Received: 25 July 2024 | Revised: 5 September 2024 | Accepted: 23 September 2024

DOI: 10.1002/pbc.31369

Pediatric Blood & Cancer

SIOP INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

aspho The American Society of Pediatric Hematology/Oncology

WILEY

RESEARCH ARTICLE

Feasibility of telehealth exercise and nicotinamide riboside supplementation in survivors of childhood cancer at risk for diabetes: A pilot randomized controlled trial

Rusha Bhandari[1,2] | Kara Lukas[1] | Kyuwan Lee[1] | Justin Shamunee[1] | Brady Almeida[1] | Tati Guzman[1] | Meagan Echevarria[1] | Lanie Lindenfeld[1] | Christian Nenninger[3] | Aleksi Iukuridze[1] | Sophia Albanese[1] | June-Wha Rhee[3] | Sitong Chen[1] | Charles Brenner[4] | F. Lennie Wong[1] | Saro H. Armenian[1,2]

[1]Department of Population Sciences, City of Hope, Duarte, California, USA

[2]Department of Pediatrics, City of Hope, Duarte, California, USA

[3]Department of Medicine, City of Hope, Duarte, California, USA

[4]Department of Diabetes and Cancer Metabolism, City of Hope, Duarte, California, USA

Correspondence
Rusha Bhandari, Department of Population Sciences, City of Hope, 1500 E Duarte Road, Duarte, CA 91010, USA.
Email: rbhandari@coh.org

Kyuwan Lee is currently at Ewha Woman's University, South Korea; Justin Shamunee is currently at Cedars-Sinai Medical Center, USA.

Funding information
National Institutes of Health, Grant/Award Number: K12CA001727

Abstract

Background: Childhood cancer survivors (CCS) have a 50% higher risk of diabetes mellitus (DM) compared with the general population. Interventions in survivors with prediabetes (fasting glucose 100-125 mg/dL or hemoglobin A1c 5.7%-6.4%) may mitigate the development of DM and its attendant morbidity, but there is limited information on the feasibility of secondary prevention in this setting.

Methods: This 6-week pilot feasibility 1:1 randomized controlled trial enrolled 20 CCS on a structured telehealth exercise program ± nicotinamide riboside (NR), a nicotinamide adenine dinucleotide precursor. Feasibility metrics were: (1) ≥50% of eligible CCS enrolled onto study; (2) ≥70% of participants completed baseline and end-of-study assessments; (3) ≥70% compliance with exercise and NR. Secondary endpoints included changes in biomarkers associated with glucose homeostasis and muscle health.

Results: Median age (years) at cancer diagnosis was 16.5 (range, 1.5-21.5) and 35.5 (range, 18.0-67.0) at study enrollment. Enrollment rate was 87%, and 85% of participants completed baseline and end-of-study assessments. The mean percentage of exercise sessions completed was 86.6%; NR compliance was > 90%. There were no severe adverse events attributable to study interventions. Secondary endpoints were not significantly different between study arms at study completion. Myostatin decrease was observed in participants who completed a higher median number of exercise sessions and was associated with decreased intramuscular adipose tissue and increased lower extremity muscle cross-sectional area.

Conclusions: A telehealth exercise intervention ± NR supplementation was feasible in CCS with prediabetes. Future studies in larger cohorts may be needed to evaluate their beneficial effects on muscle health and DM risk among CCS.

Abbreviations: BIA, Bioelectrical impedance analysis; BMI, Body mass index; CCS, Childhood cancer survivor; COH, City of Hope; CSA, Cross-sectional area; DM, Diabetes mellitus; Ex, Exercise; HbA1c, Hemoglobin A1c; HCT, Hematopoietic cell transplantation; HOMA-IR, Homeostatic model assessment for insulin resistance; IMAT, Intramuscular adipose tissue; LTFU, Long-term follow-up; NAD, Nicotinamide adenine dinucleotide; NR, Nicotinamide riboside; OXPHOS, Oxidative phosphorylation; SPPB, Short physical performance battery; US, Ultrasound.

KEYWORDS
Childhood cancer survivor, nicotinamide riboside, prediabetes, remote exercise

1 | BACKGROUND

Five-year survival rates exceed 85% for most pediatric malignancies,[1] and there are currently an estimated 500,000 childhood cancer survivors (CCS) in the United States alone.[2] However, cancer and its associated treatment exposures at a young age can contribute to a high burden of chronic health conditions in adulthood. CCS have a nearly six-fold higher cumulative incidence of at least one chronic health condition compared with their siblings, and conditions such as diabetes and sarcopenia, or low muscle mass, have emerged as leading contributors to morbidity and excess mortality.[3–8] Diabetes and sarcopenia are closely related, as skeletal muscle mediates > 80% of the body's insulin-stimulated glucose disposal, and hyperglycemia directly contributes to skeletal muscle atrophy.[9,10] Interventions that leverage the mechanistic link between diabetes and sarcopenia have the potential to improve insulin-stimulated glucose disposal by muscle tissue.[11] This may be especially useful for patients with prediabetes, a condition that precedes diabetes and is nearly twice as prevalent among CCS compared with age-matched controls.[4]

Exercise has been shown to improve muscle health, including muscle mass, strength, and physical function, in individuals with prediabetes.[12,13] However, studies examining the efficacy of exercise interventions to improve muscle health, and in turn diabetes risk, in long-term CCS have been limited. Historically, exercise interventions have required participants to attend facility-based, scheduled exercise programs,[14,15] which can be prohibitive for patients due to transportation requirements and scheduling conflicts. Remote programs integrating individualized exercise training with flexible schedules are needed to increase accessibility and optimize the uptake of effective doses of exercise.

Adjunctive approaches may be needed to optimize the effects of exercise on diabetes risk and muscle health, especially in CCS, who have increased exercise intolerance due to their previous treatment exposures and comorbidities.[16,17] With regard to chemoprevention, there are currently no FDA-approved medications specifically to prevent diabetes. Four nicotinamide adenine dinucleotide (NAD) coenzymes are the central catalysts of metabolism that are critical for a myriad of cellular processes including mitochondrial oxidative phosphorylation (OXPHOS), anabolic reactions, and repair capacity.[18] OXPHOS capacity is decreased in individuals with diabetes and/or sarcopenia,[19,20] which is a disease of diminished anabolism and repair.[21] NAD precursors are increasingly being investigated for their potential to improve muscle health in the general non-oncology population. Nicotinamide riboside (NR) is the nucleoside precursor of NAD[22] that is available over-the-counter, safely orally bioavailable to adults,[23,24] and has demonstrated anti-inflammatory activity when administered alone.[25–31]

The objective of this trial was to evaluate the feasibility of a remote telehealth exercise program with or without NR supplementation in adult CCS with prediabetes. Secondary objectives were to study the effects of the intervention on measures of prediabetes and muscle health. We hypothesized that this six-week intervention would be feasible and that the combination of exercise and NR would result in greater improvement in glucose homeostasis and muscle health than exercise alone.

2 | METHODS

2.1 | Participants and randomization

Study participants were identified from the institutional review board–approved City of Hope (COH) Long-Term Follow-Up (LTFU) Clinic for survivors of childhood, adolescent, and young adult cancer. The clinic provides comprehensive long-term risk-based screening for late effects for survivors who are in remission and at least 2 years off therapy. Eligibility criteria for this study included: history of childhood cancer diagnosis or hematopoietic cell transplantation (HCT) before 22 years of age; with prediabetes (most recent hemoglobin A1c [HbA1c] 5.7%-6.4% and/or fasting glucose of 100-125 mg/dL)[32]; ≥18 years of age and in remission at the time of enrollment; able to access online exercise program at home; able to participate in an exercise program; English-speaking. Exclusion criteria were: taking an NAD precursor in the 2 weeks prior to enrollment; taking medication for hyperglycemia or diabetes at the time of enrollment; females who were pregnant or planning to become pregnant. This study was registered on clinicaltrials.gov (NCT05023993).

Following a database review for eligibility, research staff sent a letter to potential participants informing them about the study. If interested, inclusion/exclusion criteria were confirmed, and informed consent was signed in person, by mail, or via DocuSign. Enrolled participants were randomized 1:1 to 6 weeks of remote exercise alone (Ex arm) or remote exercise and NR (Ex + NR arm). Randomization was stratified on whether or not participants were obese per CDC classification (BMI ≥ 95th percentile if < 20 years of age or BMI ≥ 30 if ≥ 20 years of age), as obesity is one of the strongest risk factors for DM and may also play a role in differential responses to the intervention.[32–36] The randomization sequence was developed by the study statistician.

2.2 | Interventions

All study participants received the telehealth resistance exercise intervention (3 sessions/week for 6 weeks; ~30 minutes per session). The

exercise program focused on targeting major muscle groups with a combination of exercises aimed at improving muscular strength and endurance. The intensity of the exercises was guided by Borg's category ratio scale, which ranges from 1 to 10, with 1 indicating no exertion and 10 representing maximal effort. Participants were instructed to perform each exercise at a perceived exertion level between 5 and 7, corresponding to moderate to somewhat hard intensity, with adjustments made based on their individual responses and progression over time. Each exercise session typically included 8-10 different resistance exercises, with participants performing 2-3 sets of 8-12 repetitions per exercise. As participants adapted to the program, the exercise regimen was progressively adjusted to maintain the targeted range, ensuring a consistent challenge and continued improvement. Exercise equipment (exercise mat, loop bands, and resistance bands) was provided to participants at their baseline visit. The telehealth exercise platform (MoterumTechnologies, Inc., South Salt Lake, UT, USA) was used to remotely deliver the exercise program and capture participants' adherence to the prescribed exercise sessions. The first two exercise sessions were supervised by a certified exercise trainer remotely; thereafter, participants were advised to log on to the Moterum platform and perform their prescribed exercise regimens voluntarily without supervision. The exercise adherence was automatically captured on the telehealth platform by confirming whether the prescribed exercise videos were played. Exercise regimens were modified by the trainer as needed based on participants' individual abilities and preferences.

Participants who were randomized to receive NR were instructed to take the capsules (Niagen 250 mg/capsule; ChromaDex; Irvine, CA, USA) at a dose of 1000 mg/day at around the same time each day, and to not make up doses if missed. The last dose of NR was scheduled for the day prior to the end-of-study visit. Participants returned any remaining NR capsules, and a pill count was performed to assess compliance. Study staff contacted all participants during weeks 2 and 4 of the intervention period to assess interim compliance, changes in medical status, adverse events, or questions regarding the study procedures. Adverse events were graded per the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.[37]

2.3 | Study efficacy assessments

All study objective assessments were performed in person at COH at baseline and end-of-study visits. *Biomarkers of glucose homeostasis and muscle*: Fasting peripheral blood was obtained for the following tests: glucose, HbA1c (%), insulin (uIU/mL), and C-peptide (ng/mL) levels. The homeostatic model assessment for insulin resistance (HOMA-IR) was calculated as: (fasting insulin [μU/mL] × fasting glucose [mmol/L]) / 22.5).[38] Plasma myostatin was measured using the human quantikine myostatin immunoassay solid phase enzyme-linked immunosorbent assay (ELISA; R&D Systems; Minneapolis, MN, USA). *Body composition and muscle health*: Handheld dynamometry (Camry; South El Monte, CA, USA) was performed to measure grip strength. This was performed three times per hand, and the highest value (in kg) for each hand was used in analyses. Short physical performance battery (SPPB), which included balance (ability to maintain side-by-side, semi-tandem, and tandem stances for 10 seconds each), gait speed (timed 3-meter walk, 2 attempts per participant), and chair stand (time to rise from chair 5 times with arms across the chest for "sit-to-stands"), was performed. The SPPB was scored as previously described, with individual scores for each portion added together for a maximum possible score of 12.[39,40] Ultrasound (US) of the rectus femoris, lateral gastrocnemius, and medial gastrocnemius muscles was performed using a portable Philips Lumify L12-4 ultrasound probe (Philips, Bothell, WA, USA) and software (MuscleSound, Denver, CO, USA) that provided real-time information on muscle size (thickness, cross-sectional area [CSA]) and intramuscular adipose tissue (IMAT). Measurements of whole-body fat and fat-free mass, segmental skeletal muscle mass, and visceral adipose tissue were obtained using multifrequency bioelectrical impedance analysis (BIA; Seca mBCA, Hamburg, Germany). Participants received a $50 gift card at study completion.

2.4 | Statistical analysis

We planned a priori to enroll 20 participants for this pilot feasibility study. The study was considered feasible if (1) ≥50% of eligible patients who were approached for participation enrolled in the study, (2) ≥70% of enrolled participants successfully completed all study assessments (i.e., physical function tests, blood draw, and imaging) at baseline and end of study, and (3) enrolled participants demonstrated ≥70% compliance with prescribed exercise (percentage of sessions completed) and NR (percentage of days with prescribed dose taken).

Descriptive statistics were generated for the entire cohort and by study arm. Continuous variables were compared using the Wilcoxon signed rank test or independent-samples median test. All tests were two-sided and $p < 0.05$ was considered statistically significant. All statistical analyses were conducted using SPSS 26.[41]

3 | RESULTS

3.1 | Participant characteristics

Between September 19, 2022, and July 24, 2023, 31 potentially eligible patients who had a history of prediabetes were contacted regarding this study and 27 (87%) consented to the study. Of 27 who consented, 6 were no longer deemed eligible at the time of the baseline visit (4 no longer had prediabetes, 1 had a new-onset malignancy, 1 became pregnant between the time of consent and baseline visit), and 1 withdrew prior to baseline eligibility determination. Of the remaining 20 participants who were enrolled in the study (10 participants randomized to each study arm), 3 participants withdrew prior to completing the study (Ex arm: 1 due to change in medical status prior to beginning the study intervention, 1 due to worsened avascular necrosis limiting mobility; Ex + NR arm: 1 due to changes in personal circumstances). Thus, 17 (85%) participants were evaluable at the end of study (8 in the Ex arm, 9 in the Ex + NR arm), all of

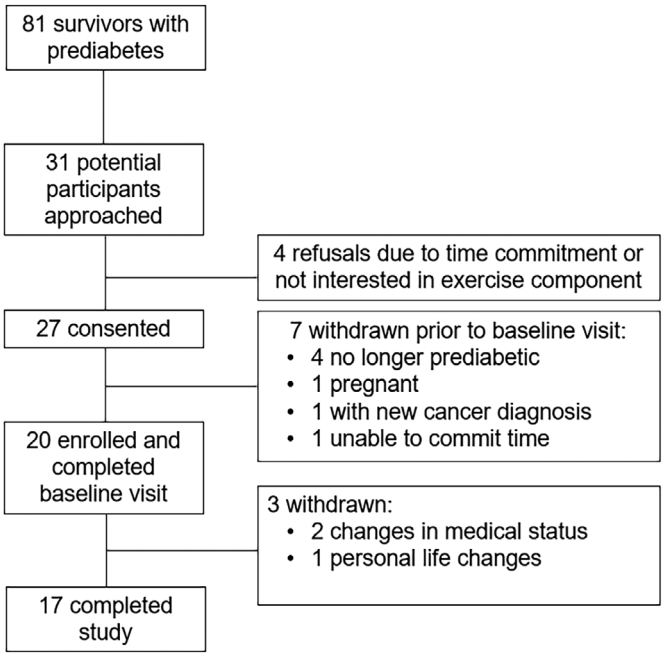

FIGURE 1 CONSORT diagram.

whom completed the required baseline and end-of-study assessments (Figure 1). The final participant completed the study in September 2023.

Participant characteristics are summarized in Table 1. Half of the participants were male, 75% identified as Hispanic or Latino, and the median age at study enrollment was 35.0 (range, 18.0-67.0). The median age at cancer diagnosis was 16.5 years (range, 1.5-21.5), 60% had undergone HCT, and the most common diagnoses were acute lymphoblastic leukemia (45%) and Hodgkin lymphoma (20%). The majority of patients had received corticosteroids (80%), alkylating agents (85%), and/or radiation (70%) as part of their treatment. The most common type of radiation exposure was total body irradiation (57.1%). Family history (grandparents or first-degree relatives) was positive for diabetes in 40% of participants.

3.2 | Exercise and NR compliance

Of the 17 participants who completed the study, the median number of exercise sessions completed (out of 18 total) was 18 (range, 3-18), with an average compliance rate of 86.6%. The median number of sessions completed was 17 (range, 3-18, average compliance rate 84.1%) in the Ex arm and 18 (range, 10-18, average compliance rate 88.9%) in the Ex + NR arm. On the Ex arm, 1 participant developed grade 1 muscle pain, which resolved within a day. Of the 9 participants randomized to Ex + NR, the mean number of days of NR completed (out of 42 total) was 37.9 (SD 6.2), for an average NR compliance rate of 90.3%. One participant developed grade 1 fatigue, which resolved the next day, and another participant developed grade 1 nausea and rash, which resolved the same day. No serious (CTCAE grade ≥3) adverse events were attributed to NR supplementation.

3.3 | Markers of glucose homeostasis

In the Ex arm, from baseline to end of study, there was no significant change in median HbA1c (6.0% [range, 5.5%-6.4%] to 6.0% [5.2%-6.7%]), fasting glucose level (101.5 mg/dL [range, 86.0-124.0 mg/dL] to 103.5 mg/dL [range, 91.0-123.0 mg/dL]), or HOMA-IR (5.3 [range, 0.8-12.0] to 3.5 [range, 0.8-15.2]). In the Ex + NR arm, there was also no significant change in median HbA1c (5.8% [range, 5.6%-6.3%] to 5.8% [range, 5.7%-6.4%]), fasting glucose level (99.0 mg/dL [range, 86.0-127.0 mg/dL] to 94.0 mg/dL [range, 86.0-123.0 mg/dL), or HOMA-IR (2.6 [range, 0.8-6.0] to 3.0 [range, 0.9-6.6]); Supporting Information Table S1. The changes in median HbA1c, fasting glucose, and HOMA-IR were not significantly different between study arms; Table 2.

3.4 | Body composition and muscle strength

Baseline median BMI and waist circumference in the Ex vs Ex + NR arms were 30.5 kg/m^2 (range, 24.8-54.6 kg/m^2) vs 31.8 kg/m^2 (range, 24.0-45.3 kg/m^2) and 96.0 cm (range, 86.0-157.0 cm) vs 99.0 cm (range, 86.0-140.0 cm), respectively, and there was no significant change in these measures from baseline to end of study for the overall study cohort, within individual study arms, or between study arms; Table 2. The median SPPB score was 11.0 (range, 10.0-12.0) out of 12 at baseline for both arms, and this was unchanged at the end of the study. There was no significant change in median grip strength or body composition measured by BIA. There was also no significant increase in muscle CSA or thickness measured by US (Supporting Information Table S1).

3.5 | Myostatin

Baseline median myostatin levels (ng/mL) in the Ex vs Ex+NR arms were 797.8 (range, 553.5-1401.6) and 775.5 (range, 536.1-1205.9), respectively, and there was no significant change in myostatin from baseline to end of study for the overall study cohort or individual study arms (Supporting Information Table S1). Nine participants had a decrease in myostatin level from 895.8 (range, 750.1-547.7) to 792.3 (range, 547.7-1123.1). These 9 participants completed more exercise sessions (median 18, range, 14-18) than the 8 participants who did not have a decrease in myostatin levels (median 15.5, range, 3-18); $p = 0.14$. These 9 participants also had decreases in median BMI and IMAT of all muscle groups, and increased rectus femoris CSA bilaterally, though this did not reach statistical significance. On the other hand, among the 8 participants who did not have a decrease in myostatin levels, there was a relative increase in median BMI, waist circumference, and IMAT of bilateral lateral and medial gastrocnemius muscles; these changes did not reach statistical significance.

TABLE 1 Participant characteristics at baseline.

	Entire cohort, *N* (%)	Exercise only, *N* (%)	Exercise + NR, *N* (%)
Sex			
Male	10 (50.0)	5 (50.0)	5 (50.0)
Female	10 (50.0)	5 (50.0)	5 (50.0)
Age at diagnosis, median (range)	16.5 (1.5-21.5)	16.0 (1.5-21.2)	17.7 (7.8-21.5)
Age at enrollment, median (range)	35.5 (18.0-67.0)	35.5 (18.0-67.0)	35.6 (24.4-48.3)
Body mass index, median (range)	30.3 (23.7-54.0)	30.3 (25.0-54.0)	30.1 (23.7-45.5)
Race and ethnicity			
Hispanic	15 (75.0)	8 (80.0)	7 (70.0)
Non-Hispanic White	3 (15.0)	1 (10.0)	2 (20.0)
Black	1 (5.0)	0	1 (10.0)
Asian	1 (5.0)	1 (10.0)	0 (0.0)
Diagnosis			
ALL	9 (45.0)	5 (50.0)	4 (40.0)
Hodgkin lymphoma	4 (20.0)	2 (20.0)	2 (20.0)
Non-Hodgkin lymphoma	2 (10.0)	0	2 (20.0)
Bone/soft tissue	2 (10.0)	0	2 (20.0)
Other leukemia	2 (10.0)	2 (20.0)	0
Germ cell tumor	1 (5.0)	1 (10.0)	0
Steroid exposure	16 (80.0)	9 (90.0)	7 (70.0)
Alkylating agent exposure (any)	17 (85.0)	8 (80.0)	9 (90.0)
Alkylating agent dose (mg/m^2)			
1-<4000	5 (29.4)	1 (12.5)	4 (44.4)
4000-<8000	7 (41.2)	4 (50.0)	3 (33.3)
≥8000	5 (29.4)	3 (37.5)	2 (22.2)
Radiation[a]	14 (70.0)	6 (60.0)	8 (80.0)
Total body irradiation	8 (57.1)	4 (66.7)	4 (50.0)
Chest/mantle	5 (35.7)	2 (33.3)	3 (37.5)
Cranial	3 (21.4)	1 (16.7)	2 (25)
Pelvic/testicular	1 (7.1)	1 (16.7)	1 (12.5)
HCT type[b]	12 (60.0)	5 (50.0)	7 (70)
Allogeneic	9 (75.0)	5 (100)	4 (57.1)
Autologous	3 (25.0)	0	3 (42.9)
History of acute GVHD	3 (15.0)	1 (10.0)	2 (20.0)
History of chronic GVHD	4 (20.0)	3 (30.0)	1 (10.0)
History of hypertension	5 (50.0)	3 (30.0)	2 (20.0)
Family history of diabetes	8 (40.0)	3 (30.0)	5 (50.0)

Abbreviations: ALL, acute lymphoblastic leukemia; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; NR, nicotinamide riboside.
[a]4 participants had > 1 radiation site.
[b]4 participants had multiple HCTs of the same type.

4 | DISCUSSION

This randomized controlled pilot trial demonstrated that it is feasible and safe to deliver a 6-week telehealth resistance exercise intervention (3 exercise sessions per week) with or without NR supplementation in adult survivors of childhood cancer with prediabetes, without any serious adverse events attributed to the study interventions. We achieved the goal feasibility metrics of ≥70% compliance with the exercise and NR interventions, demonstrating that this study approach was acceptable to our population of interest. Lifestyle modifications

TABLE 2 Change in body composition, markers of glucose homeostasis, and muscle strength.

Characteristic, median (range)	Exercise only ($n = 8$)	P^a	Exercise + NR ($n = 9$)	P^a	P^b
BMI (kg/m^2)	−0.1 (−1.3 to 1.4)	.74	−0.2 (−0.6 to 0.6)	.86	.53
Waist circumference (cm)	−1.3 (−8.0 to 2.0)	.15	0 (−2.5 to 23.0)	1.00	.25
HbA1c (%)	−0.1 (−0.4 to 0.4)	.75	0 (−0.2 to 0.2)	.89	.49
Fasting glucose (mg/dL)	1.0 (−15 to 10)	.87	1.0 (−7 to 9)	.44	.66
HOMA-IR	−0.03 (−4.42 to 3.47)	1	0.50 (−0.75 to 2.04)	.17	.63
Myostatin (ng/mL)	−8.86 (−405.75 to 115.40)	.40	−5.62 (−110.2 to 135.4)	.77	.77
Grip strength of dominant hand (kg)	2.5 (−4.1 to 10.1)	.48	−0.1 (−1.7 to 4.3)	.81	.27
Fat mass (lb)	−1.1 (−5.5 to 1.4)	.09	0.6 (−3.6 to 4.2)	.37	.11
Fat-free mass (lb)	−1.2 (−2.5 to 8.4)	.67	−1.5 (−3.1 to 2.8)	.37	.63
Skeletal muscle mass (lb)	−0.8 (−2.3 to 5.2)	.89	−0.3 (−1.3 to 1.9)	.95	.70
Visceral adipose tissue index (cm^2/m^2)	−0.1 (−3.3 to 0.3)	.48	0 (−0.4 to 5.4)	.61	.66

Abbreviations: BMI, body mass index; HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment for insulin resistance.
[a]Comparison baseline and end-of-study measures within the study arm.
[b]Comparison of median change between two study arms.

including increasing exercise are a first-line intervention for prediabetes, have successfully improved glycemic control and fitness,[42] and have been shown to mitigate the progression to diabetes in non-cancer populations.[43] In fact, such interventions can have similar if not superior effects on markers of glucose homeostasis when compared with pharmacotherapy such as metformin.[43,44] This is the first study to show that this combination of interventions can be feasibly and remotely delivered to CCS, a population at high risk for developing prediabetes and subsequent comorbidities.[4]

Nearly 90% of the patients who were contacted consented to the study. Although we recruited from an engaged population of LTFU clinic patients, this high consent rate may also be due in part to the remote design of the study interventions, as previous studies have found that cancer survivors appreciate the convenient and flexible nature of remote behavioral intervention programs.[45,46] The consent rate may also reflect the strong interest CCS have in making healthy lifestyle changes, recognizing their increased risk for diabetes and cardiovascular disease. Additionally, we coordinated study visits with planned clinic appointments when possible to minimize participant burden. The exercise equipment in this study (resistance bands and exercise mat) is readily available and portable, and we leveraged an online platform to deliver virtual coaching and personalized exercises to each participant's needs. This platform also enabled tracking of adherence to the prescribed exercise program, which is preferable to the self-report method used in previous remote interventions. Compliance rates were > 80% for exercise, which may reflect the impact of a convenient and flexible exercise program, with the hybrid approach of initial instructor-led exercise sessions followed by independently conducted sessions, and consistent check-ins from the research team. Our study intervention may also be easily applied to other patient populations as well, such as survivors of adult-onset cancers. Although our study incorporated resistance exercises alone, which have shown benefit in improving some glycemic indices,[47] future studies may need to consider evaluating the role of combining resistance with aerobic exercise in CCS with prediabetes.

NAD coenzymes are vital for key cellular processes including OXPHOS and energy production. In the general population, NAD declines with age, and mitochondrial OXPHOS capacity is decreased in the setting of both diabetes and sarcopenia.[19,20,48] NAD precursors have been found in some studies to improve insulin sensitivity in prediabetic women[49] and aspects of muscle health and exercise performance in older men.[50] Moreover, NR has shown activity in depressing inflammation in adults.[25–31] NR at a dose of 1000 mg/day was specifically selected for this study, which included survivors at risk for accelerated aging, diabetes, and sarcopenia, due to its safety in previous human studies, favorable side effect profile, oral bioavailability, and the potential of NR to synergize with exercise to improve both glycemic indices and muscle health.[23,26,51] To our knowledge, this is the first study to report on the feasibility or effects of combination of exercise and NR in any population. None of the participants in this study developed serious adverse events attributable to NR supplementation. Additional studies of combination exercise programs with NR supplementation are underway (NCT04907110, NCT05194397) and will provide valuable insight regarding the potential of NR to enhance the effects of exercise on overall fitness and metabolism.[52]

A key strength of our study was our large proportion of historically underrepresented populations. Participants were recruited from our LTFU clinic, in which 50% of our patients are Hispanic. A substantially larger proportion (75%) of participants who enrolled in this study were Hispanic. This may be reflective of the higher prevalence of prediabetes and diabetes among Hispanic individuals in the general and cancer survivor populations.[53–55] In our clinic, 40% of CCS have received HCT; however, 60% of participants in this study had a history of HCT. Although this in part is representative of our high proportion of HCT survivors at COH, it also reflects the increased risk of prediabetes among HCT recipients. Larger studies in similarly diverse patient

populations are needed to determine whether race and ethnicity are risk factors for the development of diabetes among CCS in the context of their treatment exposures and, if so, to what extent.

There were no statistically significant changes in markers of glucose homeostasis (i.e., fasting glucose, HbA1c, HOMA-IR) or muscle health (i.e., muscle mass, grip strength, thickness, or CSA) following the 6-week intervention in either study arm. However, this pilot study was not powered to detect such changes. Furthermore, HbA1c represents blood glucose levels over a period of about 90 days; thus, it is unlikely to change substantially over this shorter study period. We hypothesized that following the intervention, there would be a decrease in levels of plasma myostatin, which is a myokine that inhibits muscle growth and has been shown to decrease with resistance exercise.[56–58] There were notable changes in muscle US findings among participants who had a decrease in myostatin. Specifically, myostatin decreases were seen among participants who completed ≥ 75% of the prescribed exercise, and were accompanied by decreased IMAT and increased rectus femoris CSA. This provides important insight and preliminary data regarding favorable changes in myokines and body composition in response to exercise and/or NR, which may represent biomarkers of early response to interventions. Larger studies are needed to disentangle how therapeutic exposures and individual factors affect changes in body composition and related biomarkers, including those related to mitochondrial OXPHOS, during interventions.

All participants who remained enrolled for the duration of the study completed the required study assessments at both time points, highlighting the feasibility of noninvasively measuring body composition and muscle health. Similar to the markers of glucose homeostasis, we did not find any significant changes in measures of body composition (i.e., BMI, waist circumference, BIA measures) or muscle health (i.e., grip strength, SPPB score, muscle US). Again, a longer duration of exercise intervention may be required to see clinically meaningful changes in body composition and grip strength. Regarding the SPPB, participants had relatively high scores at baseline (median 11.0 out of 12.0); all participants had a baseline score of ≥ 10, which is considered normal range.[59] These high baseline scores may preclude the ability to detect significant increases in SPPB scores. It is possible that patients who were interested in participating in this exercise intervention were more likely to have higher baseline physical performance. These findings emphasize the need for larger studies with longer intervention periods to examine the effects of exercise and NR on glycemic indices, body composition, and muscle health.

Our study had several limitations. The relatively small study sample size and short duration precluded our ability to evaluate the actual effects of the study interventions on markers of glucose homeostasis and muscle health. This study also included survivors of all childhood cancer types, and thus was comprised of a heterogeneous study population with regard to underlying diagnosis, age at diagnosis, current age, and treatment exposures. Larger studies focused specifically on survivors identified to be at highest risk for prediabetes are needed. This study did not include additional monitoring to measure physical activity, which is an important aspect to incorporate in future studies. Lastly, there was little variation in our participants' SPPB scores, indicating that different functional assessments (e.g., combination of lower and upper extremity dynamometry) may be necessary to study changes in muscle function over relatively short periods of time in this relatively young patient population.

Nevertheless, this study demonstrates that a randomized trial of telehealth exercise and NR supplementation is feasible and safe in a diverse cohort of CCS with prediabetes. The data provide the foundation for future studies of remote exercise and nutritional supplementation among survivors who are particularly at risk for developing metabolic diseases. The growing population of CCS necessitates the development of accessible, convenient, effective, and sustainable interventions to improve health outcomes and decrease morbidity and mortality among this vulnerable patient population.

ACKNOWLEDGMENTS

Nicotinamide riboside was provided by ChromaDex, Inc. Research reported in this publication was supported in part by the National Cancer Institute of the National Institutes of Health under Award Number K12CA001727 (Mortimer) and by the TREC Training Workshop R25CA203650 (Irwin). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

CONFLICT OF INTEREST STATEMENT

Charles Brenner is the chief scientific advisor of ChromaDex.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available upon request from the corresponding author.

ORCID

Rusha Bhandari https://orcid.org/0000-0003-2069-1518
Kara Lukas https://orcid.org/0000-0002-7273-1158
Saro H. Armenian https://orcid.org/0000-0003-2604-8603

REFERENCES

1. Erdmann F, Frederiksen LE, Bonaventure A, et al. Childhood cancer: survival, treatment modalities, late effects and improvements over time. *Cancer Epidemiol*. 2021;71:101733.
2. Robison LL, Hudson MM. Survivors of childhood and adolescent cancer: life-long risks and responsibilities. *Nat Rev Cancer*. 2014;14(1):61-70.
3. Gibson TM, Mostoufi-Moab S, Stratton KL, et al. Temporal patterns in the risk of chronic health conditions in survivors of childhood cancer diagnosed 1970–99: a report from the Childhood Cancer Survivor Study cohort. *Lancet Oncol*. 2018;19(12):1590-1601.
4. Dixon SB, Wang F, Lu L, et al. Prediabetes and associated risk of cardiovascular events and chronic kidney disease among adult survivors of childhood cancer in the St Jude Lifetime Cohort. *J Clin Oncol*. 2023:JCO2301005.
5. Hayek S, Gibson TM, Leisenring WM, et al. Prevalence and predictors of frailty in childhood cancer survivors and siblings: a report from the Childhood Cancer Survivor Study. *J Clin Oncol*. 2020;38(3):232-247.
6. Ness KK, Armstrong GT, Kundu M, Wilson CL, Tchkonia T, Kirkland JL. Frailty in childhood cancer survivors. *Cancer*. 2015;121(10):1540-1547.

7. Mostoufi-Moab S, Seidel K, Leisenring WM, et al. Endocrine abnormalities in aging survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *J Clin Oncol*. 2016;34(27):3240-3247.
8. McCastlain K, Howell CR, Welsh CE, et al. The association of mitochondrial copy number with sarcopenia in adult survivors of childhood cancer. *J Natl Cancer Inst*. 2021;113:1570-1580.
9. Kalyani RR, Corriere M, Ferrucci L. Age-related and disease-related muscle loss: the effect of diabetes, obesity, and other diseases. *Lancet Diabetes Endocrinol*. 2014;2(10):819-829.
10. DeFronzo RA, Tripathy D. Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. *Diabetes Care*. 2009;32:S157-S163. Suppl 2.
11. Meex RC, Schrauwen-Hinderling VB, Moonen-Kornips E, et al. Restoration of muscle mitochondrial function and metabolic flexibility in type 2 diabetes by exercise training is paralleled by increased myocellular fat storage and improved insulin sensitivity. *Diabetes*. 2010;59(3):572-579.
12. Huang Y, Han J, Gu Q, et al. Effect of Yijinjing combined with elastic band exercise on muscle mass and function in middle-aged and elderly patients with prediabetes: a randomized controlled trial. *Front Med (Lausanne)*. 2022;9:990100.
13. Miller CK, King D, Nagaraja HN, Fujita K, Cheavens J, Focht BC. Impact of an augmented intervention on self-regulatory, dietary and physical activity outcomes in a diabetes prevention trial among adults with prediabetes. *J Behav Med*. 2023;46(5):770-780.
14. Atkinson M, Murnane A, Goddard T, et al. A randomized controlled trial of a structured exercise intervention after the completion of acute cancer treatment in adolescents and young adults. *Pediatr Blood Cancer*. 2021;68(1):e28751.
15. Schutz S, Aidar FJ, Souza RLM, et al. Different Methods of physical training applied to women breast cancer survivors: a systematic review. *Front Physiol*. 2021;12:639406.
16. Wisse W, Boer Rookhuizen M, de Kruif MD, et al. Prescription of physical activity is not sufficient to change sedentary behavior and improve glycemic control in type 2 diabetes patients. *Diabetes Res Clin Pract*. 2010;88(2):e10-e13.
17. Ness KK, Plana JC, Joshi VM, et al. Exercise intolerance, mortality, and organ system impairment in adult survivors of childhood cancer. *J Clin Oncol*. 2020;38(1):29-42.
18. Belenky P, Bogan KL, Brenner C. NAD+ metabolism in health and disease. *Trends Biochem Sci*. 2007;32(1):12-19.
19. Mogensen M, Sahlin K, Fernstrom M, et al. Mitochondrial respiration is decreased in skeletal muscle of patients with type 2 diabetes. *Diabetes*. 2007;56(6):1592-1599.
20. Migliavacca E, Tay SKH, Patel HP, et al. Mitochondrial oxidative capacity and NAD(+) biosynthesis are reduced in human sarcopenia across ethnicities. *Nat Commun*. 2019;10(1):5808.
21. Tieland M, Trouwborst I, Clark BC. Skeletal muscle performance and ageing. *J Cachexia Sarcopenia Muscle*. 2018;9(1):3-19.
22. Bieganowski P, Brenner C. Discoveries of nicotinamide riboside as a nutrient and conserved NRK genes establish a Preiss-Handler independent route to NAD+ in fungi and humans. *Cell*. 2004;117(4):495-502.
23. Trammell SA, Schmidt MS, Weidemann BJ, et al. Nicotinamide riboside is uniquely and orally bioavailable in mice and humans. *Nat Commun*. 2016;7:12948.
24. Conze D, Brenner C, Kruger CL. Safety and metabolism of long-term administration of NIAGEN (nicotinamide riboside chloride) in a randomized, double-blind, placebo-controlled clinical trial of healthy overweight adults. *Sci Rep*. 2019;9(1):9772.
25. Brakedal B, Dolle C, Riemer F, et al. The NADPARK study: a randomized phase I trial of nicotinamide riboside supplementation in Parkinson's disease. *Cell Metab*. 2022;34(3):396-407.e6. e396.
26. Elhassan YS, Kluckova K, Fletcher RS, et al. Nicotinamide riboside augments the aged human skeletal muscle NAD(+) metabolome and induces transcriptomic and anti-inflammatory signatures. *Cell Rep*. 2019;28(7):1717-1728.e6. e1716.
27. Han K, Singh K, Meadows AM, et al. Boosting NAD preferentially blunts Th17 inflammation via arginine biosynthesis and redox control in healthy and psoriasis subjects. *Cell Rep Med*. 2023;4(9):101157.
28. Remie CME, Roumans KHM, Moonen MPB, et al. Nicotinamide riboside supplementation alters body composition and skeletal muscle acetylcarnitine concentrations in healthy obese humans. *Am J Clin Nutr*. 2020;112(2):413-426.
29. Wang DD, Airhart SE, Zhou B, et al. Safety and tolerability of nicotinamide riboside in heart failure with reduced ejection fraction. *JACC Basic Transl Sci*. 2022;7(12):1183-1196.
30. Wu J, Singh K, Lin A, et al. Boosting NAD+ blunts TLR4-induced type I IFN in control and systemic lupus erythematosus monocytes. *J Clin Invest*. 2022;132(5).
31. Zhou B, Wang DD, Qiu Y, et al. Boosting NAD level suppresses inflammatory activation of PBMCs in heart failure. *J Clin Invest*. 2020;130(11):6054-6063.
32. American Diabetes A. 2. classification and diagnosis of diabetes: standards of medical care in diabetes-2021. *Diabetes Care*. 2021;44(Suppl 1):S15-S33.
33. BMI percentile calculator for child and teen. 2019; https://www.cdc.gov/healthyweight/bmi/calculator.html
34. About adult BMI. 2020; Accessed October 26, 2020. https://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html#InterpretedAdults
35. Kovac L, Goj T, Ouni M, et al. Skeletal muscle gene expression signatures of obese high- and low- responders to endurance exercise training. *J Clin Endocrinol Metab*. 2024 Apr 19;109(5):1318-1327.
36. Dollerup OL, Christensen B, Svart M, et al. A randomized placebo-controlled clinical trial of nicotinamide riboside in obese men: safety, insulin-sensitivity, and lipid-mobilizing effects. *Am J Clin Nutr*. 2018;108(2):343-353.
37. Common Terminology Criteria for Adverse Events (CTCAE). 2018; https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40
38. Muniyappa R, Madan R. Assessing insulin sensitivity and resistance in humans. In: Feingold KR, Anawalt B, Boyce A, editors. *Endotext*. South Dartmouth (MA): MDText.com, Inc.; 2000.
39. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. *N Engl J Med*. 1995;332(9):556-562.
40. Cassidy B, Arena S. The short physical performance battery as a predictor of functional decline. *Home Healthc Now*. 2022;40(3):168-169.
41. *IBM SPSS Statistics for Windows* [computer program]. Version 26. IBM Corp; 2019.
42. Rowan CP, Riddell MC, Gledhill N, Jamnik VK. Aerobic exercise training modalities and prediabetes risk reduction. *Med Sci Sports Exerc*. 2017;49(3):403-412.
43. Diabetes Prevention Program Research G. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. *Lancet Diabetes Endocrinol*. 2015;3(11):866-875.
44. Azocar-Gallardo J, Ramirez-Campillo R, Afonso J, et al. Overweight and obese adult patients show larger benefits from concurrent training compared with pharmacological metformin treatment on insulin resistance and fat oxidation. *Int J Environ Res Public Health*. 2022;19(21):14331.
45. MacDonald AM, Chafranskaia A, Lopez CJ, et al. CaRE @ Home: pilot study of an online multidimensional cancer rehabilitation and exercise program for cancer survivors. *J Clin Med*. 2020;9(10):3092.

46. Rabin C, Simpson N, Morrow K, Pinto B. Intervention format and delivery preferences among young adult cancer survivors. *Int J Behav Med*. 2013;20(2):304-310.
47. Bennasar-Veny M, Malih N, Galmes-Panades AM, et al. Effect of physical activity and different exercise modalities on glycemic control in people with prediabetes: a systematic review and meta-analysis of randomized controlled trials. *Front Endocrinol (Lausanne)*. 2023;14:1233312.
48. Braidy N, Berg J, Clement J, et al. Role of nicotinamide adenine dinucleotide and related precursors as therapeutic targets for age-related degenerative diseases: rationale, biochemistry, pharmacokinetics, and outcomes. *Antioxid Redox Signal*. 2019;30(2):251-294.
49. Yoshino M, Yoshino J, Kayser BD, et al. Nicotinamide mononucleotide increases muscle insulin sensitivity in prediabetic women. *Science*. 2021;372:1224-1229.
50. Dolopikou CF, Kourtzidis IA, Margaritelis NV, et al. Acute nicotinamide riboside supplementation improves redox homeostasis and exercise performance in old individuals: a double-blind cross-over study. *Eur J Nutr*. 2020;59(2):505-515.
51. Fan W, Evans RM. Exercise mimetics: impact on health and performance. *Cell Metab*. 2017;25(2):242-247.
52. Song M, Armenian SH, Bhandari R, et al. Exercise training and NR supplementation to improve muscle mass and fitness in adolescent and young adult hematopoietic cell transplant survivors: a randomized controlled trial 1. *BMC Cancer*. 2022;22(1):795.
53. Force USPST, Davidson KW, Barry MJ, et al. Screening for prediabetes and type 2 diabetes: US Preventive Services Task Force recommendation statement. *JAMA*. 2021;326(8):736-743.
54. Formagini T, Brooks JV, Roberts A, et al. Prediabetes prevalence and awareness by race, ethnicity, and educational attainment among U.S. adults. *Front Public Health*. 2023;11:1277657.
55. Noyd DH, Liu Q, Yasui Y, et al. Cardiovascular risk factor disparities in adult survivors of childhood cancer compared with the general population. *JACC CardioOncol*. 2023;5(4):489-500.
56. Severinsen MCK, Pedersen BK. Muscle-organ crosstalk: the emerging roles of myokines. *Endocr Rev*. 2020;41(4):594-609.
57. Jeong D, Park K, Lee J, et al. Effects of resistance exercise and essential amino acid intake on muscle quality, myokine, and inflammation factors in young adult males. *Nutrients*. 2024;16(11):1688.
58. Balakrishnan R, Thurmond DC. Mechanisms by which skeletal muscle myokines ameliorate insulin resistance. *Int J Mol Sci*. 2022;23(9):4636.
59. Lee K, Shamunee J, Lindenfeld L, et al. Feasibility of implementing a supervised telehealth exercise intervention in frail survivors of hematopoietic cell transplantation: a pilot randomized trial. *BMC Cancer*. 2023;23(1):390.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Bhandari R, Lukas K, Lee K, et al. Feasibility of telehealth exercise and nicotinamide riboside supplementation in survivors of childhood cancer at risk for diabetes: A pilot randomized controlled trial. *Pediatr Blood Cancer*. 2025;72:e31369. https://doi.org/10.1002/pbc.31369