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Adjuvant pharmacological strategies for the musculoskeletal system during long-term space missions

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Abstract

Despite 2 h of daily exercise training, muscle wasting and bone loss are still present after 6-month missions to the international space station. Some crew members lose bone much faster than others. In preparation for missions to the Moon and Mars, space agencies are therefore reviewing their countermeasure portfolios. Here, we discuss the potential of current pharmacological strategies. Bone loss in space is fuelled by bone resorption. Alendronate, an oral bisphosphonate, reduced bone losses in experimental bed rest and space. However, gastrointestinal side effects precluded its further utilization in space. Zoledronate (a potent bisphosphonate), denosumab (RANKL antagonist) and romosozumab (sclerostin antagonist) are all administered via injection. They effectively suppress bone resorption and are routinely prescribed against osteoporosis. Their serious adverse effects, namely, osteonecrosis of the jaw and atypical femur fractures occur very rarely when the usage is limited to 1 or 2 years. Hence, utilization of one of these compounds may outweigh the bone risks of space travelling, in particular in those with high bone resorption rates. Muscle wasting in space is likely due to hampered muscle protein synthesis. Even though this might theoretically be countered by the synthesis-boosting effects of anabolic steroids, the practical grounds for such recommendation are currently weak. Moreover, they reveal their full potential only when combined with an anabolic exercise stimulus, for example, via strength training. It therefore seems that a combination of exercise and pharmacological countermeasures should be considered for musculoskeletal health on the way to the Moon and Mars and back.

KEYWORDS
endocrinology, nutrition, pharmacotherapy, physiology

1 | DEFINING THE PROBLEM

Muscle wasting in space has been known since the early days of space travel. It primarily affects the anti-gravity muscles, which have an atrophy rate of up to 15% in 2 weeks.[1] The loss in muscle strength exceeds the decrease in size,[2] which can be explained, for example, by fibre atrophy[3] in the likely absence of intramuscular connective tissue shrinkage,[4] reduction in myosin heavy chain content,[5] and disturbed actin-myosin filament alignment.[3] Although no data exist from spaceflight, one would expect by analogy with bed rest and other ground-based immobilization models that muscle wasting in space is primarily due to depressed protein synthesis, rather than excessive protein

breakdown.[6] However, there is currently little agreement on the mechanisms responsible for this. In this context, recent publications suggest that oxidative stress and mitochondrial electron transfer disruption seem to play an important role in the internal environment of microgravity.[7,8]

In parallel to muscle atrophy, astronauts also experience bone losses in space. This occurs mostly in the legs and spine, not, or only to a lesser extent, in the upper extremities.[9,10] The losses amount to 1% to 2% of bone mass per month on average. However, there is enormous inter-individual variability in bone losses,[11] so that some individuals can lose approximately 25% of their bone mineral content at specific bone sites within 3 months of experimental bed rest[12] or after a 6-month space mission.[9] These individuals with pronounced bone losses are often colloquially referred to as 'fast losers'.

The bone losses need to be seen in the context of bone turnover: osteoclasts resorb bone tissue by acidic solution of mineral and enzymatic degradation of extracellular matrix proteins, and osteoblasts replenish the incurred deficits by bone formation, which involves deposition of de novo extracellular matrix proteins and assistance in the primary mineralization. The resorption-formation cycle is known as 'remodelling',[13] and it is orchestrated by the so-called osteocytes. These are former osteoblasts that have become embedded in the bone matrix, and which coordinate, among other things, bone's sensitivity to mechanical signals. Communication between cells of the osteoblast lineage with osteoclasts is effectuated by various biological agents, such as receptor activator of NF-kB (RANK), RANK-ligand (**RANKL**) and **sclerostin**.[14]

Bone losses in space are caused by an increase in bone resorption, rather than hampered bone formation.[15] It has been argued that bones adapt to their mechanical environment,[16] and that the greatest forces acting on them arise from muscle contractions.[17,18] This, and the fact that no bone loss or muscle loss is observed in astronauts' arms, supports the view that bone loss in space is primarily a mechanically induced problem. In-flight, serum ionized calcium is moderately elevated, parathyroid hormone (PTH) levels are low[19] and urinary excretion of calcium and phosphate are enhanced. Accordingly, there is a known risk of kidney stones in bed rest[20] and in space.[21] However, absence of mechanical loading may not be the only reason for space-induced bone losses, but can also be due to exposure to ionizing radiation in space.[22] However, the fact that space-related bone losses are most pronounced in the lower extremity, and that the arm bones are spared suggests that radiation is unlikely to be the exclusive cause.

1.1 | Bed rest as a ground-based analogue model

Since the late 1960s, space research has used the −6° head-down model, also referred to as anti-orthostatic hypokinesia, as a ground-based analogue for weightlessness.[23] Although originally developed to reproduce the neuro-ophthalmic effects of zero gravity and facial swelling, it has also proven capable of modelling numerous space medicine problems, including muscle and bone loss,[24,25] cardiovascular deconditioning and orthostatic intolerance,[26] and also the only recently described spaceflight-associated neuro-ocular syndrome.[27,28] Experimental bed rest is therefore considered a necessary step in the development of any space countermeasure. However, for obvious ethical reasons, bed rest does not model the effects of ionizing radiation.

1.2 | Physical training as countermeasure

Physical training has been an integral part of space travel since the early 1970s, with an original focus on aerobic training. However, since a 17-week bed rest study has demonstrated the suitability of strength training for maintaining muscle strength and bone mass,[29] resistive training has become the main physical countermeasure in space.[30] One has to consider, however, that the currently implemented countermeasure regimen is still not fully effective.[31]

Combining resistive exercise with whole body vibration is another option.[32] Thus, when exhaustingly performed 11 times,[33] resistive vibration exercise preserved muscle mass, muscle strength and bone mass of the lower extremities.[34] It is crucial to understand that the countermeasure was effective not by mitigating exaggerated resorption in response to bed rest, but rather by stimulating a commensurate bone formation in response to exercise.[35] Moreover, a follow-up study has demonstrated the genuine effects by the vibration component for preserving bone.[36] However, these effects were only partly confirmed by others,[37,38] which raises questions regarding the standardized implementation and compliance with training programmes across studies and study centres. Perhaps the best countermeasure results so far are reported from a 60-day bed rest study that used reactive jumps as exercise countermeasure on 5 days per week.[39,40] That training programme has proven to be very effective not only for maintaining muscle strength and power, but also as a countermeasure against bone loss in the lower extremities. These results have led to the idea that plyometric training principles (i.e., exercises that involve active stretch-shortening cycles and thus high amounts of elastically stored energy in the muscle-tendon complexes[41]) may constitute an ideal countermeasure exercise modality, which not only engenders large musculoskeletal forces, but also contains elements of high-intensity interval training, and thereby helps to reap cardiovascular benefits as well.[42] Accordingly, space agencies are currently undertaking substantial efforts to make such exercise modalities available in space.

The principle requirements for successful countermeasures are highlighted in Table 1. It is also important that the countermeasure

TABLE 1 Requirements for successful physical countermeasures for preservation of muscle and bone.

What to train?	• Large muscle groups of lower extremity and trunk
How often?	• At least five times per week
How hard to train?	• Maximal exertion unto exhaustion. The aim is to achieve large musculoskeletal forces

battle for preserving bone has so far been won only by boosting bone formation, rather than by suppressing bone resorption. The latter could suggest uncoupling bone formation from bone resorption as the underlying problem,[43,44] which would imply that uncoupling is insensitive to physical interventions. That notion, and also the consideration that physical countermeasures involve risks for humans and challenges for flight hardware (e.g., failure of exercise machines, shocks to the vehicle structure, challenges to nutrition and oxygen supplies), lead us to wonder which pharmacological treatment options might exist for the medical support of long-term missions in space.

1.3 | Recovery of incurred bone losses

The observation that bone losses due to immobilization depict incomplete recovery has raised the question of whether or not astronauts can recover bone that is lost in space.[45] However, the analogy between clinical use and space is deceptive, since astronauts fully recover their physical capabilities post-landing, while patients often experience protracted functional deficits. As evidenced by recovery data from experimental bed rest studies, the adult skeleton does retain the ability to recover bone losses even when they are substantial.[46] However, incomplete recovery of bone losses is still a problem in astronauts,[47] in particular in the upper extremity. Unfortunately, it is currently unclear, to what extent incompletely recovered bone losses affect the individual's future fracture risk.

2 | PHARMACOLOGICAL OPTIONS FOR BONE PRESERVATION

2.1 | Background: Therapy of osteoporosis and countermeasures

In the treatment of osteoporosis, a distinction is made between (1) primarily preventing declines in bone mass from healthy bone density levels, (2) secondarily preventing bone losses from osteoporotic levels and (3) tertiary prevention after fractures have incurred. While specific drug therapy is only provided for secondary and tertiary prevention, basic therapy is recommended in all three stages of prevention. Moreover, it is recommended to implement the general measures for fracture prophylaxis in all risk groups and that modifiable risk factors should be minimized.

In analogy to this, the prevention of bone mass loss in astronauts could be approached by:

- Primary prevention before the mission, with the measures listed below under 'basic therapy'.
- Secondary prevention, which is dependent on an initial bone density scan and mission duration. Available therapeutic options are listed below. The measures can be carried out before launch, for example, by long-acting antiresorptive drugs on Earth or, in the case of oral bisphosphonates, during the mission. A combination with basic therapy measures is crucial.
- After returning to Earth, depending on bone density readings and the clinical course, it must be determined whether medication needs to be intensified. This would have to be considered in any occurrence of fragility fracture and depending on the amount of bone loss exceeding the expected bone loss.

2.2 | Basic therapy

The supply of calcium is essential for the development and maintenance of bone mineralization in all phases of life. Hence, daily intake of 1000 mg calcium through nutrition is recommended on Earth and also for astronauts, either through the diet, or by supplementation if needed.[48]

Vitamin D plays a central role in calcium balance and bone mineralization. The current recommendation for osteoporosis patients on Earth is 800–1000 international units (IU) per day. 2000–4000 IU cholecalciferol per day should not be exceeded. As part of the basic therapy, 800–1000 IU of vitamin D3 are recommended daily in addition to sufficient calcium intake.[49] For low-Earth orbit, a daily intake of 800 IU per day is currently recommended.[50]

In addition, an adequate supply of vitamin K,[51] vitamin B and folic acid[52] and an adequate supply of protein[53] are generally recommended. Underweight (BMI < 18.5 kg/m^2), that is, inadequate energy intake, smoking and excessive alcohol consumption should be avoided.

Oestrogen deficiency of any cause, including depot-medroxyprogesterone-acetate (DMPA), will results in bone loss. In premenopausal women, the regular cycle and oestrogen levels play an essential role in maintaining bone mass. If amenorrhoea is pharmacologically induced for space missions, then this would probably not increase the risk of fractures,[54] except for DMPA, which leads to a decrease in bone density, and may increase fracture risk.[55] This should be taken into account in the selection of the contraceptive: as with all medications, attention should be paid to the expected drug adherence before prescription in order to prevent intermenstrual bleeding.

Oestrogens are essential to bone health. Their principle of action on bone is through modulating the number of osteoblasts and osteoclasts and the viability of osteocytes.[56] Under the influence of oestrogen, the entire skeletal system is renewed every 10 years. However, lowering oestrogen levels induces osteoclast differentiation, which shifts the balance towards bone resorption and results in bone losses. Therefore, in women with early menopause before the age of 40, international guidelines stipulate hormone replacement therapy, among other things, in order to compensate for the negative effects of oestrogen deficiency on the bone. In the case of permanent cycle disorders, a hormone-containing pill with oestradiol should be considered taking into account the benefit–risk profile in such cases.

Finally, regular exercise and mechanical loading is crucial to maintain bone health in patients on Earth.

2.3 | Drug therapy guidelines on Earth

The approval status for treating osteoporosis in postmenopausal women and men varies for the available treatment options (see Table 2). The best-documented drug benefits for fracture reduction in postmenopausal women according to the German Guidelines for diagnosis, prevention and treatment of osteoporosis[59] recommend **alendronate** (10 mg daily and 70 mg weekly), **bazedoxifene**, **denosumab**, **ibandronate**, oestrogens, **raloxifene**, **risedronate** (35 mg weekly), **romosozumab**, **teriparatide** (rhPTH 1–34) and **zoledronate**.

For men, alendronate (10 mg daily), risedronate (35 mg weekly), zoledronate, denosumab and teriparatide are approved for the treatment of osteoporosis. However, these therapeutic approaches have been less extensively studied in men than in women, and the evidence mainly stems from equivalence studies with postmenopausal osteoporosis on the surrogate bone density and bone remodelling parameters, and only few studies have demonstrated a reduction in vertebral fractures in men.[60,61] Therefore, if there is less sufficient data for fracture reduction in men, it seems appropriate to adopt the women's guideline recommendations also for osteoporosis therapy in men.

2.4 | Antiresorptive drugs as countermeasure

2.4.1 | Bisphosphonates

Published data suggest positive effects by combining exercise training and the oral bisphosphonate alendronate (70 mg weekly) during space flight.[62] In experimental bed rest, oral application of alendronate (10 mg daily) or a single dose of intravenous pamidronate have both proven beneficial without any additional exercise,[20,63] which, taken together, validates the principle of preventing space-induced bone loss with antiresorptive drugs. Another important aspect is that bisphosphonates reduce urinary calcium excretion, thereby mitigating the risk of renal stone formation on long-duration missions.

So far, there are no published data on the administration of the intravenous bisphosphonate zoledronate under spaceflight conditions. Of note, zoledronate is the bisphosphonate with the strongest antiresorptive potency in osteoporosis therapy due to its high binding affinity to bone mineral, thus leading to pronounced inhibition of mature osteoclasts. Because of its protracted effectiveness over 1 year, it could be timely administered prior to the planned mission, so that its side effect (acute phase response similar to flu symptoms over a period of 2–3 days which can be substantially reduced by a 3-day course of dexamethasone prior and after infusion[64]) would not affect the mission. Therapeutic options for astronauts have already been discussed in the past[65] and are recommended by NASA in internal documents.[66]

In addition, parenteral administration would circumvent difficulty in swallowing and stomach pain, which are known side effects of oral bisphosphonate therapy on Earth that must be expected to be aggravated in microgravity. There are of course more side effects to consider before initiating a bisphosphonate or denosumab therapy. However, the rare and severe complications linked to the strong antiresorptive capacity of denosumab and zoledronate, such as osteonecrosis of the jaw or atypical femoral fracture are associated with longer therapy durations of 3 years and more. When presented as absolute numbers, the incidence of osteonecrosis of the jaw in patients prescribed oral bisphosphonates for the treatment of osteoporosis is rather low. The reported upper ranges are 69 and 90 cases per 100 000 patient-years for intravenous and oral application of bisphosphonates, respectively (Table 3). For denosumab, an upper

TABLE 2 Evidence-based recommendations for pharmacological treatment of osteoporosis.

Risk reduction for	Vertebral fractures	Peripheral fractures	Hip fractures
Bisphosphonates-antiresorptive			
Alendronate	A	A	A
Ibandronate	A	B	-
Risedronate	A	A	A
Zoledronate	A	A	A
Oestrogen and selective oestrogen receptor modulator-antiresorptives			
Oestrogens	A	A	A
Bazedoxifene	A	B	-
Raloxifene	A	-	-
Monoclonal RANK-ligand antibody-antiresorptive			
Denosumab	A	A	A
Osteoanabolic drugs			
Romosozumab-sclerostin antibody	A	A	A
Teriparatide-parathyroid hormone derivate	A	A	A

Note: A and B indicate evidence levels, translating into strong recommendation for A and recommendation for B. The German recommendations are in line with international recommendations, for example, the European Guideline for the diagnosis and management of osteoporosis[57] or the SIGN Guideline for the management of osteoporosis.[58]

range of 30.2 per 100 000 patient-years has been reported.[67] Atypical femur fractures are another rare side effect that needs to be considered. That risk increases with the duration of bisphosphonate use; as shown in an analysis by the Kaiser Permanente foundation of Southern California, the risk increases 8.9-fold (95% confidence interval [CI], 2.8–28.2) after usage between 3 and 5 years and 43.5-fold (95% CI, 13.7–138.2) after usage for 8 years or more. However, atypical fractures are still a rare event, in particular if the therapy duration is less than 3 years (Table 4). A risk factor to be highlighted is ethnicity (hazard ratio for Asians *vs*. Whites, 4.84; 95% CI, 3.57–6.56).[69]

2.4.2 | Denosumab

Another powerful antiresorptive treatment option is the monoclonal human antibody denosumab, the first RANKL inhibitor developed to target osteoclasts. The monoclonal antibody denosumab shows antiresorptive activity by selectively blocking the binding of RANKL on osteoclasts to RANK. RANK signalling is essential for osteoclast differentiation, activity and survival.[70] Denosumab is injected subcutaneously every 6 months, and it acts as a strong antiresorptive to prevent bone loss in different metabolic challenges. The subcutaneous route of administration and infrequent (twice-yearly) administration schedule suggest potential utility for denosumab in male and female astronauts that are expected to lose significant bone mass during long-duration spaceflight. Although it has not been tested on astronauts or in bed rest, the compound has demonstrated effectiveness in mice in space, where treatment with a denosumab equivalent 24 h prior to launch[71] led to higher bone mineral density (BMD) than spaceflight or ground control mice treated with inert vehicle.

Similar to zoledronate, denosumab could also be administered prior to space missions. One injection of denosumab leads to a suppression of bone turnover over a period of 6 months. Denosumab potentially also leads to musculoskeletal pain, therefore the first injection should be given on Earth. Due to its strong antiresorptive capacity, the potential side effects of denosumab are similar to those of zoledronate. Again, the rare, severe and dreadful complications of a prolonged therapy with denosmab such as osteonecrosis of the jaw or atypical femoral fracture are associated with therapy durations of 3 years and longer.

If a longer therapy becomes necessary, then the so-called rebound phenomenon may occur after discontinuation of denosumab, which is due to the RANK-receptor being exposed once the duration of action is exceeded. That rebound involves osteoclast activation, and it significantly increases fracture risk, leading, for example, to multiple vertebral fractures in about 10% of cases.[72,73] Therefore, follow-up therapy with a bisphosphonate (e.g., zoledronate) is required after prolonged denosumab medication in order to prevent rebound.[73]

TABLE 3 Risk of osteonecrosis of the jaw with usage of bisphosphonates or denosumab.[67]

Drug class	Administration	Risk of osteonecrosis of the jaw (cases per 100 000 patient-years)
Bisphosphonates	Oral	1–69
Bisphosphonates	Intravenous	0–90
Denosumab	Subcutaneous	0–30

TABLE 4 Risk of atypical femur fracture with usage of bisphosphonates[68] or denosumab.

Drug class	Administration	Risk of atypical femur fracture (age adjusted incidence rate per 100 000 person years)—use under 2 to > 8 years
Bisphosphonates	Oral and intravenous	2–113
Denosumab	Subcutaneous	No summarizing data available

2.4.3 | Oestrogens and selective oestrogen receptor modulator (SERM)

Oestrogens and SERMs such as raloxifene and bazedoxifene are approved for postmenopausal women only. More importantly, the antiresorptive potency of raloxifene is lower than that of bisphosphonates.[74] Therefore, it seems plausible that bisphosphonates (and also denosumab) should be preferred over SERMs for preventing spaceflight-associated bone loss.[75] On the other hand, postmenopausal hormone replacement therapy does prevent postmenopausal bone loss and reduces the risk of fractures.[76,77] However, data on hormone replacement therapy and BMD are not available in postmenopausal astronauts.

2.5 | Osteoanabolic drugs

2.5.1 | Teriparatide

Teriparatide is a synthetic peptide comprising the first 34 amino acids of PTH. As PTH receptor agonist, teriparatide stimulates the PTH 1 receptor to activate bone metabolism and to increase renal calcium absorption. The number and activity of osteoblasts is increased with teriparatide, resulting in a positive bone balance, most of which occurs in active bone remodelling sites on trabecular and endocortical bone surfaces (remodelling-based bone formation).[78,79] Teriparatide has the same actions as endogenous PTH on calcium and phosphate homeostasis (i.e., increasing serum calcium and lowering serum phosphate). The duration of teriparatide therapy is limited to 24 months, and teriparatide is injected subcutaneously on a daily basis. So far, this compound has not been tested in space. It should be emphasized that a contraindication for teriparatide is a history of ionizing radiation involving the skeleton due to a preclinical finding of osteosarcoma in rats treated with high doses of teriparatide for near lifetime. However, in patients treated with teriparatide, there has been no increase in

osteosarcoma incidence.[80] Therefore, and although the option of an osteoanabolic drug is intriguing for astronauts with hampered bone recovery or who experienced fragility fractures, the known effects of ionizing radiation in space[81] warrant further studies before drawing further conclusions.

2.5.2 | Romosozumab

Romosozumab is a sclerostin antibody with a development history that literally started in space. Two companies developed a molecule called sclAB to block sclerostin's activity and tested it on 30 mice on board the STS-135 Space Shuttle flight. Mice treated with sclAB in space developed higher BMD than the untreated flight mice and the ground-based control animals.[82,83] Romosozumab effectively reduces the risk of fractures in patients and produces faster and greater increases in BMD and bone strength than any other current osteoporosis treatment. Romosozumab is injected subcutaneously once monthly for 12 months, and this is followed by a bisphosphonate or denosumab therapy. Due to the ease of use and the strong effect on the bone mass as well as the risk of fractures, studies with romosozumab in astronauts are highly desirable, but are not yet available. Thus, the possibility remains to use romosozumab in returnees from space who have lost excessive and non-reversible bone mass or have suffered a fragility fracture.

In summary, with the exception of alendronate, none of the pharmacological options for osteoporosis have been tested in astronauts. However, it can be assumed that zoledronate, denosumab and also romosozumab, for which data from mouse experiments in space exist, could be helpful through their suppressive effect on bone metabolism. Due to their antiresorptive capacity, zoledronate and denosumab are expected to cause greater suppression of bone metabolism over time than alendronate or romosozumab.

3 | PHARMACOLOGICAL OPTIONS FOR MUSCLE

There is currently no approved drug to combat muscle wasting on Earth. And although mechanistic studies investigating muscle atrophy in astronauts are limited, more evidence has emerged from ground-based studies. Further to that, there are salient challenges that have to be considered when addressing muscle loss. Firstly, bed rest-related atrophy does not occur uniformly across all muscles, but rather affects different muscles to different extents, even if they are located in the same limb.[84,85] While proximal muscles seem to be more impacted by hypoxic exposure,[86] posterior calf muscles atrophied faster than the knee extensor muscles during experimental bed rest.[84] Secondly, within an atrophied muscle, different muscle fibre types are differently affected. Especially during longer periods of inactivity, such as a prolonged space flight of 180 days, the loss of fibre cross-sectional area by histochemical staining was greatest in soleus type I fibres, followed by soleus type II fibres and gastrocnemius type I fibres and least in gastrocnemius type II fibres.[87] Similarly, loss of fibre cross-sectional area of the vastus lateralis was greater in type I than in type II fibres following 35 days of bed rest.[88] However, this muscle fibre type specificity in response to disuse has not been observed in other studies.[89–91] Thirdly, it needs to be considered that the rate of muscle wasting is greatest during the first 3–14 days, while later further loss of muscle happens at a slower rate despite continued unloading.[92] Although methodological challenges in assessing muscle protein breakdown prevail, it is now well established that decreased muscle protein synthesis seems to be the major driver mediating disuse muscle atrophy, at least on the ground. The precise reason for muscle loss during spaceflights remains to be determined. While during Skylab missions, increased excretion in most amino acids was reported, indicating increased protein catabolism,[93] urinary 3-methylhistidine as a marker for myofibrillar protein breakdown was unaffected in subsequent shuttle missions.[94] Data from tissue-cultured avian skeletal muscle cells carried for 9–10 days on a Space Shuttle flight, demonstrating decreased protein synthesis rates without alterations in protein degradation[95] support reduced protein synthesis in astronauts and cosmonauts during long-duration (>3 months) flights on MIR.[96] It has to be noted, however, that these reductions correlated with reduced energy intake. Thus, in the spaceflight context, the inability to maintain energy balance, hormonal disruptions or psychological stress response with increased cortisol and catecholamine concentrations are important factors contributing to muscle loss. Along these lines, inflammation or infection in addition to disuse may further exacerbate muscle loss in space.[97,98] This underlines the necessity for assessment of the full scope of contributing factors in future studies in order to derive effective countermeasures.

3.1 | Hormonal and nutritional cues

In general, muscle mass is maintained when muscle protein synthesis is balanced with muscle protein breakdown. Physiologically, nutrients, in particular amino acids, and anabolic hormones, in particular insulin and growth hormone, play a crucial role in maintaining muscle mass. Amino acids are the building blocks stimulating muscle protein synthesis. Branched-chain amino acids, in particular leucine, can activate pathways involved in initiating muscle protein synthesis.[99] Although it is challenging to determine the maximal anabolic response after protein intake, maximal rates of myofibrillar protein synthesis derived from infused labelled phenylalanine are reached when 0.4 g/kg of rapidly digesting protein is provided with the diet.[100,101] Collective evidence further suggests a minimum of 1.6 g/kg/day of protein to optimize gains in muscle mass and strength.[102] On the other hand, insulin released upon ingestion of carbohydrates is neither necessary nor sufficient to stimulate muscle protein synthesis.[103] However, insulin exerts a powerful anti-catabolic effect acting on suppressing muscle protein breakdown at concentrations of just 15 IU/mL.[104] A recent meta-analysis underlined the effect of insulin on suppressing muscle protein breakdown and its minor role in impacting muscle

protein synthesis.[105] This illustrates the prominent role of amino acids and insulin in maintaining muscle homeostasis.

3.2 | Pharmacological approaches

Currently, only few effective pharmacological approaches are available to counter disuse-associated muscle loss. Although molecular events resulting in muscle atrophy can vary from condition to condition, there is general agreement that increased degradation is the result of proteolytic pathways, including the autophagy lysosomal system, the ubiquitin-proteasome pathway, calpains and the caspase (or apoptotic) protease pathway.[106–109] In order to derive effective countermeasures for each condition, an understanding of the underlying mechanisms is necessary. In the spaceflight context, microgravity-induced unloading is the most obvious factor mediating muscle atrophy, but loss of appetite with subsequent reduced caloric intake,[110] sleep deprivation,[111] radiation, high workloads and a general stress response with increased cortisol and catecholamine concentrations could also be involved. Thus, all these components are potential targets to reduce muscle atrophy in space.

The following section discusses a selection of possible pharmacological approaches to maintain muscle mass and function during disuse.

3.2.1 | Anabolic–androgenic steroids

Steroidal androgens, including the naturally occurring hormone testosterone, exert their effects by binding to and activating androgen receptors, which activates genes involved in promoting protein synthesis. It needs to be pointed out that the majority of anabolic–androgenic steroid trials have been conducted in elderly individuals.[112] This limits conclusions that can be drawn from these trials for healthy, middle-aged individuals eligible for space missions. However, one study involving healthy young men in 70-day experimental bed rest provides promising results regarding testosterone as an aid to preserve muscle functioning during space missions. Testosterone enanthate injections in combination with an exercise programme on 6 days/week preserved body composition and strength compared to exercise alone and bed rest alone during 70 days of bed rest.[113] While fat mass increased with exercise alone and bed rest alone, testosterone in combination with exercise did not alter fat mass and exclusively improved lean mass and calf concentric strength.[113] Testosterone treatment in combination with exercise also indicated a favourable response towards preserving insulin sensitivity after bed rest in this trial.[114] Of note, 200 mg/week of testosterone helped to preserve protein balance but failed to prevent loss in muscle strength in the absence of mechanical or gravitational loading during 28 days of head-down bed rest.[115] The additive effect of exercise has also been demonstrated in a controlled trial involving ambulatory men.[116] Testosterone's ability to improve muscular strength and performance—albeit small—has also been shown in a recent meta-analysis involving men with varying endogenous testosterone levels.[117] Although treatment was associated with side effects such as prostate enlargement, 200 mg of testosterone every 2 weeks had the potential to also improve BMD, at least in the elderly.[118] This is of particular interest in the spaceflight context. However, no data with regard to fracture reduction exist.

Testosterone is an effective pharmacological approach to preserve both muscle mass and function and potentially metabolic deterioration and BMD. Yet, its clinical use is considerably limited by severe side effects including behavioural abnormalities (which could be crucial in the spaceflight context) and amplified risk for developing prostate hypertrophy, cancer, sleep apnoea, masculinization or thrombosis complications. Furthermore, the effects of testosterone supplementation vary with endogenous testosterone levels.

3.2.2 | Androgen receptor modulators

Selective androgen receptor modulators (SARMs) are small molecule drugs selectively targeting androgen receptors to elicit anabolic effects on muscle and bone tissue while reducing side effects associated with testosterone use.[119] In a double-blind, placebo-controlled phase II trial, the SARM GTx-024 administered over 12 weeks dose-dependently increased total lean body mass and stair-climbing ability as well insulin sensitivity in healthy elderly men and postmenopausal women.[120] The same SARM increased total lean body mass in male and female patients with cancer, without serious side effects after 113 days of treatment.[121] In healthy younger men, the SARM LGD-4033 dose-dependently increased lean body mass, without drug-related serious adverse events but also without affecting fat mass or stair-climbing ability.[122] To date, none of these candidates has been approved for therapeutic use by the Food and Drug Administration and certainly not moved towards the market. Although SARMs are being used as performance-enhancing support by athletes or bodybuilders, their recreational use is associated with serious or life-threatening health problems.[123] Further to that, they are considered a prohibited substance according to the World Anti-Doping Agency. While trials exploring therapeutic use of SARMs involve both men and women, they have not shown consistent improvement in functional outcomes, and they have further been discredited due to their potential hepatotoxicity.[124]

3.2.3 | β2-Adrenergic receptor agonists

When inhaled at low doses, β2-adrenoceptor agonists induce bronchodilatation and are used for the treatment of asthma. Given at higher doses systemically, β2-adrenergic receptor agonists act on β2-adrenoceptors in muscle to regulate myogenesis, that is, the formation of skeletal muscular tissue, and promote muscle hypertrophy by enhancing muscle protein synthesis and reducing protein degradation.[125] In this way, oral formoterol (80 μg/day) improved quadriceps volume assessed by MRI and induced a non-significant, yet clinically meaningful increase in quadriceps and handgrip strength in cachectic patients with advanced malignancy.[126] Clenbuterol, 20 μg twice daily

for 4 weeks, resulted in faster rehabilitation of the operated leg after meniscectomy and slightly increased strength in the normal leg of healthy male patients.[127] Muscle mass was not affected in this study. In trained men, terbutaline given orally at 5 mg/30 kg body weight for 28 days improved muscle force and power output during 30 s of maximal cycling.[128] This ergogenic effect could be advantageous during space missions, where deconditioning occurs despite regular exercise training.[129] In a hind limb suspension unloading mouse model, treatment with the β2-adrenergic receptor agonist formoterol diminished loss of soleus muscle mass compared to control mice.[130] This study also assessed for the first time the use of an implantable drug delivery device in mice in a microgravity environment aboard the international space station (ISS) for 29 and 55 days. This nanofluidic delivery system provides sustained systemic formoterol delivery.[130] Tested during spaceflight conditions, hypertrophy was observed in various muscle tissues of the formoterol-treated animals compared to respective vehicle controls. Although experimental at this stage, such a system provides a proof-of-concept and may someday be used for long-term space missions for promoting muscle anabolism and potentially enhancing the response to regular exercise training. These agents can also create adverse effects by stimulating off-target alpha or beta receptors. The most common side effects include tachycardia, muscle tremor and malaise.[131]

3.2.4 | Molecules targeting the transforming growth factor-β (TGF-β) network

The myokine **myostatin** (MSTN) is a signalling molecule negatively regulating muscle mass via signalling through activin type II receptors **A** and **B**.[132] Myostatin can further be regulated by different binding proteins such as follistatin. In C57BL/6 mice, inhibiting circulating activin A and activin B, dimeric glycoproteins of the TGF-β family involved in the regulation of muscle growth, by local injection of adeno-associated viral vectors encoding antagonists against activin A and activin B prodomains induced a ~20% increases in tibialis anterior muscle mass.[133] Using myostatin prodomains to inhibit myostatin resulted in a ~45% gain in muscle mass in the tibialis anterior of the same animals. When myostatin and activins were inhibited together, however, the hypertrophic response amounted to an increase in muscle mass by ~150%, caused mainly by complete inhibition of Smad2/3 signalling.[133] Of note, elevated protein synthesis was the main driver mediating the observed hypertrophy, in addition to only moderately reduced expression of genes involved in the ubiquitin-dependent protein degradation pathway.[133] Moreover, wild-type mice exposed to microgravity for 33 days aboard the ISS lost muscle and bone mass, $Mstn^{-/-}$ mice maintained their muscle strength, and pharmacological inhibition of MSTN/activin A signalling via a soluble form of the activin type IIB receptor resulted in significant increase in muscle and bone mass in ground and flight mice.[134] These and other studies fuelled a widespread effort to develop myostatin inhibitors for clinical use. An overview of the current state of clinical trials testing targets of the myostatin regulatory system can be found elsewhere.[135] Trials have largely used biologics that fall in two categories, namely, (i) molecules that are relatively specific for myostatin with some cross-reactivity for the related protein growth and differentiation factor (GDF)-11 and (ii) molecules with a broader range of ligand specificity covering not only myostatin and GDF-11 but also activin A.[135] Generally, and in agreement with mouse studies, agents of category (ii) induced larger gains in muscle mass compared to those targeting only one molecule. Although gains in thigh muscle volume by MRI and lean body mass by dual-energy x-ray absorptiometry ranging between 3% and 9% were reported,[135] these fall behind those being described in animal studies in the range of 10% to 50% or even more.[133,136,137] While these trials show that both signalling molecules are involved in regulating muscle growth, it also became evident that activin A is possibly more important in humans compared to mice.[138] Another drawback is that gains in muscle mass did not always translate into improved functional outcomes in human trials. Trials failing to show clinical functional benefits involve patients with muscular dystrophy,[139] sporadic inclusion body myositis[140] and patients with cachexia from cancer[141] or chronic obstructive pulmonary disease.[142] Only when tested in the elderly, were improved grip strength or gait speed, walking distance, stair climbing or chair rising ability reported.[143,144] While one reason for these deviating results may be related to the relatively small gains in muscle mass observed in human trials, inconsistencies in defining and measuring appropriate functional endpoints also need to be resolved. Nevertheless, agents targeting the myostatin regulatory system may hold promise for space missions as they leverage mainly protein synthesis, which is depressed during space flights. Future trials will need to answer questions related to appropriate clinical indications and the more effective broader range of ligand specificity that probably goes hand in hand with possible adverse effects on other cell types and tissues. Further to that, defining and assessing meaningful functional endpoints will be another critical issue in determining potential suitability for space missions.

4 | CONCLUSION

The problem of musculoskeletal deconditioning in space has not yet been fully solved. While the muscle atrophy that is incurred in space seems to be recovered, incomplete rehabilitation of bone losses may predispose individuals to increased fracture risk in the long run. Moreover, space-induced bone losses induce kidney stone formation, and muscle wasting likely impairs glucose metabolism with the possibility of accelerated ageing.[145] Space missions will become longer and more challenging in the future, which makes crew health even more important than it is for low-Earth orbit missions. We therefore recommend consideration of the usage of appropriate supportive medication for the upcoming missions to the Moon and Mars.

This suggestion is encouraged by the previous experiences with alendronate, which effectively prevent space-related bone losses. Since the days of alendronate, newer drugs, with safer ways of administration, absence of gastrointestinal side effects and greater therapeutic effectiveness have entered the market. In particular, zoledronate,

denosumab and romosozumab are nowadays routinely prescribed for treating osteoporosis in terrestric medicine. While data exist for use of romosozumab in space, the greater suppression of bone resorption may speak in favour of zoledronate and denosumab, as bone resorption is the primary problem in space. Hence, we argue here that the preventive benefits of bone antiresorptive treatment in deep-space missions can outweigh the remote risks, in particular for the select space travellers who depict pronounced and rapid bone loss.

As for muscle, there is much less certainty. The limited information available suggests that, unlike bone, the problem arises on the side of synthesis, and not on the breakdown side. It might therefore be best to aim at safeguarding muscle protein synthesis for preserving muscle in space. Boosting protein synthesis is a classical action on muscle, which, however, works best in combination with strength training. It therefore seems that a combination of physical and pharmacological strategies should be applied for maintaining crew health on their way to the Moon and Mars.

4.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22.[146]

AUTHOR CONTRIBUTIONS

All authors have jointly conceived, drafted, discussed and finalized the manuscript.

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CONFLICT OF INTEREST STATEMENT

F.T. reports personal fees, consultancy, lecture fees and honoraria from AMGEN, Fresenius, Gedeon-Richter, Hexal, HOLOGIC, Kyowa-Kirin, Stadapharm, Theramex, UCB, outside the submitted work. J.R. has received speaker's fees from Kyowa-Kirin in 2020 and from UCB pharma in 2021.

DATA AVAILABILITY STATEMENT

Not applicable.

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