employ endurance exercise, resistance exercise, and high intensity interval training (HIIT), as well as combinations of modalities to ameliorate diabetic pathology.[48−51] Within these studies, the reduction of glycated hemoglobin (HbA1c) served as the primary outcome measure over weeks to months of training. Consistently, many of these studies captured a reduction in HbA1c, concurrent with improvements in body mass index (BMI), blood pressure, and enhanced quality of life.[48−51] In this regard, there is an assured consensus in the field related to the efficacy of exercise to mitigate diabetic pathology, but investigation of exercise modalities and preclinical application of translatable exercise models have not been well-explored, limiting investigations into molecular mechanisms of exercise impacts on metabolic syndrome.

Differentiation of exercise modalities has been investigated in several studies as a means to manage diabetic pathology.[52−58] Within these studies, recommendations for exercise largely fall in line with the American College of Sports Medicine frequency, intensity, time, and type (FITT) principles and

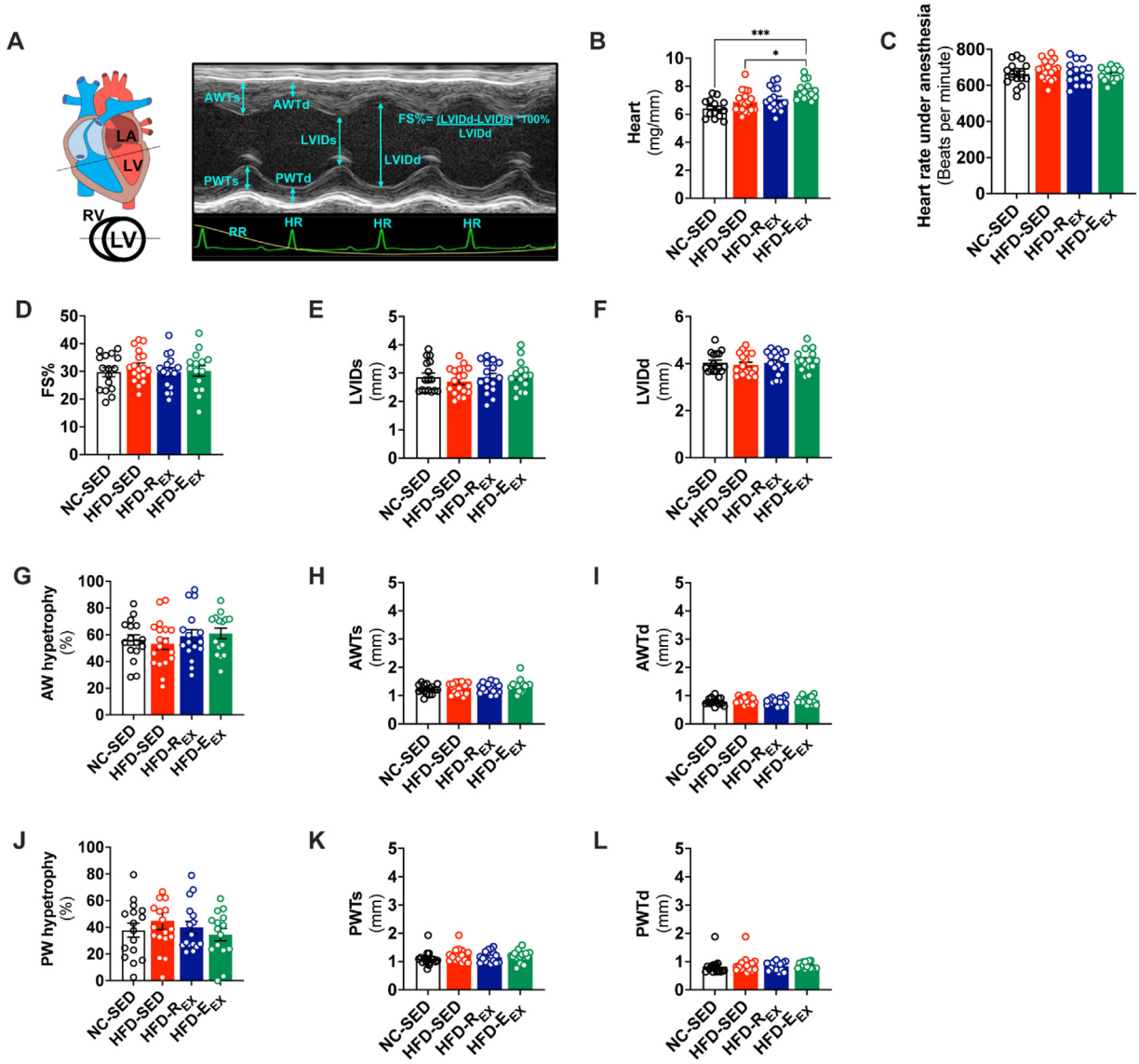

Fig. 4. Endurance exercise results in physiological cardiac hypertrophy under the condition of HFD feeding without detectable change of cardiac function. Following 8 weeks of diet and exercise interventions, all mice were assessed for cardiac function by echocardiogram under anesthesia. (A) Standard m-mode echocardiography was performed to determine LV morphology during diastole (d) and systole (s) for the LVID, PWT and AWT and % hypertrophy, HR under inhaled isoflurane, RR (data not shown), and calculation of FS%. (B) Heart weight at endpoint normalized to tibia length (mg/mm). (C−J) Additional measurements taken for heart rate, FS%, LVIDs, LVIDd, AWTs, AWTd, PWTs, and PWTd, and AW and PW % hypertrophy. Data presented as mean ± standard error of the mean. Statistical analysis performed by analysis of variance between groups: * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$. NC-SED $n = 16$ (white); HFD-SED $n = 18$ (red); HFD-R_{EX} $n = 16$ (blue); HFD-E_{EX} $n = 15$ (green). AWT = anterior wall thickness; E_{EX} = endurance exercise; FS% = percentage of fractional shortening; HFD = high fat diet; HR = heart rate; LA = left atrium; LV = left ventricle; LVID = left ventricle internal diameter; NC = normal chow; PWT = posterior wall thickness; R_{EX} = resistance exercise; RR = respiratory rate; RV = right ventricle; SED = sedentary.

consist of (a) endurance exercise for 40−60 min with 60%−85% of heart rate reserve 2−3 times/week and (b) resistance exercise for 30−60 min with 2−3 sets of 8−12 repetitions at 60%−80% of 1 repetition maximum 2−3/week.[59] Although many studies agree on the efficacy of endurance and resistance exercise to decrease HbA1c independently, there are mixed results in comparing the impact of one modality over another. Endurance exercise has been demonstrated to be acutely more effective at achieving glucose homeostasis but to have similar impact as resistance training for long-term management of metabolic homeostasis.[57] In patients with T2D who have normal weight (BMI < 25 kg/m^2), resistance exercise training proved more efficacious than endurance training for reduction of HbA1c.[56] In a recent study, Luo and colleagues[58] demonstrated that endurance and resistance exercise could improve HOMA-IR and insulin resistance but that the effects of resistance exercise surpassed endurance exercise in terms of improved HOMA-IR. These investigations suggest that resistance exercises, such as weightlifting, may lead to improved insulin sensitivity and muscle quality beyond the glycemic control that is associated with weight loss and endurance training. Further, while the current report demonstrates an

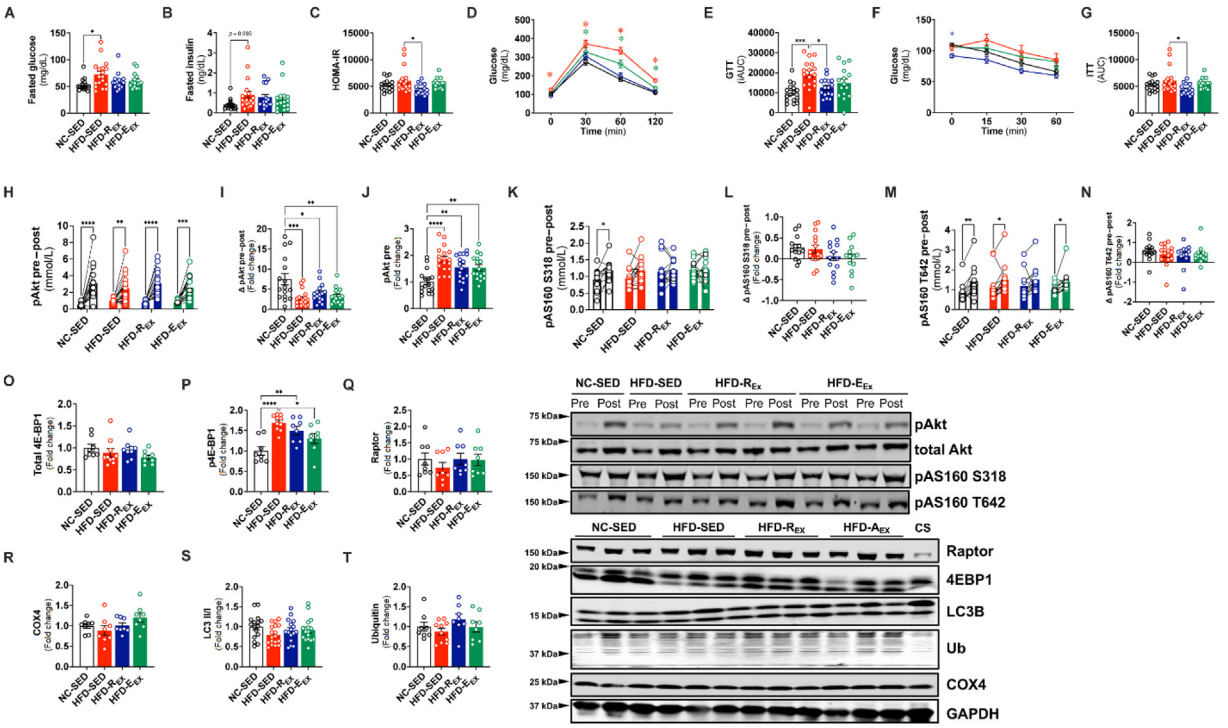

Fig. 5. Resistance exercise exceeds the benefits of endurance exercise in ameliorating metabolic dysfunction. Following 8 weeks of diet and exercise interventions, all mice were assessed for their metabolic function by GTT, ITT, and skeletal muscle response of Akt and AS160 phosphorylation to injection of insulin measured by Western blot. (A−C) HOMA-IR taken after an overnight fast for baseline glucose and insulin. (D and E) GTT from 0−120 min and calculated AUC; colored * indicates significant difference from NC-SED. (F and G) ITT from 0−60 min and calculated AUC; colored * indicates significant difference from NC-SED. (H−N) pAkt stimulation, AS160 S318, and AS160 T642 in hindlimb muscles before and after insulin injection and the pre−post *Δ* in phosphorylation. (O and P) Total and phosphorylated 4E-BP1. (Q−T) Western results for Raptor, COX4, LC3 II/I, and ubiquitin staining. Representative western blot images inset right. Data presented as mean ± standard error of the mean. Statistical analysis performed by analysis of variance between groups: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, and **** $p < 0.0001$. NC-SED *n*: 8−16 (white); HFD-SED *n*: 8−18 (red); HFD-R_{EX} *n*: 8−16 (blue); HFD-E_{EX} *n*: 8−15 (green). 4E-BP1 = Eukaryotic translation initiation factor 4E binding protein; Akt = protein kinase B; AS160 = Akt substrate 160; COX4 = cytochrome c oxidase 4; CS = citrate sythase; E_{EX} = endurance exercise; GAPDH = glyceraldehyde 3 phosphate dehydrogenase; GTT = glucose tolerance test; HFD = high fat diet; HOMA-IR = homeostatic model assessment for insulin resistance; iAUC = integrated area under the curve; ITT = insulin tolerance test; LC3 II/I = microtubule-associated protein light chain 3; NC = normal chow; pAkt = phospho-Akt; R_{EX} = resistance exercise; SED = sedentary; Ub = ubiquitin.

initially progressive model of weightlifting training and then remains at a steady load for most of the study, an advanced progressive weightlifting training regimen may have advanced benefits.[60,61] Future studies may consider a combination of endurance and resistance exercise interventions that have proven effective rather than a single modality alone[62–64] and/or a greater load of R_{EX} training as mitigation if HbA1c is correlated with resistance exercise intensity.[65] Nonetheless, the results of the current report provide a vital contribution to the literature when considering exercise modality through effective modeling of resistance and endurance exercise in a preclinical context, and they are largely in line with several outcomes of the clinical data.

Clinical studies have many limitations, including heterogenicity in study populations, adherence to exercise protocols, population dynamics, and patient burden to participation. These limitations may severely impede mechanistic molecular investigation into exercise impacts on obesity, T2D, and many other disease conditions. In contrast, preclinical models allow for more discrete and invasive comprehensive measures; however, there are to this point an insufficient number of translatable resistance exercise models.[18] Our resistance exercise apparatus solves this problem by closely mimicking a squat-like exercise with natural concentric and eccentric muscle contractions. Similarly, voluntary wheel running is a very translatable model for physical activity in mice. RCTs for exercise-based treatment of T2D typically employ a supervised model where patients are required to attend regular exercise sessions under the guidance of an exercise professional. However, unsupervised (i.e., telehealth, home-based, coaching) exercise interventions for T2D have demonstrated similar efficacy for improvement in glycemic control, body composition, functional capacity, muscle strength, and quality of life.[48,66–69] Importantly, unsupervised (i.e., voluntary) exercise has an increased self-efficacy for adaptations of a physically active lifestyle that may have lasting benefits for management of T2D.[70] In this regard, the voluntary modeling of exercise in our report may have improved translatable potential over other available models.[18,20]

Within diabetic skeletal muscle, the synergistic effects of insulin resistance and decreased physical activity create a toxic feedforward loop between increased fat mass and decreased skeletal muscle mass and quality, prospectively exacerbating diabetic pathology.[71,72] In many diabetic patients, this phenotype is produced concurrent with sarcopenic obesity, even with a normal BMI.[73] Herein, we report no significant changes to lean mass in the HFD-SED condition or with exercise intervention, yet studies of diabetic individuals have shown a decrement in lean mass;[74] however, the current report utilizes young mice exclusively, which may account for this difference. Relatively increased visceral and subcutaneous fat levels are associated with the development of metabolic dysregulation,[74] and patients with diabetes are known to have increased fat mass.[72] Further, visceral fat is strongly associated with diabetes, more so than subcutaneous fat or BMI.[75] Interestingly, our data suggest that R_{EX} and E_{EX} are effective at limiting fat mass gain over 8 weeks of HFD feeding, as demonstrated by endpoint body composition analysis. Meanwhile, R_{EX} was marginally more effective at limiting body weight gain but significantly more impactful in reducing subcutaneous and visceral fat. Based on our results, resistance exercise appears to be a more effective intervention for limiting these risk factors. Lastly, adipose tissue metabolism is highly sensitive to exercise and plays a significant role in the diabetic phenotype,[76–78] and future studies may benefit from evaluation of the crosstalk between skeletal muscle and adipose tissue in the current study design.

Resistance exercise, and our model of voluntary weightlifting in particular, has been demonstrated to lead to muscle hypertrophy (quantity) and improved insulin sensitivity (quality) in acute and training study modalities.[19,79] However, resistance exercise has been consistently demonstrated to mitigate anabolic resistance and exercise intolerance in diabetic populations.[14,80–83] Skeletal muscle with anabolic resistance is less responsive to exogenous stimuli that characteristically cause increased muscle protein synthesis, such as amino acid consumption, insulin stimulation, and exercise. The combinatorial effects of exercise intolerance and anabolic resistance may be detrimental to exercise interventions, as several studies have demonstrated that mitigation of T2D pathology with exercise is dose-dependent.[49,65] In this regard, the more directly hypertrophic stimulus of resistance training may increase anabolic sensitivity to a larger degree than endurance exercise, a theory that has been demonstrated in several reports.[84–86] RCTs have demonstrated that resistance exercise can effectively improve muscle strength in T2D patients independent of improved lean mass,[83,87] a hallmark of increased anabolic sensitivity. The current report demonstrates an absence of detectable improvements of contractile properties and hypertrophy in skeletal muscles in the context of resistance exercise during HFD in young mice. As HFD did not result in significant impairment of muscle contractile function, it may not be surprising to observe no significant changes with exercise interventions. While E_{EX} did increase muscle weight at endpoint, this may be as a synergistic effect of body weight gain and voluntary wheel running. However, R_{EX} appears to improve anabolic sensitivity as demonstrated by improved GTT, ITT, and HOMA-IR measurements, which were not all observed in E_{EX}. A singular resistance exercise bout has been shown to improve glucose clearance while also influencing insulin action at 18 h post exercise in diabetic individuals.[88] Multiple studies have demonstrated an increase in insulin sensitivity with resistance or strength training, which is in line with our data;[89–91] however intra-study comparison with endurance training is not commonly addressed. Putatively, R_{EX} leads to increased anabolic sensitivity due to amplified activation of muscle protein synthesis pathways through the Akt-mTOR pathway.[92] Interestingly, randomized crossover study demonstrated increased mTOR activity with resistance as opposed to endurance training.[93] We have confirmed hindlimb skeletal muscle response to insulin and showed that HFD diminished pAkt activation in all groups, with subtle trends of improvements by E_{EX} and R_{EX}. Additional molecular signaling pathways could explicate the beneficial effects of R_{EX}, such as myostatin signaling, which is a negative

regulator of muscle mass and is decreased in humans and mice after resistance exercise, possibly through the impedance of the Akt-mTOR signaling axis.[80]

The RCTs and preclinical investigations we have discussed herein thoroughly demonstrated the benefits of resistance and endurance exercise training regimens to mitigate diabetic pathology and restore euglycemia. One limitation of the current study is the use of only male mice given that sex variation in exercise performance has been demonstrated in the literature.[94–96] It is important to also note that diabetic women have diminished physical fitness compared to age-matched uncomplicated diabetic women, something that was not observed in men and may account for increased cardiovascular morbidity and mortality in women.[97] A recent meta-analysis demonstrated that adult men with diabetes are more likely to meet the physical activity guidelines than women,[98] putatively impacting the efficacy of autonomous exercise as a strategy for mitigating diabetes. However, in a structured setting, two recent systematic reviews and meta-analyses[98,99] demonstrate similar responses to exercise in the diabetic men and women. Indeed, no sex-based differences were observed for muscle size or physical performance for resistance exercise training alone.[99] Physical activity interventions of mixed modality showed diminished cardiovascular risk as well as improvements to cardiorespiratory fitness and glycemic and insulin sensitivity that were irrespective of sex.[100]

5. Conclusion

HFD feeding is the most highly validated and established model of obesity and T2D in mice, as it mirrors the etiological and pathological indications in human patients. However, the discrete mechanisms of this relationship and the ability of exercise to mitigate the pathology of DIO are not well understood and require further investigation. Herein, we explored the efficacy of weightlifting (R_{EX}) and voluntary wheel running (E_{EX}) in mitigating the consequences of HFD feeding in mice. We found that R_{EX} showed greater efficacy than E_{EX} in mitigating metabolic dysfunction as demonstrated by a greater reduction of subcutaneous and visceral fat mass accumulation as well as improvements in metabolic tolerance testing and HOMA-IR caused by HFD feeding. These results were independent of significant alterations to exercise capacity, muscle contractile performance, and skeletal muscle hypertrophy. In this regard, R_{EX} training demonstrates a superior benefit of anabolic sensitivity, even in the context of HFD.

Authors' contributions

RJS conceptualized the work, performed primary data collection of all outcomes, and assisted with writing of the original draft; RNM performed data analysis, compiled and analyzed the outcomes for publication, generated figures, and drafted/edited the manuscript for its final form; WS, QY, and MZ contributions were equal for the generation of primary data related to this manuscript in all outcomes, apart from echocardiography; YG performed and analyzed echocardiographic outcomes and contributed to data collection of all other outcomes; ZY conceptualized the work, provided oversight to study design and implementation, acquired funding to support the work, oversaw data analysis, reviewed and edited the preparation of the manuscript. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Declaration of competing interest

The authors declare that they have no competing interests.

Data availability

Data will be made available from the corresponding author upon reasonable request.

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Supplementary materials

Supplementary materials associated with this article can be found, in the online version, at doi:10.1016/j.jshs.2025.101100.

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