In the Name of God

Rehabilitation & Exercise intervention in BMT & GVHD

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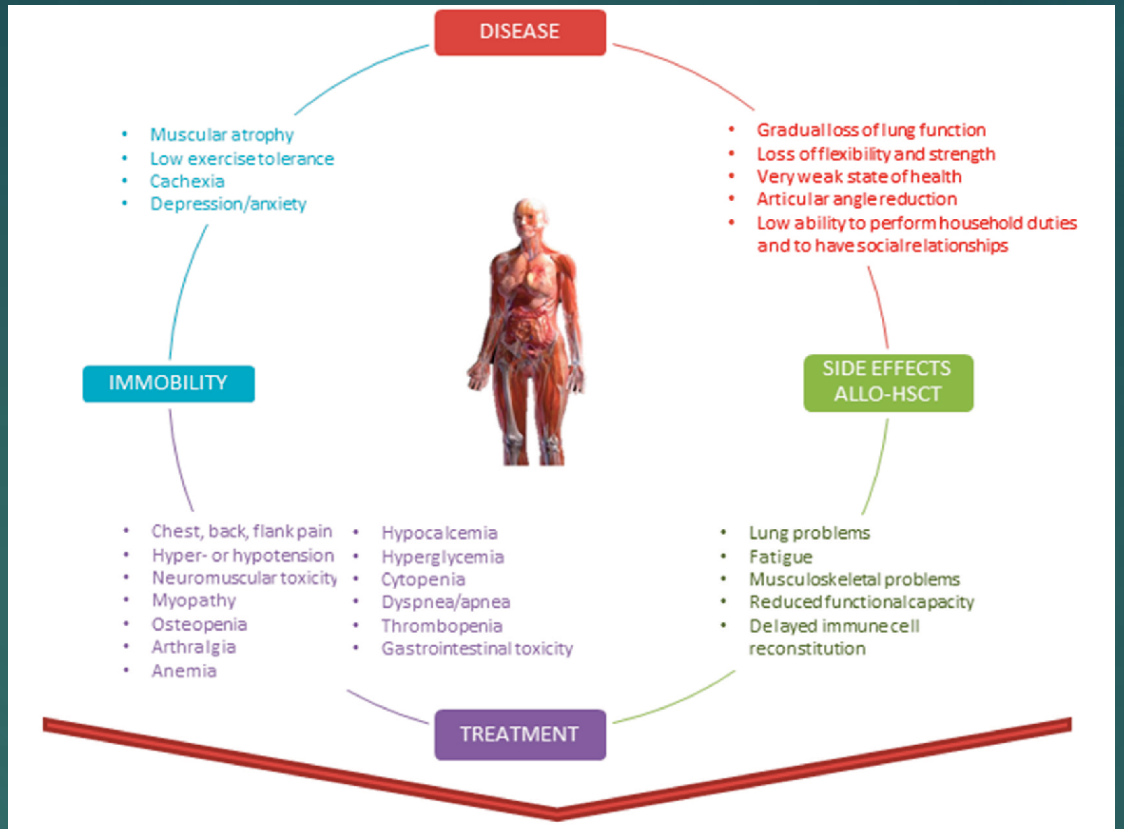
Challenges and Shortcomings of Research on Rehabilitation for cGVHD

- Challenges in Studying Rehabilitation Issues in cGVHD
  - Chronic GVHD has not traditionally been a **focus of rehabilitation** (compared with stroke, spinal cord injury, amputation, etc)
  - **Polymorphic clinical presentation**, so outcome measurements and standardization of trials is difficult
  - Patient populations are essentially **limited to tertiary care centers** with a BMT program
  - BMT physicians **may not be familiar with rehabilitation physician** skill sets, may not collaborate frequently

Challenges and Shortcomings of Research on Rehabilitation for cGVHD

- Examples of Topics in cGVHD Rehabilitation Needing More Research
  - Effects of **aerobic exercise** on reversing cGVHD
  - Bracing and/or splinting trials for sclerotic cGVHD
  - **Inpatient rehabilitation** and the benefits of multidisciplinary assessment
  - Prevalence of **steroid myopathy** and its impact on patient function and health
  - Correlation between loss of physical function and **hospital readmission**



aGVHD

- Liver
- Gastrointestinal tract
- Skin

cGVHD

- Eyes
- Nerves
- Mouth
- Heart
- Lungs
- Hematopoietic and immune systems
- Liver
- Gastrointestinal tract
- Skin
- Nails
- Tendons
- Skeletal muscle
- Joints
- Bones

ain clinical features of acute (aGVHD) and chronic graft-versus-host disease (cGVHD). Abbreviation: allo-HSCT

Common Rehabilitation Issues in cGVHD

Organ	Problem	Intervention
Skin/fascia	Sclerodermatous contractures	OT for ROM and strengthening, splinting, iontophoresis. Surgery likely ineffective and may have negative outcomes.
Muscle	Myopathy	PT for fall prevention and strengthening. Bracing for weak muscles. Adaptive equipment (canes, walkers) as indicated.
Bone	Osteoporosis	Core stabilization, bracing for pain or stability
Peripheral nervous system	Peripheral neuropathy	Bracing for motor weakness, nerve stabilizing agents for pain, wound prevention (proper footwear, frequent skin checks)
Cardiopulmonary	Physical deconditioning	Exercise program (possibly through PT), consider pulmonary or cardiac rehab for specific issues in these organ systems

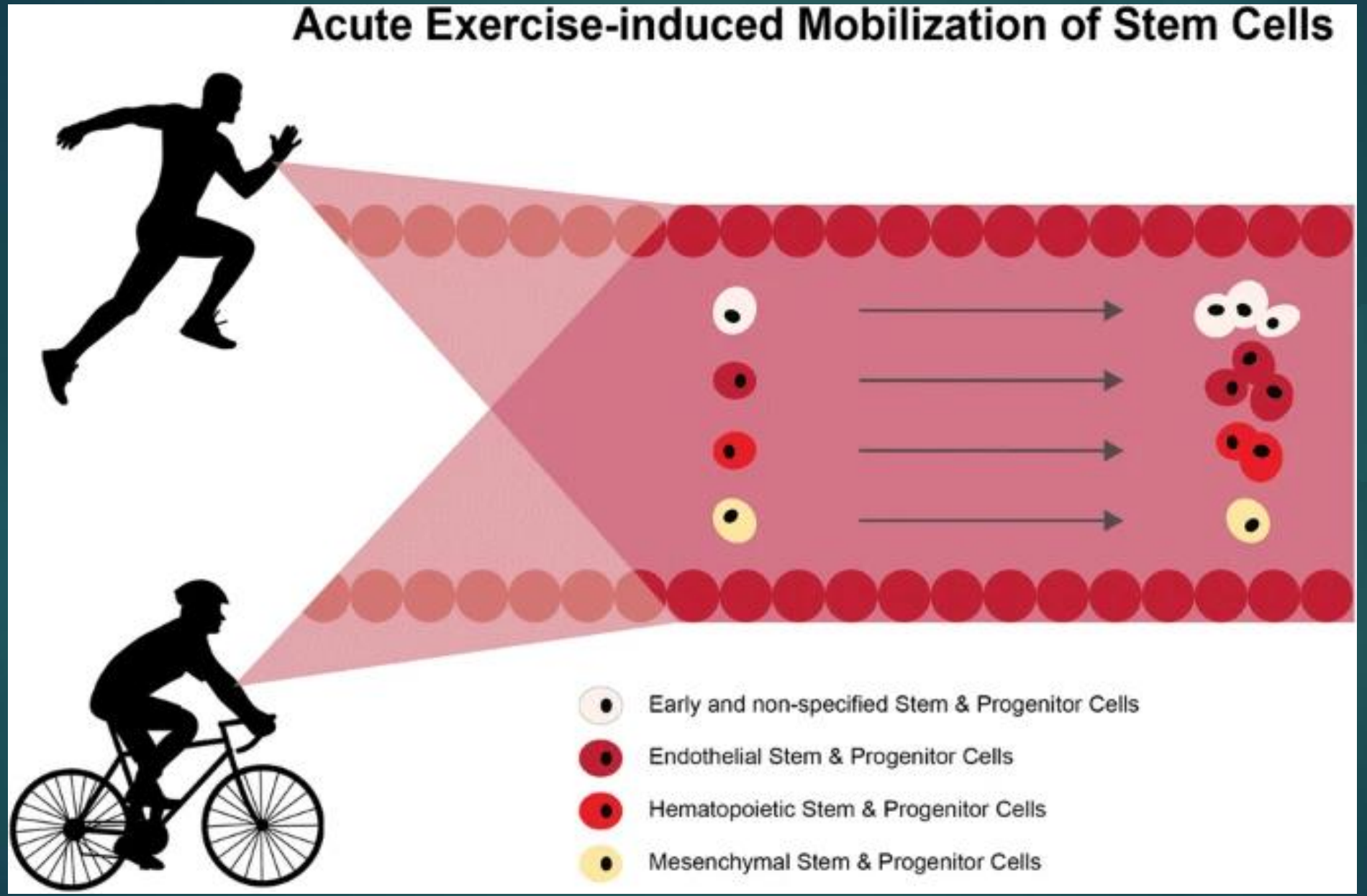
OT indicates occupational therapy; ROM, range of motion; PT, physical therapy.

Exercise as an Adjuvant Therapy for Hematopoietic Stem Cell Mobilization

- HSPC collection protocols rely on pharmacological agents to mobilize hematopoietic stem cells (HSPCs) to peripheral blood.
- Limitations including variable donor responses and long dosing protocols merit further investigations into adjuvant therapies to enhance the efficiency of HSPCs collection.

- Exercise, a safe and feasible intervention in patients undergoing HSCT, has been shown to **robustly stimulate HSPC mobilization** from the bone marrow.

Stem Cells International Volume 2016, Article ID 7131359


Acute Exercise-induced Mobilization of Stem Cells
Early and non-specified Stem & Progenitor Cells
Endothelial Stem & Progenitor Cells
Hematopoietic Stem & Progenitor Cells
Mesenchymal Stem & Progenitor Cells

Future Perspectives

- **First**, the precise **parameters of exercise need to be better defined**. The optimal mode, intensity, and duration of exercise for maximal mobilization of HSPCs need to be established,

- **Second**, a better understanding of the **mechanisms responsible** for exercise-induced mobilization is needed.

- **Finally**, the efficacy of HSPCs mobilized by exercise needs to be **established in the transplantation setting**

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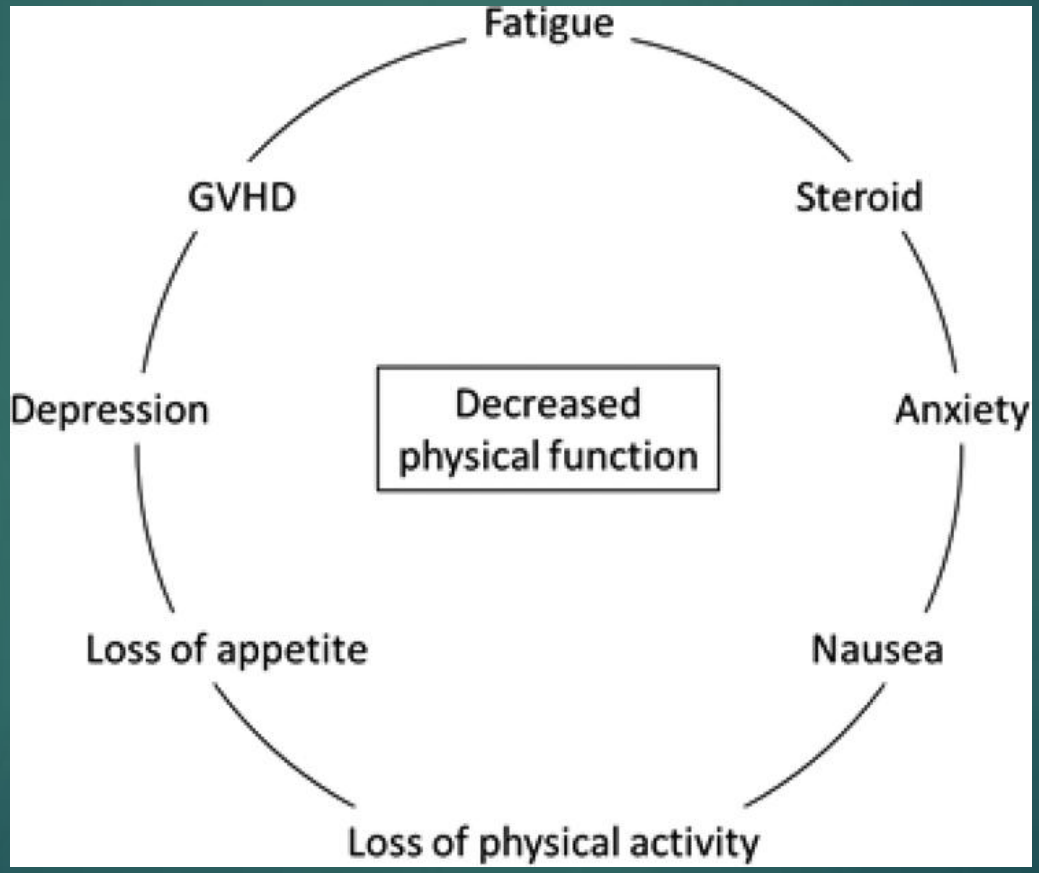
The Benefit of Exercise in Patients Who Undergo Allogeneic Hematopoietic Stem Cell Transplantation



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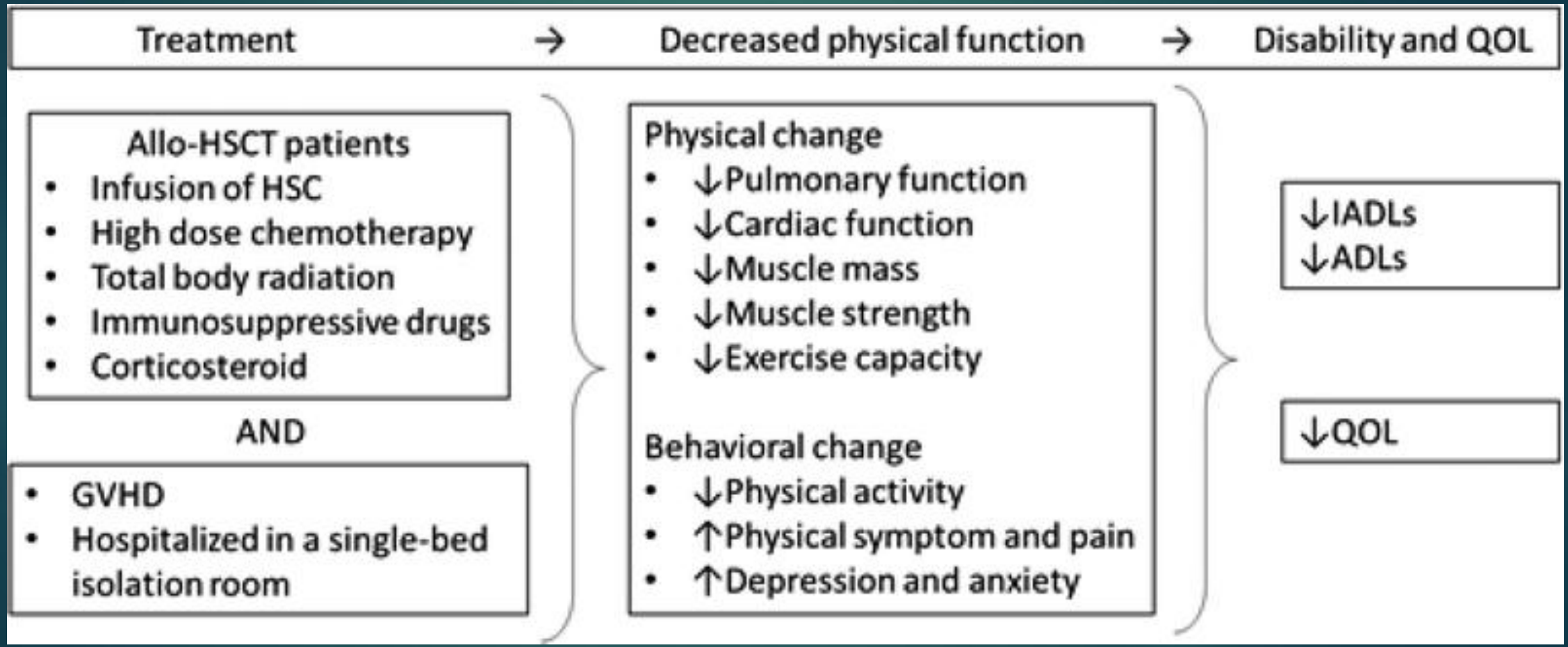
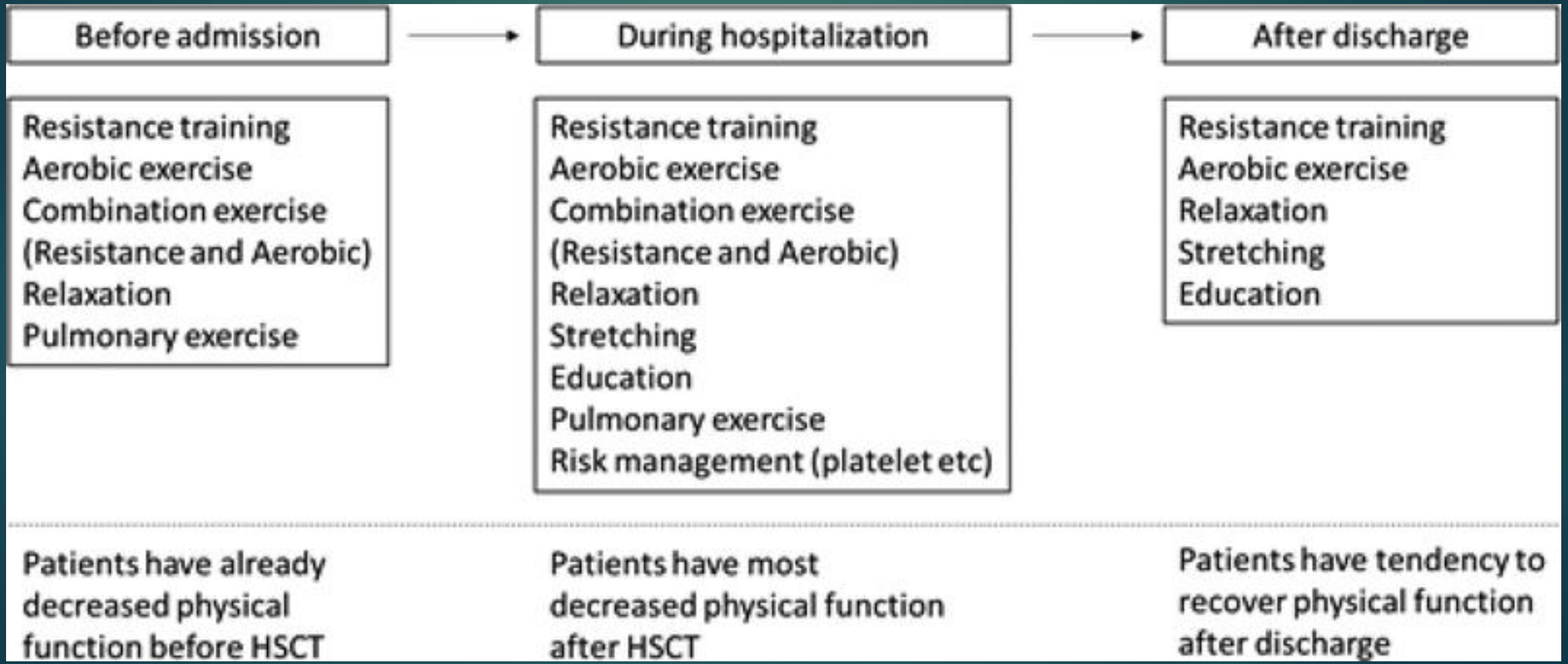
Decrease in physical function, disability, and QOL in patients with allo-HSCT after treatment



Physical exercise before admission, during hospitalization, and after discharge



- Allo-HSCT patients **require physical exercise** to prevent a decrease in physical function or improve physical function.

- The **use of corticosteroids** and decreases in physical activity post-HSCT seem to be related to decreases in physical function.

- These patients experience **nausea, loss of appetite, and GVHD**, and tend to experience a **decline in nutritional status and weight**, which leads to muscle loss and loss of physical vitality.

- Therefore, future studies on the effects of **nutritional therapy combined with physical exercise** for allo-HSCT patients are needed.

- Moreover, as **exercise capacity** may be related to mortality in allo-HSCT patients, it is possible that **muscle strength** and **physical activity** could have a relationship with mortality in these patients.
- Future studies should investigate these possible relationships.

- Future **long-term follow-up studies** focusing on the long-term physical function and overall QOL are needed.

- The **survival rates** of allo-HSCT patients have been improving, with many allo-HSCT patients living longer than those in the past.
- Thus, the maintenance of physical function, and its relationship to physical exercise, should be investigated in long-term survivors of allo-HSCT in addition to inpatient populations.

- The review suggests that physical exercise is beneficial for the **physiological**, **psychological**, and **psychosocial health** of allo-HSCT patients.

- Clinicians should encourage patients to perform physical exercise **before, during, and after transplantation**, and physical exercise **should be integrated** into the conditioning and recovery plans for all allo-HSCT patients.

Rehabilitation after Allogeneic Haematopoietic Stem Cell Transplantation: A Special Challenge

- Acute Rehabilitation as an Inpatient
- Acute Rehabilitation as an Outpatient
- Acute Rehabilitation as an Inpatient Later in the Time Course
- Rehabilitation with Chronic GvHD

Cancers **2021**, 13, 6187. https://doi.org/10.3390/cancers13246187

Acute Rehabilitation as an Inpatient

- Malnutrition
- Muscle Loss
- Risk of Infections
- Psycho-Oncological Aspects
- Psychosocial Aspects

Acute Rehabilitation as an Inpatient

- Occurs **around day +25 (ranging between 19 and 35 days)** after the transplantation

- Suffer from the same side effects and discomforts as other cancer patients soon after therapy, such as:
  - fatigue, nausea, vomiting, neurocognitive deficits, and perhaps diarrhoea.

Muscle Loss

- After admission to alloHCT, the patients stay about ~40 days on the transplantation ward, mainly in their **single isolation room**, usually **lying in their bed**;
  - their physical activities diminish dramatically (to 10–15%) and their muscles shrink.
- Additional drugs like **corticosteroids and CNIs** cause myopathy, which is then aggravated by the polyneuropathy induced by several drugs (e.g., CNIs).

- Paradigmatic change has happened over the last 25 years, and after the first evidence of its benefits was published, **exercise was introduced on the transplantation wards**, and the patients are now motivated to exercise.

- **Developing muscles** is a further challenge for the rehabilitation centre; patients feel weak, experience fatigue, are too exhausted to climb a few stairs, and have, due to the continued medication, worsening polyneuropathy.

- Three different kinds of exercise should be encouraged for patients:
  - Endurance
  - Strength
  - Balance

- Training can be done in groups, but many patients after alloHCT need an **individualised training program**.

- **Whole body vibration** has been introduced without major side effects on the transplantation ward;
- it increases the muscle tissue and improves functional capacity.

- It is also safe and effective in the rehabilitation setting as well, as are **Nordic walking, ergometric training, electro muscle stimulation (EMS), and low-weight training.**

- The main task during rehabilitation is to improve the patient's physical performance so that they can go home and live without assistance in their own rooms.

- Special attention should be paid to the **climbing of stairs**, which is impaired by the aforementioned myopathy.

- One often neglected aspect is **balance**; patients with balance problems carry a high risk of falling, and osteoporosis leads to fractures.

- As infections should be avoided, training the **breathing muscles** is a further target of special exercise in this patient group.

- Because these patients are severely immunosuppressed, training in a group may be impossible because of the high risk of infections, which is why **individualised training** programs are preferable and should be offered.

Acute Rehabilitation as an Outpatient

- Outpatient rehabilitation in the first three months will primarily consist of **physical exercise**, as mentioned above, involving the training of strength, power, and balance.

- This should be done **at least twice a week** at two- to three-day intervals.

- An alternative is **web–based training programs,** which are individualised by the physiotherapists or sports scientists in the transplant centre.
- These programs can be adopted if the patient's fitness is improving

Acute Rehabilitation as an Inpatient Later in the Time Course

- If patients come in for rehabilitation later as an inpatient in their **post-alloHCT time course (mainly on days +60–90),** then their recovery has started, accompanied by the main side effects, and patients are more capable of participating in their tasks in the rehabilitation clinic

- These patients can participate in **group exercise**, lectures, and eat in the clinic restaurant.

- If they have not engaged in an intensive outpatient sports programme after discharge from the transplant centre, they will still be struggling with **muscle loss, weakness, and a certain amount of fatigue**.

Rehabilitation with Chronic GvHD
What role does the rehabilitation centre play?

- The **main goal** of a planned intensive rehabilitation period is **physical therapy**.
- The patients' **physical limitations** are what mainly prevent them from participating in their ADL.
- To achieve this goal, the therapist **should possess a great deal of experience** in treating this alloHCT complication in particular, especially in patients suffering from skin/fascia related GvHDs.

Rehabilitation with Chronic GvHD
What role does the rehabilitation centre play?

- A list of possible interventions is:
  - Massage
  - breathing exercise
  - connective tissue massage
  - lymph drainage
  - polyneuropathy training
  - wraps
  - light therapy with UVA A and B
  - whole body vibration (WBV)

- These should be done very often (not just once a week);
- furthermore, repeated intense weeks in the rehab-centre really helps these patients.

- Such cGvHD-associated impairments can affect the patients emotionally, and psychologically as well;
  - they **cannot move** as they used to (reduced performance),
  - can suffer from **shortness of breath** (which is extremely frightening),
  - their **appearance** is altered (hair loss, dyspigmentation),
  - **sexual activity** is impaired in cases of cGvHD of the genitals (in females and males).

- These problems also **require experienced psycho-oncologists** because their treatment differs from the follow-up care of “normal” oncology patients

- With longer and more frequent support during **a 3–4-week rehabilitation programme**, these discomforts can be dealt with effectively.

- In cases of severe cGvHD involving severe impairments, rehabilitation **twice a year**, or at the very least once a year, helps these patients.

- Side effects of the CNIs are damage to the vessel endothelia, which leads to **hypertension**, and **vascular diseases of the heart and brain**.

- These impairments should be diagnosed and handled again mainly through exercise during follow-up care.

- The clinical manifestation has implication for **patients' physical function**, limiting a patient's ability to carry out activities of daily living and subsequently reduces the quality of life.

- Impairments in the physical domain is a result of both the **disease** itself and its **treatments**.

- Unfortunately, **usage of glucocorticoids** is associated with a variety of side-efects, especially at higher doses and with longer duration of therapy,
  - such as **osteoporosis**, **osteonecrosis**, **diabetes** and
  - **myopathy** with weakness primarily found in the proximal lower muscles, with particularly the pelvic girdle muscles being involved.

- In view of the poor treatment respond and the toxic effects of the GvHD therapy, **new supportive strategies** that will help maintain or even improve patients' quality of life are needed.

- Such supportive therapies should particularly target the physical domain, hence, reducing impacts on activities of daily living resulting in the **preservation of public participation and autonomy**

- A 2021 systematic review yielded that **exercise interventions** may be beneficial on **physical functioning and quality of life** in patients undergoing HSCT.

- The findings of **the positive effects of exercise on HSCT** patients are supported by another review which found beneficial effects for muscle strength and physical fitness.

- Specifically in patients receiving an allo HSCT, randomized controlled studies showed that exercise is capable of **counteracting the negative consequences of cancer** and its treatment and may **improve survival**

- Pre-clinical findings in a chronic GvHD murine model under standard immunosuppressive therapy suggest beneficial effects of **exercise on survival, clinical course of GvHD and on physical capacity** in the exercising mice group compared to control animals.

- Moreover, the exercising mice showed **lower TNF-α and IL-4 levels** after 12weeks post transplant, reflecting **a weaker inflammatory state.**

- These findings give first insight on how exercise may affect the clinical and biological course of GvHD patients.

- A prospective study authored by Morishita et al. showed that the cumulative corticosteroids dose is associated with **weak handgrip and knee extension**.

- This is in line with recent findings of a small single-arm cohort study by Ngo-Huang et al. , who investigated acute GvHD patients on high-dose steroids and their decline in objective functional tests.

- They found a significant association between cumulative corticosteroid dose and the following functional tests: **6min walk test, hip flexors and knee flexors strength, manual muscle testing strength, sit to stand test.**

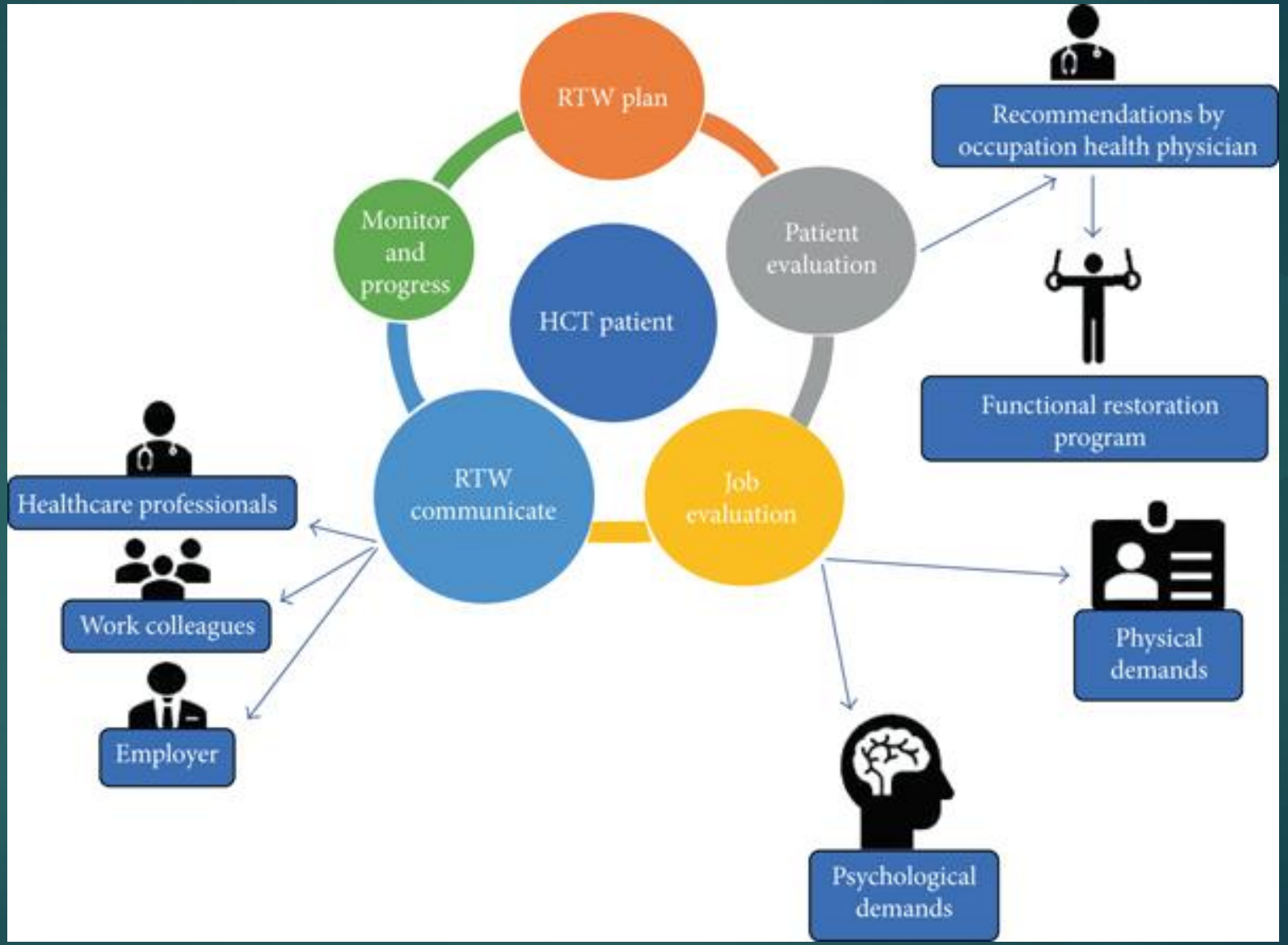
- In terms of the timing of the decline, weakness can be detected **as early as day 14**, suggesting that **early supportive interventions** are needed to mitigate these changes.

- Interestingly, Morishita et al. found that physical therapy is positively associated with physical function, indicating that exercise may be capable **of ameliorating the detrimental effects of GvHD** and its treatment.

Combined exercise and nutritional support

- it is likely that a **combination of an exercise and nutritional** intervention will be of greater benefit than one intervention in isolation.

Understanding the Process and Challenges for Return-to-Work Post-Hematopoietic Cell Transplantation from a Musculoskeletal Perspective: A Narrative Review



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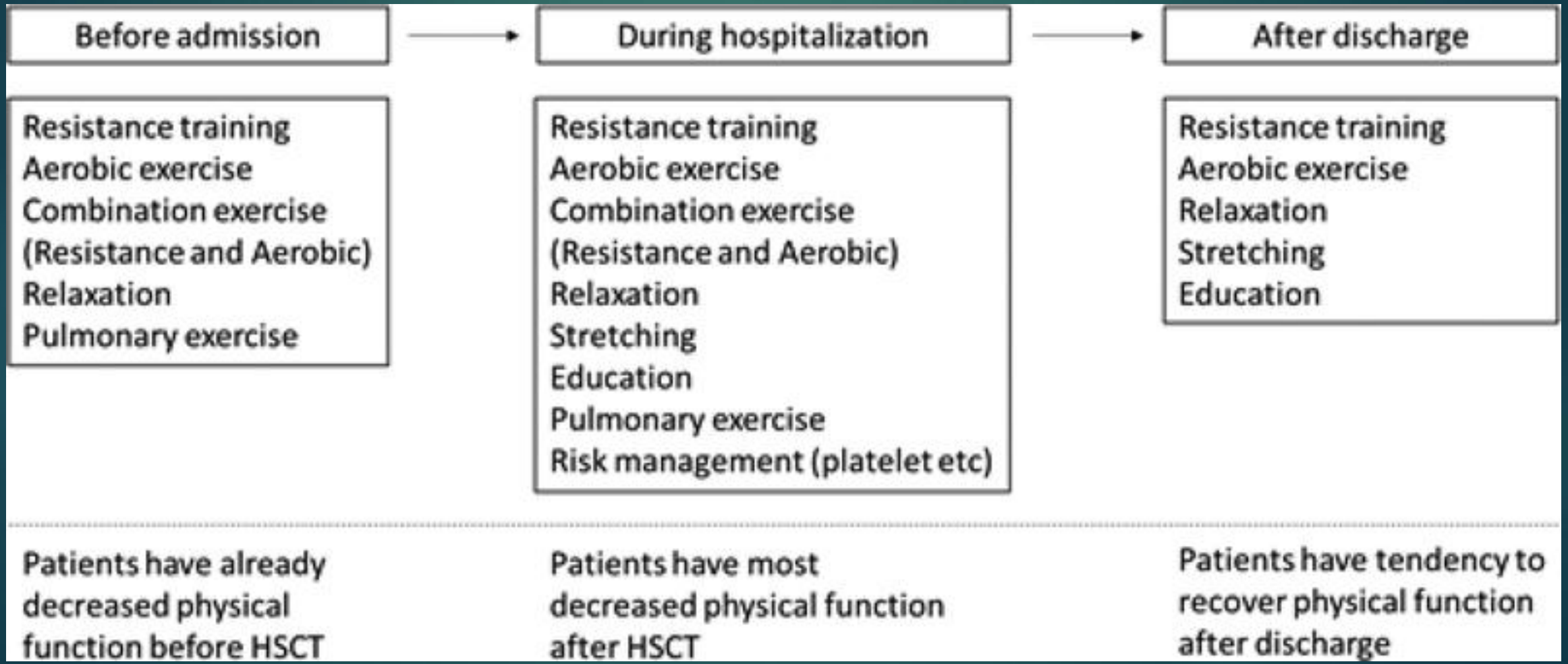

Thanks