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REVIEW

Which physical activity in patients affected by hypoparathyroidism? A review of the literature and practical recommendations

V. Bonavolontà[1] · L. Cianferotti[2] · G. Iolascon[3] · A. Moretti[3] · M. L. Brandi[4] · F. Fischetti[1] · A. Lenzi[5] · C. Baldari[6] · S. Migliaccio[7]

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Abstract

Background Hypoparathyroidism (HypoP) is a rare endocrine condition characterized by hypocalcaemia and hyperphosphatemia, as a consequence of absent or improperly low parathyroid hormone (PTH) levels. Patients affected by HypoP have a clinical condition often characterized by paresthesias and muscle spasms, as well as long-term consequences as nephrolithiasis, extraskeletal calcification, and fractures. In the literature, likely due to these symptoms, few data exist regarding the appropriate physical activity (PA) in subjects suffering from HypoP.

Purpose This review evaluates the literature on exercise-based approaches to the management of individuals affected by HypoP and evaluates: (1) the effects of physical exercise on muscle cramps and other clinical symptoms; (2) the effects of exercise on PTH and calcium level; (3) the most suitable clinical exercise testing; and (4) the most suitable exercise combination.

Methods and results A systematic search was conducted using the databases MEDLINE, Google Scholar using "hypoparathyroidism AND Physical Activity", "Training AND hypoparathyroidism", "Exercise AND muscle cramps", "Exercise AND Fatigue" as keywords. In addition, references list from the included articles were searched and cross-checked to identify any further potentially eligible studies. A total of 50 manuscripts were found among which 39 manuscripts were selected. A few clinical studies have been performed in HypoP patients to evaluate PA training protocols.

Conclusion Although further research is needed to draw solid conclusions regarding best PA protocols in subjects affected by HypoP, a PA protocol has been proposed within the manuscript to encourage patients to attempt exercise to improve their clinical conditions and their quality of life.

Keywords Parathyroid hormone · Hypoparathyroidism · Physical activity · Muscle cramps · Fatigue

✉ S. Migliaccio
silvia.migliaccio@uniroma4.it

[1] Department of Basic Medical Sciences, Neuroscience and Sense Organs, University of Bari "Aldo Moro", Bari, Italy

[2] Bone Metabolic Diseases Unit, Department of Experimental and Clinical Biomedical Sciences, University of Firenze, Firenze, Italy

[3] Department of Medical and Surgical Specialties and Dentistry, University of Campania "Luigi Vanvitelli", Napoli, Italy

[4] Fondazione Firmo, Firenze, Italy

[5] Department of Experimental Medicine, Sapienza University of Roma, Roma, Italy

[6] Department of Theoretical and Applied Sciences, eCampus University, Roma, Italy

[7] Department of Movement, Human and Health Sciences, University Foro Italico of Roma, Piazza Lauro De Bosis 6, 00195 Roma, Italy

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Introduction

Hypoparathyroidism (HypoP) is a rare endocrine condition characterized by hypocalcaemia and hyperphosphatemia, as consequence of absent or improperly low parathyroid hormone (PTH) levels [1–3]. Furthermore, pseudohypoparathyroidism (PHP) is a less common alteration, due to resistance of target organs to PTH, characterized by similarly abnormal biochemical abnormalities, in the presence of elevated circulating concentrations of PTH [1]. Moreover, alterations of bone remodeling are present [4].

Neuromuscular hyperexcitability is one of the main features of HypoP, and affected patients have significant long-term consequences such as an increased risk of renal insufficiency, cardiovascular diseases, neuropsychiatric complications, infections, seizures, cataracts, and fractures at the upper extremities [2, 5, 6]. Due to these clinical and biochemical features, subjects often modify lifestyle, decreasing physical activity (PA) with a deterioration of their quality of life [2].

The goal of long-term replacement treatment with calcium and active vitamin D metabolites is to maintain calcium in the low normal range to avoid complications such as hypercalciuria, nephrolithiasis, and soft-tissue calcifications. Nevertheless, even well-replaced individuals with the disease are constantly prone to drops in serum calcium, especially during PA, and might suffer quality-of-life alterations [7]. Indeed, a recent study [8] evaluated four impact domains in subjects affected by HypoP in pharmacological therapy (physical functioning, including the ability to exercise and mobility; daily life, including the ability to do things at home, and interference with work productivity; psychological well-being; social, including the ability to participate in social activities and relationships) demonstrating a significant deterioration of all these items.

Likely, even in spite of normal serum calcium, the decline of calcium in the extracellular milieu can alter skeletal muscle cell polarization. Conversely, PA, per se, is able to modulate bone and mineral metabolism and decrease serum calcium [8]. Subjects affected by HypoP or PHP often report the occurrence or the increase in the frequency of paresthesia and muscle spasms during endurance exercise, leading to stop exercise [1]. This could further alter the quality of life in these patients [10], since these problems can affect daily living. Interestingly, it has been hypothesized that the absence of PTH per se might be responsible, at least in part, for HypoP-related myopathy and impaired muscle performance, since skeletal muscle cells express the PTH receptor (PTHR1). Indeed, a HypoP-related myopathy showing atrophy of type 2 fibers and accompanied by an increase in muscle enzymes has been described in the past in various cases of mostly idiopathic HypoP [7, 11, 12]. The histological features were reversed by appropriate therapy with calcium salts and calcitriol [11, 12]. Nonetheless, short-term treatment with the full-length PTH (PTH1-84) has shown contradictory results as far as the restoration of muscle function is concerned [13–15]. Thus, data on this specific issue are still not conclusive.

For the management of chronic HypoP, current treatment options comprise oral calcium, and vitamin D (including its metabolites and analogs) supplementations, and thiazide diuretics, to reduce urinary calcium excretion [16]. Over the past 2 decades, studies of teriparatide (PTH 1–34) and recombinant human PTH (rhPTH 1–84) have ushered a new era in the management of this disease [13] with an improvement of calcium homeostasis as well as of quality of life [17].

However, even though these replacement therapies improve clinical outcomes in these subjects, very few studies have been conducted to evaluate the correlation between PA and PTH regulation. Interestingly, physical exercise (PE) appears to be per se an important modulator of serum PTH levels [9] depending on both duration and intensity of exercise. For instance, PA above a certain threshold can increase PTH levels both in euparathyroid, supposedly healthy, young and elders [9]. Moreover, some studies have shown that the increase in PTH, caused by high-intensity exercise in either young women (running) and men, was accompanied by a decrease in ionized calcium concentration [17, 18]. The transient decrease in extracellular calcium induced by exercise could explain the increase in neuromuscular symptoms in HypoP subjects during exercise. Moreover, HypoP patients often suffer of myopathies, further leading to cramps and other symptoms [19]. Thus, as a matter of fact, these patients could benefit of pre- or post-exercise stretching recovery session for preventing and reducing muscle spasms, respectively. Moreover, appropriate PA in terms of both quality and quantity of specific exercise should be determined and clarified. Therefore, this manuscript will evaluate specific literature and will attempt to delineate potentially appropriate PA (and eventual salt integration), which could be managed by patients affected by HypoP to maintain satisfactory quality of life.

Interaction between physical exercise and PTH secretion

The effects of PE and PA on PTH secretion are not clearly established, and a few studies were conducted to address this point as primary outcome.

Previous research showed that there is a correlation between PTH levels and PE, suggesting that greater PA may be associated with lower PTH levels [20]. It is also known

that calcium homeostasis, and consequently PTH response, is perturbed during exercise and that its maintenance is dependent on energy costs; moreover, PE can modify PTH levels, as recently shown [9].

In particular, acute bouts of exercise, as well as chronic training, have been reported to induce different and contrasting effects on PTH secretion in various populations. Nonetheless, the role for PTH in health benefits associated with PE has not yet been established [9].

PTH response to acute and chronic physical exercise and training status

Existing literature demonstrated that PE is an important modifier of PTH concentration, and this effect is dependent on both intensity and duration of exercise [21].

Indeed, PE acts as a form of stressor that perturbs homeostasis and a more intense and longer exercise bout leads to a stronger perturbation [22]. Acute PA induces a hormone response that acts to re-establish homeostasis and the endocrine response to acute exercise occurs in several phases with effects depending on the volume and intensity parameters [9].

Previous studies have demonstrated exercise-associated changes in calcium and PTH concentrations even after a single bout of exercise, while PTH secretion levels change upon PE duration and intensity [21]. Specifically, PTH increases when exercise intensity is 15% above the Individual Ventilatory Threshold (IVT) for a workload prolonged for 50 min; similarly, PTH increase has been reported in situations of low work intensity (50% of the maximal aerobic power, VO_{2max}) protracted for a very long period, i.e., more than 5 h [23]. Conversely, in a study by Bouassida [24], it was reported that maximal intensity short bouts of PE (30 s), as well as long-lasting-low intensity (15% below IVT), do not affect PTH secretion. However, in a previous work, the same author found independence on exercising time, since both a continuous and an intermittent intervention protocol induced an increase in PTH level and a decrease in ionized calcium concentration [18].

Thus, it appears that a threshold related to intensity and time of workload, or properly, a combination of these two factors, does exist to induce PTH secretion changes. Intensity dependency appears to be relevant as compared to the period of exercising and this is supported by several studies [9]. In addition, Townsend et al. [25] found that circulating PTH concentrations decreased with the onset of exercise and then increased in an intensity-dependent manner, with the highest levels recorded at the end of exercise performed at 75% VO_{2max}.

In contrast, other studies were not able to demonstrate acute effects on PTH secretion following 50 min cycling at − 15% IVT in male cyclists, 50 min running at 3.3 m/s in male firefighters, and 30 s of modified Wingate test exercise at maximal intensity in male athletes [24].

Regarding chronic exercise, usually referred to as training, this leads to a progressive adaptation to the endocrine reactions that attenuates the body's response to acute exercise intensity and volume, without, anyhow, abolishing it [9]. Previous research [26] demonstrated that 6 weeks of endurance training (75–80% of maximal heart rate, 1 h/day, 4 days/week) enhanced the release of PTH in elderly men. Conversely, Brahm et al. [27] suggested that trainability (referred to the gain in VO_{2max}, due to training) decreases resting PTH secretion.

Some studies also reported a grade of unresponsiveness to PTH changes after specific training regimens for different populations such as highly trained elite cyclists after a 3 week stage race, young active men after 8 week repeated sprint training and in militaries after 13 weeks of intense training [9].

Physical activity and hypoparathyroidism

Literature has even more rarely addressed this topic with controversial findings. Thus, it has become crucial to further investigate this specific issue, to better understand the potential link between hypoparathyroidism (HypoP) and PA as previously advocated by Lankhaar and colleagues [28] who concluded that there are not enough studies on the effect of physical training programs.

Interestingly, Vaidya et al. [21], in a large prospective cohort study, reported that participation in higher weekly PA (> 16.6 MET-hours per week, which is approximately equivalent to brisk walking > 5 h per week or running > 2.5 h per week) might reduce the risk by 50% of developing primary Hyperparathyroidism in women when compared with a more sedentary lifestyle, suggesting an important role of PA in maintaining parathyroid gland homeostasis and function.

Recently, Brod et al. [8] reported that HypoP impacts on functioning and well-being also in terms of exercise inability leading subjects with HypoP to be less physically active during the day compared to healthy control peers. Several studies [29–32] have focused on hypothyroid patients, that sometimes show similar symptoms to HypoP population (i.e., muscle cramps, fatigue, and loss of concentration), showing a lower daily steps number in women with subclinical hypothyroidism compared to healthy controls (about 6200 steps vs 9370, respectively) and a general lower PA level [30]. Moreover, among the few studies available, Santos et al. [31] reported increased HDL concentration after 20 weeks of resistance training program in women with hypothyroidism compared to controls; likewise, Sefat et al. [33] found that concurrent aerobic-resistance training improves blood

glucose homeostasis and body composition of adolescent girls with hypothyroidism. In addition, Wernech et al. [34] indicated that 16 weeks of aerobic exercise training significantly improved health-related quality of life (HRQoL) in women with hypothyroidism.

In contrast to this abundant amount of data in hypoT patients, only a few studies have been focused on PA in HypoP subjects [1]. In particular, an interesting study [34] stated that women with hypothyroidism should participate in training programs to increase PA and muscular strength, possibly with the presence of a specialist counselor. Thus, similar indications should also be given to patients affected by calcium disorders. Lankhaar et al. [28] also reported that the most common exercise-related constraints in patients affected by hypothyroidism are fatigue, prolonged recovery post-exercise, low-performance outcomes, and muscle complaints, advocating a multidisciplinary integral health approach. Indeed, postsurgical complication of thyroidectomy might include all the above-described complaints, as more recently described [35]. Conversely, a study by Vokes [36] reported that some patients affected by HypoP can manage relatively normal life, including high levels of PA (like running marathons at professional levels), while others are extremely limited and constrained in terms of physical functioning. Due to these recent descriptions of symptoms of HypoP subjects similar to the HypoT patients, it might be hypothesized that similar PA protocol might be developed for these patients, as well.

In particular, it appears that a combination of aerobic and resistance training could represent a valid PA modality for HypoP patients. It is well known that in all people performing physical activity, it is needed an appropriate integration of both fluid and minerals. Thus, it is strongly advisable, and even mandatory, that HypoP individuals carefully evaluate both minerals and liquid integration to prevent alteration of electrolyte homeostasis.

Lines of inquiry

In the future, it would be of interest to deeply investigate the impact of those physical activities performed at high intensity with rest intervals (high-intensity interval training, HIIT) such as CrossFit®, a training modality that alternates high-intensity workouts based on functional exercises, that showed a positive impact on healthy population [37] as an alternative and enjoyable training strategy that could also be adapted for HypoP people.

In addition, since HypoP patients are prone to hypocalcemia, abdominal pains, muscle cramping, and paraesthesia [38], it appears crucial to pay particular attention to fluids intake and to electrolytes integration during PA to prevent these possible manifestations.

Physical activity intervention recommendations

Regarding therapeutic chronic management of HypoP, in almost all cases included in the previously presented studies, standard treatment options have been used, including oral calcium and vitamin D (its metabolites and analogues), except for only a few cases treated with PTH 1–34 [38, 39]. The data collected have shown, at baseline evaluation, several cases with values above or below the normal range of corrected serum calcium, serum phosphorus, and 24 h urinary calcium and phosphorus, in accordance with the known difficulty to maintain these levels within the range of normality. This phenomenon of serum calcium imbalance can cause paresthesia, brain fog, prolonged QcT on electrocardiogram, impaired renal function, or life-threatening and a generally reduced quality of life.

Several studies have been performed in hypothyroid patients, in whom it is advisable a multicomponent approach that, besides pharmacological and medical intervention [45, 46], would comprise a specific moderate-to-vigorous PE program (55–80% of VO_{2max}), with a frequency varying from 3 to 5 days a week, in relation to the relative PA intensity, and lasting 12–20 weeks [43, 44]. These PA programs should include aerobic and resistance training or a combination of these two modalities such as concurrent training or HIIT. In addition, circuit training, which could be defined as a time-efficient form of strength training utilizing a repeated sequence of exercises with short rest periods, could represent an easy and enjoyable training strategy. PA programs must necessarily be followed by a multidisciplinary team including a PE professional, possibly an Adapted Physical Activity (APA) specialist who owns specific competences to modulate the training parameters in special populations. Thus, a similar type of interdisciplinary approach should be advisable also in HypoP patients to improve their physical activity ability and optimize their QoL. Table 1 depicts potential exercises and training to suggest to individuals affected by HypoP to improve their physical fitness and quality of life.

Main limitations of the review

This document provides recommendations based on the most recent scientific evidence; however, caution is recommended when prescribing a specific exercise protocol due to the limited amount of robust, longitudinal experimental studies available on HypoP population. Another limitation of our manuscript is the fact that this review cannot be considered a systematic review, due to the limited number

Table 1 Exercise protocol proposal for patients affected by hypoparathyroidism

Type	Exercise description	Intensity	Duration	Frequency
Warm-up: aerobic exercise and passive stretching	Treadmill running or cycling; stretching of proximal muscles and those involved in resistance exercise	Up to 30% VO_{2max} (60% HR max) 3 sets, 30 s for each muscle group	10 min	3–5 times/week
Aerobic exercise	Treadmill running or cycling	40–50% VO_{2max} (70% HR max)	15 min	3 times/week
		65–80% VO_{2max} (80% HR max)	15 min	
Resistance training	Bench press, back press, arm curl, double-leg extension, bent-leg incline sit-up, lateral pull down, leg press	60–80% of maximal effort (1RM)	10 repetitions, 3 sets Resting period between sets: 2 min	2 times/week (no consecutive days)
Cooldown: aerobic exercise	Treadmill running or cycling	Up to 30% VO_{2max} (60% HR max)	10 min	3–5 times/week

References: [18, 21–23, 40–42]

of publications on this topic. However, specific keywords such as hypoparathyroidism, calcium homeostasis, physical activity, and physical exercise were used to search specific manuscripts dedicated to this issue.

Conclusion

Hypoparathyroidism is a rare endocrine disorder, with difficult clinical and therapeutic management and severe complications, whose incidence and prevalence have not been well defined. This study aimed to systematically review the more recent literature about the relationship between PTH function and PA as well as HypoP and PA.

It is advisable a multicomponent approach that, besides pharmacological intervention, would comprise a specific moderate-to-vigorous PA program (55–80% of VO_{2max}), with a frequency varying from 3 to 5 days a week, that should include aerobic and resistance training or a combination of the two. In addition, a PE protocol is proposed to increase mobility, muscular strength, and aerobic fitness in everyday activities.

In conclusion, to enhance exercise and sports participation for the HypoP population, more robust longitudinal research is strongly advisable: specifically, additional studies are needed to further define which intensities and training modalities better fit to manage physical activity in these patients and improve quality of life.

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Author contributions SM and MLB had the idea for the manuscript, VB, LC, and AM performed the literature search; VB, AM, FF, GI, CB, and SM drafted and critically revised the work. AL, CB, GI, and MLB reviewed the manuscript.

Declarations

Conflict of interest The authors declare no competing financial or non-financial interests. LC and SM are members of the Editorial Board of JEI.

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