Home-Based Grouped Telerehabilitation Program in Early-on Survivors of Childhood Acute Lymphoblastic Leukemia

A Pilot Cohort Exploring Quantitative and Qualitative Feasibility

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List of Abbreviations

ALL: Acute Lymphoblastic Leukemia

ALLs: Acute Lymphoblastic Leukemia Survivors

B-LL: B-cell Lymphoblastic Lymphoma

BMC: Bone Mineral Content

BMD: Bone Mineral Density

vBMD: volumetric Bone Mineral Density

BMI: Body Mass Index

CRT: Cranial Radiotherapy

CSA: Cross-Sectional Area

e.g: exempli gratia

Etc.: Et cætera

HBM: Health Belief Model

i.e: id est

ISCD: International Society of Clinical Densitometry

LAEs: Late Adverse Effects

MDD: Minimal Detectable Difference

MSK: Musculoskeletal

M2LH: Multiple Two-Leg Hopping Test

ON: Avascular Osteonecrosis

PHM: Pediatric Hematological Malignancies

pQCT: peripheral Quantitative Computed Tomography

RCT: Randomized Controlled Trial

RR: Relative Risk

SD: Standard Deviation

SSI: Stress-Strain Index

S2LJ: Single Two-Leg Jump

TAM: Technology Adoption Model

USA: United States of America

VF: Vertebral Fracture

WHO: World Health Organization

6MWT: Six-Minute Walk Test

Abstract

Background: Pediatric Hematological malignancies such as Acute Lymphoblastic Leukemia (ALL) and B Lymphoblastic Lymphoma (B-LL) take their origin in the stem cells from the bone marrow and are some of the most common types of pediatric cancer. The origin of the diseases, and their treatments, cause patients' altered bone-mineral homeostasis state, which can contribute to osteopenia, orthopedic fractures most commonly those of the lower vertebrae. The increasing number of survivors highlights the presence of the disease- and treatment-related musculoskeletal (MSK) comorbidities and late adverse effects (LAEs) of long-term survivors which are also influenced by inactivity. However, physical activity has been shown to increase mechanical workload to the bone, mitigating the bone impairment in other cancer-specific populations. Nonetheless, since it is hard to have pediatric survivors come in hospital to receive specialized intervention, this thesis will investigate 1. the use of telerehabilitation to deliver home-based supervised exercise programs for early-on survivors of bone marrow-related hematological malignancies, further exploring 2. the impact of such programs on survivors' MSK and functional health, and 3. the participants' experience with the program. We hypothesized that telerehabilitation is feasible with ALL survivors, expecting significant adherence rate (>80%) and completion rate (>75%).

Methods: Survivors of bone-marrow-related hematological malignancies (n=12; 7.9 to 14.7 years old) within 6 months to 5 years of their complete remission were recruited to participate with a parent. The 16-week program included 40 potential home-based exercise interventions supervised by a kinesiologist through a telerehabilitation Internet platform, with monthly progression. Evaluation before and after the intervention protocol included measurements of functional capacities (Six-Minute Walk Test; 6MWT), and MSK health (mechanography, grip force test, and pQCT) of patients, in addition to a semi-structured interview at the post-intervention evaluation with the patients and parents separately.

Results: Of the 12 patients recruited, two were excluded (1=relapse; 1=failure to comply with technical criteria) and 1 abandoned. The nine patients who completed the program (6 girls; 10.93±2.83 years; BMI: 21.58±6.55; time since complete remission: 36.67±16.37 months) had a mean adherence of 89%, representing a completion rate of 75%. These patients showed functional improvements in absolute and relative lower-limb muscle power, relative muscle force and 6MWT. However, no improvement was observed in grip strength. Additionally, participants exhibited improved bone health after the interventions, when compared to the initial assessment: BMC, SSI, total and cortical CSA at the 14% (*P*=.03, *P*=.01, *P*=.01, & *P*=.001, respectively) and 38% sites of the tibia (*P*=.003, *P*=.04, *P*=.001, & *P*=.003, respectively). Lastly, the overarching themes identified throughout the post-intervention interviews were the benefits and challenges of the program modalities (the group approach, with patient-parent paired trainings, supervised by a kinesiologist) and the telerehabilitation system, the participants' perception of the training's benefits, in addition to the recommendations and suggestions from the families. Both patients and parents were highly satisfied with the program and perceived benefits.

Conclusion: Telerehabilitation seems to be a feasible way of delivering exercise interventions to ALL early-on survivors and might bring benefits to patients' functional performance in addition to bone health parameters, by means of improved adherence. The telerehabilitation method of delivering the training program was perceived by some as a decisive argument in choosing to participate, whereas the supervision and the intra- and inter-family interactions were perceived as motivating factors, which are key to program adherence. A longer intervention, with more participants, would be needed to truly assess the impact of such programs on bone health.

Keywords: Exercise therapy, Rehabilitation, Acute Lymphoblastic Leukemia, Lymphoblastic Lymphoma, Hematologic Malignancies, Survivorship, Muscle-Bone Complex, Intervention study, Plyometric and Resistance Training, Patients' perspective

Abrégé

Contexte: Les hémopathies malignes pédiatriques telles que la leucémie lymphoblastique aiguë (LAL) et le lymphome lymphoblastique B (B-LL) prennent leur origine dans les cellules souches de la moelle osseuse et font partie des types de cancer pédiatrique les plus courants. L'origine des maladies, ainsi que ses traitements, entraîne une altération de l'homéostasie minérale osseuse des patients, ce qui peut contribuer à l'ostéopénie, ou aux fractures orthopédiques, plus couramment celles de la vertèbre inférieure. Le nombre croissant de survivants met en évidence la présence de comorbidités et d'effets indésirables musculo-squelettiques liées à la maladie et aux traitements, pour les survivants à long terme. Ces effets indésirables sont également influencés par l'inactivité. Néanmoins, il a été démontré que l'activité physique augmente la charge de travail mécanique de l'os, atténuant la déficience osseuse dans d'autres populations spécifiques du cancer. Cependant, comme il est difficile de faire venir des survivants pédiatriques à l'hôpital pour recevoir une intervention spécialisée, ce mémoire examinera 1. l'utilisation de la téléréadaptation pour offrir un programme supervisé d'exercices à domicile pour les survivants précoces d'hémopathies malignes liées à la moelle osseuse, ainsi qu'explorera 2. l'impact d'un tel programme sur la santé musculo-squelettique et fonctionnelle des survivants, et 3. l'expérience des participants avec le programme. Nous avons émis l'hypothèse que la téléréadaptation est faisable avec les survivants LAL, en prévoyant un taux de participation (> 80%) et un taux de participants complétant le programme (> 75%) significatifs.

Méthodes: Des survivants d'hémopathies malignes liées à la moelle osseuse (n = 12; 7,9 à 14,7 ans) dans les 6 mois à 5 ans suivant leur rémission complète ont été recrutés pour participer avec un parent. Le programme de 16 semaines comprenait 40 interventions potentielles d'exercices à domicile supervisées par un kinésiologue via une plateforme Internet de téléréadaptation, avec une progression mensuelle. L'évaluation avant et après le protocole d'intervention comprenait des mesures des capacités fonctionnelles (test de marche de 6 minutes; 6MWT) et de la santé musculo-squelettique (mécanographie, test de force de préhension et pQCT) des patients, en plus d'un entretien semi-structuré à l'évaluation post- intervention avec les patients et les parents, séparément.

Résultats: Sur les 12 patients recrutés, deux ont été exclus (1 = rechute; 1 = non-respect des critères techniques) et 1 abandonné. Les neuf patients ayant terminé le programme (6 filles; 10,93 ± 2,83 ans; IMC: 21,58 ± 6,55; délai depuis la rémission complète: 36,67 ± 16,37 mois) avaient un taux de participation moyen de 89%, pour 75% des participants complétant le programme. Ces patients ont montré des améliorations fonctionnelles de la puissance musculaire absolue et relative des membres inférieurs, de la force musculaire relative et du 6MWT. Cependant, aucune amélioration de la force de préhension n'a été observée. De plus, les participants ont présenté une amélioration de la santé osseuse après les interventions, par rapport à l'évaluation initiale: BMC, SSI, CSA totale et corticale à 14% (*P*=0,03, *P*=0,01, *P*=0,01 et *P*=0,001, respectivement) et 38% des sites du tibia (*P*=0,003, *P*=0,04, *P*=0,001 et *P*=0,003, respectivement). De plus, les thèmes dominants identifiés comme transcendant les entrevues post-intervention étaient: les bénéfices et les défis des modalités du programme (l'approche de groupe, avec des paires patient-parent, supervisées par un kinésiologue) et du système de téléréadaptation, la perception des participants sur le les bénéfices de la formation, ainsi que les recommandations et suggestions des familles. Les patients et les parents ont été très satisfaits du programme et des avantages perçus.

Conclusion: La téléréadaptation semble être un moyen réalisable de fournir des interventions d'exercice aux survivants de la LAL et pourrait apporter des avantages aux performances fonctionnelles des patients en plus des paramètres de santé osseuse, grâce à une meilleure participation. La méthode de téléréadaptation pour prodiguer le programme d'entraînement a été perçue par certains comme un argument décisif dans le choix de participer, tandis que la supervision ainsi que les interactions intra et inter-familiales ont été perçues comme des facteurs de motivation, qui sont essentiels à l'adhésion au programme. Une intervention plus longue, avec plus de participants, serait nécessaire pour évaluer les vrais impacts d'un tel programme sur la santé osseuse.

Mots clés: Thérapie par l'exercice, réadaptation, leucémie lymphoblastique aiguë, lymphome lymphoblastique, tumeurs malignes hématologiques, survie, complexe musculo-osseux, étude d'intervention, entraînement pliométrique et résistance, perspective des patients

In Memory of

Myriam Boudreau Landry,1998 – 2009

Mimi, you left way too soon. And yet you found a way to inspire me in every challenging moment I have encountered. You are part of all my success over the years, and, therefore, you needed a special place in this thesis. You loved sport in all forms, and laughing, which is why I know you would have loved this project.

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Contribution of the Authors

As this is a Manuscript-based thesis, the work had multiple contributors. To this extent, here are the respective contributions of the students and co-authors to each chapter. Please find below the list of authors and respective tasks and contribution:

- *Genevieve Lambert (GL), BSc and MSc(c)*: Co-created the exercise prescription, co-created the semi-structured interview questionnaire, recruited patients, scheduled and assessed participants for evaluation, managed the communications with the ethical review board, supervised 93% of the interventions, collected data and conducted the statistical analysis for the First Manuscript, transcribed 8 interviews, conducted the qualitative analysis for the Second Manuscript and wrote the First and Second Manuscripts as the first author (Chapters 3 and 4).
- *Nathalie Alos*, M.D.: Was a co-investigator for the project, supervised the health of patients during the program, and reviewed and edited both Manuscripts.
- *Pascal Bernier, BSc and MSc(c):* Reviewed recruitment list for exclusion criteria and medical background.
- *Caroline Laverdière:* Was a collaborator for the project, approved the participation of patients recruited for the study as their oncologist, and revised the First Manuscript.
- *Dahlia Kairy:* Was a co-investigator for the project, supervised the creation of the semi-structured interview questionnaire for the Second Manuscript and supervised GL in conducting the qualitative analysis and writing the Second Manuscript (Chapter 4), reviewed and edited both Manuscripts.
- *Kenneth Drummond, BSc and MSc(c)*: Co-created the exercise prescription and supervised 8% of the interventions, reviewed both Manuscripts (Chapter 3).
- Noémi Dahan-Oliel: Was a co-investigator for the project, and reviewed both Manuscripts (Chapters 3 and 4).
- Martin Lemay: Was a co-investigator for the project, and reviewed both Manuscripts (Chapters 3 and 4).
- Louis-Nicolas Veilleux: Was the Principal Investigator, applied for the funding, developed the documents for the ethical review board, supervised GL in the creation and administration of the program, in conducting the statistical analysis and in the writing of the First Manuscript (Chapter

3), wrote part of the introduction of the Second Manuscript (Chapter 4), and edited and reviewed both Manuscripts (Chapters 3 and 4).

The first Manuscript, titled: "Home-Based Telehealth Exercise Intervention in Early-On Survivors of Childhood Acute Lymphoblastic Leukemia: a Feasibility Study", was submitted to the Journal of Medical Internet Research on mHealth and uHealth on November 6, 2020, received a decision of minor revisions in January 2021 and in March 2021, and has received a provisional acceptance on April 9, 2021, in the Journal of Medical Internet Research on Cancer for publication. The preprint is available at: https://preprints.jmir.org/preprint/25569 .

The second Manuscript, titled: "Patient and Parent Experiences with Group Telerehabilitation for Child Survivors of Acute Lymphoblastic Leukemia", was submitted to the International Journal of Environmental Research and Public Health on February 15, 2021, and was published on March 31, 2021 (https://www.mdpi.com/1660-4601/18/7/3610).

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Chapter 1 - Introduction

1.1. Statement of the Problem

In Canada, there are nearly 900 children younger than 15 years diagnosed annually with cancer (1), whereas in the United States of America (USA) this number can easily be thirteen times higher (2). Their survival rate varies among types of malignancy; however, ranges are from 64% to almost 100% (3). As the number of pediatric malignancies survivors increases due to advancements in curative therapies, these survivors are at risk of having late-adverse effects (LAEs), even 5 years after treatment completion. The Public Health Agency of Canada estimates that two thirds of survivors will experience LAEs at some point in their lifetime following treatment completion. To this extent, hematological malignancies, such as Acute Lymphoblastic Leukemia (ALL) or B-cell Lymphoblastic Lymphoma (B-LL), are of interest to musculoskeletal (MSK) LAEs such as pathological fractures, pain, decreased muscle mass and strength (4), as the origin of the malignancy takes place in the bone marrow. The disease therefore poses a detrimental effect to the bone structure, and the therapies further target and affect the overall bone health. Moreover, lifestyle habits, such as the practice of physical activity, have been known to be poorer in pediatric cancer patients and survivors (5). This lack of physical activity may impact MSK health, as it decreases the mechanostimulation prompting periosteal apposition. The culmination of the disease, treatments, and modification of lifestyle habits has been identified as the trilogy of factors prompting LAEs to ALL survivors (ALLs) such as fractures, osteoporosis, and decreased muscle strength and mobility.

Although some studies aimed at testing the use of mechanical stimulation to improve bone health, the only randomized control trial (RCT) study demonstrating such effects in the pediatric oncological population was through the use of vibration platforms (6). Further, the only other RCT assessing the potential of mechanical stimulation, using physical activity, did not show conclusive results nor discuss the role of adherence to explain their lack of evidence (7). ALLs have been observed to not reach governmental recommendations in terms of physical activity even 5 years after remission, and childhood survivors were more inactive than their healthy peers (8). Patients have expressed their preferences for exercising at home or school, rather than at a hospital or physiotherapy clinic (9). However, unsupervised modalities of intervention may be associated with low adherence rates (7,10). Therefore, to investigate the potential of physical activity as a means to improve bone health, a new method of delivering services must be used to prompt high adherence.

1.2. Purpose

This thesis primarily aims to assess the feasibility of implementing a new adjunct therapy to early survivors of ALL, at home, using a telerehabilitation system. Furthermore, secondary purposes will be to assess the preliminary efficiency of the program on MSK and functional health and to explore the participants' experience with the program.

1.3. Hypothesis

It is hypothesized that delivering telerehabilitation services to ALLs will be feasible and will be accompanied by improved MSK and functional health.

Chapter 2 - Literature Review

2.1. Acute Lymphoblastic Leukemia

In 2010, a study by the National Cancer Institute reported that 23% of all cancers among children younger than 15 years in Canada, and 28% in the USA, were leukemia, making it the most common type of pediatric malignancy. Leukemia has been reported to have a yearly incidence ranging from 2.17 to 3.78 per 100,000 individuals, depending on the country, in a study published in 2015 (11), whereas the US National Cancer Institute reported a yearly incidence of 4.7 per 100,000 (12). Specifically, more than 3,000 children are diagnosed with ALL yearly in the USA alone (13). The peak of incidence is between the ages of 2 and 8 years (14).

The disadvantageous prognosis factors of ALL include, but are not limited to age of 10 years or more at diagnosis, having a high white blood cell count (≥ 50,000/mm3 for children, or ≥300,000/mm3 for infants), T-cells ALL, medication adherence, race and socioeconomic status (15). Depending on these factors, patients are assigned a "risk of relapse" classification (e.g., standard risk, high risk, and very high risk) which determines the modalities and intensity of their treatment protocol.

Rapid advancement of therapies in the last half-century has significantly increased the 5-year survival rate of patients diagnosed with hematological malignancies, reaching almost 85% between 2010 and 2016 (12). This leaves a growing number of survivors at risk of experiencing MSK late adverse effects (LAEs). In this population of survivors, the modalities and aggressiveness of treatment received to eradicate ALL malignant cells will become additional risk factors for MSK LAEs.

2.2. Pathophysiology of Musculoskeletal (MSK) Deficits

The Disease

ALL and other pediatric hematological malignancies (PHM), such as lymphoma, originate from blood stem cells situated in the bone marrow of the trabecular bone. The latter is mostly contained within the epiphysis of long appendicular bones (such as the tibia or femur), vertebrae, and large irregular bones (such as the hips). Malignancies originating in these parts of bones result in liquid forms of cancer, as it is where blood cells are produced. The liquid characteristic of the PHM renders them more versatile because malignant cells are carried by the bloodstream in the cardiovascular system throughout all other physiological systems. Upon diagnosis, ALL patients commonly exhibit defects in bone-mineral homeostasis due to the combination of osteolysis and abnormal bone formation (16). Osteolysis is a process by which osteoclast will increase their activity to break down mineralization in the bone structure, resulting in bone resorption. This dysregulation of the bone microenvironment, embedded in the disease characteristics, contributes to deficits in bone health (17–21). Furthermore, it has been reported that leukemic cells secrete parathyroid hormones, and other related peptides, causing bone mineral density (BMD) deficits (22). In fact, 10 to 20% of patients have BMD deficits at diagnosis (22,23).

The Treatment

In the context of their disease, ALL patients receive many modalities of treatments, curative or as treatment of the side effects, including the following: a) chemotherapies, b) radiotherapy, c) hematopoietic stem cell transplants, in addition to d) pharmacological and e) non-pharmacological therapies of side effects and long-term effects. In North America, one of the most prominent protocols for the treatment of hematological ALL and B-LL is the Dana-Farber Cancer Institute of Boston, USA, ALL Protocol (DFCI-ALL). The protocol is dependent on the prognosis, which is coded as the risk of relapse: standard risk, high risk, or very high risk of relapse. The regimen for standard risk of relapse is typically constituted of pharmacological interventions such as chemotherapies. Cranial radiotherapy is also used in high and very high risk of relapse patients (24), and bone marrow transplant in cases of non-responsiveness to treatments or relapse (25). The goal of all these therapies, whether pharmacological or radiological, is to destroy cancer cells, by targeting the physiological pathways to limit the reproduction of hematological cells. However, by doing so, therapies further induce side effects on other systems, most predominantly on the cardiovascular system, as drugs are given intravenously and circulate in the blood to reach their intended target: the bone marrow contained in the trabecular bone.

<u>a) Chemotherapies</u>

Chemotherapies are pharmacological therapies that are standard usage in the treatment of cancer. Depending on the specific medication, the drug will act in different ways to limit cancer cell reproduction and lead to apoptosis. The most common chemotherapeutic agents include doxorubicin, vincristine, asparaginase, methotrexate, glucocorticoids (dexamethasone, Decadron, prednisone, and hydrocortisone (26)) (27), which can be classified into the following chemotherapy agents: anthracycline, plant alkaloid, antimetabolite, enzyme, and corticosteroids drugs. However, in the case of hematological malignancies, L-asparaginase would also be considered one of the most pertinent medications. The main medications documented to negatively affect bone health are doxorubicin (28–30), methotrexate (26,31–33), and glucocorticoids, such as dexamethasone (32–36). Further, muscle functions are also impacted by dexamethasone-induced reductions in sex and growth hormones (29,32), and vincristine-induced dose-dependent neurotoxic effects (37), mediated through axonal inflammation, thereby impairing motor functions (38) and muscle weakness (39). Moreover, intravenous administration of doxorubicin may induce side effects and LAEs such as cardiotoxicities (40). Further, no direct MSK LAEs have been reported related to the administration of L-asparaginase, however, common side effects observed during administration phases of the treatments are allergic response, diabetes and drug-induced liver disease (more frequent during maintenance phase), in addition to hematological and gastrointestinal comorbid conditions and septic shock (more frequent during remission induction phase) (41).

b) Radiotherapy

In the fight against cancer, radiotherapy is usually used to specifically target the localization of the tumor using high-energy gamma rays to fragment the genetic material of malignant cells. However, in the treatment of PHM, there is no specific original tumoral site to target, as cancerous cells are in the bloodstream of the cardiovascular and lymphatic systems. Cranial Radiotherapy (CRT) is avoided as much as possible for younger patients, as it is associated with many side effects and LAEs such as endocrine dysregulation, neurological deficits, abnormal metabolic activity, and secondary tumors (24,42,43). Studies reporting results of long-term survivors observed that the negative effects on growth hormones persist longer for CRT than corticosteroids or other chemotherapies (24,44,45), prompting an increased prevalence of LAEs such as BMD deficits in ALLs (24).

c) Anti-Thrombosis Medications and Their Effect on Bones Health

Anti-Thrombosis Medications, such as enoxaparin (i.e., Lovenox), can be administered to childhood ALL patients, as venous thromboembolism is a common serious complication of cancer therapies reported to occur in 2.5 to 11.6% of ALL patients (46). Enoxaparin is used to prevent blood clots, but can further induce side effects impacting the bone integrity, by inhibiting the mesenchymal stem cells' differentiation into osteoblasts (47). Receiving enoxaparin for longer than 3 months is associated with a progressive reduction of BMD (48), and may impose a long-term burden on bone repair (47).

Inactivity: The Impact of the Mechanostat Theorem

Multiple studies have reported the low level of physical activity of childhood cancer patients and survivors (8,49–52). This increased inactivity in the population may further prompt MSK LAEs. This can be explained by the Mechanostat theorem developed by Frost (2003 (53)). The latter stipulates that bone structure adapts to maximal mechanical stimulation from muscle contractions and unfavorable lever arms, by adding thickness to its cortical bone in order to be able to withstand these maximal forces. This phenomenon is called periosteal apposition and usually starts after 8 to 10 years of age, as it is associated with the pre-pubescent stage and older. It involves activation of the osteoblast activity in the outer layers of cortical bone leading to osteogenesis, with slight osteoclast activity in the lumen of the cortical bone. The combination of both phenomena leads to cortical bone adapting faster than trabecular bone by increasing its cross-sectional area (CSA), while maintaining or increasing its bone mineral content (BMC) without increasing its mineral density during bone remodeling (54). The combination of both phenomena may not lead to short-term improved BMD, as new bone needs time to acquire the same mineral quantity as older bone material, but will improve the CSA, cortical thickness, in addition to stress-strain index. Ultimately, periosteal apposition increases bone solidity in view of future forces and stress, decreasing the theoretical likelihood of fractures (55). This relationship between maximal muscle forces applied to the bone and the bone solidity is called the muscle-bone functional unit. It was first investigated in baseball players when noticing that their throwing arm had bigger bones than their other arm. However, in the cases of pediatric cancer patients and survivors, inactivity may play a reversed role in reducing maximal contractions that would lead to periosteal apposition. Nonetheless, forces applied to the MSK system can be increased due to growth (which is accompanied by increased overall weight, without necessarily changing the percentile of Body Mass Index; BMI), or metabolic syndromes such as obesity (which would be associated with increased relative weight, indicated by increased BMI percentile), which have been observed to have a protective role for BMD (56).

2.3. Musculoskeletal Late Adverse Effects

Almost two thirds of childhood cancer survivors will experience some kind of LAEs in their lifetime, and survivors are more likely to experience chronic conditions (Relative Risk; RR: 3.3) and life-threatening conditions (RR:8.2) compared to their siblings (57). As the therapies are mostly systemic for PHM, which means that treatments are not administered locally, the patients are at risk of developing various LAEs, such as adverse cardiovascular events, metabolic syndrome, or peripheral neuropathy. Moreover, the therapies are aimed at bone cells; therefore musculoskeletal LAEs are also prevalent in this population. The most common musculoskeletal LAEs reported in the literature include sarcopenia, myosteatosis, decreased bone density, osteopenia, osteoporosis, avascular osteonecrosis, pathological and vertebral fractures. Some of these LAEs, such as avascular osteonecrosis or vertebral fractures (VF), are usually managed through standard care and may prevent patients from exercising. However, sarcopenia, myosteatosis, or decreased BMD, without a diagnosis of osteoporosis, may be a good target for adjunct exercise therapy.

Musculoskeletal LAEs Treated with Standard of Care that Limits Exercising:

a) Vertebral Fractures and Non-Vertebral Fractures

Due to the decrease in bone mineralization in all phases of the disease, from diagnosis to survivorship, ALL patients are considered to have fragile bones and are therefore more at risk of fractures. Two types of fractures can be highlighted in the literature: VF and non-vertebral fractures (Non-VF). Non-VF include all fractures that do not affect the axis skeletal bones, and predominantly happen by "falling from a standing height or less at no more than walking speed" in the ALL population (58). It was reported in a literature review that 25 to 39% of patients during the course of their treatments had a fracture, either traumatic or pathological (58), and the risk of fracture increases for every BMD Standard Deviation (SD) under peak bone mass (58). Studies have revealed that 16% of patients experienced VF at diagnosis (in greater proportions than Non-VF (59)), and an additional 16% of patients developed VF within the first year of diagnosis (60), or 26% within 4 years of diagnosis (17). Similarly, the study by Ward et al. published in 2018 followed 186 patients for 6 years from diagnosis and found that 36% had a fracture at some point during the study (36). They also revealed that all occurrences of Non-VF reported in their sample were low trauma pathological fractures, resulting from treatment-related low bone mineral density in appendicular bones (36). Lastly, the study reported 25% of VF lead to spinal deformities, even more so in older children and in those with more severe compaction (36), which may further limit their ability to perform physical activities.

b) Avascular Osteonecrosis

Avascular Osteonecrosis (ON) is suggested to be the result of treatment-related emboli inducing reduced blood flow, ischemia, and osteocyte apoptosis (18,40). The most predominant form of ON is asymptomatic ON (18), defined as the presence of one or more lesions (61), whereas symptomatic ON also involves persistent pain in the affected limbs (61). The peak incidence of ON is during the first year from diagnosis (reported in 2 to 25% of patients during treatment (40,62)). However, it is a rare and severe LAE that can be present during survivorship (2.5% (63)), up to 11 years after diagnosis (40).

Musculoskeletal LAEs Possibly Subject to Adjunct Exercise Therapies:

a) Sarcopenia and Myosteatosis

Decreased muscle function has been reported in the literature among ALLs, partly attributed to the disease and its treatments (64). Inactivity during treatment, among other things due to bed rest, may further exacerbate these deficits in muscular strength (65). If untreated, this can lead to sarcopenia; the latter being defined as decreased muscle function accompanied by loss of muscle mass and muscle quality. Muscle quality deficit can be attributed partly to fat infiltration within, and in between, the skeletal muscles, i.e. myosteatosis (66). Both sarcopenia and myosteatosis can negatively impact muscle integrity, which may contribute to future bone impairments. This is due to the positive relationship that is generally observed between muscle force and bone strength in healthy and pathological populations. Sarcopenia has been documented to improve after treatments; however, muscle weakness has been reported to have lasting effects, still imposing limitations on the execution of daily activity 25 years into survivorship (65). Additionally, endocrine LAEs, such as metabolic syndromes, may suggest that myosteatosis would remain into survivorship; however, there is limited to no evidence on the subject, preventing any conclusion in the literature for the time being (66).

b) Decreased Bone Density, Osteopenia and Osteoporosis

The presence of bone mineral deficiency in survivors of ALL has been reported in some studies, while others report no, or low, decreased mineralization of the bone (67). This can cause osteopenia and, in more severe cases, osteoporosis. The World Health Organization (WHO) defines osteopenia as thinning of the bone, or an intermediate level of bone loss (T-score: [-1 to -2.5SD[), less severe than osteoporosis (T-score<-2.5SD) (68). The term has been used in other studies in patients and survivors (62,69,70), however, in the official statement of the international society of clinical densitometry (ISCD), published in 2008, the ISCD deemed the term as an inappropriate diagnosis for children (71). This is due to the WHO classification being based only on evidence from postmenopausal women (68). Based on the ISCD statement, the correct formulation to identify bone thinning in children would be "low bone mineral content, or area bone mineral density, for the age of the child" (71). Moreover, the diagnosis of osteoporosis can be provided if the patient has a low BMD combined with significant fracture history, or in the presence of VFs regardless of BMD (if VF occurs in the absence of high velocity trauma or local lesion) (71).

During survivorship, abnormally low BMD has been reported to occur in 21% of patients who completed at least 4 years since their end of treatments (70). This was similar to the results of the study by Rogalsky et al. published in 1989 (24.3%) and the study by Donmez et al. 2019 (osteopenia: 23%, osteoporosis: 7%). This contrasts with studies reporting low or no differences with a healthy population, such as the ones by Brennan et al. and Molinari et al. (62,72). Possible explanations for these discrepancies in the literature are the heterogeneity of the samples related to the puberty stage of the patients and the time until achieving peak bone mass (67). Furthermore, many factors have been investigated for their possible relationship with BMD, such as the disease itself, growth and sex hormones, usage of corticosteroids in the treatment regimen, calcium intake, or inactivity (31,73).

2.4. Addressing MSK Deficits in ALL Survivors

The Standard of Care

a) Pharmacological Treatment

Bisphosphonates are used in children for the treatment of primary and secondary osteoporosis (e.g., Glucocorticoid- or immobility-induced osteoporosis), in addition to malignancy-induced hypercalcemia, chemotherapy-related osteonecrosis (74). This category of medication aims to reduce bone resorption to improve bone integrity. The most common bisphosphonates given to ALL patients and survivors are zoledronic acid (i.e., Zometa) and, or pamidronic acid (i.e., Pamidronate). The former is more convenient to administer.

b) Nutritional Supplementation

Nutritional supplementation with calcium and vitamin D is well documented in the literature to improve bone integrity and is currently prescribed to patients and survivors as needed (58). Vitamin D (i.e., 25hydroxyD) is classified as a steroid hormone, and it acts as a regulator, most notably of intestinal calcium and phosphates absorption(75), in addition to bone homeostasis (76,77) and renal reabsorption of calcium and phosphates (76,77). Calcium, phosphate, and magnesium are minerals that are stored in the bone matrix in order to be available if needed by other systems, as a reserve. This process of depositing and releasing minerals from the skeletal tissue through bone formation and resorption is also called bone remodeling. However, minerals such as calcium are not only stored in the bone, they also serve the essential function of maintaining the bone structure to provide its characteristics essential to movement (rigidity, strength, and elasticity) (78). Supplementation in vitamin D and minerals, such as calcium, phosphate and magnesium, is essential in this population as more than 70% of survivors fall short of the recommendations (vitamin D: 200IU, calcium: 1300mg, phosphorus: 1250mg, and sex- age-specific recommendations: potassium: 4500 to 5400mg and magnesium 240 to 410mg), even 5 years after treatment completion (79). Further, in cases of hypocalcemia, patients can receive calcitriol, an active form of vitamin D (i.e., 1,25(OH)2D3; (76)).

Adjunct Exercise Therapy

The option of increasing levels of physical activity and function in patients and survivors has been explored in other studies, either by observing retrospectively the level of physical activity and its association with BMD (80,81) or by performing prospective interventional programs with the objective of observing differences in BMD (7,82). Despite the retrospective observational studies reporting an association between level of physical activity and BMD, the interventional studies were unable to demonstrate that exercise would be a tool to improve bone health. Therefore, the impact of exercise on bone integrity has not reached the level of evidence required to be prescribed clinically in response to low BMD. The rationale behind these prospective studies is to impose an incremental maximal force on the bone by gradually increasing the exercise modalities (frequency, duration of sessions, intensity). Physical or mechanical stimulation, such as vibration stimulation or exercise, has been investigated for its potential benefits on bone physiology in healthy and pathological populations, however, only one RCT study on the usage of low-magnitude high-frequency mechanical stimulation (i.e., vibration platform) has shown a positive effect on BMD in PHM patients, compared to patients receiving a placebo intervention who had a decrease in BMD (6). Another RCT study, by Hartman et al. (2009), aimed to demonstrate that exercise, as mechanical stimulation, may prevent a reduction in BMD for ALL patients during treatments. However, the study did not report any differences between the intervention and standard care groups, which authors attributed to the poor adherence rate (7).

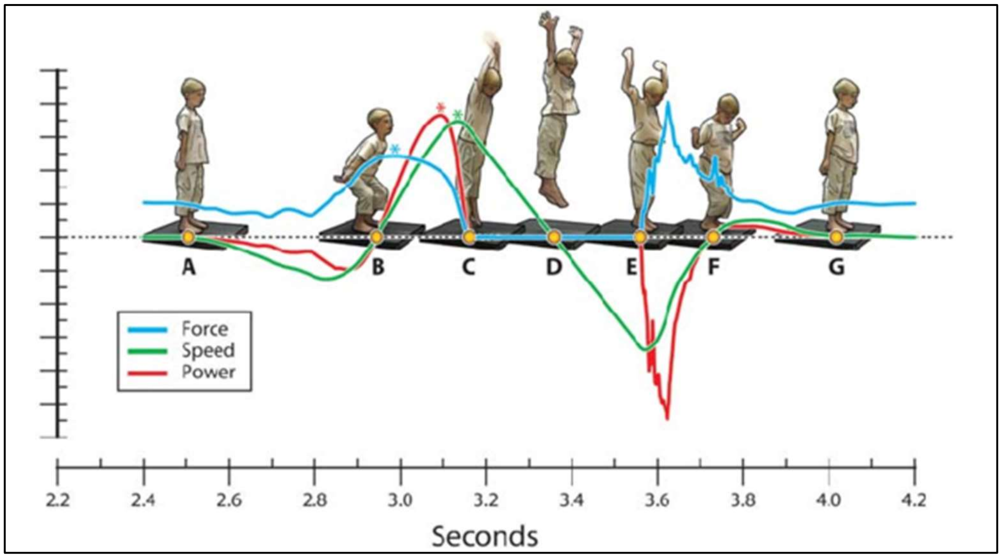

Figure 1. Mechanotransduction stimulation to induce periosteal apposition by imposing incremental maximal force on the bones (83)

Specific exercises have been recognized to be efficient in improving maximal muscle forces in other populations. In fact, plyometric exercises (i.e. jumps) stimulate osteogenesis in two ways: first, with an acute effect of creating maximal forces and unfavorable lever arms in reaction to ground force resistance upon landing the jump; and secondly by building muscle mass, which will increase all muscle contraction forces applied to the bone in a chronic effect. In addition, exercises with a component of dorsiflexion of the foot should be given priority, as the latter is a generalized weakness in the ALL population (84,85).

2.5. Current Approaches in Adjunct Exercise Interventions for the Management of MSK Deficits

There are only a handful of studies reporting the impact of physical activity on MSK health in ALL patients and survivors. Interventions vary between phases of treatment or survivorship, duration, frequency, and objectives. These differences between studies, in addition to bone adaptation time, make it difficult to draw conclusions related to the efficacy of such programs. The following section reports the few interventional studies that were found to report either bone health or muscle function outcomes.

To our knowledge, only two studies assessed the impact of a home-based exercise program on bone health throughout treatment (7,82). The RCT study by Hartman et al., published in 2009 (7), compared patients, aged one to eighteen years, within a group assigned to home-based exercise (n=25) with a control group following standard care (n=26), and failed to show any added benefit on bone health for the intervention group. The intervention involved physiotherapy sessions at the hospital every six weeks for the whole trial, in addition to a home-based exercise program. The authors attributed the lack of effect of the program to the low adherence: 11% of patients exercised daily, 37% exercised more than once a week, 16% exercised once a week and 36% exercised less than once a week (7). Taken altogether, results from these studies suggest that adherence rate may be a key element in evaluating possible bone health improvements in PHM patients in maintenance or early-on remission. The RCT study by Cox et al. published in 2018 (82) aimed to improve BMD of patients aged [4 to 19[years, for a duration of 2.5 years from diagnosis. The patients were randomized within the first 10 days to either the intervention or control group: the intervention group (n=53) received a) in-hospital, or clinic, appointments with a physiotherapist (1st month: weekly; 2nd month: every other week, and monthly for the rest of the 2.5-year trial) and an advance practice nurse for behavior-change strategy (1st month: biweekly; 2nd month: weekly, and monthly for the rest of the 2.5-year trial), and b) a home-based exercise program to perform 5 days a week (30 minutes per session) independently or with parental support, whereas the control group (n=54) received usual care. Only 62% of patients and parents in the intervention group (n=33) completed all four physical performance and HRQL evaluations (baseline, 2-month, 3.75-month, 2.5-year), which was similar to 76% in the control group. The results of this study (82) are very similar to the previous study (7) reporting results of bone health in ALL during treatments: the authors did not report a difference on the lumbar spine BMD, evaluated by DXA, or in the level of physical activity, evaluated through the use of an accelerometer worn for 7 days prior to each assessment. To this extent, their results aligned with the previous study concerning low adherence, as they documented a decrease in vigorous exercise from 37 to 16 minutes throughout the trial.

Both studies addressing bone health were, however, a) not specific to the context of early survivorship and b) not able to provide program structure towards achieving good adherence rates for exercise interventions. Thus, the following interventional exercise studies reporting muscle functions may be able to provide insight to draw conclusions on program modalities inducing high adherence:

Table 1: Interventional Studies Reporting Exercise Program Modalities, Efficiency, and Feasibility and/or Adherence.

Authors, Year	**Design, Inclusion Criteria and Groups**	**Modalities of Programs**	**Program Efficiency: MSK and Functional Results**	**Feasibility and Adherence**
Marchese et al., 2004 (10)	*RCT study* Inclusion criteria: patients aged 4 to 15 years; during the maintenance phase of the treatments Groups: Intervention, n=13; Controls, n=15.	Duration: 4 months Modalities: • Home-based exercise program regimen: - aerobic (7 days/week), - lower-limb strength (3 days/week), and - stretching (5 days/week). • Five sessions of in-person physical therapy.	• Increased knee extensors strength, • Increased range of motion for ankle dorsiflexion. No improvement on cardiopulmonary function.	The authors were unable to quantify the adherence: • Patients did not consistently log their activities, and • Patients did not wear their heart monitor, as they found it "inconvenient and uncomfortable".
Keats and Culos-Reed, 2008 (86)	*Feasibility study* Inclusion criteria: pediatric cancers patients in treatment, and survivors, aged 14 to 19 years. Group: Cohort, n=10.	Duration: 4 months Modalities: • University-based exercise program: first two months 1 session /week: - education: 30 minutes, - aerobic: 45 minutes, - core strength and flexibility: 15 minutes. And two months of various physical activities. • All interventions were grouped .	Improvements after the 4-month program, compared to the baseline evaluation: • Upper body strength, • Lower limbs flexibility, • QoL.	Adherence: an average 81.5% attendance rate (ranging from 64 to 100%).
Takken et al., 2009 (87)	*Feasibility study* Inclusion criteria: ALL survivors aged six to eighteen years. Group: Cohort, n=9.	Duration: 3 months Modalities: • Community-based exercise program 2 sessions/week at a local physical therapy clinic (45 minutes): - aerobic, and - strength. An additional 2 times/week home-based program.	No significant difference in muscle and cardiopulmonary functions and fatigue.	Feasibility: • Five patients abandoned the trial within the first three weeks after baseline; • The most common reason for abandoning was that patients felt biweekly appointments were "too physically demanding and/or difficult to

		• The program included an objective for each month (1st month: increase muscle strength; 2nd month: increase aerobic cardiopulmonary function; 3rd month: interval training).		combine" with other activities (n=3). • Participants completing the program mostly considered the trainings in clinic "fun but demanding" but considered the interventions at home "boring and demanding". Adherence: an average 14.8 hours completed out of 24 possible hours of intervention (n=4).
Tanir and Kuguoglu, 2012 (88)	*RCT study* Inclusion criteria: ALL patients aged 8 to 12 years and within their first remission. Groups: Intervention, n=19; Controls, n=21.	Duration: 3 months Modalities: • Home-based exercise program: - stretching 5 times/week, - muscle strength 3 times/week, - aerobic 3 times/week. Included an initial exercise session supervised at the hospital, with a parent for support and motivation, and two additional home visits. • Phone calls (twice during the first month and once for the following months).	Improvements from baseline to post-intervention evaluation in: • Flexibility, • Muscle function and • Cardiopulmonary functions	The authors did not quantify the adherence: • "[patients] had performed the exercises regularly and marked their progress on the exercise worksheet".
Esbenshade et al., published in 2014 (89)	*Pilot study* Inclusion criteria: ALL patients, aged 5 to 10 years, during the maintenance phase of treatments. Group: Cohort, n=17	Duration: 6 months Modalities: • Home-based intervention program 3 days/week (30 to 45 minutes/session): - stretching, - muscle strength, and - aerobic exercises. And an additional 3 days/week of general physical activities. • Written exercise prescription personalized to patients' ability and access to Internet-based videos of the exercises.	Improvement reported in: • Muscle function and • Cardiopulmonary functions.	Feasibility: n=12/17 patient completed the program. Adherence: adherence rate of 81.7 ± 7.2%.

		• Called weekly by a research team member.		
Saultier et al. , 2021 (90)	*RCT study* Inclusion criteria: pediatric cancer patients aged 5 to 19 years, enrolled in the study on average a year after diagnosis. Groups: Intervention, n=41; Controls, n=39.	Duration: 6 months Modalities: • Hospital-based adapted physical (30 sessions, 30 to 90 minutes each): - muscle strength, - balance, and - proprioception exercises. And multi-activity sessions (15 sessions, 90 to 240 minutes each). • 20 days of preparation, two 2-day stays, and one 5-day stay at an outdoor camp. • Gender- age- and disease-sub-grouped interventions.	The intervention group revealed significant improvements compared to the controlled group at the six-month evaluation: • Upper and lower limb strength, • Trunk and abdominal muscle endurance, • Flexibility, and • Distance walked during six minutes.	The authors did not report the mean adherence rate or missed sessions to either in-hospital sessions or the multi-activity sessions. Feasibility: • The authors discussed that the program "evaluated shorter intervention, decreasing the risk for loss of follow-up and lack of compliance".

2.6. Barriers in Adjunct Exercise Interventions for the Management of MSK Deficits

The studies in Table 1 show a large variety of study designs, intervention modalities, objectives, and evaluation modalities, which complicates the interpretation of the results in view of establishing the role of exercise as a mechanical stimulus in order to improve the MSK health of ALL patients and survivors. The review of the literature underscores the importance of patient adherence in order to demonstrate efficacy of exercise interventions. There is therefore a need to recognize and address the barriers to adherence for this population.

Barriers and Facilitators to Home-Based Adherence

Traditional home-based exercise programs have been under scrutiny for some time for their association with multiple barriers to adherence (91), and therefore their efficacy. The barriers reported in the literature, with strong evidence, are a) not having time for exercise, b) forgetting to exercise, c) daily stress, d) having negative cognitions or emotional experience. However, in addition to overcoming these barriers, people receiving an exercise prescription to perform at home may need intrapersonal or interpersonal facilitators. There are many intrapersonal factors strongly associated with good adherence to a home-based program (e.g., perception of health status, perceived ability to complete the program, intention to adhere, and/or self-motivation, history of adherence, and current physical activity level), but limited interpersonal factors (i.e., support such as social support and guidance). These barriers and facilitators were the results of a systematic literature review by Essery et al. (91) involving studies with participants older than 14 years receiving physiotherapy for various conditions. The authors conclude that interventions done by practitioners should aim to address patients' individual barriers and enhance facilitators in order for patients to adhere to and reap full benefits from the interventions.

In addition, a systematic review published in 2018 by Stout et al. provided evidence on the subject of supervision of exercise programs in cancer care in relation to the efficacy. The authors discussed that supervised programs had a better effect on health than unsupervised programs, such as traditional home-based programs. They attributed this improved efficiency to the individual attention from healthcare professionals to patients, prompting better-controlled volume of exercise (92).

In the field of pediatric home-based exercise programs, involving parents has become common practice. Despite this, there is minimal research on the role of the relationship between the parents and healthcare providers on the adherence to exercise programs. A study by Medina-Mirapeix et al., published in 2017 (93), investigated predictors of adherence to home-based exercise programs for parents of children with disabilities. Their results showed that low perception of barriers, high knowledge and ability, and high self-efficacy were predictors of adherence to frequency and duration of sessions and that social support was an additional predictor of frequency. The results of the study also informed on the healthcare providers' behaviors that may prompt higher adherence. Providing information to the parent about the child's progress and the usefulness of exercises, in addition to providing instructions on how to insert exercise into the daily schedule, and following up on treatment by verifying the acquisition of skills and inquiring about adherence were all predictors of adherence to frequency. High satisfaction of the parent with the attention provided by the healthcare professional may also possibly have a role to play on adherence to the frequency of home-based exercise programs. The authors of this survey study mention that this highlights that factors influencing adherence to programs for parents of children with disabilities may be different than for people receiving programs for themselves. The statement that barriers and facilitators to intervention may be population-specific was highlighted in the comparison with a study with pediatric cancer patients in treatments where the main barriers to exercise reported by patients' caregivers were feeling unwell, lack of time, and low motivation (94).

The large variety of population-specific barriers and facilitators mentioned above prompts the question of what are the factors to adherence of ALL patients and survivors that future exercise programs in pediatric oncology should address for patients to access their full benefits?

Barriers and Facilitators to Intervention in Pediatric Oncology Survivors

Wu et al., in 2015 (95), explored the barriers and facilitators to healthy lifestyle modification in adolescent and young adult survivors of pediatric cancer and their supporters. The main barriers to exercise and healthy eating mentioned in this study were the lack of financial and professional resources, the negative thoughts and emotions related to healthy behaviors, and the negative interpersonal influences. Concerning the lack of resources, the participants had a hard time finding professionals tooled to address their specific needs, and that many resources available would be too general to be useful to their specific situation. Survivors further explained the negative thoughts and emotions towards exercise as they "felt ''depressed,'' ''embarrassed,'' and "frustrated" about not being able to do physical activities in the same way as before cancer", in addition to fatigue preventing them from exercising. They also mentioned the difficulties of having people with different health goals in their surroundings, and everyone pushing advice onto them, to explain the negative interpersonal barriers to exercise and healthy eating. Nonetheless, the survivors mentioned facilitators to healthy behaviors too. Cognitive motivators, tools for implementation of healthy behaviors, and social interactions were important facilitators for survivors. Related to the cognitive motivators, they mentioned that the desire to prevent future health issues or to gain control over their health again was a significant motivator to engage in healthy behaviors. They further elaborated on the role that tools, such as wellness programs or gyms, play in the implementation of actions towards their health. Lastly, they specified the important role of family and friends to adopt companionship behaviors when engaging in healthy behaviors. The survivors and supporters recommended that interventions specific to their situation be embedded in the continuum of care, as the transition from treatments to survivorship may be difficult. They also expressed their interest in receiving more information about LAEs and having access to survivor-specific exercise programs. They elaborated on two aspects for accessing such programs: firstly, to be able to interact with others who can relate, and secondly, to receive interventions tailored to their survivor-specific needs. The authors of the literature review, however, discussed the challenges of proposing such programs for survivors, as cancer patients and survivors are usually treated in tertiary care centers, potentially far from their home (95).

Moreover, in younger and earlier survivors, the completion of ALL treatment regimen for survivors does not signify that survivors do not experience lasting effects of the disease, treatments, and modified lifestyle. In fact, survivors are more likely to have exercise intolerance, pain, and fatigue (22,96,97) limiting them in the execution of daily tasks. More precisely, it has been reported in the literature that 21 to 59% of survivors may experience MSK pain (22,58). "Pain and fatigue contribute to a cycle of reduced activity, diminished strength and fitness, increased fatigue, and decreased quality of life." (82) Additionally, the completion of treatment adds the need for patients and their families to incorporate new challenges into their everyday life such as going back to daily activities (i.e., school or work), prompting more strain on family schedules and cohesion (98). The barriers to adherence to physical activities in the early ALLs may be influenced by the misalignment of patients' preferences and lasting effects.

It is well known that survivors prefer exercising in non-medical facilities, such as home or at school (99). Furthermore, a qualitative study conducted with children with disabilities highlighted that interventions in rehabilitation or occupational therapy should focus on enjoyment, capability, autonomy, and social involvement in order for children to experience meaningful participation in interventions (100). In this perspective, home-based programs may fulfill patients' preferences to not exercise in a clinical context, but the experience may not be as meaningful due to its inherent lack of social involvement and enjoyment (87), impacting negatively on adherence. In itself, social interactions could be achieved within the family, with peers, or with healthcare providers (95).

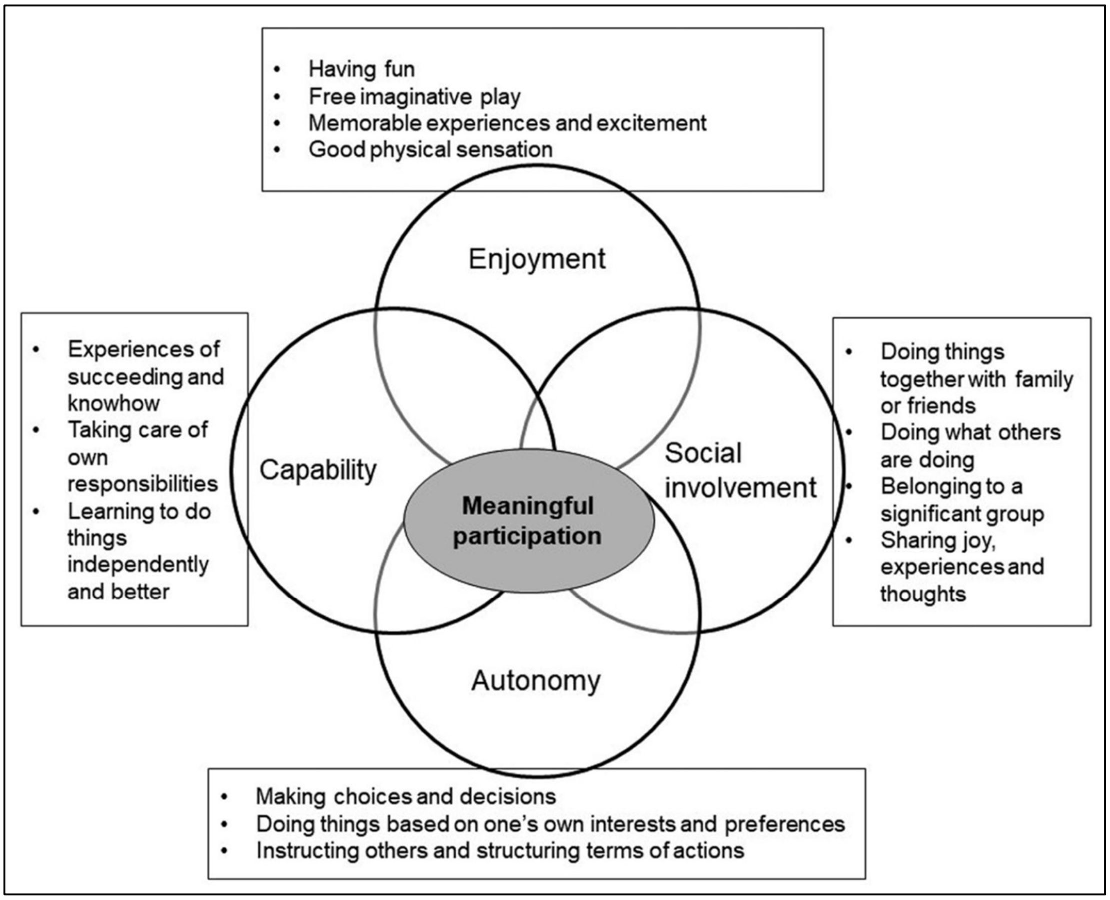

Figure 2. Elements in meaningful participation from the children's perspectives, from Vanska, Sipari, and Haataja, 2020 (100)

2.7. Telehealth: The Solution to Home-based Exercise Programs with Social Involvement?

Telehealth: The Definition

With advances in information and communication technologies in healthcare, telehealth has been shown over the years to be an important tool to provide assessment, education, monitoring, and deliver health care (101). Telehealth is defined as the distance delivery of health services to patients using communication technologies. It refers to many different types of asynchronous and real-time applications, such as websites, mobile/tablet apps, videogames, social media, wearable devices, or even virtual reality (102). With improved security of the telehealth platforms and Internet availability to several parts of the country, videoconferencing has attracted more interest. It represents an increasingly specific way to connect a patient with a provider for either real-time clinical evaluation or intervention. In the settings of a videoconferencing application, patients are closely supervised and can replicate what providers would otherwise do in on-site clinical conditions, but from the comfort of their own home. This has proven to be feasible and effective in the context of nutritional counseling (103), smoking and alcohol cessation programs, in addition to supervised deep breathing and relaxation exercise sessions(104). Along the same lines, the technologies can be used in the context of exercise interventions, aerobic, resistance, flexibility, and balance exercises can be directly supervised by a physical therapy specialist or a kinesiologist. Inappropriate posture and techniques can be corrected to improve the training effect and ensure safety (92). Patients living further away from their treating centers (95) or patients unable to travel (105) may benefit greatly from such innovations.

Telerehabilitation: Telehealth Applications in Rehabilitation Services

The field of telerehabilitation, for instance, has developed rapidly for the assessment and management of MSK diseases (106), chronic respiratory diseases (107), stroke, and other neurological conditions (108).

Interventions directly supervised, i.e. videoconferencing, coupled with digital support, e.g. a training watch, can capture patients' progress through the intervention, using functional and self-reported outcome measures throughout the duration of the intervention to obtain an optimal image of the patient's progression. Several studies and systematic reviews have shown the value of telehealth in improving access to care with an emphasis on functional outcome, quality of life, and cost effectiveness (109–111). Videoconferencing has been established as a reasonable non-inferior alternative to face-to-face therapy (112,113). Equal access to services is paramount and can be facilitated with costs potentially decreased (111).

A study reporting the patient's perspective, by Moffet et al. published in 2017(106), stated that patients value their relationship with the therapist through videoconferencing, and foster a sense of safety and support. Patients are satisfied with the service, as they feel more engaged and resilient (106).

However, three limitations in the literature highlight gaps for future research. Firstly, the need for more adequately powered studies using more robust methodological rigor in minimizing the risk of bias

(106). Secondly, while emphasis has been on the delivery of long-term physical therapy for chronic conditions, other areas of clinical practice have not been adequately investigated. This especially applies to the pediatric population who may not be able to attend regular in-hospital exercise programs (108). Lastly, some have expressed concerns about the security of the platforms used to protect confidential information and patient privacy. A systematic review has shown that a large majority of studies published in telehealth did not use, or mention, secure platforms (108). This could be explained by variable local regulations, in addition to specific research needs. However, the review encouraged emerging research to focus on system outcomes (114) such as cost-effectiveness and health outcomes that are important for the patients.

Telerehabilitation in Pediatric Cancer

As Internet services are becoming increasingly available at low cost, families of sick children are able to keep in contact with their family, peers, and healthcare team. Given the current COVID-19 situation, in times of social isolation of patients and survivors of cancers, telehealth-delivery exercise programs could serve as a safety net to provide health interventions at home using technologies already available to patients and their families (115).

Limited studies have been reported on the use of asynchronous telehealth delivery of exercise programs for patients or survivors of childhood cancer (10,89,116), and not in real-time telehealth delivery with direct training supervision. Further, only one active living 10-week program (i.e., consisted of loaning training watches and using a support group for adolescents and young adults, survivors of pediatric cancers) formally documented qualitative acceptability of the technologies (116).

Telehealth may be an ideal tool to provide patients with grouped and supervised interventions from the comfort of their home while providing social involvement, essential to having a meaningful experience (95,100). Telehealth-delivered programs may also be able to address population-specific needs and barriers to interventions, such as MSK pain (22,96,97), in order to increase patients' adherence to exercise programs (117).

2.8. Research Questions

Hence, it can be observed that the combination of the disease, the treatments, and the lifestyle changes happening during and after the treatments of ALL may lead to MSK LAEs. Hematological malignancies originate in the bone marrow, in the trabecular compartment, and are therefore the target site of cancer therapies. However, previous non-pharmacological options to limit the MSK LAEs, such as physical activity interventions, are very limited in the literature and accompanied by important limitations related to the adherence of participants. Studies about patients' and survivors' preferences regarding practicing physical activities note that they would rather exercise at home, school, or in a gym, more so than at the hospital or a physiotherapy clinic (99). However, the preferred modalities, traditionally not supervised by healthcare professionals, may also prompt low adherence to the programs (7,117,118), and are associated with lower effects of the exercise program (92). This prompts the need to assess if telerehabilitation could be used to deliver exercise programs to survivors of ALL.

This thesis will answer the following research questions; the first manuscript will answer questions 1 and 2, whereas the second manuscript will answer question 3:

1. Is it feasible to deliver a 12- to 16-week group home-based plyometric and resistance exercise program to early survivors of hematological malignancies using a telehealth system?
2. Can such a program be beneficial to the functional or MSK health of its participants?
3. What will be the participants' perspective of the modalities of intervention (i.e. telehealth system, patient-parent paired interventions, group approach, supervised training) and their perceived benefits?

Chapter 3 – First Manuscript

Title. *Home-Based Telehealth Exercise Intervention in Early-On Survivors of Childhood Acute Lymphoblastic Leukemia: a Pilot Study*

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Abstract:

Background: Acute Lymphoblastic Leukemia (ALL) is the most common type of pediatric cancer. ALL causes an altered bone-mineral homeostasis state, which can contribute to osteopenia, and bone fractures, most commonly vertebral fractures. With the increasing number of childhood cancer survivors, late adverse effects (LAEs) such as musculoskeletal comorbidities are often reported, and are further influenced by inactive lifestyle habits. Physical activity has been shown to increase mechanical workload to the bone, mitigating the bone impairment in other cancer-specific populations.
Objectives: This interventional pilot study proposes investigating (1) the use of telehealth to deliver home-based exercise intervention for early-on survivors of bone marrow-related hematological malignancies, and (2) assessing its impact on survivors' musculoskeletal and functional health.
Methods: The study aimed to recruit a group of 12 early-on survivors of ALL, within 6 months to 5 years off treatment to participate in and complete the proposed telehealth intervention with a parent. The 16-week intervention included 40 potential home-based physical activity interventions supervised by a kinesiologist through a telehealth Internet platform, with monthly progression. Patients could be recruited for the cohort if they were able to join the intervention during the first month (minimum 12 weeks of intervention). Evaluation before and after the intervention protocol highlighted differences in functional capacities and musculoskeletal health of patients using Mechanography, pQCT, six-minute walk test (6MWT), and grip force test.
Results: The recruitment rate for the intervention was low (21%), with 12 patients recruited. Three patients were excluded (1=relapse; 1=failure to meet technical requirements, and 1=abandoned). The nine patients who completed the intervention (6 girls; 10.93±2.83 years; BMI: 21.58±6.55; time since treatment completion: 36.67±16.37 months) had a mean adherence of 89%, and a completion rate of 75%. Additionally, these patients showed functional improvements in lower-limbs muscle force and power, as well as for the 6MWT distance. Participants also showed improved bone health post-intervention on the following parameters: BMC, SSI, total and cortical CSA at the 14% (P=0.03, P=0.01, P=0.01, & P=0.001, respectively) and 38% sites of the tibia (P=0.003, P=0.04, P=0.001, & P=0.003, respectively).
Conclusions: High adherence and participation rates suggest telehealth is a feasible way of delivering exercise interventions to young ALL early-on survivors. The proposed intervention seems promising in providing benefits to patients' functional performance and bone health, but a larger-scale study would be needed to confirm this assumption.

Keywords:

Exercise therapy, Rehabilitation, Acute Lymphoblastic Leukemia, Intervention study, Telehealth

Introduction

Acute Lymphoblastic Leukemia (ALL) is the most common cancer type among the pediatric population. Over the past 50 years, the survival rates for pediatric hematological malignancies have increased significantly from almost zero to over 80%, due to scientific advancements and improved therapeutic protocols [1]. Consequently, there are increasing numbers of survivors likely to experience long-term effects of the disease, treatment toxicities and increased inactive life-style [2, 3]. Further, the specific immune cells of ALL originate from the stem cells in the bone marrow. Therefore, it is not surprising that the disease, the treatments, and the modified lifestyle habits contribute to comorbidities and late adverse effects (LAEs) of the musculoskeletal system in long-term survivors [4]. Among these comorbidities, a decrease in muscle strength [5], bone mass [6, 7] and an increased prevalence of vertebral fractures [8, 9] have been reported. These musculoskeletal adverse effects can be apparent upon initial diagnosis, increase in severity during the acute phase of treatment [9], and remain present [10], or appear during remission [11] and survivorship [12, 13].

Physical activity and exercise provides physiological and mechanical stimulations proven to be beneficial for muscle and bone health [14] as well as for the cardiovascular system [15]. Specific types of exercises such as plyometric (defined as high impact, e.g. jumps) and resistance exercises have been shown to decrease bone impairments in other cancer populations with bone-specific deficits (breast and prostate cancer) [16]. Therefore, an exercise rehabilitation intervention administered to early-on survivors of hematological malignancies, with plyometric and resistance exercises aiming at improving muscle function and bone strength, could limit the long-term musculoskeletal LAEs reported in long-term survivors.

Medical follow-up visits for ALL survivors are generally done 1-4 times/year in pediatric oncology centers, limiting the feasibility of an in-clinic exercise intervention. In that regard, studies have shown that patients and survivors would rather exercise at home, school or a gym, than at the hospital or at a physiotherapy clinic [17, 18]. For these reasons, home-based exercise interventions have been considered the most appropriate method of intervention for this population. Only a few studies have addressed the effects of home-based exercise intervention on muscle function of children with ALL in maintenance or early-on survivorship, with equivocal results. In a study by Tanir and Kuguoglu [19], a home-based physical exercise intervention was provided to the patients for a three-month duration, with muscle strength, aerobic and stretching exercises. Results showed significant improvements in flexibility, muscle and cardiopulmonary functions. Similarly, a study by Esbenshade et al. [20] yielded similar results for a six-month home-based exercise intervention. In contrast, a study by Marchese et al. [21] and another one by Hartman et al., showed only minor improvements in muscle functions (increased knee extensors and ankle dorsiflexors strength) [21], and no improvement on cardiopulmonary function [21] and bone health [22]. Both studies showing significant physical function improvements i.e., the Tanir and Kuguoglu and Esbenshade et al. studies, reported high adherence rates (81.7 ± 7.2% [20]), whereas the Marchese et al. and the Hartman et al. studies reported low adherence rates. Taken altogether, results from these studies suggest that ALL patients in maintenance or early-on survivorship can benefit from a home-based exercise intervention but that high adherence rates are required to achieve significant improvements on the musculoskeletal system.

Adherence rates tend to be lower in the absence of supervision in home-based exercise interventions. For example, both studies (Marchese et al. and Hartman et al.) showing minimal or no effect of the home-based exercise intervention, reported a minimal follow-up approach (between bi-weekly and monthly phone calls with sole objective to assess adherence) likely resulting in the reported low adherence rates [21, 22]. In contrast, both studies showing improvements following the home-based exercise intervention had set up stringent supervision (weekly or bi-weekly follow-up calls to discuss factors of adherence), leading to high adherence rates [19, 20]. In that regard, a recent literature review suggests that home-based exercised interventions with telehealth supervision improves adherence rates compared to no supervision [23] due to patients receiving positive reinforcement [24], improving on exercise technique [24] and feeling self-efficient [25]. Another potential positive impact of supervision is the greater overall volume of exercise achieved during individual sessions, which can be associated with better structured and controlled exercisd sessions under supervision, compared to no supervision [26]. These observations suggest that supervision from health care providers during home-based exercise training may help patients achieve higher adherence rates and obtain added benefits compared to no or minimal supervision.

Telehealth is defined as a method of delivering health interventions (e.g. physical activity, nutritional, psychological counselling) or follow-ups from a remote location through information technologies (e.g. Internet). The research field associated with telehealth has experienced significant growth in the last 10 years, leading to an exponential increase in its application in light of the current COVID-19 global pandemic. Over the last decade, telehealth has been shown to be efficient in achieving high adherence rates compared to traditional home-based exercise intervention in patients with musculoskeletal, neurological, cardiorespiratory and various other conditions [27, 28]. However, to our knowledge, the present study is the first reporting feasibility of implementing a home-based exercise intervention with telehealth supervision in early-on survivors of pediatric cancer.

The primary aim of the present study is to assess the feasibility of implementing a home-based exercise intervention with telehealth-based supervision for early-on ALL survivors. Telehealth can be administered through various technologies. Desktops, laptops, tablets and smartphones all have capacities to provide and receive telehealth services. Although tablets and laptops provide mobility options compared to a desktop solution, the current study was designed to favor accessibility, and therefore, families were able to select the technology of their choice to receive the intervention, whether a fixed desktop, mobile phone or tablet. In addition, since having companions for exercising has been identified as a facilitating element in adherence [17], we grouped together patient-parent pairs with one or two other pairs. Feasibility of the pilot intervention was evaluated by assessing the completion and adherence rate of patients, in addition to occurrence of training adaptation due to participants' pain, and adverse events. It is hypothesized that direct supervision, possible through telehealth technologies, will lead to an adherence rate of 80% and a completion rate of 75% [15]. The secondary aim of the study is to explore the effects of the intervention on functional performance, muscle function and bone health. It is hypothesized that the intervention will lead to improvement in musculoskeletal and cardiopulmonary function.

Methods

Study Design and Recruitment

This prospective pre- and post-intervention cohort pilot study was initiated in 2018 at Sainte-Justine University Health Center to assess the feasibility of home-based exercise interventions with early-on survivors of hematological bone marrow-related malignancies treated under Dana-Farber Cancer Institute-ALL (DFCI) 2005 or 2011 protocols. As the research design was of a pilot interventional study, no sample size calculations were made, and a convenience sample of 10 participants for intervention completion was set as the aim. The initial inclusion criteria were: 1) diagnosis of ALL or B lymphoblastic lymphoma, 2) age between 6 and 18 years, 3) within 6 months to 5 years of treatment completion. Exclusion criteria were: unresolved fractures, unresolved avascular osteonecrosis, and bone marrow transplant as part of their treatment, physical or functional impairment at the time of recruitment were excluded. If patients had no or unstable Internet connection, they would further be excluded. Due to challenges in recruitment for the first cohort, a first amendment was submitted to the Ethical Review Board to increase the oldest age of eligibility from 10 to 14 years. Due to recruitment challenges remaining present in the second cohort, a subsequent amendment was submitted to further increase the age range to between 6 and 18 years, in addition to modifying the criterion of time since treatment completion from between 6 months and 2 years to between 6 months and 5 years. Patients could be included in a cohort if they joined the exercise intervention within the first month of the intervention in order to receive between 12 and 16 weeks of intervention.

Patients were screened for eligibility by the hematology oncology service medical team (nurses and physicians) at Sainte-Justine University Health Center.

Healthy, age- and sex-matched participants were retrospectively added as controls for the muscle function and bone analyses. Due to the retrospective nature of this cohort, participants in the control group were not subjected to the intervention, and muscle and bone data were available at only one time point. These controls were drawn from our local historical database including healthy siblings of patients and hospital staff's children who were part of a previous study. Control participants were selected only based on sex and age to avoid any selection bias, for example in selecting patients who would decrease the difference between controls and patients in muscle and bone parameters.

Sainte-Justine University Health Center's Institutional Review Board approved the study (2018-1555: e-S@@VIE). Parents of patients below 18 years of age provided signed informed consent; patients between 6 and 17 years of age provided informed assent. Families were contacted over the phone to provide details of the project and check for interest. If they were interested in the study, a baseline evaluation was scheduled.

Study Procedures

The study procedure was divided into four phases: 1. baseline evaluation, 2. home-based visit, 3. intervention, and 4. post-intervention evaluation.

Baseline Evaluation: After informed consent/assent was provided, patients completed baseline (and post-intervention) measurements at two pediatric health care centers in the Montreal area: Sainte-

Justine University Health Center and Shriners Hospital for Children – Canada. The baseline and post-intervention visits schedule followed the same pattern: at Sainte-Justine University Health Center, patients' weight and height measurements were taken, and six-minute walk test (6MWT), upper limbs grip force test and lower-limb mechanography evaluations. All the participants were assessed by the same trained evaluator (GL). At Shriners Hospital for Children, patients underwent bone imaging testing (peripheral Quantitative Computed Tomography; pQCT).

Home-Based Visit: Following the baseline evaluation, a kinesiologist visited the families in their home to help them prepare for the intervention. The kinesiologist delivered material to the patients: an exercise step, a training elastic, a weighted 5-pound ball, a training watch (Polar A370, © Polar Electro Oy 2020, Polar FlowSync 3.0.0.1337, Finland) and its charger. At the same time, an assessment was done for the suitability and safety of the space (1.8m^2 of free space required). Support was provided for the installation of the software (for the watch and the videoconferencing system) on their own technologies (tablet, laptop, and computer) [29].

Intervention: All home-based exercise interventions were done through a teleconferencing system (Zoom license Pro, Zoom Video Communications, Inc., USA) with the kinesiologist at the hospital center and the study patients and their parents in their home. This system was chosen because it provides encrypted communication between the kinesiologist and the families compliant with the Canadian federal law on privacy for companies, the "Personal Information Protection and Electronic Documents Act" (PIPEDA). Families were sent an email in the 24 hours before every training with the link to connect to the virtual "meeting room" for their respective group. Interventions were live interactions enabling direct supervision and immediate correction or adaptation of the exercise intervention when needed (for safety purposes). Study patients were divided into three groups of two families and two groups of three families based on language (English or French), age and availabilities. Three cohorts were supervised at different times (May-August 2018, January-April 2019, September-December 2019). The original 16-week intervention included a progression every four weeks. Week 1 to 4 involved 2 sessions of 35 minutes per week. There was an additional five minutes of training per session during weeks 5 to 8, i.e. 2 sessions of 40 minutes/week. During weeks 9 to 12, one session was added every week, i.e. 3 sessions of 40 minutes/week. Lastly, during weeks 13 to 16, an additional 5 minutes were added to each of the 3 sessions per week, bringing the duration to 45 minutes per sessions [30]. For the first 8 weeks, training sessions occurred on weekday evenings and for the last 8 weeks, a third training session was added either on weekday evenings or on a weekend day. The general organization of a training session was as follows: a 5-minute warm-up, followed by whole-body resistance exercises (of progressive duration through the 16-week intervention) and finally 5 minutes of stretching. The resistance exercises part of the trainings was composed of whole-body exercises (e.g. push-ups, squats, deadlifts, etc.), combined with plyometric exercises (e.g. drop jumps, hopping, jumping lunges, etc.). Training sessions and exercises were adapted according to the participant's pain report. The pain was evaluated at the beginning and end of the session, in addition to during sessions when pain was present at the beginning of the session. The pain was assessed on a scale from 0 to 10 (NRS-11 [31]), a description of the perception of pain (sensation and location) and its evolution through time and movements. The adaptations were personalized according to the location and intensity of the pain. For example, patients with moderate knee pain would not do impact exercises such as "high-knees jogging" but would do low impact exercises such as "walking" or no impact with "chair squats" or "calves raise" instead.

Post-Intervention Evaluation: The same evaluations assessed at baseline were performed at the end of the home-based exercise intervention, in the same context as the baseline evaluation.

Outcome Measures

Primary Endpoints: Feasibility

To determine feasibility of administrating a home-based intervention through telehealth to this population, recruitment rate and reasons for declining participation, as well as mean adherence and completion rates to the intervention, were computed. Recruitment rate was defined as number of consented patients divided by contacted potential patients. Adherence rate was defined as the number of sessions attended by the patients divided by the total of possible sessions. Individual reasons for missing sessions are reported. Additionally, the specific information-technologies (tablet, mobile phone or computers) used for the interventions was reported for each household. Completion rate was defined as number of patients who finished the intervention divided by the total number of patients consented. The number of training sessions that required adaptation due to pain of the participants were recorded. Lastly, the nature and extent of adverse events during the training sessions was assessed by the kinesiologist, according to the type and severity of event defined as potentially sequelae in the study by Ory et al. [32].

Secondary Endpoints: Functional Performance and Bone Health

Muscle Parameters: Mechanography and Grip Force Test

Mechanography is a technique developed to investigate lower-limbs' muscle function using a ground reaction force-measuring platform (Leonardo Mechanograph Ground Reaction Force Plate; Novotec Medical GmbH, Pforzheim, Germany). Forces were recorded over time at a sampling rate of 800 Hz. All parameters reported here were derived from these force-time data using proprietary software (Leonardo Mechanography GRFP Research Edition software, version 4.2-b05.53-RES; Novotec Medical GmbH) (28).

Two tests were done using mechanography: the single two-legged jump test (S2LJ) for maximal power and the multiple two-legged hopping test (M2LH) for maximal force. The methodology is described in detail elsewhere [33, 34]. Briefly, the S2LJ is a countermovement jump and maximal power (kW), and maximal relative power (W/kg) are the main outcome parameter for this test. The M2LH test consists of hopping on the forefeet with stiff knees and without the heels touching the ground (similar to skipping rope). The M2LH provide information about near maximal ground reaction forces during eccentric contraction generated by patients. Relative muscle force (calculated in multiples of body weight) has been identified as the main parameter of this objective as it is strongly associated with bone strength [35]. Participants were asked to perform three trials of each test. A trial for the S2LJ consisted of performing one jump whereas a trial for M2LH consisted of ten consecutive hops. In case the trials were not done properly, an additional two trials were attributed to acquire three valid test results. The trial with the highest peak power and peak force for the S2LJ and the M2LH, respectively, were selected for analysis.

The grip force test was done using a handgrip dynamometer (JAMAR Hand Dynamometer, Jamar Technology Inc., USA); this test evaluates the maximal isometric force of upper limb muscles. The patients were instructed to stand, feet shoulder-width apart, with arms in neutral resting position on both sides of the body. They were then given a dynamometer that had previously been fitted to the individual patients' hand. Finally, patients were instructed to press as hard as possible on the handle until they were told otherwise. The test was performed one arm at a time, both sides repeated twice, and the best result of both sides was selected as the participant's result. A dynamometer provides force data as kilograms (kg), and the evaluator was instructed to round the result to the nearest kg [36].

Scores were calculated based on grip force test-references data to compare the patients' results to a healthy sex- and age-specific population [37].

Cardiopulmonary Function: Six-Minute Walk Test (6MWT)

6MWT evaluates the ability of an individual to maintain a moderate level of physical activity over a six-minute period [38]. Therefore, the result of the 6MWT is reflective of the patient's daily activities [39]. The 6MWT correlates significantly with VO_2max in typically developing children, in addition to patients and survivors. This indicates that these two tests measure related functional capacities [39-41]. Study patients followed the instructions from the American Journal Respiratory and Critical Care Medicine published guidelines (2002): to walk back and forth in a hallway, between 2 cones distanced by 30m, for six minutes as fast as possible, at a pace that would make them tired by the end of the walk; encouragement and feedback are given every minute. During the test, patients can rest if needed. Expected results equations are available for calculating percent of age- and gender-specific norms [42]. The 6MWT has been shown to be reliable and valid in normal developing (2-4 weeks apart between test and re-test) and obese children (same day test-retest), with a reliability reported from 0.73 to 0.949 [40, 43]. Expected results were used to compare the results of the patients to a healthy sex- and age-specific population ("Equations to predict the 6-minute walk distance in children and adolescents" [42]).

Bone Health: Peripheral Quantitative Computed Tomography (pQCT)

PQCT was performed on the left tibia, unless there was medical history of fracture to that bone, using the Stratec XCT2000 (Stratec Inc, Pforzheim, Germany). The method is described in detail elsewhere [44, 45]. The lower leg was scanned at 4 (metaphysis, trabecular bone), 14 (metaphyseal-diaphyseal transition site, cortical bone), 38 (diaphyseal transition site, cortical bone), and 66% (Muscle parameters scan; midsection of the gastrocnemius muscles, therefore being the largest outer calf diameter; [46]) of tibia length, measured as the distance from the reference line. The tomography images were then ranked on the movement artefact scale from one to five, one being an image without artefact and 5 being too much movement to have a proper image. Scans scoring three or less were deemed usable. If the scan scored four or five, the test was redone [47].

The main bone outcomes parameters of pQCT analysis at the tibia are measured at the 4, 14 and 38% sites. The following parameters are measured: total bone cross-sectional area (Total CSA; mm^2); cortical bone cross-section area (Cortical CSA) excluding marrow space (Cortical CSA; mm^2); the bone mineral content (BMC) per millimeter of cross-sectional slice thickness (mg/mm;); total volumetric bone mineral density (vBMD; mg/cm^3); the trabecular cross-section (Trabecular CSA; mm^2 4% site only); the trabecular volumetric bone mineral density (trabecular vBMD; mg/ cm^3; 4% site only); the cortical volumetric bone mineral density (cortical vBMD; mg/cm3); the polar stress-strain index was assessed as a surrogate of bone strength (SSIp; unit: mm^3). The two main pQCT muscle outcome parameters are measured at the 66% site: muscle cross-sectional area (Muscle CSA; unit: mm2; 66% site) and muscle density (Muscle Density; unit: mg/cm3; 66% site) [44].

Statistical Analysis

As this study was a pilot study with the purpose of investigating feasibility, no sample size calculation was performed. Normality of the data was tested using Shapiro-Wilk Test (n=9) [48]. Mean and standard deviations were reported when data were normally distributed, and median and range were reported when normality assumption was violated.

To assess feasibility, the recruitment, completion and adherence rates were analyzed. A one-sample Wilcoxon Signed-Rank test was performed on the adherence rate of patients with a set threshold of 80%, based on the hypothesis. The threshold was based on a study involving home-based distance-delivery exercise interventions administered to ALL patients in remission, which showed an 80% adherence rate for a 75% completion rate [15].

To determine the effect of the exercise intervention on patients' functional and musculoskeletal health, pre- and post-intervention test results from the pQCT, mechanography, grip force, 6MWT were compared using Paired-Samples T-test, when data were normally distributed and the Related-Sample Wilcoxon Signed-Ranked test when they were not. In addition to these pre- to post- analyses, pQCT, mechanography and grip force [37] post-intervention results were compared to sex- and age-matched typically developing controls using Independent Samples T-tests (for normally distributed parameters) and Independent-Samples Mann-Whitney U Test (for parameters not normally distributed). Additional analysis included a One-Sample T-test analysis to determine if mechanography results were clinically significant, and were done by comparing patients' change in lower-limbs muscle function to the minimal detectable difference reported by Veilleux et al. [33]. For the 6MWT, an Independent-Samples T-test was performed on post-intervention distance traveled and expected distance of 6MWT from sex- and age-related calculations [42]. Patients' change in 6MWT distance were compared in a One-Sample T-test analysis to the standard error of 15 meters reported by Li et al. (2005) in order to establish if results were deemed clinically significant [40].

To assess the muscle-bone functional unit, a Spearman correlation, for non-normally distributed parameters, was performed. The correlation between maximal force (absolute; N) and bone mineral content at 14% of the tibia was established for both pre- and post-intervention patients' related data as well as for the typically developing controls [35].

All statistical tests were performed using the PASW Statistics software version 24.0, with confidence interval and significance level pre-set at 95% and .05, respectively (SPSS Inc., Chicago, Illinois).

Results

Feasibility and Baseline Characteristics

The recruitment flow chart is illustrated in Figure 1. One hundred four patients aged from 6 to 17.1 years within five years of complete remission were considered as potential participants. Among the 57 potential participants contacted, 12 patients (nine girls) provided informed consent or assent (see Table 1 for participants' clinical information), representing a 21% recruitment rate. The specific motive to decline participation was recorded in 12/45 refusals: a) parents' overloaded schedules (n = 2), b) the patients were deemed too active by their parents, as they engaged in other physical activities multiple times per week (n = 4), c) the patients did not want to come to the hospital for the evaluation (n = 2), or d) the patient did not find the idea of an organized training session interesting (n = 3).

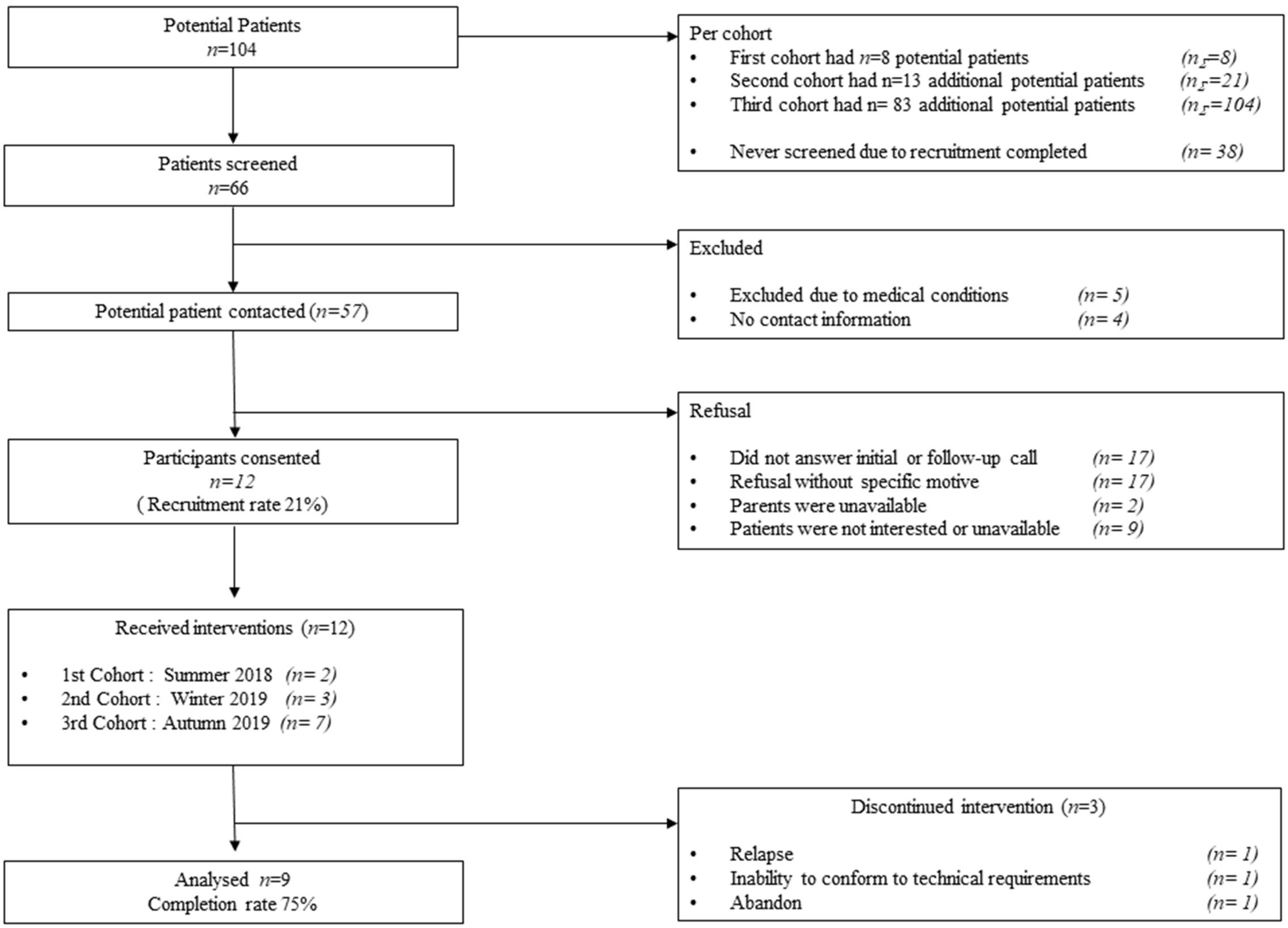

Figure 1. Recruitment process flowchart
n represents the number of individuals in the sampling; nΣ represents the summation of all potential participants at that timepoint.

Table 1. Clinical Information

	Baseline (n=9)	Post-intervention (n=9)	Controls
Age; years [a]	9.17 (8 – 14.5)	9.5 (8.25 – 15.1)	9.87 (7.48-14.72)
Sex, female; n (%)	6 (75%)	6 (75%)	6 (75%)
Height; cm [b]	143.27 (23.63)	145.19 (23.63)	146.03 (17.54)
Weight; kg [b]	46.92 (24.67)	47.88 (24.92)	40.71 (11.64)
BMI; kg/m^2 [b]	21.58 (6.55)	21.46 (6.53)	18.83 (3.39)
Diagnosis; n (%)			
Acute Lymphoblastic Leukemia	8 (89%)		
Lymphoblastic Lymphoma	1 (11%)		
Prognosis; n			
SR: HR: VHR.	6: 2: 1		
Time since end of treatment; months [b]	36.67 (16.37)		
Recurrence; n	1		
Treatment protocol; n			
DFCI-ALL 2005	2		
DFCI-ALL 2011	7		
Cumulative Dose of Glucocorticoids			
Dexamethasone [a]	352.00 (256 – 870)		
Prednisone [a]	390.00 (252.5 – 2199.5)		
Cranial Radiotherapy; n	1		
Duration of Hospitalization During Treatments; days [b]	44.89 (13.54)		
Musculoskeletal Comorbidities During Treatments; n			
Vertebral Fracture	4		
Osteonecrosis	1		
Non-Vertebral Fracture	2		
Osteoporosis	4		
Low Bone Mineral Density	8		
Received Bisphosphonates; n	4		
Cumulative Dose of Zoledronic Acid [a]	3.13 (1.7 – 4.05)		
Other Comorbidities During Treatments; n			
Thrombosis	4		
Neuropathy	1		
Home distance from Health Care Center (round trip); km [a]	65.8 (7.2 – 72.4)		

[a]Median (range), [b]Mean (Standard deviation), *BMI* Body Mass Index, SR: HR: VHR: Standard Risk: High Risk: Very High Risk, DFC I– ALL Dana-Faber Cancer Institute – ALL treatment regimen.

From the twelve enrolled patients, nine patients completed the 12- to 16-week intervention and had full pre- and post-intervention datasets, representing a 75% completion rate (see Figure 1). Three out of the twelve patients did not complete the final evaluation due to technical issues (poor Internet connection; n = 1), relapse (n = 1), or dropped out due to lack of interest (n = 1). Out of the nine patients who completed the intervention, five had 40 potential training sessions whereas the other ones had 31, 32, 34 and 38 potential training sessions. Overall, the group's average adherence rate was of 89% (median: 95%, range: 70–98; *P*=.04) i.e. an average of 33 sessions attended out of 37 possible sessions. All participants required adaptations due to pain, on average, for 16 sessions (range: 14-27), representing 48% of the training done. Figure 2 illustrates the reasons provided for missing a training session and the overall proportion it represents.

With regard to the information technology used to receive the telehealth intervention: one family used a desktop computer plugged into their television, resulting in a fixed set-up; two families used a tablet and six used a laptop for interventions. From the six households using a laptop, three of them connected the device to the television to allow larger screen view. The mobile technology was also used outside home settings (i.e., at the hotel during family vacation, n=2; at family members' house such as divorced parents, grandparents, uncles or aunts, n=3; or to benefit from outdoor settings, n=1). The kinesiologist provided most of the sessions within the hospital setting using a fixed system, except for six training sessions delivered outside hospital settings using mobile technology (laptop) for two weeks while on conference travel abroad.

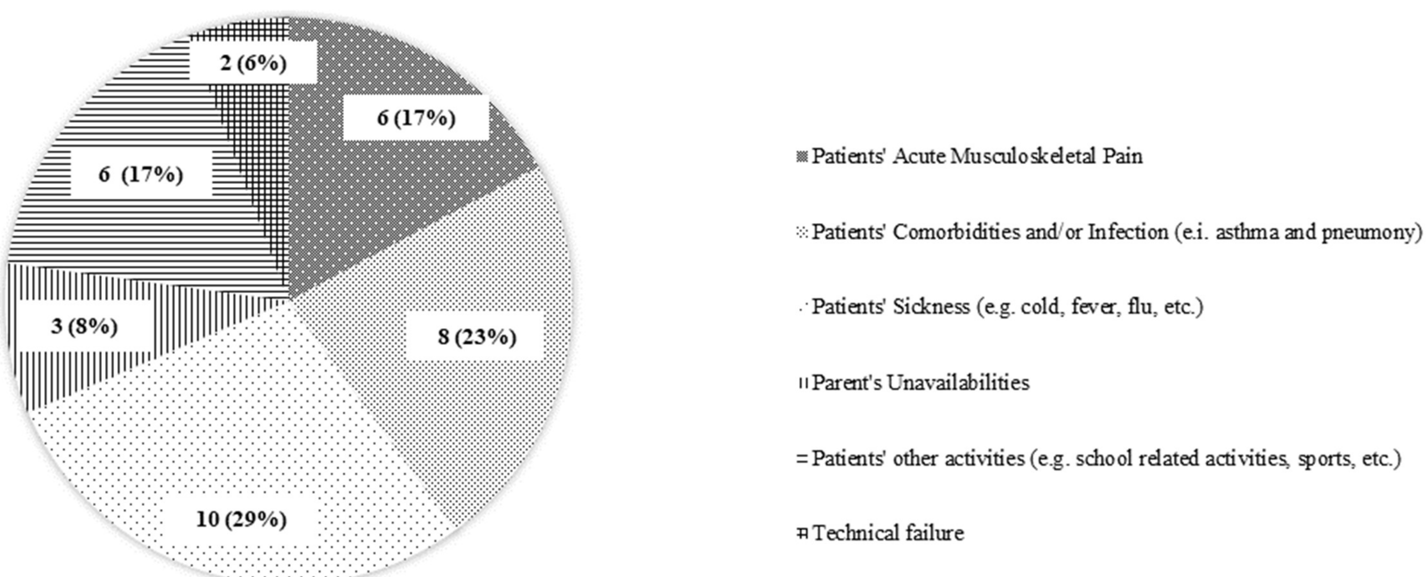

Figure 2. Pie chart picturing reasons for participants' absences to the exercise sessions.
The total of missed sessions is 35 out of 335; the number presented on the chart represents the absolute number of absence (in percentage) according to their respective reasons for absence.

The kinesiologist reported four occurrences of mild adverse events over a total of 300 training sessions. The events were interventions-related and resulted from falls (n = 2) or missteps (n = 2). All patients were able to resume training within minutes after the event had occurred. None of the patients had lasting effects and it did not prevent patients from taking part in any of the following sessions.

Functional Performance and Bone Health

Muscle Parameters

All functional performance parameters are reported in Table 2 except for the lower-limb relative maximal force and power illustrated in Figure 3. Lower-limb muscle function showed a significant increase from pre- to post-intervention for relative maximal force (11%; Figure 3A), in addition to absolute (11%) and relative maximal power (9%; Figure 3B). The lower-limbs' absolute force data showed no significant difference between pre- and post-intervention. The analyses comparing study patients' mechanographic post-intervention data to typically developing controls showed no significant difference (all *P*-values >.05).

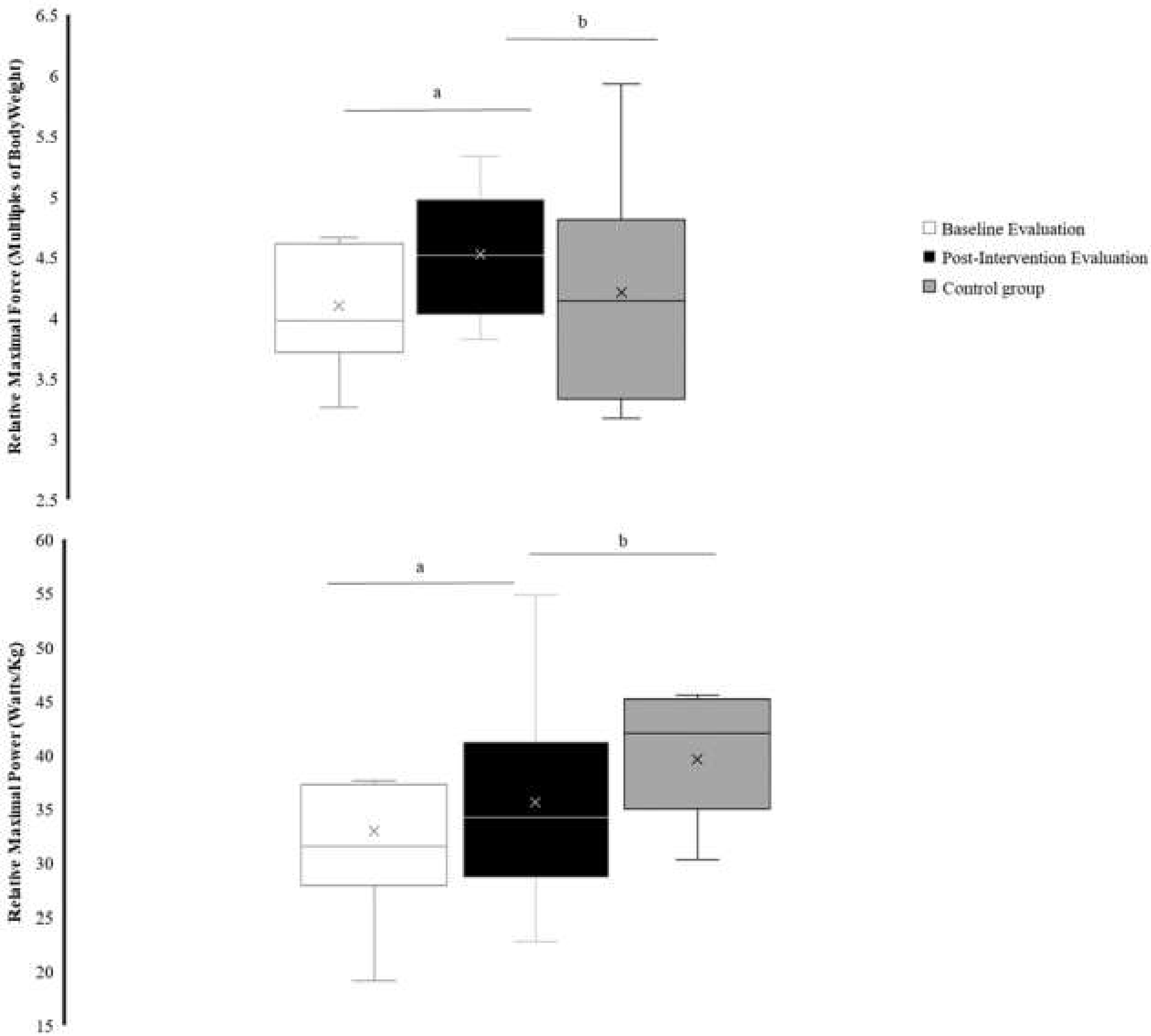

Figure 3. Box-and-whiskers plots of the mechanography results.
Upper panel: Relative maximal muscle force at baseline, post-intervention and for controls; [a] Paired sample T-test comparing baseline and post-intervention data, significant at *P*=.05; [b] Paired-sample T-test comparing post-evaluation data to control data, non-significant (*P*>.05); Lower panel: Relative maximal muscle power at baseline, post-intervention evaluation and for sex- and age-matched controls; [a] Paired sampled T-test significative comparing baseline and post-intervention data, significant at *P*=.002; [b] Paired-sample T-test comparing post-evaluation data to control data, non-significant (*P*>.05).

Absolute upper-limb isometric grip force showed no significant difference between pre- and post-intervention results. Isometric grip force results showed that patients had lower grip force than normal (Average z-score right hand: pre-intervention = -1.06 ± 0.66; *P*= .001; post-intervention: -0,73 ±0.94; *P*=.05; Average z-score left hand: pre-intervention = -1.63 ±0.86; *P*<0.001; post-intervention: -1.19 ±0.97; *P*=.006) when compared to age and sex reference data. Patients showed a trend in improving isometric grip force from pre- to post-intervention (Right: 7% and Left: 18%), but it did not reach significance (Right: *P*=.16 & Left: *P*=.21).

Table 2. Functional Outcomes

	n	Baseline Evaluation	Post-Intervention Evaluation	Controls or Expected Results	*P*-value[a]	*P*-value[b]
Mechanography						
Absolute Force (kN)[d]	9	1.17 (0.96 – 4.06)	1.60 (1.08 – 3.72)	1.63 (1.02 – 2.63)	0.10	0.73
Absolute Power (kW)[d]	9	0.97 (0.66 – 3.03)	1.07 (0.72 – 3.14)	1.57 (0.95 – 2.73)	**0.008**	0.73
Hand Dynamometer						
Grip Test R (kg)	9	16.6 (8.4)	17.3 (7.7)	-	0.50	0.16 [c]
Grip Test L (kg)	9	14.6 (8.7)	15.6 (7.7)	-	0.52	0.21[c]
6MWTD (m)	9	593 (100)	646 (97)	598 (43)	**0.01**	0.90

[a] P-values of paired sample T-test and Wilcoxon matched-pairs signed-ranked test comparing baseline and post-intervention evaluations; [b] P-values of independent sample T-test and independent sample Mann-Whitney U test comparing post-intervention to controls' data ; [c] P-value of the paired sample T-test of the grip strength Z-scores comparing baseline and post-intervention evaluations; [d] Parameters not normally distributed;. 6MWTD : Six minutes walking test distance; R: right; L: left.

Cardiopulmonary Function

Regarding cardiopulmonary function (Table 2), the results of the 6MWT showed a significant 10% increase in the distance walked from pre- to post-intervention. To test whether the increase was clinically significant, a one-sample Wilcoxon Signed Rank Test analysis showed that the median improvement of 40 m (range: 7-159) was significantly different than the 15m threshold suggested as the clinically MMD (*P*= .003) [40]. The comparison between the post-intervention average distance walked and the reference values was not significant. The pre-intervention data were not compared to reference values but would most likely not differ since pre-intervention walked distance was within normal range (593m walked vs. 598 ± 43m).

Bone Health

The pre- and post-intervention pQCT bone parameters data are reported in Table 3. A significant increase in the following parameters were reported: Cortical CSA increased by 4% (14% site; *P*=.001) and 3% (38% site; *P*=.003) and total CSA by 2% and 4% at the 14% (*P*=.01) and 38% (*P*=.001) sites, respectively. A 6% and 4% increase in SSI was also observed at the 14% and 38% (*P*=.001 and *P*=.04), respectively. Bone mineral content increased significantly by 4% at the 14% (*P*=.02) and the 38% site (*P*=.003). No other pQCT bone parameters showed significant difference between pre- and post-intervention evaluations. To ascertain that change in bone parameters were associated with the exercise training and not entirely to growth, we ran supplementary bivariate correlations between change in height and weight and change in bone parameters. No significant association (all p-values > 0.15) was found between any growth associated factors and bone parameters suggesting that changes in bone parameters are associated with the mechanical workload of the exercise interventions rather than with growth itself. The post-intervention bone parameters comparison between patients and typically developing controls revealed that the only bone parameters significantly different from controls at the post-intervention evaluation were total CSA at the 4% site, which was 21.2% (*P*=.01) larger in patients than in controls and the SSI at the 14% site, which was 7% (*P*=.007) greater in patient than in controls. No other bone related significant differences were observed between patients and controls.

Table 3. Bone Health Parameters Assessed with pQCT

[a]Parameters not normally distributed; [b] one pQCT scan removed due to movement artifact; [c] *P*-values of paired sample T-test and Wilcoxon matched pairs signed-ranked test comparing baseline and post-intervention parameters; [d] *P*-values of independent sample T-test and independent sample Mann-Whitney U Test comparing post-intervention to age and sex-matched controls' data. Units for the parameters are respectively mm² for CSA, mg/mm for BMC, mg/cm³ for muscle density and vBMD parameters, and mm³ for SSI.

	n	Baseline Evaluation	Post-Intervention Evaluation	Controls	*P*-value[c]	*P*-value[d]
Calf muscle						
Muscle CSA [a]	8[b]	3503 (2687 – 7222)	3606 (2766 – 6921)	4618 (2966 – 6828)	0.26	0.86
Muscle density	8	68.7 (4.0)	68.6 (3.3)	71.9 (1.8)	0.97	**0.05**
Tibia 4% site						
Total CSA	9	819 (325)	830 (332)	675.86 (227)	0.12	**0.01**
Total BMC	9	234 (99)	239 (103)	207.02 (58)	0.17	0.10
Total vBMD	9	289.46 (37)	289 (32)	312.98 (31)	0.98	0.14
Trabecular vBMD	9	218.92 (38)	216 (38)	212.74 (19)	0.53	0.77
Tibia 14% *site*						
Total CSA [a]	8[b]	341 (188 – 517)	349 (194 – 528)	292 (85)	**0.01**	0.38
Total BMC [a]	8	170 (104 – 268)	175 (112 – 272)	188 (111 – 222)	**0.03**	0.72
Cortical CSA	8	120 (44)	124 (44)	133 (34)	**0.001**	0.68
Cortical vBMD	8	1000 (32)	1004 (30)	994 (50)	0.26	0.62
SSI	8	891 (510)	932 (519)	837 (310)	**0.001**	**0.007**
Tibia 38% site						
Total CSA	9	292 (116)	301 (116)	282 (85)	**0.001**	0.47
Total BMC	9	222 (78)	229 (79)	233 (62)	**0.003**	0.89
Cortical CSA	9	191 (70)	198 (71)	206 (53)	**0.003**	0.86
Cortical vBMD [a]	9	1056 (927 – 1088)	1045 (930 – 1096)	1036 (959 – 1094)	0.86	0.80
SSI	9	906 (498)	939 (507)	948 (387)	**0.04**	0.37

The pQCT analysis showed that muscle density, evaluated at the post-intervention assessment, was 5% lower (P=.05) in patients, compared to typically developing controls. However, the muscle density did not change after the intervention.

For the muscle-bone functional unit (Figure 4), there was a significant positive relationship between absolute peak force and BMC at 14% at pre-intervention (P=.01), post-intervention (P=.004) and for controls (P=.007) (Fig. 4). The slopes were similar with both patient's slopes within 10% of the controls.

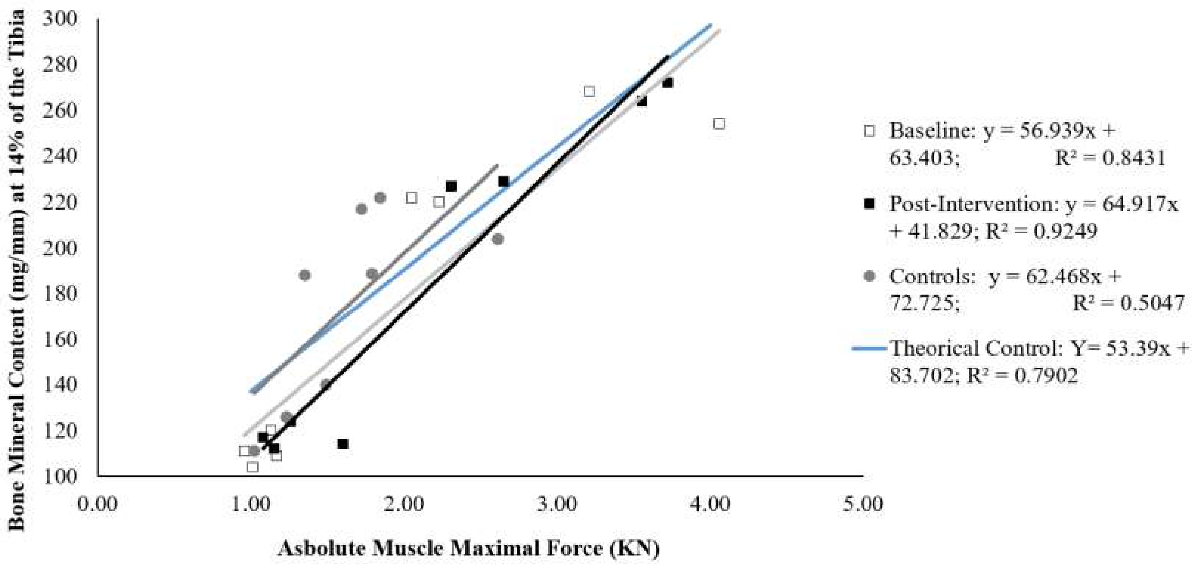

Figure 4. Muscle force and bone strength relationship.
Linear correlation between BMC (mg/mm) at the 14% site and muscle force (kN) as a function of the disease status (Early-on ALL survivors vs. age- and sex-matched controls) and testing phase (Baseline vs. Post-intervention). Light grey line and white squares depicts Baseline ALL data; Black line and squares depicts post-intervention ALL data; Dark grey line and circles depicts age and sex-matched controls data. Blue line depicts theoretical control muscle-bone relationship.

Discussion

The main objective of this study was to assess the feasibility of administering a supervised telehealth home-based exercise intervention for early-on survivors of ALL. The hypothesis was confirmed, and the approach was deemed feasible as demonstrated by the 75% completion rate and mean of 89% adherence rate. Our second objective was to explore benefits of the exercise intervention on functional outcomes and bone health parameters. In line with our exploratory hypothesis, an improvement in lower-limbs muscle function and bone health parameters was observed between pre- and post-intervention evaluations.

Feasibility

Compared to an unsupervised home-based exercise intervention, the adherence and completion rates (89% and 75%, respectively) reported in the current study are high [15], suggesting that having direct supervision contributes to a high adherence rate. These numbers are similar to those from the Esbenshade et al. [20] study reporting adherence rates of 81% and completion rates of 71%. Both our study and that of Esbenshade showed similar improvements in muscle and cardiopulmonary functions.

In the Esbenshade study, no direct supervision was provided but weekly follow-up phone calls were done. Direct supervision has many advantages that can lead to increased adherence and participation rates [23]. Receiving positive reinforcement [24], improving on exercise technique [24] and feeling self-efficient [25] are all benefits associated with increased adherence and indirectly, health benefits. Another positive impact of supervision is the greater overall volume of exercise achieved during individual sessions which can be associated with better structured and controlled exercise sessions under supervision compared to no supervision or only phone-call follow-ups [26]. In the current study, having direct supervision might have led to more efficient training because many sessions needed exercises to be adapted due to patients' pain. Being able to adjust the exercises to avoid pain in real time may have prevented injuries that could have led to a decrease in participation and adherence rates. According to our data, the high proportion of training that required adaptation for pain management would suggest the need for direct supervision for safety purposes for this specific patient population prone to musculoskeletal related pain [49, 50].

A favorable aspect of the telehealth approach used in the current study is that patients showed similar improvement in musculoskeletal and cardiopulmonary functions to other studies using indirect supervision (phone calls and video recordings of the exercises to perform) but with lower volume and frequency. In the study by Tanir and Kuguoglu [19], muscle function training was required 3 days per week, 3 times per day, in addition to 3 times per week once a day of aerobic training, whereas the Esbenshade study required 3 times per week of resistance training and 3 times per week of aerobic training, for a total training time ranging between 3.5 to 5.25 hours per week. In comparison, the weekly amount of time devoted to training in our study reached a maximum of 2.25 hours (3 X 45 minutes). Taken together, this suggests that having a qualified kinesiologist supervising the training sessions improves the efficiency with which the patients are performing the trainings [26].

Functional Performance and Bone Health

Although the current study aimed at evaluating feasibility, it was nevertheless hypothesized that improvements would be observed for muscle, bone and cardiopulmonary function parameters. Regarding muscle parameters a previous study in a patient population showing similar muscle weaknesses established [33] the minimal detectable difference (MDD) to be of 0.42 multiples of body weight for relative force (M2LH test) and 3.19 W/kg for relative power (S2LJ). In the current study, and once the patient who relapsed was removed from analysis, the improvements were 0.55 multiples of body weight for relative force and 3.05 W/kg for relative power. Of note, all patients showed improvements on these parameters. Those results are similar to the reported MDD, suggesting clinically relevant improvements in our patients.

In terms of cardiopulmonary function, the 6MWT walking distance showed an increase of 53 m from pre- to post-intervention. This is more than the 15m limits of agreement reported in a previous study evaluating between sessions reproducibility of the 6MWT walking distance [40]. Again, this suggests that the improvement represents true changes rather than measurement variability.

At the bone level, the Mechanostat theory, developed by Frost [51], stipulates that bones adapt to maximal mechanical loading applied from muscle contractions and unfavorable lever arms. In the current study, a special emphasis was put on increasing lower limb muscle force, and indirectly, mechanical loading of patients' bones. Results indicated significant improvements on multiple bone related parameters, such as bone mineral content and cross-section. Figure 4 shows that the linear relationship associating muscle force and bone strength parameters was normal in the ALL patient population and maintained post-intervention. These results suggest that the bone mechanotransduction and modeling process are normal in young early-on survivors of hematological malignancies and that intervention aiming at increasing muscle force may lead to increased bone strength [44].

Limitations of the study

Two major challenges in the recruitment process were identified: 1) only a fifth of the patients contacted provided informed consent (n=12; 21%), and 2) creating the groups revealed to be difficult, leading to multiple cohorts. Regarding the families that declined participation, the four families that declined because patients were too active, were more advanced in their survivorship (> 2 years) and got back to their daily living activities of pre-diagnosis. This suggests that implementing a home-based exercise intervention may be more feasible earlier (1-2 years) than later (3-5 years) in their survivorship. The group approach was also challenging due to two factors: a) the age range of the participants and b) the availabilities of families leading to bilingual groups. a) Due to difficulty in recruiting patients, the protocol was amended to increase the age range of the study participants going from 6 to 10 years to 6 to 18 years. This resulted in one group having two 9-year-olds training with a 14-year-old patient, which is not ideal. b) Quebec has very large proportions of French- and Englishspeaking populations and both were represented in the current study. English- and French-speaking participants had to be grouped together due to family availability constraints, leading to providing bilingual training sessions.

Due to administrative constraints, the intervention was offered to participants approximately 2 weeks prior to the beginning of the interventions. To avoid the above-mentioned challenges, it is recommended that such interventions for early-on survivors be offered to families during routine checkups, months prior to their participation. This would provide sufficient time for families to organize their schedule to integrate the training intervention with school activities and other obligations. This would also provide the clinician the opportunity to avoid the recruitment pitfalls and challenges reported above.

The positive impact of mobile technology on families' experience was unforeseen, hence the limited results reported. The current project was originally designed to be a traditional home-based intervention, however mobile technology allowed accessibility to the interventions outside the household, favoring everyday life activities vs. exercise training balance. As such, families took full opportunity of using their own technologies to train in different environments, such as on their family vacations at the hotel or during family dinners. Without mobile technologies, families would have had to choose between attending the training session or their social events. Similarly, the clinician was able to deliver interventions while on a scientific conference travel outside the country over a two-week period. Nonetheless, the use of personal technologies can be disadvantageous to some families with lower socioeconomic status who may have limited access to personal technologies and high-speed Internet. In the current study, no patient declined participation due to lack of accessible information technology, but one family was excluded because the available Internet connection in their geographical area was too unstable to allow communication and safe exercise supervision.

In terms of health benefits, the results of the intervention are promising, showing improvements in most muscle, cardiopulmonary function and bone measured parameters. However, the current study was designed to assess feasibility of a home-based exercise intervention delivered through telehealth, and therefore was not powered nor designed to detect the physiological changes associated with the intervention. In that regard, functional performance and bone health results were analysed simply and may suffer from statistical artifacts, such as the multiple hypothesis testing effect, because no statistical corrections were applied. Improvements in functional performance and bone health should thus be interpreted with these considerations in mind despite the fact that improvement was observed in 8 out 9 study participants. Another limitation of this study is that the control group was formed of healthy individuals, rather than early-on survivors who would not receive the intervention. This prevents any conclusion regarding whether the proposed approach provides added benefits compared to standard care. A second limitation is associated with the retrospective nature of the control group who only had data for one time point. This prevented performing adequate statistical analyses comparing two groups pre- and post-intervention. Therefore, any control group comparison should be interpreted in this context.

Conclusions

The results of the current study suggest that providing early-on survivors of ALL with home-based exercise intervention through telehealth is a feasible approach. This approach has multiple advantages, even more so in the context of the current COVID-19 pandemic. ALL patients are usually treated in specialized (tertiary) health care centers, located in large cities. As a result, patients treated at these centers are scattered across large distances, making implementation of frequent adjunct therapies impossible. Finally, although exploratory in nature, the comparison between pre- and post-intervention muscle and bone parameters suggest that the proposed exercise regimen is suitable to induce musculoskeletal benefits in youth early-on survivors of bone-marrow-related hematological malignancies.

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Abbreviations:

ALL: Acute Lymphoblastic Leukemia
LAEs: Late Adverse Effects
pQCT: peripheral Quantitative Computed Tomography
BMC: Bone Mineral Content
vBMD: volumetric Bone Mineral Density
CSA: Cross-Sectional Area
SSI: Stress-Strain Index
6MWT: Six-Minute Walk Test

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Chapter 4- Second Manuscript

Title. Patient and Parent Experiences with Group Telerehabilitation for Child Survivors of Acute Lymphoblastic Leukemia

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Abstract:

Background: Acute Lymphoblastic Leukemia (ALL) is the most common pediatric cancer. ALL and its treatment cause altered bone-mineral homeostasis, which can contribute to musculoskeletal late adverse effects (LAEs). With the increasing number of childhood cancer survivors, LAEs are reported often, and are aggravated by inactive lifestyles. A telerehabilitation program is proposed to strengthen the muscle–bone complex and prevent future impairment. Objective: This study aimed to explore and better understand patient and parent experience of a telerehabilitation program after completion of ALL treatment. Methods: ALL survivors (n = 12), 75% girls, 7.9 to 14.7 years old, within six months to five years of treatment, were recruited to participate in the proposed study, along with a parent. The 16-week group program included 40 potential home-based physical activities, with monthly progression, supervised by a kinesiologist, through an online telerehabilitation platform. Patients could be included in the study if they joined during the first month of intervention of their group (minimum 12 weeks of intervention). A semi-structured post-intervention interview was conducted with the patients and their parent during the final assessment, along with a review of the kinesiologist's clinical notes, to obtain a portrait of the participants' experience with the telerehabilitation program. Overarching themes were identified by one author and confirmed by two senior authors before extracting the various aspects of each theme. Results: Of the 12 patients recruited, three were excluded from the analysis because they did not complete the minimum 12 weeks of intervention (one = relapse, one = failure to meet technical requirements, and one = abandoned due to parent's disinterest). The nine patients who completed the program (six girls; 10.93 ± 2.83 years) had a mean adherence of 89%. The overarching themes identified were the program modalities (group approach with patient–parent paired training, supervised by a kinesiologist), the telerehabilitation system, the participants' perception of the benefits, and recommendations and suggestions from the families. Both patients and parents expressed very high satisfaction with the program and perceived benefits. Conclusion: Participants appreciated the program and reported they would all recommend it to other families in similar situations. The telerehabilitation method of service delivery was perceived by some as decisive in choosing to participate, while the supervision and intra- and inter-family interactions were the motivating factors that were key to program adherence.

Keywords:
exercise therapy; rehabilitation; acute lymphoblastic leukemia; intervention study; telehealth; patient perspective

1. Introduction

Acute Lymphoblastic Leukemia (ALL) is the most common of pediatric hematological malignancy. The survival rate of patients with ALL currently exceeds 85% [1], which highlights the potential for long-term consequences of the disease. These consequences, known as late adverse effects, include cardiopulmonary impairment and musculoskeletal deficits. Physical activities and exercise programs provide physiological and mechanical stimulation proven to benefit muscle and bone as well as cardiovascular health [2,3]. However, while physical activity and exercise are beneficial to cardiopulmonary and musculoskeletal function in young patients in remission or survivorship, studies show that they have lower levels of physical activity than their healthy counterparts and do not reach the required level of recommended physical activity [4].

Over the years, studies have identified multiple barriers to participation and adherence to exercise programs [5,6,7]. Due to the complexity of management and the rarity of the diagnosis, children affected by ALL often have to attend subspecialized tertiary care centers. Those centers are usually located in large cities and, consequently, not necessarily close to the patient's home. Travel to the training facility has been shown to be a barrier to adherence and participation. However, a recent study has reported that young patients are more inclined to perform such activities at home, school, or at the gym than at the hospital or rehabilitation clinic [6]. Pain and fatigue may be another barrier to exercise in patients and early survivors. A study of long-term survivors showed that approximately a third of the sample experienced pain requiring the use of analgesics [8]. Studies involving home-based physical activity and exercise training programs for ALL patients in remission or survivorship have reported low recruitment, adherence, and completion rates [9]. These findings suggest that alternative approaches are needed to make home-based exercise programs appealing to children and teenagers in remission and long-term survivors of ALL.

We recently completed a study to evaluate the feasibility of implementing a home-based supervised telerehabilitation program for children and teenagers in ALL remission [10]. Results confirmed a low recruitment rate (21%), as reported previously, which was mostly attributed to the recruitment methodology (i.e., research assistant calling families 2–3 weeks prior to the program, at various time in the survivorship period). To address the recruitment challenges, the previous article proposed integrating the recruitment to patient's routine medical appointments in early survivorship. Nonetheless, results also showed that adherence and completion rates were high (89% and 75%, respectively). During the post-intervention evaluations, semi-directed interviews were conducted with patients and parents who completed the program, to better understand the role of supervised telerehabilitation in the high adherence rate reported. This study explored the patient and parent experience of a telerehabilitation program [11] after completion of treatment for ALL.

2. Methods

2.1. Study design and Recruitment

This qualitative exploratory study [12] was embedded in a telerehabilitation trial initiated at Sainte-Justine University Health Center, after receiving ethical approval from the Institutional Review Board (2018-1555: e-S@@VIE) in 2018. The trial aimed to recruit a sample of 10 patient–parent pairs to complete a telerehabilitation exercise program after their treatment for ALL. Participants were screened by the hematology oncology service medical team (nurses and physicians) for eligibility. Patients were eligible for the trial if they (1) had a diagnosis of ALL or B lymphoblastic lymphoma, (2) were between 6 and 18 years old, (3) were within six months to five years of treatment completion, and (4) were able to join their group within the first four weeks of the program start for a minimum of 12 weeks of intervention. They were ineligible if they had, as seen in the first publication emerging from this pilot project [10], unresolved fractures or avascular osteonecrosis, a treatment regimen that included bone marrow transplant, or major physical or functional impairment preventing from exercise at the time of recruitment. Technical reasons for exclusion included having an unstable or no Internet connection. Twelve patient–parent pairs were recruited, and nine completed the program, including the initial and final evaluation.

2.2. Study Procedures

The Telerehabilitation Program

The telerehabilitation trial was a single-arm interventional pilot study to assess the feasibility of group telerehabilitation programs for early ALL survivors. Patients were contacted to provide information and to screen for interest. Families who were interested were invited for an initial assessment at the hospital. Upon arrival at the hospital, parents of patients under 18 years old provided signed informed consent, and patients between 6 and 17 years old provided written informed assent. After the baseline evaluation of patients' functional health and musculoskeletal parameters, the kinesiologist visited the families' home to help them with the technologies and room set-up before starting the 16-week program. Each family was provided with training material and a training watch (Polar A370, © Polar

Electro Oy 2020, Polar FlowSync 3.0.0.1337, Finland). A videoconferencing application (Zoom Pro license, Zoom Video Communications, Inc., USA) was installed on the preferred technological tool of each family (tablet, laptop, or desktop computer) [13]; the layout of the videoconferencing interface is shown in Figure 1.

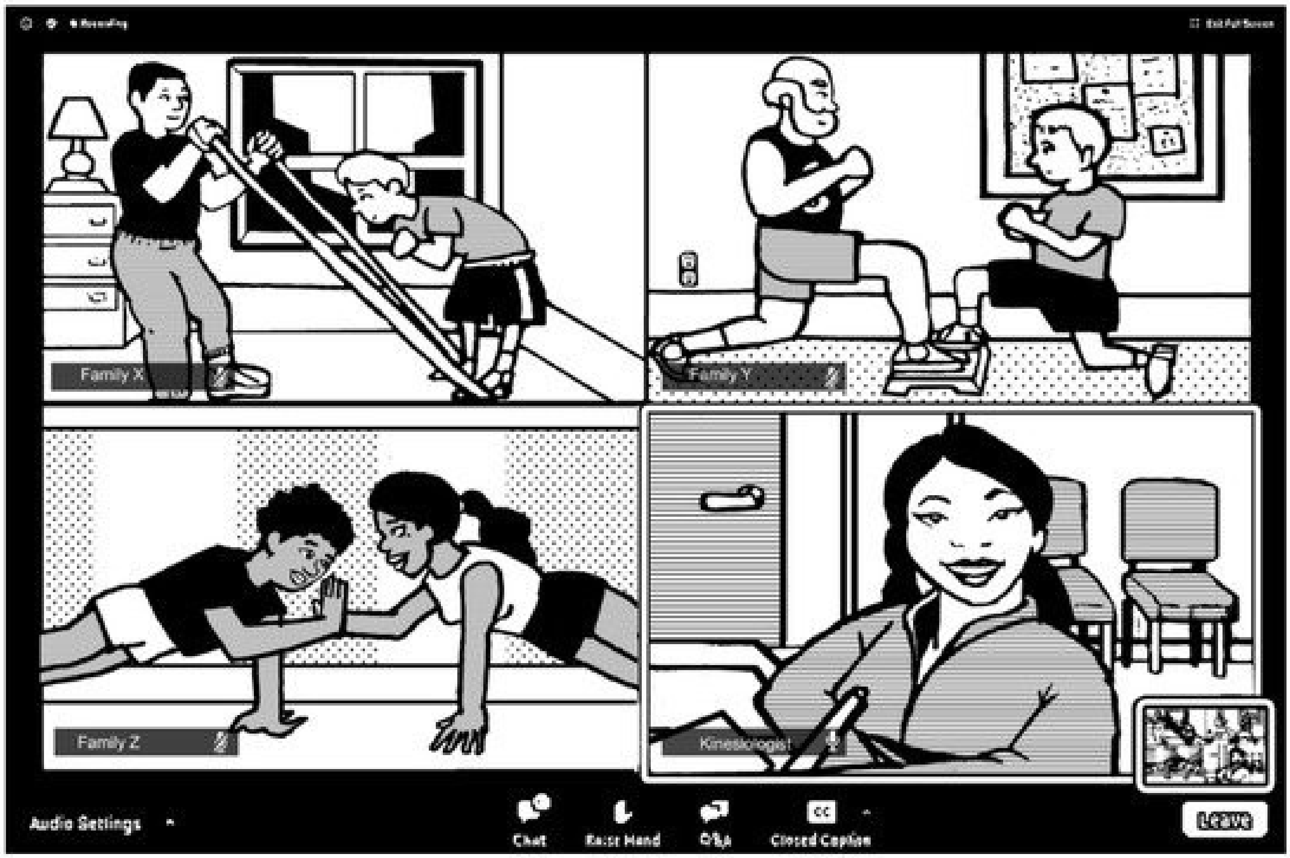

Figure1. Illustration representing the screen during a group session, by Nizar Laarais

The training program itself was designed to be progressive, to increase either in duration (from 35 to 45 min) or frequency (from two to three times per week) each month. During each session, exercises were adapted or changed according to individual participants' pain, reported as a number on a scale from zero to 10 (NRS-11) [14], along with a description of the sensation and its location, in addition to its evolution over time and with movement. The patients were reassessed after completing the 16-week intervention. The full study procedures are provided in Reference [10] (Lambert, G., et al. 2021 doi:10.2196/preprints.25569). The study was approved by the Sainte-Justine University Health Center Research Ethics Committee.

2.3. Data collection

As part of the final evaluation, individual semi-structured interviews were conducted with the nine families that completed the study, in French or English, to explore the patients' and parents' experience of the telerehabilitation service provided [11]. All interviews were conducted in the same manner, following a semi-structured interview guide, including open and closed questions (see **Appendix A** for interview questionnaire). The interview guide was adjusted as new information emerged. This led to the addition of a question about the perceived benefits of the program after the second cohort, as the first three families mentioned many perceived benefits throughout the program. Patients and parents were interviewed separately using an in-person format with a research team member. The kinesiologist who had conducted the 16-week intervention program was not present during the interviews to limit participant's bias in answering. Interviews were audio-recorded, transcribed verbatim, and anonymized during the analysis with the senior authors. Additionally, notes from the kinesiologist supervising the program were reviewed for relevant content reporting participants' feedback regarding the service or system, in addition to their barriers to interventions.

2.4. Data analysis

The first author (G.L.) identified major overarching themes, using the interview transcripts. The themes were then discussed with two of the senior authors (K.D. and L.N.V.), to confirm that the themes reflected and transcended the interviews. A second read-through of the interviews was done, using the Taguette free application for qualitative analysis (**https://app.taguette.org**, accessed on 19 November 2020) to identify quotes representing different aspects of the themes, and the number of participants (parents or patients) mentioning them. The results are presented according to overarching themes, reporting similarities, and divergences between patients' and parents' experience of the program. Quotes selected for reporting from the French interviews were translated to English by a bilingual author (G.L.).

To complement the perspective captured in the interviews, a list of barriers encountered throughout the program by participants was compiled. The kinesiologist's clinical notes were reviewed to identify two principal types of barriers: (1) technological challenges and (2) pain reported by either the participant or parents. Since pain varied in location, intensity and duration, we reported the number of sessions where adaptations were required due to pain relative to the total number of sessions completed. Technical challenges were considered major for the Zoom videoconferencing system if it led to discontinuation of the session, and minor if it hampered communication between the families and the kinesiologist (e.g., video or audio lag). Technical challenges for the training watch were coded as major if no data were acquired (e.g., uncharged watch or patient forgetting to put it on, resulting in an absent HR monitor and step count), and minor if there were difficulties charging the watch, low battery, or the participant forgot to start the watch at the beginning of the session, resulting in inconsistent data collection (incomplete or absent HR monitor).

3. Results

3.1. Participants' characteristics

Of the 12 patient–parent pairs recruited for the telerehabilitation program, nine from four different groups completed the program and final interview. The three families that did not complete the program were either excluded (n = 1 relapsed; n = 1 did not meet technical requirements) or dropped out due to parents' lack of interest (n = 1). The characteristics of the 16 participants who completed the program (parents and children) are found in **Table 1**.

Table 1. Participants' characteristics and technologies used for the program

Patients' Characteristic					**Parents' Characteristic**			**Families' Characteristic**	
ID	**Sex**	**Age [a]**	**Diagnosis and Prognosis**	**Time Since TC**	**ID**	**Sex**	**Age [a]**	**Group No.**	**Technology Used**
Patient 03	F	14	ALL; HR	14	Parent 03	F	51	1	Tablet
Patient 04	F	9	ALL; SR	27	Parent 04	F	41	1	Laptop computer connected to television
Patient 05	F	9	ALL; SR	53	Parent 05	F	40	1	Laptop computer connected to television
Patient 06	F	13	ALL; SR	44	Parent 06	M	44	2	Desktop computer connected to television
Patient 07	M	8	ALL; VHR	13	Parent 07	M	43	3 [b]	Laptop computer
Patient 09	F	8	ALL; SR	34	Parent 09	F	33	4	Laptop computer
Patient 10	F	9	ALL; SR	36	Parent 10	F	36	4	Laptop computer connected to television
Patient 11	M	13	B-LL; SR	57	Parent 11	F	52	2	Laptop computer
Patient 12	M	15	ALL; HR	52	Parent 12	M	44	2	Tablet

[a] Age reported at the final interview. [b] The family in Group 3 is presented alone in this table because they started the program with the family that abandoned mid-program, then joined Group 4 but had to finish the last month alone, due to schedule restrictions. ALL, Acute Lymphoblastic Leukemia; VHR, very high risk

of relapse; HR, High Risk of Relapse; SR, Standard Risk of Relapse; TC, Treatment Completion (month); B-LL, B-cell Lymphoblastic Lymphoma.

3.2. Overarching Themes

The interview results confirm that patient and parent experiences were influenced by the modalities of the program (i.e., group training, patient–parent pairing, and kinesiologist supervision), the perceived benefits of the intervention, and the telerehabilitation system itself. Participants also offered recommendations for other families and healthcare professionals considering such a program. The themes identified and confirmed by the authors are shown in **Figure 2**.

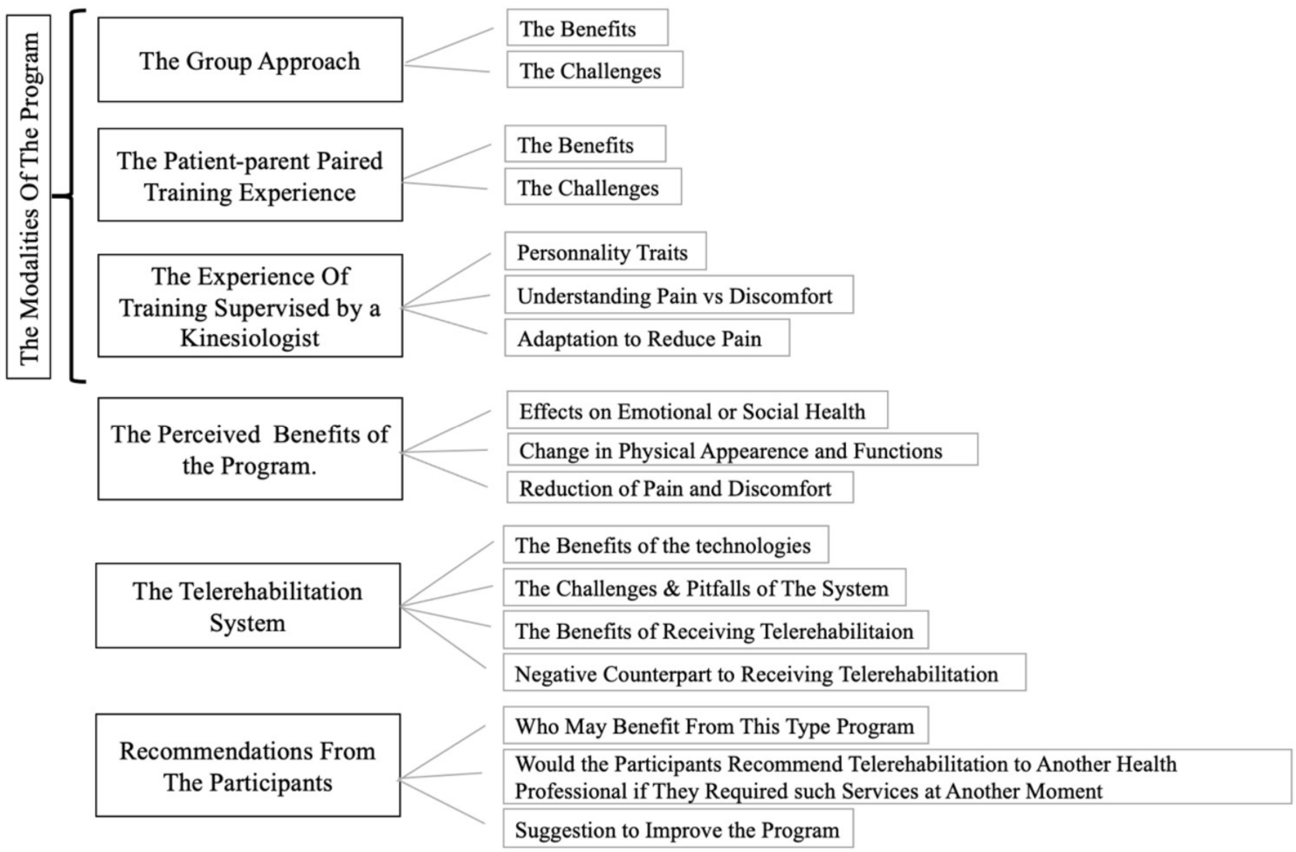

Figure 2. Overarching themes

3.3. The Group Approach

The role of the group approach in participants' experience was widely positive. Participants reported few challenges. Only one parent reported a major challenge.

While only some parents mentioned the telerehabilitation program would have been impossible without the group approach, many patients mentioned that when the other families were unable to attend the session, they felt it was “a little boring” (Patient 06) or “monotonous” (Patient 12), suggesting it was less motivating. In fact, the group approach was identified as a motivating factor by all participants, parents and patients alike. The underlying motivational phenomena were mostly healthy competition and a collaborative atmosphere between families, in addition to feeling able to relate to each other. Patients reported “healthy competition, because when you’re next to someone, you’re always going to try to do like the person next to you (during in-person trainings). But now, it is in our home… (everyone feels comfortable) That’s it, everyone’s doing their work. When someone feels tired, others can go on, or stop, you don’t feel like you have to force or anything” (Parent 12). The second motivating phenomenon of the group approach was the collaborative atmosphere: “It was like teamwork” (Patient 09). It was reported that if “someone had a problem, we could give ideas, we could help each other” (Patient 11) and encourage each other: “It’s actually more than positive, because when (Patient 09) would see the other girl exercising, she would be like, ‘*Yeah, let’s do this’!* and they would high-five each other at the end” (Parent 09). Moreover, participants appreciated being able to relate to others about their health: “I wasn’t comparing myself, but I could see that I wasn’t the only one who wasn’t used to it. So that made me feel comfortable, I was not alone” (Parent 05). “There was a father who had a knee problem, and I have a shoulder problem” (Parent 12). “It was good because you could meet more people and could see others who had the disease, what it is like, and if they have the same booboos as you do, things like that” (Patient 04). They also mentioned shared challenges: “Because sometimes they’d say things to each other. Let’s say, if it’s advice, it can also apply to me too. Even if she (the kinesiologist, G.L.) isn’t talking to me, I can still listen to her” (Patient 10). “We are not alone in our living room doing this” (Parent 10).

The level of interaction varied between groups. Group 1 did not communicate very much with other families, while Groups 3 and 4 had patients that played together when hospitalized during treatments. “I like exercising with someone—another family I’ve met in the hospital. Before, it was kind of a hospital friend” (Patient 09). This may have elicited a higher level of interaction among both patients and parents. Participants in Group 4 did not know each other before the program, but became friends: “(today we) met for the first time (during the final evaluation), it’s like (we have) known each other for years” (Parent 12).

During the interviews, very few challenges were mentioned related to the group approach. Parents commented that families “were not always in sync” (Parent 10), which made the parent anxious to keep pace, although she added that the kinesiologist did not pressure them. Another parent mentioned not really hearing the other families "people were still discreet" (Parent 04). On the other hand, challenges regarding the group approach reported by patients included families disappearing from the screen, or not seeing everyone all the time; however, only one patient said this approach was distracting. Another patient reported that, at times, another participant looked like he did not want to be there.

The major challenge cited earlier referred to a parent experiencing discomfort overhearing an incident in another family: "We didn't have to hear that" (Parent 11). The parent said, "We don't all have the same values", and concluded, "Afterwards, I don't know if someone spoke to them or not, but it was less disturbing (the training), and more fun".

3.4. The Patient–Parent Paired Training Experience

According to the parents, the patient–parent paired training was also beneficial. Limited challenges and no major challenges were cited by study participants.

The main benefits reported were the motivation it provided, the time spent together, the healthy competition, and the opportunity for parents to help their child. Motivation was mentioned by several participants: "It also helps motivate (Patient 06) because sometimes she doesn't want to do it, sometimes she does. It depends on her mood" (Parent 06). Many patients or parents mentioned that training sessions were an opportunity to spend quality time together: "It's rare that you have a lot of time together because, at school, you always have to hurry. When it comes to training, you are more relaxed" (Patient 04). Many parents found it to be a time to develop their relationship with their child: "We do it together. The exercises with the elastic band also created a bond because we watch each other and do it together. I think that it gave me a (sense of) complicity with my daughter (a desire) to do activities (together), and it really makes me see that training should not be seen as an overload of activity, but rather as a family moment" (Parent 05). One of the parents reported that his relationship with his son improved. The child "has ADHD with an opposition disorder, so there's always parent–child conflict. (The program) allowed me (Parent 12) to spend time with him, and at the same time, to do something with him, (…) to get closer—well not to get closer, but (for him) to see someone other than the father who says stop doing that, or whatever" (Parent 12). Both parents and patients also appreciated that there was healthy competitiveness between them. This rivalry was perceived as motivating: If patients saw they were able to do one more repetition than their parent, it empowered them to continue. Moreover, patients appreciated the opportunity for their parent to assist them: "It helped (to do the training with my mother) because my mother, even if (the kinesiologist) didn't say it, she (referring to the mother) could tell me things that I had to improve" (Patient 05). Parents recognized and valued the supportive role they played in their child's experience: "(…) him just doing the exercises wouldn't have worked. First, (he has to understand), and also there are exercises you (referring to Patient 07) needed a little help with and stuff—like holding the carrot (referring to assisted drop jump)—it went really well. And then, I also participated, and that makes me feel good, too" (Parent 07).

As indicated above, the pairing of parents and patients caused no critical issues; however, some challenges were raised, such as conflicts: "sometimes, if we quarrelled (…) everyone could hear us" (Patient 04). One family mentioned that a parent was less motivated, which reduced the motivation of the patient. Another child mentioned that sometimes the parent was anxious to finish quickly to continue doing housework. Differences in strength between partners was also reported twice as a possible limiting factor by two teenagers, which had an impact on the partner they chose to exercise with: One decided to exercise with her parents instead of her siblings; another chose his father instead of his mother as his exercise partner.

3.5. The Training Experience While Supervised by A Kinesiologist

When asked about their experience of training while supervised by a kinesiologist, participants unanimously said they felt the kinesiologist had a positive impact. All participants said that they received enough information to do the exercises correctly, and that the information was clear. Some mentioned that, if they misunderstood or an audio-video lag occurred, the kinesiologist took the time to explain and demonstrate the exercise again. This was greatly appreciated by participants, as expressed by one parent: "If (…) we didn't understand, she would go down on the ground to demonstrate the exercise" (Parent 03). Participants expanded mainly on three elements regarding the kinesiologist: (a) the kinesiologist's personality, which helped foster the therapeutic relationship; (b) their understanding and attention paid to pain and discomfort; and (c) their knowledge and ability to adapt the training to individual limitations.

The kinesiologist's personality was the factor most often mentioned by study participants. Many parents used qualifiers such as attentive, knowledgeable, motivating and motivated, inclusive, accommodating, accessible or approachable, and open to questions. Additionally, almost all parents used at least one of the following adjectives, warm, kind, playful, positive, dynamic, or enthusiastic, when describing the kinesiologist's personality. For their part, patients described the kinesiologist as friendly, nice, happy, funny, playful, motivating, and engaged. Patients appreciated the incorporation of games in the training "We do games, yes it's going to be exercise, but in activities" (Patient 06). Some patients mentioned that the kinesiologist was a mix of serious and comical, or relaxed, that they were supportive, and that they provided constructive criticism. To describe their relationship with the kinesiologist, some made the following comparisons: "like my teacher" (Patient 11) or "a fourth cousin who you don't know, but play well with" (Patient 12), illustrating the friendly therapeutic relationship that developed between the patient and trainer.

Furthermore, some parents and patients emphasized that they appreciated the opportunity to understand the nuance between pain and discomfort that the patients were experiencing. As seen in **Table 2**, patients frequently reported pain throughout the program which demanded adaptation (varying among patients from 42% to 96% of sessions). The kinesiologist took the time in each instance to discuss and understand the pain or normal discomfort that the participant was feeling. On this topic, one parent interviewed said that, before the program, he did not know how to react when his son was complaining of pain, but he was now able to ask questions and help his son understand what he was experiencing: "Yes, he had pain in his feet, because it is normal after treatments. But now, we learned something: *'is it pain or discomfort'?* Sometimes, he does physical education at school, then he comes home, and he's tired. And '*yes, you have done physical activities, so, of course, you are a little uncomfortable*'. (…) Then he understood the difference" (Parent 07).

Table 2. Barriers to interventions reported in the kinesiologist's clinical notes for each family

Families	**Patients' Pain (sessions with adaptation due to pain/ total sessions completed)**	**Parents' Pain (sessions with adaptation due to pain/ total sessions completed)**	**Level of Technological Challenges: Zoom**		**Level of Technological Challenges: Polar watch**	
			Major	**Minor**	**Major**	**Minor**
03	21/30	2/30	2	1	1	1
04	27/28	1/28	1	7	4	3
05	18/39	1/28	-	2	-	1
06	16/37	9/37	-	4	2	4
07	25/38	0/38	3	-	-	-
09	16/39	1/39	-	4	-	2
10	14/33	1/33	-	-	-	2
11	15/31	15/31	-	4	-	1
12	16/25	9/25	1	2	-	-
Total	168/300	39	7	24	7	14

Lastly, the kinesiologist paid careful attention to pain, in order to adapt the exercises and training to participants' individual condition and limitations. The ability to adapt the exercises and training to all participants was greatly appreciated by both parents and patients. "And really, it worked" (Patient 11), "I had back pain before, and she gave me tips to have less back pain" (Patient 04). Parents appreciated the adjustments for their children as it made the training "adapted to their needs" (Parent 04). But they also appreciated having access to the service for themselves: "because, even though we are parents, we have little booboos" (Parent 12), and "she always had a plan B and a plan C when someone was having pain; you know, like me. Sometimes I had pain in my knee, and I would tell her and (she would say:) *Okay, do this exercise instead*" (Parent 06). This allowed parents "to be active, without doing the same exercises" (Parent 12).

3.6. The Perception of Training Benefits

Although the program aimed to improve physical function, participants perceived benefits that extended beyond this outcome. The interviews and kinesiologist's clinical notes revealed that participants recognized positive effects on emotional or social health, and changes in appearance and function. Some participants also reported less pain and discomfort as a result of the program.

The effects on emotional or social health were reported mainly by the parents on behalf of their children. Almost half the parents spoke of the effects of the program on their child's self-esteem, ability to focus, general motivation, or socialization and communication skills. Two patients also mentioned this aspect during their interviews:

> Patient 09, "It also helped me get less distracted".
> Interviewer, "Less distracted? Do you mean during the training, or just in general"?
> Patient 09, "In general".
> Interviewer, "In general"?
> Patient 09, "It helped me get less distracted, because I'm always distracted".

The main changes in physical function cited by parents and patients alike were improved strength, increased endurance either during trainings or in everyday life, and increased energy or less fatigue. Participants mentioned, among other things, the ability to do exercises at the end of the program that they could not do at the beginning (such as push-ups or burpees), or being able to wear their backpack to school, walk to school, jog in a corridor, or pick up grocery bags more easily than before, with less tiredness or fatigue. “At first, he was really, in physical terms, he was really not at all in shape. I even met his physical education teacher at school, and he said, ‘*Ah! (Patient 07) has improved. He is doing very well! Are you doing anything special*’? I explained the program to him a bit. We were also able to start playing other sports, and he is good at them: We play badminton and soccer, and it’s going well. Before, I tell you, five minutes and he was ready to give up” (Parent 07). Another patient decided to take up a new sport: “Because I wasn’t there for a few years. Just after I finished chemo, and I wasn’t able… I was weak… I didn’t have enough energy, strength so—I felt like, during the training I did, I bounced back, so I want to take advantage of it to try to start karate again” (Patient 06). Parents also spoke of appearance. A third of parents reported changes in their child’s appearance, mainly patients looking thinner or having more muscle definition. One parent also reported that they, too, lost weight.

Some patients and parents saw a reduction in pain and discomfort as a result of the program. Two parents expressed a reduction in either chronic or acute knee pain due to the program exercises or movement corrections. Patients mentioned chronic pain such as headaches, and back, leg or foot pain, which they attributed to the lasting effects of ALL treatments. Patients did not report diminished frequency of headaches in daily life, however, some said that other types of pain decreased or disappeared: “All the pain went away while doing the exercises. I may still be in pain sometimes (referring to headaches), but the physical pain, doesn’t happen that much anymore” (Patient 10). Another patient reported disappearance of pain multiple times during the program: “I used to get up (in the morning), and there was a leg like, it just didn’t work. It was stiff, and it hurt. I had to find a (different) way to go down the stairs, or it hurt. But now, that has stopped” (Patient 11). Clinical notes confirmed that some patients reported specific sensations as pain at the beginning, and over the weeks reported it as discomfort or no longer reported it at all. This was most notably the case for Patient 07 and Patient 12.

3.7. The Telerehabilitation System

One of the main benefits of telerehabilitation technologies mentioned by the parents was that the system was adaptable. The families valued being able to use their own technologies. For example, a family that used their tablet mentioned, “it wasn’t distracting me from anything and, you know, if it had been a big screen, and I would have seen them (the other families) live, then I would have been uncomfortable. But the way it was set up, it was fine" (Parent 03). Another family said, "We really had a great set-up at home. I was able to take my laptop and put it (the video feed) on the television" (Parent 05). Furthermore, many patients and parents described the system technologies as user-friendly, which allowed patients in more than half the families to sometimes connect by themselves to the telerehabilitation sessions. A specific detail mentioned that facilitated the experience was that links for the training sessions were sent by email the day before the session: "It was easy. Well, we just had to click on a link (…) in an email. Because we had the codes, and we were given them as we went through the sessions" (Patient 12).

However, even if the technologies were generally easy to use for all families, when asked about minor or major challenges, most participants mentioned occasional video or audio malfunctions, "It happened from time to time, sporadically" (Parent 12). System difficulties were reported if other family members were using the Internet simultaneously, if the weather was poor, or sometimes if families were doing the training from somewhere other than at home. Some families said that issues occurred mostly in the early sessions, while they were adjusting their Internet consumption: "At home, the children all have devices that use the Internet. So, at the beginning, we weren't sure. We didn't really know how much consumption it was going to take. So, at the beginning, the first and second week we had a lot of, you know, lags, because the Internet was in great demand, because the children were already listening to videos with voices, and we had the camera live with the voice. Well, there was one point when the Internet jumped a bit there. (…) We had stopped the devices (for the other) children during the training; to dedicate the Internet just to that" (Parent 06). "No, nothing went wrong. But at first the camera froze a lot". (Patient 09). Two other factors were mentioned as limiting by some parents. The first was the sound, "As soon as someone spoke, we couldn't hear what was happening elsewhere (…) we could no longer hear what the instructor was saying. It was hard to manage sometimes. It was not all the time" (Parent 10). The second limiting factor was the watch, "Sometimes we forgot, it's our fault, but we forgot to plug in the watch, and things like that" (Parent 04).

Overall, the telerehabilitation method of delivering the service was identified as beneficial by all participants, because the program did not require travel and could be done from the comfort of their home, allowing families to balance training with personal and professional activities. Some mentioned that it might not have been possible for them to participate if the program had been in-person: "We don't waste 20 or 30 min to get there and come back. It sounds like nothing, but it's still precious. Because if we had to go to (the hospital), (…) it's not certain that we could have participated" (Parent 06). Others said that the telerehabilitation delivery was crucial in their decision to participate "Three evenings, it was going to be a little more difficult. (…) The fact that I knew I didn't have to go out, that was one of the characteristics that made me say yes" (Parent 11). Patients also liked not having to come to the hospital for interventions: "Before the telehealth, I was like '*Why don't we go to the hospital? That would be better*'. It would be weird to do it on the computer. But then I noticed it was better, because you can do it in your living room. You don't have to be like, '*Okay, it's 6:30 a.m. I have to go to the hospital*'. Because it takes an hour to get there, and it will be at 7:30 a.m. You can say like, '*It's 7:15. Okay, I'm going to turn on the television, and I'm going to start this*'. There you go, you didn't have to go to the hospital and do everything" (Patient 05). Doing the training at home was appreciated by all parents, but this subject was not addressed as much by patients. Parents mentioned that their children felt at ease doing their exercises, and that it was even more beneficial in winter that they did not need to leave the house. Moreover, they agreed on the convenience of the delivery method. Most parents mentioned that it helped to balance the training in the family's everyday life: "In family life with children, it fits well, it makes it much easier. I don't need to call a babysitter for the others while we go to his appointment. For family management, I think it's something very useful" (Parent 10). As indicated in the kinesiologist's notes, it was common for families to have the other parent involved in the training ($n = 7$), as well as siblings ($n = 4$), cousins ($n = 1$), grandparents ($n = 2$) or even friends ($n = 2$).

However, in some cases, the increased accessibility of the telerehabilitation method of delivery led to a sense of obligation, especially among the teenagers: "(I) felt a bit like I had to do it even though I didn't feel like it sometimes. Then, like when I was in pain, I felt bad for not doing it" (Patient 03).

3.8. Recommendations and Suggestions from the Families

When asked if they would recommend the program to other patients and their families, all parents and patients agreed that they would, some even going so far as to propose that it become part of the ALL treatment protocols: "This should be a part of the treatment. It has (been) five years (since) she (Patient 09) got sick, she has (had) two years of chemotherapy. This type of program should be included in her treatment, as a follow-up with the hospital, because she would benefit a lot. (It would be) beneficial for all kids in her situation" (Parent 09). Similarly, most parents and patients also thought that the telerehabilitation delivery method could be useful not only for cancer survivors but for anyone interested in exercising. Some patients specifically mentioned that it would be ideal for populations with factors that limit travel or mobility. Others mentioned that if the person is able to do the training in person, it may not be needed.

Many parents agreed that they would propose the telerehabilitation method of delivery to another health or sport professional if they ever needed such rehabilitation services again, mainly due to the aforementioned general benefits of the telerehabilitation service delivery method: no travel time, being able to do it from the comfort of their own home, and the balance of training with personal and work life.

During the program, a few families said that they would have appreciated at least a few in-person training sessions to help correct movements that were more technically difficult for the patient and to get tactile feedback. Other suggestions from the families to the research team for improving the system or service were as follows:

1. Provide more material (such as yoga mats, or wider variety of weighted balls, and elastic bands).
2. Provide the system to families with fewer technologies at home, or with better quality cameras that could be controlled by the kinesiologist to focus on participants so that they would stay in the frame while in motion (Parent 06), or even to use a set of three cameras to see different angles.
3. For the kinesiologist to “have (real-time) access to the data from the training (to) watch” on the screen, to help motivate and set goals (Parent 10).
4. Have a more flexible schedule for families to do a different session if they couldn’t attend one earlier in the week. “Let us decide when our training is. (…) Sometimes, we might have an exam on Thursday, so we can’t do it on Wednesday evening because it takes too long and we couldn’t study” (Patient 04), or for families to select their preferred times without selecting the age group.
5. Offer a longer program to gain more benefits (“a full school year” (Patient 11) was proposed by two families).
6. Incorporate a wider variety of exercises, or exercises that each child likes, and more games.
7. Encourage families to include friends, siblings, and other family members to shift the focus and make it playful.
8. Offer the service earlier to help families plan their schedules ahead of time.
9. Offer the service to more families “As a part, included in the treatments” (Parent 09).
10. The hospital should better advertise the service to families, such as having the treating physician recommend the program to patients during the final months of treatments.

4. Discussion

Parents and patients were very satisfied with the program, as confirmed by the semi-structured interviews. All participants said they would recommend the program to other families in their situation. In addition, they all spoke in great detail of the benefits of the program and its modalities, and were less concerned by its challenges.

Factors that contributed to the high satisfaction identified in this study, i.e., primarily the method of delivery and the intervention modalities, may explain the high adherence rates recorded in this study (89% [10]), and for some, may have contributed to the initial decision to participate. The current findings illustrate that the telerehabilitation method of delivering the rehabilitation service was critical in choosing to participate, played an important role in facilitating participants' access to the program, and, subsequently, to their satisfaction with the program. Pairing, grouping, and supervision also positively influenced participants' experience once they chose to enroll in the program. The frequency and quantity of benefits mentioned during the interviews concerning these aspects of the program far outweighed the challenges. Therefore, it would seem that the modalities of the telerehabilitation service (i.e., pairing, grouping, and supervision) impacted adherence to the program, while its accessibility contributed to the initial decision to participate.

The literature examining factors influencing ALL survivors to participate in, adhere to, and complete a rehabilitation or exercise program is limited. Nevertheless, the findings of the current study are consistent with the earlier study done by Wright et al. (2015). Both highlight that participants prefer to exercise at home rather than at a hospital or clinic [6].

Furthermore, the current study parallels the findings of Kairy et al. (2013) in certain respects. The latter explored the patient perspective of adults who received an eight-week home-based telerehabilitation program following total knee arthroplasty [11]. That study used a system similar to the current study, to provide supervised intervention to patients; however, their program was neither paired nor grouped. Although each study targeted very different populations, their findings are astonishingly similar, indicating that the aspects interviewees appreciated most were being able to receive the services at home, and their relationship with the physiotherapist. In both studies, participants reported that the physiotherapist and kinesiologist were capable of adequately evaluating patient's technique, pain, and discomfort. Furthermore, patients in both studies mentioned that some in-person sessions might be useful to facilitate a clinical follow-up, such as physical correction. Lastly, in both studies, telerehabilitation was not viewed by patients as an impediment to their satisfaction with the program.

However, the differences between the populations and modalities (i.e., paired and grouped trainings) may have influenced the perspective of the participants: Patients in the current study highlighted the playfulness of both the training regimen and their kinesiologist. Additionally, while in the study by Kairy et al. the patients preferred the telerehabilitation delivery method over in-person, due to saved preparation and travel time, they did not mention the advantages of better balancing of personal, family and work life, a factor raised repeatedly in the current study. The increased social interactions, due to the paired and grouped approach of the current study, may have imposed some challenges, but motivated participants to adhere to the program [15].

To this extent, a study revealed that children with disabilities considered their participation in physiotherapies and occupational therapies meaningful when they were enjoying themselves, felt capable and autonomous in their activity, and when there was a social component to the activity [16]. The modalities of the present study had an intrinsic social component. Participants took full advantage of the social involvement. The original "patient–parent paired" experience very often expanded to not just two but three participants, including other family members or friends. Furthermore, participants mentioned the perceived benefit of being able to do exercises or tasks that had once been difficult. This finding aligns with the essential role of capacity in creating a meaningful rehabilitation experience. Lastly, participants highlighted the importance of enjoyment in their experience of the current program. This enjoyment is noted, in their perspective, concerning the modalities: Patients appreciated the healthy competition between families, as well as with their parents. Enjoyment is also observed in their perspective of the kinesiologist's personality. Both patients and parents described her as playful. It is also noted in their recommendations for future programs.

Early survivors of ALL are known to be a difficult population to recruit for exercise interventional study. Their adherence to such programs tends to be low, since they are less active than the general population. Furthermore, after ALL treatment completion, patients and their families may experience challenges related to family cohesion [17] and the addition of school-related activities to the schedule [18]. In these respects, the modalities of the current program were beneficial, since they reduced the burden on the family's schedule by increasing the accessibility of the rehabilitation services. The social intra- and inter-family interactions might also provide a valuable tool to improve patient motivation to adhere to such rehabilitation programs.

Study Limitations

The main limitation of this study was the small sample size: Results from nine parent–patient pairs cannot be generalized to the entire population of early survivors of ALL. Furthermore, interviews were conducted only with participants who completed the program, and their perspectives may differ from participants excluded prior to intervention completion.

The current study used a hybrid approach (i.e., not all interactions with the kinesiologist were done remotely) that may have allowed the therapeutic relationship with the participants to develop, but it is impossible to infer whether this would be better than other telerehabilitation approaches, such as conducting all activities online. One of the main aspects appreciated by both parents and patients was supervision by the kinesiologist during the telerehabilitation training sessions. However, it is important to note that the therapeutic relationship fostered between participants and the kinesiologist was not created exclusively through the use of telerehabilitation. Participants met the kinesiologist twice before starting the program: once for the baseline evaluation in the hospital (three to four hours), and once for a home visit to help the families prepare the technologies and their training environment (45 to 90 min). Consequently, it is not possible to infer from the results of this study alone that a therapeutic relationship can be created through the use of telerehabilitation alone.

Moreover, regarding the benefits perceived by participants, it remains unclear if the decreased pain that patients reported was due to actual changes in the pain sensation (i.e., whether it decreased to discomfort or the sensation was no longer present), or was the result of the educational role of the kinesiologist in gaining a better understanding of the pain. Nonetheless, pain is a very important issue and was raised as limiting in this study. This finding raises the need to address pain in this population, using a multidisciplinary approach.

5. Conclusion

5.1. Summary

The telerehabilitation program with early survivors of ALL yielded very high satisfaction among participants. The telerehabilitation method of delivery may have been a key factor in their consent to participate in the project, but the group approach, patient–parent paired training, and supervision by a kinesiologist were the main factors that spurred participants to adhere to the program throughout the 16 weeks of interventions.

5.2. Future Avenues

Future studies should further explore the impact of personal and family factors on adherence to telerehabilitation, in order to address challenges and promote participation in such programs. In a similar vein, the reasons why some ALL survivors chose not to participate or abandon during the course of the intervention should be explored, in order to provide solutions and programs that are accessible and appealing to a larger group of patients and survivors. Lastly, future interventional research should focus on assessing the impact of the program on the emotional and social well-being, in addition to quality of life (QoL) and health-related QoL, of participants using validated tools, and should also examine other formats of telerehabilitation interventions, compared to in-person services.

Author Contributions

Conceptualization, L.-N.V., N.A., D.K., C.L., N.D.-O., and M.L.; methodology, G.L., L.-N.V., K.D., N.A., P.B., and D.K.; software, G.L.; validation, G.L., N.A., and L.-N.V.; formal analysis, G.L.; investigation, L.-N.V.; resources, L.-N.V. and D.K.; data curation, G.L.; writing—original draft preparation, G.L., L.-N.V. and D.K.; writing—review and editing, G.L., D.K., L.-N.V., N.A., C.L., N.D.-O., and M.L.; visualization, G.L.; supervision, L.-N.V.; project administration, G.L., N.A., K.D., P.B., and C.L.; funding acquisition, L.-N.V., N.A., D.K., C.L., N.D.-O., and M.L. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Ethics Committee of CHU Sainte-Justine (protocol code 2018-1555, approval date: 15 March 2018).

Informed Consent Statement

Informed consent/assent was obtained from all subjects involved in the study. Parents of patients below 18 years of age provided signed informed consent; patients between 6 and 17 years of age provided informed assent.

Data Availability Statement

All data supporting results can be found coded at the Center of Motion Analysis of the Shriners Hopital for Children–Canada.

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Conflicts of Interest

The authors have no competing interests to declare.

Abbreviations

ALL	Acute Lymphoblastic Leukemia
B-LL	B-cell Lymphoblastic Lymphoma
HR	High Risk of Relapse
SR	Standard Risk of Relapse
TC	Treatment Completion (month)
VHR	very high risk of relapse
LAEs	late adverse effects

Appendix A: Semi-Structured Interview Questionnaire

General clarification—for use with any question:

- Can you elaborate a little more?
- What do you mean by that?
- Could you give me an example of this?
- Why do you think this is so?

Appendix A.1. Introduction

We know that you have had acute lymphoblastic leukemia, and that you have been offered telemedicine services to limit side effects on the musculoskeletal system. This project seeks to follow up with patients who have received this type of service, in order to better understand their experience. In this way, we hope to better identify the factors that have harmed or helped the process and thus improve the experience of users in general. This project is specifically looking at telemedicine, so I will not ask you about the delivery of more traditional rehabilitation services, if you have received any. I would like you to tell me about your personal experience with telemedicine services and technologies. Your participation in this project remains confidential. We are recording this interview to enable the interview to be transcribed. Your participation is important and much appreciated. That said, if you see fit to end the interview, you are free to do so at any time, and this without consequences for you. Moreover, feel free to ask questions as needed, whether about the interview or the study. We are very interested in your feedback, whether positive or negative, and keep in mind that there is no right or wrong answer. Would you be ready to start?

Appendix A.2. Interview Questions

(1) We define telemedicine as any offer of remote rehabilitation services using telecommunication technologies, so by computer, smartphone, iPhone…. Can you give me your general opinion on telemedicine? This is not strictly limited to the services you have received.

Follow-up questions:

Can you give me an example of a benefit of telemedicine?

Can you give me an example of a disadvantage of telemedicine?

(2) We will now talk about your experience when you received the telemedicine services with the Zoom system. Above all, I would like you to tell me about what went well and what went wrong.

Follow-up questions:

What made the service easier to use/did not require too much effort?

What made you become comfortable with the service?

What made it easy to use?

What kind of difficulties did you encounter during the telemedicine sessions?

Has this changed over time?

Did you have any technical problems? If so, have these had an impact on the quality of the services offered? Have they affected the quality of care provided?

How would you describe your relationship/level of familiarity with your therapist?

(3) When you first received services from TR, was there anything that you found particularly difficult or did you have any prior concerns? If so, what was it?

Follow-up questions:

Were there any situations that you did not like/found annoying/embarrassing?

Did you have any concerns about using telemedicine at home?

Did you have any concerns about your security/privacy/the space it would occupy?

If yes, did your therapist respond to your concerns?

Have you ever observed or heard of any mishaps involving the provision of telemedicine services?

Have you ever had accidents or near misses during telemedicine sessions?

(4) What did people around you think/what was their opinion of telemedicine?

Follow-up questions:

Do people around you base their opinion of telemedicine on past experience? If so, what was their opinion from their personal experience?

(5) What did you think of the “parent–child” training experience?

Follow-up questions:

What was the attitude of the parent/child during the telemedicine sessions (e.g., was he/she enthusiastic or negative/negative)? How did your parent/child influence your training experience?

Do you feel that working out in pairs helped or hindered your experience? How and why?

(6) What did you think of the telemedicine group training experience?

Follow-up questions:

What was the attitude of other parents/children during the telemedicine sessions (e.g., was he/she enthusiastic or negative/negative)? How did group training influence your telemedicine experience?

Do you feel that being several helped or hindered the training? How and why?

(7) Did you feel that your personal experience was positively or negatively influenced by the kinesiologist?

Follow-up questions:

What was the attitude of the kinesiologist during the telemedicine sessions (e.g., was he/she enthusiastic or negative/negative)? How did your kinesiologist influence your telemedicine experience?

Was the information you received during your telemedicine sessions with your kinesiologist sufficient? Did it meet your needs? If not why?

(8) If you needed physical training again, would you suggest another kinesiologist to use Zoom?

Follow-up questions:

Can you tell me why?

(9) Who do you think could benefit from this type of service?

Follow-up questions:

Why?

Can you give me an example?

(10) I would just like to review my notes for a moment to check if I forgot anything or if I want more information on something…

Follow-up questions:

Perceived effectiveness of the program? Perceived benefits or consequences on health or well-being on the day-to-day basis or in the context of the sessions?

Can you give me an example?

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Chapter 5- Discussion

5.1. Feasibility

This thesis examined the feasibility of a telehealth-delivered program for rehabilitation post-cancer treatments. As such, challenges to the recruitment process and adherence to the program were discussed in the first article, and the technical challenges from the participants' perspective were discussed in the second manuscript, either collected through interviews or review of the kinesiologist's clinical notes. However, to complement the feasibility assessment provided in the manuscripts, this thesis discussion will address the challenges encountered throughout the creation and administration of the intervention program regarding two principal topics: the selection of a telehealth system and the interactive pain management.

The Selection of a Telehealth System

The first two participants received a month and a half of their training regimens on an application called REACTS. This is a telemedicine system created for medical education purposes but was not tailored for patients and their parents. The system was unintuitive despite training being provided during the initial visit. As a result, it would take 5 to 15 minutes for families to connect, and the kinesiologist would often need to call them to assist in connecting to the telerehabilitation sessions. This was a major challenge that was resolved by changing to a more user-friendly system: Zoom application, which is secure and Health Canada approved (108). In addition to the problem of connection, the first system also brought forth challenges for families to stay connected throughout sessions. Both of these issues were easier to manage for participants using the second system, which required lower Internet bandwidth. In our experience with low Internet bandwidth, the REACTS system would interrupt the connection between the kinesiologist and participants, whereas the Zoom system would be pixelized and decrease the size of the participant's video output without breaking the connection. This observation aligns with the article by Hawley-Hague et al. 2021, which reported poor connectivity as a barrier to the reliability, perceived usefulness, and feasibility of a telehealth system (119). A scoping review further highlighted the need for future studies to elaborate more on the technical aspect of telerehabilitation systems, and the technical challenges of these systems (108). Nonetheless, in view of the COVID-19 pandemic, and its associated increase in remote working and schooling, this thesis suggests that the post-pandemic era may emerge with a different degree of reliability for videoconferencing telehealth systems.

The Interactive Pain Management

Pain was only documented as described in the "methods – study procedures" section of the first manuscript (120) to adapt the interventions; the aims of the telerehabilitation project were not specifically related to pain management. Nonetheless, the authors felt it was crucial to add overall information sessions requiring training adaptations for pain in the first manuscript, as it turned out to be a predominant aspect of the feasibility of administering the program and considering that pain is rarely reported in interventional studies despite its presence in the literature (22,58,82). Additionally, a detailed table of occurrence of patients' and parents' pain was added in the second manuscript, because of the importance given to the aspect of pain education and adaptation in the interviews, when discussing their experience of supervised training with the participants. Therefore, pain management may be a key aspect of future telerehabilitation studies (121). In this perspective, the present thesis suggests that future interventional studies should quantify MSK pain during exercise in this population, and provide educational tools on the matter (122,123). To this extent, the second manuscript proposed that an interdisciplinary approach may be beneficial for patients. However, the nature of the collaboration that best benefits patients remains to be determined (86).

5.2. Exploration of MSK and Functional Improvement

The first manuscript provides only an overview of the MSK and functional parameters given the small sample size. However, this thesis discussion will elaborate on the effect of the exercise intervention on muscle, bone, and cardiopulmonary parameters, to provide more context with the literature.

Muscle Parameters

Sarcopenia (i.e. decreased muscle function and muscle mass) and myosteatosis (i.e. muscle adiposis infiltration) has been reported in patients with ALL at diagnosis, at the end of the induction phase, and at the end of the delayed intensification phase (64). Keeping in mind that pre-intervention results were not compared to controls, the first manuscript suggests that muscle density was lower in patients at the post-intervention assessment than in controls, but without significant difference between groups for muscle mass or functions. Further, contrary to muscle function, muscle mass and density did not increase with the intervention. This aligns with the literature suggesting that myosteatosis may remain inferior to controls (66). However, there are no comparative studies allowing the authors to conclude if adiposis infiltration in skeletal muscles may be resistant to exercise (64,66). Additionally, the increased muscle function at the post-intervention evaluation, and its similarity to controls' results, suggests that patients in early survivorship may be able, to some extent, to recover from decreased muscle mass and function, which aligns with other findings of the literature (10,88–90).

More specifically, related to lower limbs muscle function, the targeted intervention resulted in significant muscle force and power improvements reported in the first manuscript. This is not surprising given that the training intervention mainly focused on lower limbs. To indicate the clinical significance of the improvement, the between sessions, 1 week apart, minimal detectable difference (MDD) was assessed in a similar pathological population. In the first manuscript, the average increase in relative force was of 0.42 multiples of body weight, which is slightly under the 0.53 MDD reported in the literature (124). Similarly, relative peak power showed an average increase of 2.67 W/kg which is also under the 3.19 MDD reported in this previous study. These results suggest that the observed change could be due to variability in the measurements. However, once a patient diagnosed with relapse a couple of weeks after the end of the program was removed from the analysis, the average increase in relative peak force and power was respectively of 0.55 and 3.05, suggesting that improvements may be true changes rather than artifact due to measurement variability. The latter would align with lower limbs muscle function improvements reported in the literature, in both feasibility (89), and RCT (84,88,90) studies.

In opposition with observations of lower limb functions, no improvement was noted in the first manuscript for the upper-limbs force despite the presence of a deficit. This contrasts with a study from Esbenshade et al. showing improvement in upper-limb force even if they did not target it specifically. It could be hypothesized that the general volume of exercise imposed in this other study was higher than in the current thesis (3.5-5.25 > 2.25 hours/week) and could have led to more upper-limb stimulation (89). The fact that patients showed a significant deficit in upper-limbs muscle force indicates that exercise programs in youth survivors of cancer could benefit from targeted training aiming at improving upper-limb muscle force.

Bone Health

The first manuscript further reports increased total BMC, total and cortical CSA, in addition to SSI at both the 14% and 38% sites of the tibia at the post-intervention evaluation, compared to the baseline assessment, in accordance with the Mechanostat theorem (53). Increases in BMC and CSA could, however, be associated with the children's growth. To ascertain that change in bone parameters was associated with the exercise training and not entirely with growth, we ran supplementary bivariate correlations between change in height and weight and change in bone parameters. No significant association (all p-values > 0.15) was found between any growth-associated factors and bone parameters suggesting that changes in bone parameters are associated with the mechanical workload of the exercise interventions rather than with growth itself. To this end, the results of the correlation analysis between BMC at 14% and absolute force generated during the M2LH showed a positive relationship between muscle force and bone strength indicating that stronger muscles are associated with stronger bones. These results suggest that the bone mechanotransduction and modeling process are normal in young early-on survivors of hematological malignancies and that increasing muscle strength may lead to increased bone strength.

Furthermore, we can observe that all improvements happened in the cortical bone (i.e., 14% and 38% sites), rather than in the trabecular bone (i.e., 4% site). Results of the present study showed that most cortical bone parameters, except for cortical density, increased following the intervention. This is in line with the literature, indicating that cortical bone adapts faster than trabecular bone by increasing its CSA while maintaining or increasing its BMC without increasing its mineral density during bone remodeling (54,55). Studies looking at bone improvement following an intervention will often only report or measure bone density because it is a well-accepted surrogate of bone strength. In the current thesis, bone strength increased as shown by the increase in SSI, without any significant change in BMD. This suggests that future studies on bone health should include parameters other than BMD, such as Total CSA, total BMC, or SSI, to understand what is truly happening at the bone strength level.

Cardiopulmonary Functions

It is well documented that cardiopulmonary functions in patients with childhood malignancies are impaired compared to their normal state, even in their survival phase (5,81,125). Additionally, the 6MWT is a well-validated test to assess indirect cardiopulmonary function in pediatric clinical settings (126). The average 53 m (median 40 m) improvement, from pre- to post-intervention evaluations, in addition to the supplementary one-sample Wilcoxon Signed Rank Test comparing patients' improvement to the 15m threshold (i.e., limits of agreement, testing sessions 2 to 4 weeks apart, from a validity and reliability study (127)), both summarized in the first manuscript, seem to indicate that the program brought clinically meaningful cardiopulmonary benefits to the patients. It appears that the duration of the training sessions and intensity of the resistance and plyometric training were sufficient to generate cardiopulmonary stimulation, similar to other programs (88–90), although the training program did not specifically aim at improving cardiopulmonary function, nor did it involve traditional aerobic exercises (e.g., walking, running, biking).

Significance of the MSK and Functional Results

The above-mentioned physiological benefits need to be interpreted in light of the small study sample size, preventing any concrete conclusions on this aspect of the intervention. However, and despite the small sample size, there are some indications that true physiological changes occurred following the intervention: (1) Eight out of nine patients showed improvements, the only one who did not was relapsing as they performed the second evaluation; (2) Both muscle and cardio showed improvements above the MDD; (3) Bone improvements did not correlate with changes in height or body mass suggesting that the exercise intervention led to the improvements. Nonetheless, the answers to these interrogations might be found in a study from a Spanish research group that published a protocol aimed at determining if an asynchronous telehealth-delivered exercise program could improve bone health in survivors of pediatric cancer (128).

5.3. Exploration of Patients' and Parents' Perspectives

When discussing qualitative studies, conceptual frameworks are often used to interpret the results. With regards to telerehabilitation that includes both the adoption of new technology and the adoption of action towards health. Two models (Technology Adoption Model: TAM (129); and Health Beliefs Model: HBM (130)) could provide additional insights into the factors leading to a successful implementation of such therapeutic intervention. The first model describes how external variables may influence the behavioral intention to use the technologies, by the perceived usefulness and ease of use of the technology to moderate the attitude of the user (i.e., patients) towards using the technology, with the final objective of having patients use the technological system. The HBM provides additional variables regarding the process of patients taking action to improve their health. It describes how the patient considers the severity of their health condition, their health motivation, and their balance of perceived benefits vs. barriers to act towards their health when cues motivate actions. In both models, the goal is to describe user motives and reasoning to take action.

In fact, a systematic literature review published in 2018 by Rahimi, B., et al., showed the different conceptual models used to interpret technology adoption in the field of health (131). In this systematic review, 17 studies provided information on the perspective of the patients, however, the large variety of technological applications revealed that only a few studies showed the use of an integrative model for TAM with HBM. However, the latter integrative model was not specific to telerehabilitation, where the desired behavior reoccurs frequently (i.e., adherence (130)). In this perspective, it seems rather improbable that participation in the current program could be interpreted using only one of the previously mentioned models, as the pediatric context relates to multiple stakeholders to achieve actions. This is why this thesis proposes an integrative model specific to telerehabilitation, inspired by the Ahadzadeh et al. model (130), to interpret its results.

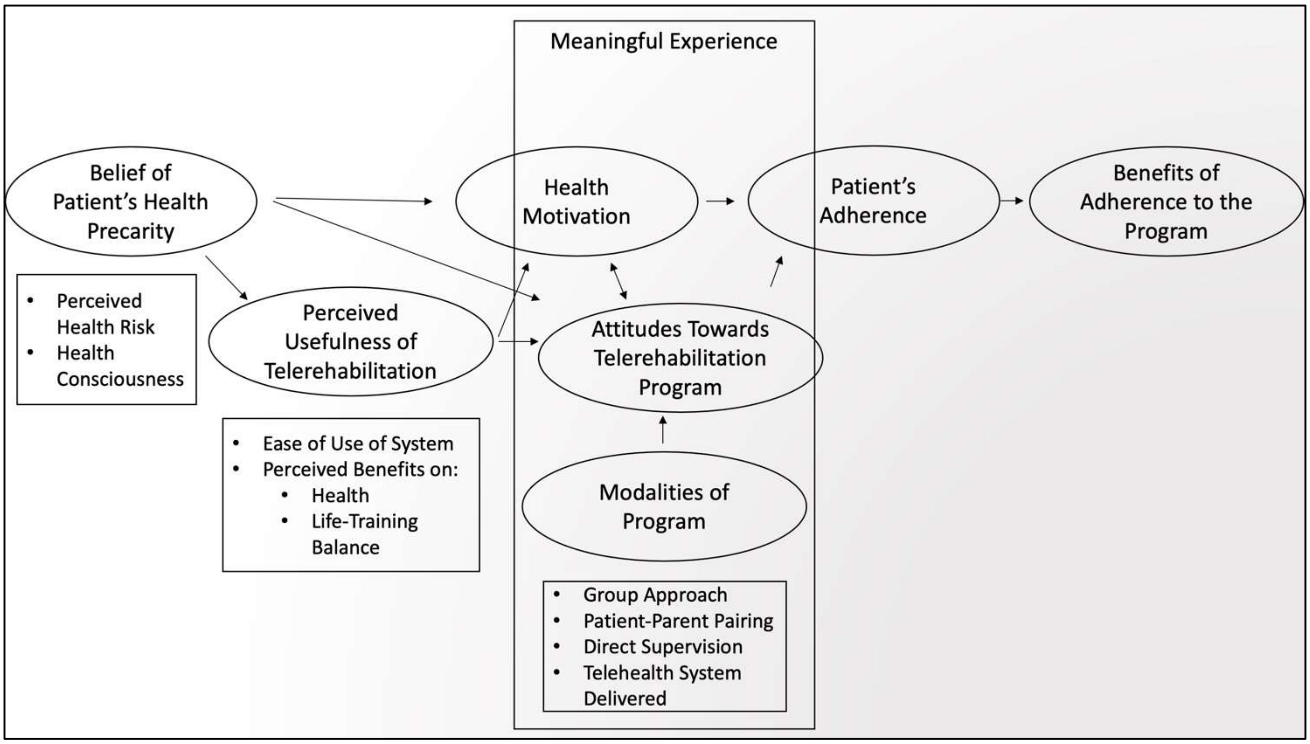

Figure 1. Integrative Model of Adherence to Telerehabilitation.
The definition of meaningful experience in the model is based on the conceptual framework illustrated in the literature review (figure 2) by Vanska, Sipari, and Haataja (100)

Respective Roles of Stakeholders

<u>a) The Role of the Parent</u>

Although it was previously determined that parents play an essential partnership in the delivery of rehabilitation services (93), the combination of the manuscripts has helped to highlight some of their important roles in a patient's adherence to a telerehabilitation program. Firstly, when recruiting, parents are the first point of contact between the family and the research team; they become the decision maker. As such, taking the engagement to participate in a telerehabilitation program may be based on two main factors: the belief of a child's health precarity, relating to the perceived health risk and health consciousness, and the perceived usefulness of telerehabilitation. The belief of a patient's health precarity may explain the poor recruitment rate reported in the first manuscript, because families who were further into survivorship may not perceive their risk of potential LAEs, or may lose sight of it because of the new challenges of going back to daily activities. Therefore, the target period of recruitment may be when families are adapting to the new reality of survivorship, as was recommended by the participants, and as families may be more aware of the value of health interventions during that period, instead of when they are established in their new reality (98,132). Secondly, parents are most commonly attributed a motivational and supportive role (88,93). This is a role that was valued by both patients and parents because assisting their child was described as one of the benefits of the patient-parent paired training. Thirdly, a last important role put forth in the results of the second manuscript was for parents to be participants themselves, in order to provide companionship to their child. Their role as a participant would then be to fully engage in the activity and live the meaningful training experience with the child (100). However, in order to do so, the parent must have their needs fulfilled as well: this is why, in the interviews, parents greatly appreciated the opportunity to access pain management and adaptation for themselves, in addition to their child. If parents experienced pain or inability to do the exercises, due to the level of difficulty, they would then fall back into their supportive role. Further, to take on the role of companion for the patient, parents must consider their own health motivation.

Briefly, the first role of decision makers would be related more to the recruitment, whereas their supportive and companion roles would be important for patients' adherence to the program.

<u>b) The Role of the Patient</u>

As mentioned in the second manuscript, in order for patients to have a meaningful experience in the telerehabilitation program, they need to have fun, interact with others, and experience situations where they feel capable and autonomous (100). However, in the context of a grouped program, they also have the role of contributors to the attitude towards the program of other families. Therefore, proactivity of the child towards modalities (e.g., choosing to connect to the training themselves or connecting a couple of minutes earlier to talk with other families) would be a situation where they have positive effects on the meaningful experience of their parent or other participants, in addition to experiencing capability themselves. Further, like the parent, active participation in the exercises can be an opportunity for the child to feel autonomous and influence the attitude towards the telerehabilitation program of others. To encourage such behavior, the kinesiologist formulated some exercises such as challenges or games and would let patients decide the order of the exercises or choose between versions of exercises.

Health Motivation

Lastly, it is recognized that the perception of health risk, and therefore the belief of health precarity, is positively associated with the motivation to adopt behaviors favorable to health, as demonstrated in the HBM (130). This is also reflected in the literature on home-based programs and adherence (91). This is why, in creating the proposed model presented above (figure 9), the authors added a motivational variable (Health Motivation) as a direct predictor of the patient's adherence behavior to the telerehabilitation program, in an effort to improve the representativeness of the model. The results discussed in both manuscripts (relating to self-efficiency: first manuscript; and modalities being facilitators to adherence: second manuscript), are coherent with the theory of self-determination (133). The latter states that intrinsic motivation, based on autonomy, competency, and relatedness, "facilitates more autonomous forms of behavioral regulations" (134), which also aligns with elements of the meaningful participation framework mentioned in the literature review. This theoretical similarity demonstrates that future studies should further promote approaches conscious of motivation, in order to maximize telerehabilitation program adherence and its potential patient benefits.

Chapter 6- Conclusion

In response to the research questions included at the end of chapter 2, the first manuscript aimed to a) assess the feasibility of a grouped telerehabilitation service and b) explore the program's benefits to the MSK health of patients. Therefore, it was hypothesized that a) delivering telerehabilitation services to ALLs would be feasible, with high adherence to the program (>80% of sessions attended), and b) that patients completing the program may have improved MSK or functional health. The second manuscript aimed to c) explore patients' and parents' experience with a grouped telerehabilitation program.

In response, the results of the first manuscript showed a) an 89% adherence rate for a 75% completion rate, suggesting that grouped telerehabilitation may be feasible; and b) improved lower limbs muscle force (relative) and power (absolute and relative), cardiopulmonary function (6MWTD), and cortical bone at the 14% and 38% sites of the tibia (total CSA, total BMC, cortical CSA, SSI) at the post-intervention evaluation. This suggests that the program may have been beneficial to the MSK and functional health of patients. In fact, it is also one of the first interventional studies to suggest bone health benefits of exercise through increased cortical bone parameters observed.

The second manuscript provided results on c) the perceived challenges and benefits of each modality by patients and parents completing the program at the post-intervention interview, in addition to providing information on their technical barriers to intervention (pain, videoconferencing application, training watch). Related to the telehealth delivery of services, the telerehabilitation perceived usefulness was deemed a critical aspect in choosing to participate. Further, the appreciation of the participants towards the program provides good information about facilitators and limiting elements which will help to improve the program and increase its accessibility to families. The modalities of the telerehabilitation service would have impacted adherence more than recruitment, as participants were already aware of their health condition requiring modification of lifestyle habits and to the possible benefits of the program on the patient's health and life-training balance.

In the literature, many studies with home-based interventions have considered the health value of providing exercise programs to patients and early survivors of ALL (7,10,82,86–89), in addition to making interventions accessible to the families, however, not all programs considered including modalities fulfilling the needs and motivators of patients (86,87,90). Therefore, the results of the second manuscript suggest that modalities of intervention prompting satisfaction of the patients and their families (i.e., grouped approach, patient-parent paired training, and supervision) may be as important for patient adherence as the health value (i.e., improving MSK health in early ALL survivors) and accessibility (i.e., telehealth, schedule).

The next step would be to confirm the MSK findings in a large cohort and assess whether there are added health benefits compared to standard care. This program should take into account the findings of this thesis related to modalities, and promote a multidisciplinary approach for better pain management, in order to provide tools to survivors in view of future exercise experiences. This future project should also integrate the following outcome measures: pain, exercise intensity monitoring, and extensive bone health parameters.

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Appendix: Physical Training Protocol

This training plan should be viewed as a guide rather than a rigid protocol. Thus, the kinesiologist will be able to recommend the variants of an exercise best suited to the condition of participants. The training will be done in pairs. This feature is advantageous. To promote intrafamily interactions, the exercises in green in the program below included a specific instruction to do the movement between parent and patient. Additionally, games and challenges were incorporated in the training to stimulate interfamily interactions (9).

Block 1, Training 1

Warm-up Exercises	Duration	Comments & Modifications
Butt kick	45s	Possibility with or without jumps/jog.
Guided tapping	45s	
Jumping jack	45s	idem
High knees	45s	idem
Step tapping	45s	idem
Side-to-side step	45s	
Worm	45s	
Select 3 out of the 7 exercises; repeat twice (2 sets) Total time of the warm-up = 5 m		
Resistance Exercises	**Comments & Adaptations and Progressions Examples**	
90º Squat & stiff leg deadlift (with elastic)	Squat options: Easier option 1= Chair squat, Easier option 2= Touch squat (with chair) Harder option 1 = Slower Harder option 2 = Arms up	
Stiff leg deadlift & squat (with elastic; reversing the roles)	Stiff leg deadlift options: Easier option 1= Stand 15 cm in front of a wall and touch it with butt while keeping back straight (helps children understand the essence of mvt) Easier option 2= Hold the elastic in supination (helps with retraction of scapula) Harder option 1 = Tabletop Harder option 2 = Hands pulling the elastic behind the hips (more triceps and core activation)	
Push-up & plank	Push-up options: Easier option 1= Knees on the floor (decreases unfavorable lever arm) Easier option 2= Start from the ground (working eccentric when concentric is too difficult)	

	Harder option 1 = Feet on the step (increases proportion of weight on upper limbs) Harder option 2 = Hand under armpit (more triceps activation)	
Plank & push-up	Plank options: Easier option 1= Knees on the floor (decreases unfavorable lever arm) Easier option 2= Hands on the step Harder option 1 = Feet together (increases instability) Harder option 2 = Raise one foot off the ground, hold for 2 seconds, and lower, and alternate raising legs	
Hopping 2 feet	Hopping options: Easier option 1= Calf raise (no impact) Easier option 2= Single leg calf raises (no impact) Harder option 1 = Feet together (increases instability) Harder option 2 = Hopping on one foot or jumping jacks	
Alternate front lunges	Lunges options: Easier option 1= Wall-lunge (guide the front knee to not increase tibio-patellar pressure) Easier option 2= Chair lunge, in a lunge position, back knee resting on the ground, push up to extended lunge position, while holding a chair Harder option 1 = Pulse lunges (5 pulses per side then switch) Harder option 2 = Alternate jumping lunges	
Week 1: 2 sets of 8 reps Week 2: 3 sets of 8 reps Week 3: 3 sets of 10 reps Week 4: 3 sets of 12 reps Concentric-Eccentric tempo: 1-2 * Breaks = 20-30s between exercises & 1m30s between sets		
Cool-down Exercises	Duration	Comments
Stretching hamstring	30s (L) & 30s (R)	
Stretching quadriceps	30s (L) & 30s (R)	
Stretching glutes and hip flexors	30s (L) & 30s (R)	
Stretching lumbar	30s	
Mobilization ankles	30s (L) & 30s (R)	
Number of sets = 1; Total time of the cool down = 5 m		

Block 1, Training 2

Warm-up Exercises	Duration	Comments
Butt kick	45s	Possibility with or without jumps/jog
Guided tapping	45s	
Jumping jack	45s	idem
High knees	45s	idem
Step tapping	45s	idem
Side-to-side step	45s	
Worm	45s	
Select 3 out of the 7 exercises; repeat twice (2 sets) Total time of the warm-up = 5 m		

Resistance Exercises	Comments & Adaptation and Progression Examples
Squat (with weighted ball)	Squat options: Easier option 1= Chair squat, Easier option 2= Touch squat (with chair) or sumo squat with weighted ball Harder option 1 = Slower Harder option 2 = Arms up
Stiff leg deadlift & bicep curl (with elastic)	Stiff leg deadlift options: Easier option 1= Stand 15 cm in front of a wall and touch it with butt while keeping back straight (helps children understand the essence of mvt) Easier option 2= Hold the elastic in supination (helps with retraction of scapula) Harder option 1 = Tabletop Harder option 2 = Hands pulling the elastic behind the hips (more triceps and core activation)
Bicep curl & Stiff leg deadlift (with elastic)	Bicep curl options: Easier option 1= Both hands holding the elastic together Easier option 2= Full bicep curl with elastic, bending knees when contracting Harder option 1 = Increase the resistance in the elastic Harder option 2 = Arms lifted 90 degrees from body, bicep curl (arm in line with shoulder)
Push-up high-fives	Push-up options: Easier option 1= Knees on the floor (decreases unfavorable lever arm) Easier option 2= Start from the ground, push tummy up first Harder option 1 = Feet on the step (increases proportion of weight on upper limbs) Harder option 2 = Hand under armpit (more triceps activation)
Drop jump 2 feet (with step 10 cm)	Drop jump options:

For the sock hold: Apple picking	Easier option 1= Jump on the step, with parent's help for safety (less eccentric force) Easier option 2= Parent holds sock high in the air, the child jumps off the step and reaches for sock Harder option 1 = If a stair case is available, jump down from a stair onto the ground, then jump onto step then onto ground Harder option 2 = Jumping with two feet together, jump off the step towards left side on the ground, jump 180 degrees, jump back onto step, jump off towards the right side, jump 180 degrees, etc. (over the river and on the bank)
Alternate back lunges	Lunges options: Easier option 1= Wall-lunge (guide the front knee to not increase tibio-patellar pressure) Easier option 2= Chair lunge, in a lunge position, back knee resting on the ground, push up to extended lunge position, while holding a chair Harder option 1 = Pulse lunges (5 pulses per side then switch) Harder option 2 = Alternate jumping lunges

Week 1: 2 sets of 8 reps
Week 2: 3 sets of 8 reps
Week 3: 3 sets of 10 reps
Week 4: 3 sets of 12 reps
Concentric-Eccentric tempo: 1-2
* Breaks = 20-30s between exercises & 1m30s between sets

Cool-down Exercises	Duration	Comments
Stretching hamstring	30s (L) & 30s (R)	
Stretching quadriceps	30s (L) & 30s (R)	
Stretching glutes and hip flexors	30s (L) & 30s (R)	
Stretching lumbar	30s	
Mobilization ankles	30s (L) & 30s (R)	

Number of sets = 1; Total time of the cool down = 5 m

Block 2, Training 1

Warm-up Exercises	Duration	Comments
Butt kick	45s	Possibility with or without jumps/jog
Guided tapping	45s	
Jumping jack	45s	idem
High knees	45s	idem
Step tapping	45s	idem
Side-to-side step	45s	
Worm	45s	
Select 3 out of the 7 exercises; repeat twice (2 sets) Total time of the warm-up = 5 m		
Resistance Exercises	Comments & Adaptation and Progression Examples	
Squat & stiff leg deadlift (with elastic)	*Put the elastic behind the knees (not under feet) Squat options: Easier option 1= Chair squat Easier option 2= Touch squat (with chair) (halfway down in the squat) Harder option 1 = Pulse squats with (5 pulses then raise) Harder option 2 = Squat jumps	
Stiff leg deadlift & squat (with elastic)	If possible, increase the resistance in the elastic deadlift options: Easier option 1= Halfway down deadlift without elastic Easier option 2= Full deadlift without elastic Harder option 1 = Deadlift, increase the resistance in the elastic Harder option 2 = Single leg deadlift, with/without resistance band	
Push-up & plank	*The person who does the push-up must finish their repetitions before the person doing the plank stops Push-up options: Easier option 1= Knees on the floor (decreases unfavorable lever arm) Easier option 2= Start from the ground (working eccentric when concentric is too difficult) Harder option 1 = Feet on the step (increases proportion of weight on upper limbs) Harder option 2 = Hand under armpit (more triceps activation)	
Plank & push-up	Plank options: Easier option 1= Knees on the floor (decreases unfavorable lever arm) Easier option 2= Hands on the step Harder option 1 = Feet together (increases instability)	

	Harder option 2 = Raise one foot off the ground, hold for 2 seconds, and lower, and alternate raising legs	
2 feet Hopping	Hopping options: Easier option 1= Calf raises (no impact) Easier option 2= Single leg calf raises (no impact) Harder option 1 = Feet together (increases instability) Harder option 2 = Hopping on one foot, or hop at the same pace as your parent (for a challenge)	
Rowing (with elastic)	Row options: Easier option 1 = Lying on the ground, raise shoulders slightly off the ground, W, T, I (if the patient has pain) Easier option 2 = Hands held together, two arms rowing together Harder option 1 = Pulse rows (when contracted 5 pulses, then release) Harder option 2 = Rotation: elbows at shoulder height, rotating down and back up with elastic (keeping shoulders down)	
Alternated back lunges (with elastic)	Lunges options: Easier option 1= Wall-lunge (guide the front knee to not increase tibio-patellar pressure) Easier option 2= Chair lunge, in a lunge position, back knee resting on the ground, push up to extended lunge position, while holding a chair Harder option 1 = Pulse lunges (5 pulses per side then switch) Harder option 2 = Alternate jumping lunges	
Week 1: 2 sets of 8 reps Week 2: 3 sets of 8 reps Week 3: 3 sets of 10 reps Week 4: 3 sets of 12 reps Concentric - Eccentric tempo: 1-2 * Breaks = 20-30s between exercises & 1m30s between sets		
Cool-down Exercises	**Duration**	**Comments**
Stretching hamstring	30s (L) & 30s (R)	
Stretching quadriceps	30s (L) & 30s (R)	
Stretching glutes and hip flexors	30s (L) & 30s (R)	
Stretching lumbar	30s	
Mobilization ankles	30s (L) & 30s (R)	
Number of sets = 1; Total time of the cool down = 5 m		

Block 2, Training 2

Warm-up Exercises	Duration	Comments
Butt kick	45s	Possibility with or without jumps/jog
Guided tapping	45s	
Jumping jack	45s	idem
High knees	45s	idem
Step tapping	45s	idem
Side-to-side step	45s	
Worm	45s	
Select 3 out of the 7 exercises; repeat twice (2 sets) Total time of the warm-up = 5 m		

Resistance Exercises	Comments & Adaptation and Progression Examples
Burpees	Burpees options: Easier option 1 = Walk out to plank and walk back, stand up, repeat, without jump Easier option 2 = Walk out to plank, frog jump, stand up, repeat Harder option 1 = Burpee with full push-up Harder option 2 = Burpee + 2 jump squats
Squat & stiff leg deadlift (with elastic)	*Put the elastic behind the knees (not under feet) Squat options: Easier option 1= Chair squat Easier option 2= Touch squat (with chair) (halfway down in the squat) Harder option 1 = Pulse squats with (5 pulses then raise) Harder option 2 = Squat jumps
Squat & **stiff leg deadlift** (with elastic)	If possible, increase the resistance in the elastic Deadlift options: Easier option 1= Halfway down deadlift without elastic Easier option 2= Full deadlift without elastic Harder option 1 = Deadlift, increase the resistance in the elastic Harder option 2 = Single leg deadlift, with/without resistance band
Leg raise, laying down on your back, "write your name"	*Other person has to be able to read the letters (can be a game to guess the words) Leg Raise options: Easier option 1= Leg raise 1 leg at a time, the other leg bent 45 degrees Easier option 2= Leg raises, high-five parents with feet Harder option 1 = Assisted leg pushes (have parents standing and push child's legs to different directions) Harder option 2 = V sit with high-five parents on each side
Chest press (with elastic)	Chest press options: Easier option 1= Chest press with weighted ball (continuous resistance) Easier option 2 = Wall push-up

	Harder option 1 = Standing, with elastic band, behind the partner's knees or waist (depending on child's height) and chest press, elbows in line with shoulders Harder option 2 = Single arm chest press with weighted ball or elastic, lying on the ground	
Drop jump 2 feet (with step 10 cm) For the sock hold: Apple picking	Drop jump options: Easier option 1= Jump on the step, with parent's help for safety (less eccentric force) Easier option 2= Parent holds sock in the air, the child jumps off the step and reaches for sock Harder option 1 = If a stair case is available, jump down from a stair onto the ground, then jump onto step then onto ground Harder option 2 = Jump with two feet together, jump off the step towards left side on the ground, jump 180 degrees, jump back onto step, jump off towards the right side, jump 180 degrees, etc. (over the river and on the bank)	
Alternated back lunges (with elastic)	Lung options: Easier option 1= Wall-lunge (guide the front knee to not increase tibio-patellar pressure) Easier option 2= Chair lunge, in a lunge position, back knee resting on the ground, push up to extended lunge position, while holding a chair Harder option 1 = Pulse lunges (5 pulses per side then switch) Harder option 2 = Alternate jumping lunges	
Week 1: 2 sets of 8 reps Week 2: 3 sets of 8 reps Week 3: 3 sets of 10 reps Week 4: 3 sets of 12 reps Concentric - Eccentric tempo: 1-2 * Breaks = 20-30s between exercises & 1m30s between sets		
Cool-down Exercises (all blocks)	Duration	Comments
Stretching hamstring	30s (L) & 30s (R)	
Stretching quadriceps	30s (L) & 30s (R)	
Stretching glutes and hip flexors	30s (L) & 30s (R)	
Stretching lumbar	30s	
Mobilization ankles	30s (L) & 30s (R)	
Number of sets = 1; Total time of the cool down = 5 m		

Block 3, Training 1

From the 3rd month to final evaluation: option for the exercises to be completed on one leg

Warm-up Exercises	Duration	Comments
Butt kick	45s	Possibility with or without jumps/jog
Guided tapping	45s	
Jumping jack	45s	idem
High knees	45s	idem
Step tapping	45s	idem
Side-to-side step	45s	
Worm	45s	
Select 3 out of the 7 exercises; repeat twice (2 sets) Total time of the warm-up = 5 m		

Resistance Exercises	Comments & Adaptation and Progression Examples
Jump squat (with weighted ball) Also called – The flying mummy	Jump squat options: Easier option 1 = Crab walk with elastic around knee Easier option 2 = The clock: squat hold, touch toe at each clock point Harder option 1 = Jump squat adding in 5 pulses Harder option 2 = Jumping squats in-outs with ball
Rowing (with elastic)	Row options: Easier option 1 = Lying on the ground, raise shoulders slightly off the ground, W, T, I (if the patient has pain) Easier option 2 = Hands held together, two arms rowing together Harder option 1 = Pulse rows (when contracted 5 pulses, then release) Harder option 2 = Rotation: elbows at shoulder height, rotating down and back up with elastic (keeping shoulders down)
Burpees	Burpees options: Easier option 1 = Walk out to plank and walk back, stand up, repeat, without jump Easier option 2 = Walk out to plank, frog jump, stand up, repeat Harder option 1 = Burpee with full push-up Harder option 2 = Burpee + 2 jump squats Harder option 2 if have the space = Burpee on one side of step, jump on/off step, squat jump to 180 rotation then next burpee
Hopping 2 feet	Hopping options: Easier option 1= Calf raise (no impact) Easier option 2= Single leg calf raises (no impact) Harder option 1 = Hop with weighted ball, holding at chest (hold the ball as you are giving it a hug) Harder option 2 = Hopping on one foot
Push-up & plank	*The person who does the push-up must finish their repetitions before the person doing the plank stops Push-up options:

	Easier option 1= Knees on the floor (decreases unfavorable lever arm) Easier option 2= Start from the ground (working eccentric when concentric too difficult) Harder option 1 = Feet on the step (increases proportion of weight on upper limbs) Harder option 2 = Hand under armpit (more triceps activation)
Push-up & **plank**	Plank options: Easier option 1= Knees on the floor (decreases unfavorable lever arm) Easier option 2= Downward dog into plank Harder option 1 = Mountain climbers Harder option 2 = Side plank on the knee or staggered feet (top foot in front)
Hip lift, to touch partners' feet	Hip-lift option: Easier option 1 = Glute bridges with elastic over hips, hold tight on either side Easier option 2 = Dead-bug (lying on the ground, opposite hand and leg extend at the same time, alternate and repeat) Harder option 1 = Lying on the ground, both legs in the air, straight up, crunch up, crossing opposite hand to foot Harder option 2 = Single leg glute bridges, with elastic over hips, hold tight on either side
Alternating lunge, (with front foot on 10 cm step)	Lunge option: Easier 1 = Lunge without step Easier 2 = Weighted ball on the floor, back leg knee lowering down to touch the ball Harder 1 = Pulse lunges (5 pulses per side then switch) Harder 2 = Alternate jumping lunges (without step)

Week 1: 2 sets of 8 reps
Week 2: 3 sets of 8 reps
Week 3: 3 sets of 10 reps
Week 4: 3 sets of 12 reps
Concentric - Eccentric tempo: 1-2
* Breaks = 20-30s between exercises & 1m30s between sets

Cool-down Exercises (all blocks)	Duration	Comments
Stretching hamstring	30s (L) & 30s (R)	
Stretching quadriceps	30s (L) & 30s (R)	
Stretching glutes and hip flexors	30s (L) & 30s (R)	
Stretching lumbar	30s	

Mobilization ankles	30s (L) & 30s (R)	
Number of sets = 1; Total time of the cool down = 5 m		

Block 3, Training 2

Warm-up Exercises	Duration	Comments
Butt kick	45s	Possibility with or without jumps/jog
Guided tapping	45s	
Jumping jack	45s	idem
High knees	45s	idem
Step tapping	45s	idem
Side-to-side step	45s	
Worm	45s	
Select 3 out of the 7 exercises; repeat twice (2 sets) Total time of the warm-up = 5 m		

Resistance Exercises	Comments & Adaptation and Progression Examples
Burpees	Burpees options: Easier option 1 = Walk out to plank and walk back, stand up, repeat, without jump Easier option 2 = Walk out to plank, frog jump, stand up, repeat Harder option 1 = Burpee with full push-up Harder option 2 = Burpee + 2 jump squats Harder option 2 if have the space = Burpee on one side of step, jump on/off step, squat jump to 180 rotation then next burpee
Chest press (with elastic)	Chest press options: Easier option 1= Chest press with weighted ball (continuous resistance) Easier option 2 = Wall push-up Harder option 1 = Standing, with elastic band, behind the partner's knees or waist (depending on child's height) and chest press, elbows in line with shoulders Harder option 2 = Single arm chest press with weighted ball or elastic, lying on the ground
Alternated raised-arms squat & ball-press squat (with weighted ball)	Squat options: Easier option 1= Squat with weighted ball Easier option 2= Sumo squat with weighted ball Harder option 1 = Pulse squat (5 pulses) with the ball to lateral lunge back to squat in the center, lateral lunge opposite side Harder option 2 = One leg chair squat with weighted ball (hug hold the ball)
Drop jump 2 feet (with step 10 cm) For the sock hold: Apple picking	Drop jump options: Easier option 1= Jump on the step, with parent's help for safety (less eccentric force) Easier option 2= Parent holds sock in the air, the child jumps off the step and reaches for sock Harder option 1 = If have a stair case, jump down from a stair onto the ground, then jump onto step then onto ground

	Harder option 2 = Jump with two feet together, jump off the step towards left side on the ground, jump 180 degrees, jump back onto step, jump off towards the right side, jump 180 degrees, etc. (over the river and on the bank)
Rowing (with elastic)	Row options: Easier option 1 = Lying on the ground, raise shoulders slightly off the ground, W, T, I (if the patient has pain) Easier option 2 = Hands held together, two arms rowing together Harder option 1 = Pulse rows (when contracted 5 pulses, then release) Harder option 2 = Rotation: elbows at shoulder height, rotating down and back up with elastic (keeping shoulders down)
Lateral one leg squat jumps Also called: The ninja	Squat options: Easier 1 = Lateral squat with other toe resting on the ground, no hop (more stable) Easier 2 = 2 chairs, with step in between, sit on the chair with leg nearest to step in the air, stand up jump to the other leg and sit on other chair Harder 1 = Squat pulse (2-3 times) before jumping Harder 2 = Lateral squat jump over step between switching sides
Sit-up position face-to-face (with weighted ball) with trunk rotation	Sit up options: Easier 1 = Individual crunch, opposite elbow to opposite knee Easier 2 = Individual crunch, opposite elbow to opposite knee, with weighted ball Harder 1 = Full sit up, with arms fully extended over head Harder 2 = Bicycle crunch – 2 (left + right counts as one) then give weighted ball to partner

Week 1: 2 sets of 8 reps
Week 2: 3 sets of 8 reps
Week 3: 3 sets of 10 reps
Week 4: 3 sets of 12 reps
Concentric - Eccentric tempo: 1-2
* Breaks = 20-30s between exercises & 1m30s between sets

Cool-down Exercises(all blocks)	Duration	Comments
Stretching hamstring	30s (L) & 30s (R)	
Stretching quadriceps	30s (L) & 30s (R)	
Stretching glutes and hip flexors	30s (L) & 30s (R)	
Stretching lumbar	30s	
Mobilization ankles	30s (L) & 30s (R)	
Number of sets = 1; Total time of the cool down = 5 m		

Block 3, Training 3

Warm-up Exercises	Duration	Comments
Butt kick	45s	Possibility with or without jumps/jog
Guided tapping	45s	
Jumping jack	45s	idem
High knees	45s	idem
Step tapping	45s	idem
Side-to-side step	45s	
Worm	45s	
Select 3 out of the 7 exercises; repeat twice (2 sets) Total time of the warm-up = 5 m		

Resistance Exercises	Comments & Adaptation and Progression Examples
Burpees	Burpees options: Easier option 1 = Walk out to plank and walk back, stand up, repeat, without jump Easier option 2 = Walk out to plank, frog jump, stand up, repeat Harder option 1 = Burpee with full push-up Harder option 2 = Burpee + 2 jump squats Harder option 2 if have the space = Burpee on one side of step, jump on/off step, squat jump to 180 rotation then next burpee
Drop jump 2 feet (with step 10 cm) For the sock hold: Apple picking	Drop jump options: Easier option 1= Jump on the step, with parent's help for safety (less eccentric force) Easier option 2= Parent holds sock in the air, the child jumps off the step and reaches for sock Harder option 1 = If a stair case is available, jump down from a stair onto the ground, then jump onto step then onto ground Harder option 2 = Jump with two feet together, jump off the step towards left side on the ground, jump 180 degrees, jump back onto step, jump off towards the right side, jump 180 degrees, etc. (over the river and on the bank)
Chest press	Chest press options: Easier option 1= Chest press with weighted ball (continuous resistance) Easier option 2 = Wall push-up Harder option 1 = Standing, with elastic band, behind the partner's knees or waist (depending on child's height) and chest press, elbows in line with shoulders Harder option 2 = Single arm chest press with weighted ball or elastic, lying on the ground
Alternate jumping lunges	Jumping lunges options: Easier option 1 = Lunge then back standing then alternate legs Easier option 2 = Alternating non-jumping lunges Harder option 1 = Alternating jump lunges with 5 pulses per side

	Harder option 2 = Jump lunges (two jumping lunges per side then jump switch)
Rowing (with elastic)	Row options: Easier option 1 = Lying on the ground, raise shoulders slightly off the ground, W, T, I (if the patient has pain) Easier option 2 = Hands held together, two arms rowing together Harder option 1 = Pulse rows (when contracted 5 pulses, then release) Harder option 2 = Rotation: elbows at shoulder height, rotating down and back up with elastic (keeping shoulders down)
Hopping 2 feet	Hopping options: Easier option 1= Calf raise (no impact) Easier option 2= Single leg calf raises (no impact) Harder option 1 = Hop with weighted ball, holding at chest (hold the ball as you are giving it a hug) Harder option 2 = Hopping on one foot
Superhero plank (with limb raise)	*Have to match speed with partner Plank options: Easier option 1= Knees on the floor (decreases unfavorable lever arm) Easier option 2= Hands on the step Harder option 1 = Feet together (increases instability) Harder option 2 = Raise one foot off the ground (opposite of lifted hand), hold for 2 seconds, and lower, and alternate raising legs
Week 1: 2 sets of 8 reps Week 2: 3 sets of 8 reps Week 3: 3 sets of 10 reps Week 4: 3 sets of 12 reps Concentric - Eccentric tempo: 1-2 * Breaks = 20-30s between exercises & 1m30s between sets	

Cool-down Exercises(all blocks)	Duration	Comments
Stretching hamstring	30s (L) & 30s (R)	
Stretching quadriceps	30s (L) & 30s (R)	
Stretching glutes and hip flexors	30s (L) & 30s (R)	
Stretching lumbar	30s	
Mobilization ankles	30s (L) & 30s (R)	
Number of sets = 1; Total time of the cool down = 5 m		

Block 4, Training 1

Warm-up Exercises	Duration	Comments
Butt kick	45s	Possibility with or without jumps/jog
Guided tapping	45s	
Jumping jack	45s	idem
High knees	45s	idem
Step tapping	45s	idem
Side-to-side step	45s	
Worm	45s	
Select 3 out of the 7 exercises; repeat twice (2 sets) Total time of the warm-up = 5 m		

Resistance Exercises	Comments & Adaptation and Progression Examples
Big amplitude jumping lunges	Jumping lunges options: Easier option 1 = Curtsy lunge Easier option 2 = Lunge jump up (standing with feet together) then opposite leg lunge Harder option 1 = Alternating jump lunges with 2 pulses per side Harder option 2 = Jump lunges (two jumping lunges per side then jump switch)
Left foot hop	Hopping options: Easier option 1= Calf raise on the step (no impact) Easier option 2= Single left leg calf raises (no impact) Harder option 1 = Parent holding object up – child has to reach higher to touch it Harder option 2 = Increase speed of hop
Right foot hop	Hopping options: Easier option 1= Calf raise on the step (no impact) Easier option 2= Single right leg calf raises (no impact) Harder option 1 = Parent holding object up – child has to reach higher to touch it Harder option 2 = Increase speed of hop
Rowing (with elastic)	Row options: Easier option 1 = Lying on the ground, raise shoulders slightly off the ground, W, T, I (if the patient has pain) Easier option 2 = Hands held together, two arms rowing together Harder option 1 = Pulse rows (when contracted 5 pulses, then release) Harder option 2 = Rotation: elbows at shoulder height, rotating down and back up with elastic (keeping shoulders down)
Burpees	Burpees options: Easier option 1 = Walk out to plank and walk back, stand up, repeat, without jump Easier option 2 = Walk out to plank, frog jump, stand up, repeat Harder option 1 = Burpee with full push-up Harder option 2 = Burpee + 2 jump squats

	Harder option 2 if have the space = Burpee on one side of step, jump on/off step, squat jump to 180 rotation then next burpee
Trunk rotation, slightly bent arms (with elastic)	Trunk rotation options: Easier option 1 = Hold hands to belly button Easier option 2 = Hold hands to the hip of the turning leg Harder option 1 = Increase band resistance Harder option 2 = Front lunge, with rotation (same lunge side as side you are rotating towards) turn 120 degrees NOT 180 degrees
Lateral jumping squat	Squat options: Easier 1 = Lateral squat with other toe resting on the ground, no hop Easier 2 = Lateral squat with other toe resting on the ground, with hop Harder 1 = Squat pulse (3 times) Harder 2 = Lateral squat jump, with jump squat in between switching sides
Hip lift, touch your partner's feet	Hip-lift option: Easier option 1 = Glute bridges with elastic over hips, hold tight on either side Easier option 2 = Dead-bug (lying on the ground, opposite hand and leg extend at the same time, alternate and repeat) Harder option 1 = Lying on the ground, both legs in the air, straight up, crunch up, crossing opposite hand to foot Harder option 2 = Single leg glute bridges, with elastic over hips, hold tight on either side

Week 1: 2 sets of 8 reps
Week 2: 3 sets of 8 reps
Week 3: 3 sets of 10 reps
Week 4: 3 sets of 12 reps
Concentric - Eccentric tempo: 1-2
* Breaks = 20-30s between exercises & 1m30s between sets

Cool-down Exercises(all blocks)	Duration	Comments
Stretching hamstring	30s (L) & 30s (R)	
Stretching quadriceps	30s (L) & 30s (R)	
Stretching glutes and hip flexors	30s (L) & 30s (R)	
Stretching lumbar	30s	
Mobilization ankles	30s (L) & 30s (R)	

Number of sets = 1; Total time of the cool down = 5 m

Block 4, Training 2

Warm-up Exercises	Duration	Comments
Butt kick	45s	Possibility with or without jumps/jog
Guided tapping	45s	
Jumping jack	45s	idem
High knees	45s	idem
Step tapping	45s	idem
Side-to-side step	45s	
Worm	45s	
Select 3 out of the 7 exercises; repeat twice (2 sets) Total time of the warm-up = 5 m		

Resistance Exercises	Comments & Adaptation and Progression Examples
Burpees	Burpees options: Easier option 1 = Walk out to plank and walk back, stand up, repeat, without jump Easier option 2 = Walk out to plank, frog jump, stand up, repeat Harder option 1 = Burpee with full push-up Harder option 2 = Burpee + 2 jump squats Harder option 2 if have the space = Burpee on one side of step, jump on/off step, squat jump to 180 rotation then next burpee
Superhero plank (with limb raise)	*Have to match speed with partner Plank options: Easier option 1= Knees on the floor (decreases unfavorable lever arm) Easier option 2= Hands on the step Harder option 1 = Feet together (increases instability) Harder option 2 = Raise one foot off the ground (opposite of lifted hand), hold for 2 seconds, and lower, and alternate raising legs
Lateral jumping squats	Squat options: Easier 1 = Lateral squat with other toe resting on the ground, no hop Easier 2 = Lateral squat with other toe resting on the ground, with hop Harder 1 = Squat pulse (3 times) Harder 2 = Lateral squat jump, with jump squat in between switching sides
Right foot drop jump (with step 10 cm)	Jump options: Easier option 1= One leg jump onto the step with parent standing close/holding for safety Easier option 2= Jump onto/off the step, with step in the middle, (the short side of the step facing forward) Harder option 1 = Hold in landing position for 5 seconds Harder option 2 = With 180 degree jump in landing, staying on one leg, have parent standing close/holding for safety

Left foot drop jump (with step 10 cm)	Jump options: Easier option 1= One leg jump onto the step with parent standing close/holding for safety Easier option 2= Jump onto/off the step, with step in the middle, (the short side of the step facing forward) Harder option 1 = Hold in landing position for 5 seconds Harder option 2 = With 180 degree jump in landing, staying on one leg, have parent standing close/holding for safety
Rowing (with elastic)	Row options: Easier option 1 = Lying on the ground, raise shoulders slightly off the ground, W, T, I (if the patient has pain) Easier option 2 = Hands held together, two arms rowing together Harder option 1 = Pulse rows (when contracted 5 pulses, then release) Harder option 2 = Rotation: elbows at shoulder height, rotating down and back up with elastic (keeping shoulders down)
Elevated-arms squat & squat press (with weighted ball)	Squat options: Easier option 1 = Squat press without weighted ball Easier option 2 = Squat with weighted ball, without press Harder option 1 = Jump squat press with weighted ball press Harder option 2 = In out jump squat with holding weight ball
Face-to-face full extension sit-up (with weighted ball)	Sit-up options: Easier option 1 = Full sit up without weighted ball Easier option 2 = Crunch with weighted ball Harder option 1 = Sit-up with legs in butterfly position with weighted ball Harder option 2 = Crunch to opposite leg with leg straight up, with weighted ball, switch sides
Week 1: 2 sets of 8 reps Week 2: 3 sets of 8 reps Week 3: 3 sets of 10 reps Week 4: 3 sets of 12 reps Concentric - Eccentric tempo: 1-2 * Breaks = 20-30s between exercises & 1m30s between sets	

Cool-down Exercises(all blocks)	Duration	Comments
Stretching hamstring	30s (L) & 30s (R)	
Stretching quadriceps	30s (L) & 30s (R)	
Stretching glutes and hip flexors	30s (L) & 30s (R)	
Stretching lumbar	30s	
Mobilization ankles	30s (L) & 30s (R)	

Number of sets = 1; Total time of the cool down = 5 m

Block 4, Training 3

Warm-up Exercises	Duration	Comments
Butt kick	45s	Possibility with or without jumps/jog
Guided tapping	45s	
Jumping jack	45s	idem
High knees	45s	idem
Step tapping	45s	idem
Side-to-side step	45s	
Worm	45s	
Select 3 out of the 7 exercises; repeat twice (2 sets) Total time of the warm-up = 5 m		

Resistance Exercises	Comments & Adaptation and Progression Examples
Burpees	Burpees options: Easier option 1 = Walk out to plank and walk back, stand up, repeat, without jump Easier option 2 = Walk out to plank, frog jump, stand up, repeat Harder option 1 = Burpee with full push-up Harder option 2 = Burpee + 2 jump squats Harder option 2 if have the space = Burpee on one side of step, jump on/off step, squat jump to 180 rotation then next burpee
Right foot hop	Hopping options: Easier option 1= Calf raise on the step (no impact) Easier option 2= Single left leg calf raises (no impact) Harder option 1 = Parent holding object up – child has to reach higher to touch it Harder option 2 = Increase speed of hop
Left foot hop	Hopping options: Easier option 1= Calf raise on the step (no impact) Easier option 2= Single right leg calf raises (no impact) Harder option 1 = Parent holding object up – child has to reach higher to touch it Harder option 2 = Increase speed of hop
Rowing (with elastic)	Row options: Easier option 1 = Lying on the ground, raise shoulders slightly off the ground, W, T, I (if the patient has pain) Easier option 2 = Hands held together, two arms rowing together Harder option 1 = Pulse rows (when contracted 5 pulses, then release) Harder option 2 = Rotation: elbows at shoulder height, rotating down and back up with elastic (keeping shoulders down)
Alternate jumping lunges	Jumping lunges options: Easier option 1 = Lunge then back standing then alternate legs

	Easier option 2 = Alternating non-jumping lunges Harder option 1 = Alternating jump lunges with 5 pulses per side Harder option 2 = Jump lunges (two jumping lunges per side then jump switch)
One-leg deadlift (with step 10 cm and weighted ball)	Deadlift options: Easier option 1 = Single-leg deadlift without weighted ball Easier option 2 = Two-leg deadlift ½ to step with weighted ball Harder option 1 = Hop after deadlift, after raising up Harder option 2 = Single leg deadlift with weighted ball, in rise, bring to a high knee position
Trunk rotation, with slightly bent arms (with elastic)	Trunk rotation options: Easier option 1 = Hold hands to belly button Easier option 2 = Hold hands to the hip of the turning leg Harder option 1 = Increase band resistance Harder option 2 = Front lunge, with rotation (same lunge side as side you are rotating towards) turn 120 degrees NOT 180 degrees
Drop jump 2 feet (with step) For the sock hold: Apple picking	Drop jump options: Easier option 1= Jump on the step, with parent's help for safety (less eccentric force) Easier option 2= Parent holds sock in the air, the child jumps off the step and reaches for sock Harder option 1 = If a stair case is available, jump down from a stair onto the ground, then jump onto step then onto ground Harder option 2 = Jump with two feet together, jump off the step towards left side on the ground, jump 180 degrees, jump back onto step, jump off towards the right side, jump 180 degrees, etc. (over the river and on the bank)

Week 1: 2 sets of 8 reps
Week 2: 3 sets of 8 reps
Week 3: 3 sets of 10 reps
Week 4: 3 sets of 12 reps
Concentric - Eccentric tempo: 1-2
* Breaks = 20-30s between exercises & 1m30s between sets

Cool-down Exercises(all blocks)	Duration	Comments
Stretching hamstring	30s (L) & 30s (R)	
Stretching quadriceps	30s (L) & 30s (R)	
Stretching glutes and hip flexors	30s (L) & 30s (R)	
Stretching lumbar	30s	
Mobilization ankles	30s (L) & 30s (R)	

Number of sets = 1; Total time of the cool down = 5 m