Weekly Bone Loading Exercise Effects on a Healthy Subject's Strength, Bone Density, and Bone Biomarkers

Ann Tsung; Daniel Jupiter; John Jaquish; Jean Sibonga

BACKGROUND: Bone density loss affects astronauts in long-duration spaceflight. The OsteoStrong® Company has shown increased hip (14.95%) and lumbar (16.6%) area bone mineral density (aBMD) after 6 mo of exercises with their loading devices. The devices were tested on one subject as a pilot study.

CASE REPORT: The subject performed 15 min of osteogenic exercises weekly for 24 wk. Total and regional aBMD, BAP (bone formation biomarker), NTX (bone resorption biomarker), forces exerted on devices, and weekly maximum weights lifted were collected. The control data was the subject's own lifting records 1.5 yr prestudy. The subject increased forces exerted on the devices in the upper extremity (97%, 197 to 390 kg; 435 to 859 lb), lower extremity (43%, 767 to 1097 kg; 1690 to 2418 lb), and spinal compression (22%, 275 to 336 kg; 607 to 740 lb). The monthly strength gain rate increased for snatch (2.3 vs. 0.71 kg; 5 vs. 1.56 lb), clean and jerk (2.5 vs. 0.4 kg; 5.5 vs. 0.88 lb), back squat (3.74 vs. 0 kg; 8.25 vs. 0 lb), front squat (2.15 vs. 0.2 kg; 4.75 vs. 0.47 lb), and deadlift (3.97 vs. 1.09 kg; 8.75 vs. 2.4 lb). The BAP increased by 39% (10.4 to 14.5 4 ug $\cdot$ L^{-1}) and NTX decreased by 41% (13.4 to 7 nmol $\cdot$ L^{-1} BME). aBMD increased in the head (6%), arms (4.3%), trunk (6.3%), ribs (3.8%), and pelvis (11%). There were no differences in body weight, legs, spine, and whole-body aBMD on the full-body dual-energy X-ray absorptiometry (DXA). There were no differences in lumbar, hip, and femoral neck aBMD on the regional DXA.

DISCUSSION: The osteogenic loading apparatus used for 15 min weekly increased strength for the one individual in this preliminary study. Future studies on astronauts and other healthy populations are necessary.

KEYWORDS: bone density, osteogenic loading, functional strength.

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The average area of bone mineral density (aBMD) loss in long-duration spaceflight (4–6 mo) was 1–1.5% per month before 2009. This is extremely high when compared to 0.5–1% loss per year in the terrestrial osteoporotic population.[8] Current countermeasures for astronauts include exercise, appropriate nutrition, and bisphosphonates. The ARED (Assisted Resistive Exercise Device) was introduced to the International Space Station in 2008 and provided 272 kg (600 lb) of resistive force versus the 136 kg (300 lb) from the iRED (Interim Resistive Exercise Device) previously on station. Study showed that astronauts who used iRED only lost significant bone density in all regions. Those who used only ARED showed a significant decrease in total hip and femoral neck aBMD, and a nonsignificant decrease in the trochanter aBMD. This decrease, however, was less than the group who used only iRED. The group who used both bisphosphonate and ARED did not show significant aBMD changes when compared to preflight due to the antibone resorption mechanism of bisphosphonates.[3]

In a bone biomarkers study, bone specific alkaline phosphatase – bone formation (BAP) postflight was unchanged but increased 1 mo postlanding with rehabilitation. N-telopeptide-bone resorption (NTX) increased during flight and up to 30 d postlanding ($P < 0.05$).[9] In the combination bisphosphonate and ARED group, the BAP was unchanged and NTX trended down, which is to be anticipated due to the drug's antibone

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resorption effects. These data signified bone resorption without compensatory bone formation, as BAP decreased or remained unchanged during flight despite increased NTX.[6] Astronauts typically exercise more toward the end of the mission, which could explain the increase in BAP at the end of spaceflight. But the growth in flight was likely due to bone modeling, where formation and resorption of bone occurred at different sites. It is unknown where exactly the bone formation was but was suspected to be in the cortices only.

After return to Earth, the time it takes to restore 50% of BMD ranged from 3–9 mo in the iRED and ARED population. Substantial recovery could take up to 4 times the half-life.[8] Quantitative Computed Tomography (qCT) scans were performed to assess bone geometry and thickness not accounted for by DXA scans. The hip qCT at 2-4 yr postflight showed a second phase of decline in cancellous BMD, even though it should have recovered within 2 yr postflight. Some crewmembers never recovered to baseline. But despite losing 10–15% of their BMD, none of the astronauts returned with T or Z scores less than -2.0.[7] Although this is acceptable for now, bone loss is not fully countered for future exploration missions. Using Apollo data, the predicted lumbar fracture probability on Mars is over 1% for a 2-m fall, and approach 2% for a 6.7-m fall (ladder height from lunar lander). The wrist fracture risk is 1% in men and 2% in women, with 95th percentile approaching 3.5% in men and 5.5% in women. These are higher than the 1% standard risk NASA is willing to accept.[4] In addition, the vehicle for the 18- to 36-mo Mars mission cannot accommodate the large ARED, and alternative countermeasures need to be created.

Multiple studies were performed to find the optimal exercise regimen for BMD change. Based on the Wolff's law of mechano-transduction, bone will adapt to the compression loads under which it is placed. BMD is dependent more on stress magnitudes than the number of loading cycles and duration during higher stress. High-impact loading in adult female athletes contributes to thicker cortices, larger diaphysis, and denser trabecular bone on qCTs.[5] Since gymnasts have one of the highest bone densities, the inventor designed the OsteoStrong® apparatuses (OsteoStrong® Company, Houston, TX) to achieve maximum bone stress in one maximum effort repetition per exercise. The force exerted is displayed real time on the screen for subjects. The purpose is to emulate the gymnast's impact load without the risk of injury. This is unique when compared to traditional exercises performed with multiple reps at submaximal effort, with no real time feedback.

The osteogenic loading exercises encompass three body parts per session: lower body, upper body, and spinal compression. In the initial OsteoStrong study, 14 osteoporotic and osteopenic subjects (mean age 62.5) performed the exercises weekly. The frequency was based on research showing that primary bone mineralization takes 5–15 d, as seen in measurements taken in vivo using double tetracycline labeling.[1] The mean peak loads achieved were 9.18 ($\pm$ 2.63 SD) multiples of body weight (MOB) in hip and legs, and 3.13 ($\pm$ 0.79 SD) in the spine. The aBMD ($g \cdot cm^{-2}$) increased an average of 7.02% in the hip and 7.73% in the spine ($P < 0.001$) with no injuries.[2] OsteoStrong subsequently studied a 24-wk protocol (one session per week) on 55 osteoporotic and osteopenic patients. DXA scans on nine patients showed increased hip (14.9%) and lumbar spine (16.6%) aBMD ($P < 0.01$).[9] This improvement was more than any of the current treatments with a time commitment of just 15 min a week, which may have beneficial implications for athletic, healthy, osteoporotic, and astronaut populations. This pilot study entails a healthy subject performing maximal axial bone osteogenic loading, with the intent of helping to design future prospective studies.

CASE REPORT

The subject was a 32-yr-old woman who performed 24 sessions lasting 15 min each at the Austin OsteoStrong location. Measurements include full-body and regional Dual-Energy X-Ray Absorptiometry (DXA) scans, BAP, NTX, maximum forces applied on apparatus, and maximum weights lifted in snatch, clean and jerk, back squat, front squat, and deadlifts. The weightlifting control data is the subject's own records 1.5 yr prior to the study. The regional DXA scans were performed with GE Lunar iDXA using Encore software version 13.6 (least significant change of 3%). The full body DXA scans were performed with GE Lunar Prodigy software version 16 (no LSC information). Whole-body DXA scans were performed after session 1 and 24; femoral and lumbar DXA were performed after session 9 and 24 due to scheduling and insurance reasons. Data include body weight, muscle mass, fat mass, T score, Z score, and aBMD for the head, arms, legs, trunk, ribs, spine, pelvis, lumbar spine, right femoral head, and neck. Typically, a 2% aBMD difference is considered beyond measurement error, but it is recognized that the whole body DXA scans are not as accurate as the regional scans. Regional X-ray transmissions are more focused and scanned at a slower rate. BAP and NTX were measured after week 2 and after week 8, 16, 24, and 32.

The study period spanned from July 2018 to January 2019. The measurements occurred weekly until the last 3 mo of the study. The average monthly strength gain was calculated using the differences between the initial weights lifted and maximum weights lifted divided by the number of months. Since the subject had been performing Olympic lifts (snatch and clean and jerk) for 3 yr, the control data were the maximum weights lifted 1.5 yr prior to the study (January 2017 to July 2018). These were compared to study data at 3 mo (no injury) and 6 mo (full study duration). The lifts include deadlifts (5 repetitions), front squat (2 repetitions), back squat (2 repetitions), snatch (3 repetitions), and clean and jerk (1 repetition). The number of repetitions was chosen based on the control data to have an appropriate comparison. Due to injury at month 3 from dropping a 25-lb plate on the 4th digit, and overtraining from pushing maximum effort in Olympic weightlifting, the subject did not push for maximum weights as frequently. These injuries were unrelated to the OsteStrong apparatus.

The osteogenic loading and impact emulation exercises encompassed one maximum effort repetition per apparatus:

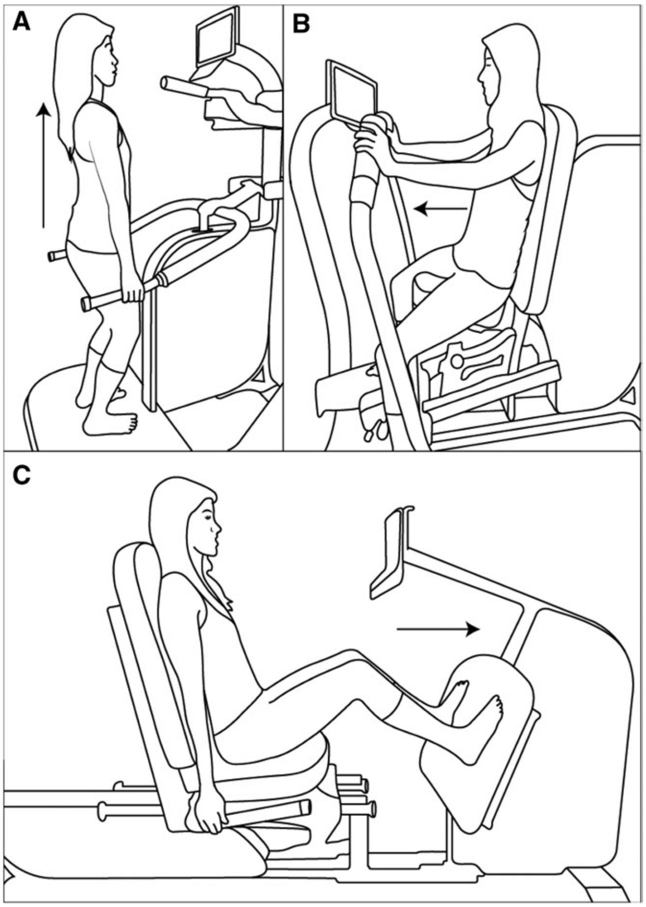

Fig. 1. OsteoStrong exercise apparatus. A. Spinal compression: subject stands with knees slightly bent and stand up while holding tight grip. B. Upper extremity compression: subject starts at 120° extension and push with maximum effort. C. Lower extremity compression: subject starts at 120° extension and push with maximum effort.

lower, upper, and spinal compression (**Fig. 1**). For the upper and lower body compression, the subject started at a 120°angle of inclination and pushed against a static bar or plate. This was not an isometric exercise as there was some range of motion. This starting angle produces peak force generation and maximal bone loading. For spinal compression, the subject stood with knees slightly bent and hands holding onto the bars on both sides. Then the subject stood up while gripping tightly onto the bars for as long as possible to achieve spinal compression. Load cells in each apparatus measured the force output in real-time, and once the subject reached peak force output (usually 5–10 s), the subject slowly released. The result was one slow loading experience with maximum bone compression using each apparatus.

After 24 wk, the maximum force generated increased in the upper extremity (435 lb to 859 lb, 97%), lower extremity (1690 lb to 2418 lb, 43%), and spinal compression apparatus (607 lb to 740 lb, 22%) (**Table I**). From week 2 to 24, the BAP increased by 39% (10.4 ug/L to 14.5 ug/L), then decreased from 14.5 to 12.3 ug/L at 9 wk poststudy. But it was still higher than baseline (10.4 ug/L to 12.3 ug/L, +18%). The NTX peaked at 15 $nmol \cdot L^{-1}$ BCE after 8 wk and quickly dropped by 41% at 24 wk (13.4 $nmol \cdot L^{-1}$ to 7.9 $nmol \cdot L^{-1}$ BME). Initially, a lab error was suspected but the recheck confirmed the true decline. NTX remained decreased at 9 wk poststudy completion compared to the initial value (13.4 $nmol \cdot L^{-1}$ to 7 $nmol \cdot L^{-1}$ BCE, - 47%) (**Fig. 2**).

On the full body DXA scans, there were no differences in weight (118.4 lb to 119.1 lb) and total body aBMD (+0.3%) (**Table II**). The fat mass increased by 4.6 lb (19.6 lb to 24.2 lb), the fat % increased by 3.7% (16.6–20.3%), and lean muscle mass decreased by 4% (93.2 to 89.3 lb). There were aBMD gains in the head (6%), arms (4.3%), trunk (6.3%), ribs (3.8%), and pelvis (11%). A nonsignificant decrease in aBMD was observed in legs (-2.3%) and spine (-2%). The Z and T scores were unchanged at 2.1 and 1.5, respectively. The regional lumbar, hip, and femoral neck DXA scans showed no large differences in aBMD and T scores for all regions: lumbar (T-score 1.8 vs 1.7), right hip (0.1 vs 0.1) and neck (-0.6 vs -0.6) (**Table III**).

The strength gain per month was calculated using the differences between initial and maximum weights lifted during the study period (**Table IV**). After 3 mo (no injuries) the rate of monthly strength gain was much faster compared to the control: snatch (6.7 lb vs. 1.56 lb, 8% vs. 2.4%), clean and jerk (6 lb vs. 0.88 lb, 5% vs. 0.88%), back squat (11 lb vs. 0, 7% vs. 0%), front squat (6.3 lb vs. 0.47 lb, 5% vs. 0.35%), and deadlifts (8 lb vs. 2.4 lb, 5% vs. 1.67%). When the results were analyzed using the max weights lifted over 6 mo (total study duration with injuries), strength gain rates were slightly lower, but still more than the control period: snatch (5 lb vs. 3 lb), clean and jerk (5.5 lb vs. 4 lb), back squat (8.25 lb vs. 5.5 lb), front squat (4.75 lb vs. 3 lb), and deadlifts (8.75 lb vs. 6 lb) (**Fig. 3**).

DISCUSSION

The subject was able to increase the peak load exerted on the apparatus by 97% in the upper extremity, 43% in the lower extremity, and 22% in the spinal compression apparatus. The gain in strength is impressive for just 6 h of maximal axial bone loading over 6 mo (15-min sessions $\times$ 24). The max load for each weekly session fluctuated based how much the subject weightlifted between sessions (usually 3–5 d per week). The forces exerted on the apparatus decreased if the subject

Table I. Force Exerted on Each Osteogenic Loading Modality from Initial to Maximum over 24 Sessions (6 mo).

	SESSION 1 (lb)	MAX SESSION (lb)	ABSOLUTE DIFFERENCE (lb)	% CHANGE
Upper Extremity Compression	435	859	424	97%
Lower Extremity Compression	1690	2418	728	43%
Spinal Compression	607	740	133	22%

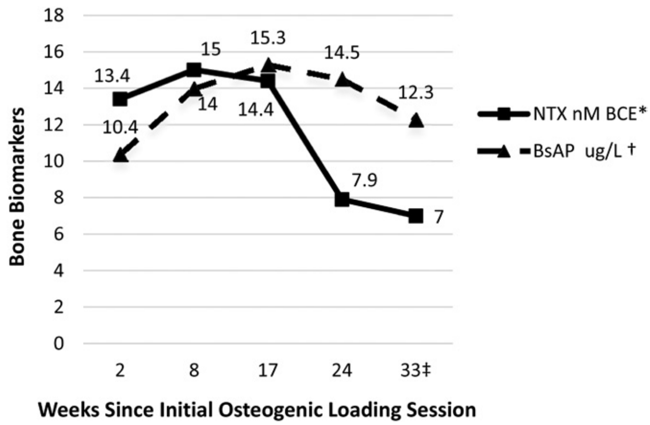

Fig. 2. Bone biomarkers vs. time since initial osteogenic loading session. From week 2 to 24, the BAP increased from 10.4 ug · L^{-1} to 14.5 ug · L^{-1} (+ 39%), and NTX decreased by from 13.4 nmol · L^{-1} to 7.9 nmol · L^{-1} BME (-41%). At 9 wk post study, the BAP decreased to 12.3 ug · L^{-1} (18% increase from baseline), and the NTX decreased to 7 nmol · L^{-1} BME (48% increase from baseline). Normal Ranges: *****NTX **–** Cross-linked N-telopeptide of Type I Collagen for Adult Male = 5.4 – 24.2 nmol · L^{-1} BCE (Bone Collagen Equivalent), and Premenopausal Adult Female = 6.2 – 19.0 nmol · L^{-1} BCE; †BsAP – Bone Specific Alkaline Phosphatase, Premenopausal Female = 4.5 – 16.9 ug · L^{-1}, and Postmenopausal Female = 7.0 – 22.4 ug · L^{-1}; ‡ 9 Weeks post study completion.

weightlifted 3 d consecutively before the osteogenic loading session. When the subject exerted over 2000 lb of force in the lower extremities, she usually had 2–3 rest days prior. No weightlifting was performed on the day of the session.

The whole body DXA showed increased trunk and pelvis aBMD, which contradicted the lack of aBMD difference on the regional DXA. The scanners were both GE Lunar but with different model, software versions, and timing between scans (total body after 1st and 24th, regional after 9th and 24th session). Since there was no baseline regional DXA performed prestudy, we were unable to assess if there was a true difference. Further, since the subject is of good health and fitness, it is more difficult to detect a robust change in aBMD in response to exercise loading. If the subject was deconditioned or had a low baseline aBMD, the skeleton might have been more responsive to the anabolic effect of resistive exercise. Another possible cause for the lack of aBMD change is that the study duration was not long enough to detect significant changes in aBMD.

The biomarkers showed an initial increase in bone resorption (NTX) and formation (BAP). The NTX dropped by 41% at 24 wk, and by 48% at 9 wk poststudy. The BAP increased throughout the study by 39%, then dropped slightly. The net increase was 18% at 9 wk poststudy. This could signify a net positive bone formation that persisted at least 8 wk after osteogenic loading.

There was no change in the subject's overall macronutrients except a 250–500/d caloric increase to gain weight, which could explain the fat percentage increase. The subject was less hydrated on the poststudy whole-body DXA, which could explain the decreased muscle mass. It could also be due to variability of testing, but the true reason of this paradoxical shift is unknown. MRI for muscle mass quantification could be useful in future studies. But despite decreased muscle mass on DXA scan, there was an astounding increase in monthly strength gain even with the weightlifting injuries. The results were evident in the analyses based on a 3-mo and 6-mo study period. The subject had been lifting for 5 yr and had never experienced this rate of strength gain. All the maximum weights lifted during the study period were the best the subject has ever achieved.

Although the subject had coaching during the control and study periods, it was more consistent during the study period, which may have partially contributed to the results. Injuries sustained also served as confounders. At 3 mo into the study the fourth digit injury led to decreased grip strength, alteration of form, and increased susceptibility to further injuries. Overtraining in weightlifting also led to muscle strain that required chiropractic care. The subject decreased the number of max rep sessions toward the latter half of the study. But despite the injuries, the rate of monthly strength gain was still more than the control period.

Table II. Whole Body DXA (Dual-Energy X-Ray Absorptiometry) Scan Results.†

	POST 1 OSTEOGENIC LOADING SESSION	POST 24 OSTEOGENIC LOADING SESSION	CHANGE PRE AND POST OSTEOGENIC LOADING	% aBMD CHANGE‡
Weight (lb)	118.4	119.1	0.7	
Fat %	16.6	20.3	3.7	
Fat Mass (lb)	19.6	24.2	4.6	
Lean Muscle Mass (lb)	93.2	89.3	−3.9	
Head BMD*	2.484	2.636	0.152	*6
Arms BMD	0.764	0.797	0.033	*4.3
Legs BMD	1.267	1.238	−0.029	*−2.3
Trunk BMD	0.945	1.005	0.06	*6.3
Ribs BMD	0.686	0.712	0.026	*3.8
Spine BMD	1.222	1.198	−0.024	−2
Pelvis BMD	1.004	1.114	0.11	*11
Total BMD	1.231	1.235	0.004	0.3
T Score	1.5	1.5	0	
Z Score	2.1	2.1	0	

* >2% change in area bone mineral density (g/cm^2); †performed with GE Lunar Prodigy Machine; ‡least significant change unknown.

Table III. Regional DXA (Dual-Energy X-Ray Absorptiometry) Scan Results.

	POST 9 OSTEOGENIC LOADING SESSIONS	POST 24 OSTEOGENIC LOADING SESSIONS	CHANGE PRE AND POST OSTEOGENIC LOADING	% ABMD CHANGE*
Lumbar BMD	1.392	1.383	−0.009	−0.6
Lumbar T Score	1.8	1.7	−0.1	
Right Hip BMD	1.021	1.018	−0.003	−0.3
Right Hip T Score	0.1	0.1	0	0
Right Hip Z Score		0.4		
Right Neck BMD	0.956	0.949	−0.007	−0.7
Right Neck T Score	−0.6	−0.6	0	

* Least significant change for testing center's iDXA GE Lunar Machine is 3% at testing center. (Anything above or below is considered significant).

There are several limitations to this study:

1. There was only 1 subject for this pilot study.
2. It is unknown how much of the strength gain was due to osteogenic loading or the frequent max weights exercise routine undertaken for the study.
3. The injuries sustained altered the results and the true trajectory without injuries is unknown.
4. There were no baseline pre-osteogenic loading bone biomarkers, total DXA, or regional DXA scans. The total DXA was obtained after 1 session, and the biomarkers were obtained after 2 sessions. The biomarkers can change after 1 wk, but it is unlikely that aBMD changes would be reflected on the DXA.
5. The timing between total and regional body DXA were different, which made them difficult to compare. There was a difference in trunk and pelvis aBMD on total body DXA but no difference on the regional DXA.
6. The positions of the handlebars and seat on the exercise apparatus were adjusted during the first half of the study. This was to prevent lockout as the subject became stronger, though this could have affected the peak force exerted during the sessions.
7. It is unknown what changes in BAP and NTX are considered significant. Do a 41% decrease in NTX and a 39% increase in BAP signify a net positive bone formation? Also bone markers usually have large coefficient of variability, and the samples were not analyzed to calculate intra- and inter-assay CV.
8. DXA scans are 2-d quantifications which are a surrogate for bone strength; in contrast, qCT scans measure 3-D structural attributes from which a more accurate estimation of bone strength can be generated. If net positive bone formation exists, DXA cannot discriminate whether it was trabecular or cortical growth.

This modality could potentially be used in the healthy, athletic, or osteoporotic population to improve their functional strength. For astronauts, it could potentially assist with strength gain preflight, and expedite bone density recovery upon return. If the exercise apparatus could be condensed to the size of a shoebox to meet the weight and volume restrictions imposed by NASA, it could potentially serve as a countermeasure for bone and strength loss on exploration vehicles. However, it is unknown how this modality compares with current exploration vehicle exercise prototypes. Although the time saved on exercise can be tremendous, the traditional daily exercise routines elevate the astronauts' mental well-being, and they may not like an exercise that is 15 min per week.

Future studies may be limited by cost and time since subjects are required to perform weekly sessions for 6 mo at a minimum. Pre- and post-qCT scans along with additional biomarkers should be obtained to assess bone strength, as DXA is not sufficient. MRI would be useful to quantify the muscle mass gained. Future questions to address include: 1.) Can this modality be used to increase strength and bone density reserve in astronauts preflight, and expedite bone density recovery postflight? 2.) Since the ARED is too large for a long-duration mission to Mars, can this modality be used to reduce bone density loss in space, and be converted to the size of a shoebox for exploration missions?

Overall, the axial bone osteogenic modality markedly increased the rate of monthly strength gain at 3 and 6 mo when compared to the control period. This was an impressive finding after just 6 h of osteogenic loading in 6 mo. The monthly strength gain ranged from 6–11 lb over 3 mo and 4.75–8.75 lb over 6 mo, vs. 0–2.4 lb during the control period. The increase in peak force exerted ranged from 22 to 95%. No aBMD differences were observed on the regional DXA, but the trunk and total hip aBMD increased based on the full body DXA. Bone biomarkers signified increased bone formation and decreased bone resorption up to 9 wk post study period. If the size and weight of the apparatus can be decreased, with the addition of

Table IV. Absolute and Monthly Rate of Change in Weights Lifted During Control and Study Period (3 and 6 mo).

	WEIGHTS INITIALLY LIFTED (lb)	MAX WEIGHTS LIFTED OVER 3 MONTHS (lb)	WEIGHT DIFFERENCE (lb)	3 MONTHS MONTHLY STRENGTH GAIN (lb)	6 MONTHS MONTHLY STRENGTH GAIN (lb)	CONTROL PERIOD MONTHLY STRENGTH GAIN (lb)
Snatch × 3 Reps	86	106	20	6.7	5	1.56
Clean and Jerk × 1 Rep	110	128	18	6	5.5	0.88
Back Squat × 2 Reps	152	185	33	11	8.25	0
Front Squat × 2 Reps	136	155	19	6.3	4.75	0.47
Deadlift × 5 Reps	165	189	24	8	8.75	2.4

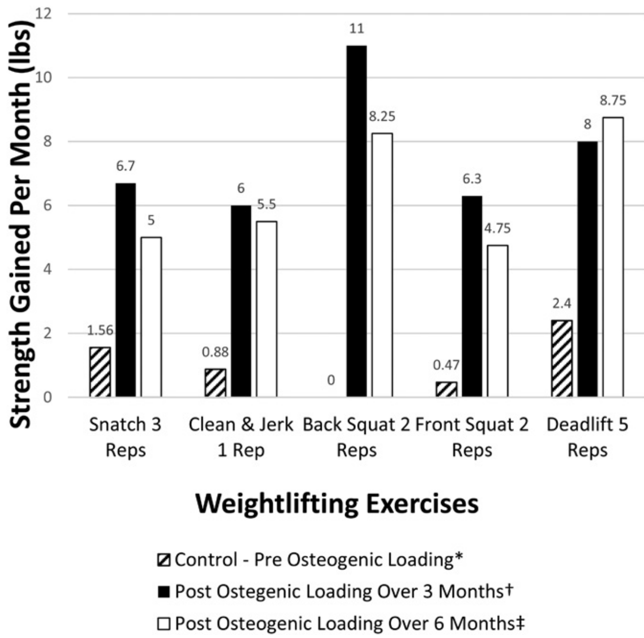

Fig. 3. Average change in weights lifted per month during control and after 12 and 24 osteogenic loading sessions. *Pre-osteogenic loading – change max weights lifted per month for each exercise; † post-ostegenic loading – change max weights lifted per month over 3 mo (preinjury); ‡ post-osteogenic loading – change max weights lifted per month over 6 mo (with injury). Pre-osteogenic loading data were calculated from 2017 to July 2018. All data were calculated from differences between initial weights and max weight lifted, divided by months in the time period. The subject was able to gain more strength per month when compared to the control period.

resistive and aerobic routines, axial osteogenic loading can potentially be used as a countermeasure in exploration vehicles. Future studies on athletic and astronaut populations are necessary to optimize the frequency of sessions, minimum effective load, aBMD, bone strength, bone architecture, muscle mass, and functional strength effects.

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