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Similar increases on muscle functions in COPD and healthy after unilateral training

A randomized controlled study

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Summary

Background: Chronic Obstructive Pulmonary Disease (COPD) characterize reduced lung functions and skeletal muscle dysfunctions. Resistance training has shown to improve muscle functions to similar degree as healthy. Previous literature has furthermore proven low exterior load to have similar effects as high exterior load in healthy. This is essential for those incapable of performing training with high exterior load.

Aims: The aim of this study was to investigate the effects of 10 weeks of lower body unilateral resistance training on maximal muscle strength (1RM), muscular endurance performance (repetitions to exhaustion at 50% of 1RM) and muscle thickness (Q_t) between Chronic Obstructive Pulmonary Disease patients (COPD) and healthy individuals (HEALTHY).

Methods: Nine COPD and 22 HEALTHY performed 10RM and 30RM resistance training in a contralateral manner for 10 weeks, preceded by three weeks of familiarization to training protocols. 1RM and repetitions to exhaustion at 50% of 1RM was measured at baseline (-3 weeks), after familiarization (0 weeks) and after 10 weeks of training (10 weeks). Q_t was measured at -3 weeks and 10 weeks with portable ultrasound.

Results: After 10 weeks of training, COPD and HEALTHY exerted similar increases in 1RM strength, repetitions to exhaustion at 50% of 1RM and Q_t ($p = 0.33$ to 0.96). Overall, there were no differences between 30RM- and 10RM-training on any of the variables.

Conclusion: Ten weeks of unilateral 30RM and 10RM resistance training led to similar increases in muscle strength, endurance performance and muscle thickness in COPD and HEALTHY. This has clinical implications for preventing and treating muscle waste, where the exterior load can be individualized according to health status and simultaneously improve muscle strength and thickness to similar degree.

Keywords Chronic obstructive pulmonary disease, elderly, resistance training, quadriceps, volitional failure

Table of Contests

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List of abbreviations

1RM	One repetition maximum
COPD	Chronic obstructive lung disease
CSA	Cross section area
FEV_1	Forced expiratory volume in one second
FEV_1% pred.	Percent of forced expiratory volume in one second of predicted value
FVC	Forced vital capacity in one second
FVC % pred.	Percent of forced vital capacity of predicted value.
FEV_1/FVC	Ratio of FEV_1 to FVC (%)
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HEALTHY	Healthy controls
HL	High load resistance training
HYPERINFLATION	Abnormal inspiration after a normal expiration
HYPERTROPHY	Increased muscle size
HYPOXIA	Diminished availability of oxygen to tissue within the body
LL	Low load resistance training
PEF	Peak expiratory flow
Q_t	Quadriceps thickness

Theory and methodology

1 Pathophysiology in COPD

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality. The variable prevalence across population groups and between countries are due diverse exposure to noxious particles (GOLD, 2017). Yet, accurate epidemiological data concerning prevalence, disease severity, morbidity and mortality is difficult and expensive to obtain because of diverse methods for measuring COPD (GOLD, 2017) and due to diverse terminology of COPD (Leivseth et al., 2013).

According to the GOLD report (GOLD, 2017), COPD is defined as *a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious gases.* Chronic airflow limitation is caused by a combination of small airway diseases (e.g. small airway fibrosis) and parenchymal destruction (emphysema) (GOLD, 2017), that can occur together or alone. Both conditions can be induced by chronic inflammation that result in airflow limitation and gas trapping by narrowing small airways, destruct connective tissue in the lungs and increase lung elasticity. As a consequence, oxygen available for working muscles are limited, causing dyspnea and reduced exercise capacity, that may contribute to muscle wasting (GOLD, 2017). Airflow obstruction increase with disease severity and can be detected by spirometry. Stages according to Global Initiative for Chronic Obstructive Lung Disease (GOLD stage) range from 1 to 4 (GOLD, 2017), that can be punctuated with episodes of exacerbations that is associated with worsening of symptoms and generally cause increased airway inflammation, abnormal inspiration after a normal expiration (hyperinflation), gas trapping and dyspnea (GOLD, 2017).

COPD is a result of a complex interaction between various factors such as genetics (α1–antitrypsin deficiency) and environmental exposures to noxious gases and particles (air pollution, dust, fumes vapours and irritants), abnormal lung development and age (GOLD, 2017). Generally are risk factors for other diseases that affects cardiac functions, diabetes, metabolic syndrome, osteoporosis and muscle waste are linked to COPD (GOLD, 2017).

2 Skeletal muscle dysfunctions in COPD

Skeletal muscle dysfunctions are frequently observed in COPD (Janaudis-Ferreira, Wadell, Sundelin, & Lindstrom, 2006; Menon et al., 2012; Shrikrishna et al., 2012). They are characterized by reduced muscle strength, muscle mass and/or endurance, reducing the capability of the muscles to perform physiological tasks adequately (Gea, Pascual, Casadevall, Orozco-Levi, & Barreiro, 2015). Muscle strength generally defines the maximal force a muscle or muscle group can generate at a specific or determined velocity (Knuttgen & Kraemer, 1987) and is often measured as one repetition maximum (1RM). Muscle dysfunctions have been detected in all GOLD stages, and especially in the lower limbs, such as the quadriceps muscles (Bernard et al., 1998; Menon et al., 2012; Shrikrishna et al., 2012). The muscular changes seem to resemble sarcopenia in the aging population (Hunter, McCarthy, & Bamman, 2004; Rosenberg, 1997), however in COPD the changes appear to be accelerated. In a previous study, a 25% reduction of rectus femoris cross-section area (CSA) compared to healthy age-matched controls was observed (Seymour et al., 2009). Improving muscle mass and strength in COPD is essential for both exercise capacity and quality of life (Iepsen et al., 2015; Vonbank et al., 2012). Muscular dysfunctions do not only apply to COPD, but also to the general population where lifestyle, diseases and possibly genetic predispositions (Mattsson, Wheeler, Waggott, Caleshu, & Ashley, 2016) are some of many influencing factors.

The underlying cause behind muscular dysfunctions in COPD is not fully understood, but has been ascribed to factors such as ventilatory limitations (Satta et al., 1997), reduced level of physical activity, lack of exercise (Vorrink, Kort, Troosters, & Lammers, 2011), systemic inflammation, diminished availability of oxygen to tissue within the body (hypoxia) and phenotypical changes (Donaldson, Maddocks, Martolini, Polkey, & Man, 2012; Gea et al., 2015; Satta et al., 1997). The ventilatory muscles are overloaded in COPD (GOLD, 2017) which can contribute to the adaptation of an inactive lifestyle, that generally is observed in patients (O'Donnell, Revill, & Webb, 2001; Vorrink et al., 2011). As a consequence of inactivity and disuse, the lower limbs are underloaded, triggering muscle wasting and more limited muscle mass compared to healthy standards (Maltais et al., 2014). An important factor in triggering muscle wasting has been proposed to include inflammatory mediators (GOLD, 2017). The inflammation seem to interfere with muscle-fiber functions and hormone levels

(Donaldson et al., 2012), as well as affecting properties of the DNA, lipids, proteins and the balance between protein synthesis and breakdown (Gea et al., 2015). Hypoxia is another contributing factor to muscle dysfunctions that acts by modifying skeletal muscle tissue (Turan et al., 2011). In general, it is presumed that exercises demanding less ventilatory capacity such as resistance training will benefit COPD patients (Constantin et al., 2013; Iepsen et al., 2015).

A shift in fiber type distribution in skeletal muscles away from type I (slow-twitch oxidative) towards type IIX (fast-twitch glycolytic) fibers is a common feature of COPD (Harry R. Gosker, Zeegers, Wouters, & Schols, 2007) and can explain the reduced strength-related endurance performance in COPD (Franssen, Broekhuizen, Janssen, Wouters, & Schols, 2005). In a previous study comparing COPD and controls, the proportion of type I fibers was 16% vs 42% and the proportion of type IIX was 23% vs 14% (H. R. Gosker et al., 2002). The underlying cause of the phenotypical changes has been suggested to include detraining (Gea et al., 2015) and neuropathic processes that cause motor denervation (Hunter et al., 2004). It is anticipated that muscular dysfunctions in COPD can partly be prevented and maintained by regular physical training.

3 Resistance training

The overall population benefits from performing resistance training to gain muscle strength and increase muscle size (hypertrophy). The World Health Organisation of public healthy guidelines for adults, recommend strength training of the major muscle groups twice weekly or more, in addition to endurance training (WHO, 2010). Resistance training has several documented benefits as reducing the risks of cardiovascular diseases, diverse cancers, prevent falls, reduce depressions and can improve functional health (WHO, 2010).

3.1 Modifications of resistance training protocols

Modifying resistance training protocols commonly known as `strength training` or `weight training` is essential for optimizing muscle strength and hypertrophy and is recommended to be performed with heavy exterior loading (Ratamess et al., 2009). The modification involves adjusting training volume (i.e. total number of repetitions, sets, rest and load performed in a training session) (Hass, Feigenbaum, & Franklin, 2001), intensity, repetitions to exhaustion, rest period between sets, rest between sessions and order of exercises (American College of Sports, 2009). Several recent training modalities have been shown to provide similar increases in muscle strength and hypertrophy (Csapo & Alegre, 2016; Morton et al., 2016; Raymond, Bramley-Tzerefos, Jeffs, Winter, & Holland, 2013; Van Roie, Delecluse, Coudyzer, Boonen, & Bautmans, 2013), suggesting that training protocols can be individualized according to preferences, health status, training status and training goals.

3.2 Low-load and high-load resistance training

For some time, the traditional high-load resistance training protocol (HL) have been challenged by low-load resistance training (LL) protocols. LL resembles the concept of “muscular endurance training” characterizing an external weight being lifted with light to moderate load (40 - 60% of 1RM) for numerous repetitions (> 15RM) (Ratamess et al., 2009). LL has been found to increase muscle strength and hypertrophy to a similar degree as HL (Morton et al., 2016), which defines an external load between one to 12RM (> 65% of 1RM). HL performed with one to three sets is currently recommended for increasing 1RM strength and hypertrophy (Ratamess et al., 2009). The similar increase from LL is therefore a contradiction to the assumption that exercising with high exterior load is necessary for increasing muscle strength and hypertrophy (Ratamess et al., 2009). For instance, young, old and cancer patients had similar or higher effect of performing LL than HL, on lower- and upper limbs (Morton et al., 2016; B. Strasser, Steindorf, Wiskemann, & Ulrich, 2013). Despite these findings, HL has generally had the tendency of improving muscle function to a higher degree than LL (Csapo & Alegre, 2016; Holm et al., 2008; B. J. Schoenfeld, Peterson, Ogborn, Contreras, & Sonmez, 2015; B. J. Schoenfeld, Wilson, Lowery, & Krieger, 2016). Overall, the studies comparing the effects of LL and HL are scarce (Mitchell et al., 2012; B. J. Schoenfeld et al., 2016), especially in diverse patient groups who might be at particular advantage of performing LL. In fragile elderly for instance, LL can reduce the risk of weight-related injuries by putting less stress on bones, muscles and tendons (Kohrt, Bloomfield, Little, Nelson, & Yingling, 2004; Lee & Carroll, 2007).

Several underlying mechanisms for the suggested increase between LL and HL have been proposed, including total training volume (Csapo & Alegre, 2016) and muscle fiber recruitment (B. J. Schoenfeld, 2013). Training volume has shown to affect neural, hypertrophic, metabolic and hormonal responses to training (Ratamess et al., 2009), and is generally high during LL (Csapo & Alegre, 2016; B. Schoenfeld, Contreras, Willardson, Fontana, & Tiryaki-Sonmez, 2014). It has been proposed that LL compensates for the lower external weight with a high training volume (Csapo & Alegre, 2016). Training volume may increase hypertrophy and strength gain by causing a high accumulation of metabolic stress and mechanical tension (B. J. Schoenfeld, 2013). Even though increasing training volume improves strength-related outcomes, a dose-response relationship is thought to exists. The upper threshold seems to be high, where one study has shown increased muscle strength after performing eight sets (Marshall, McEwen, & Robbins, 2011).

Training volume can act as a confounding factor in research settings (Csapo & Alegre, 2016). When studies have controlled for training volume, HL has increased 1RM strength and quadriceps CSA more than LL (Holm et al., 2008). Without controlling for training volume, both have demonstrated increased muscle functions (Radaelli et al., 2013; Van Roie et al., 2013). Combining a high training volume and performing exercises until muscular failure have been proposed to be essential for increasing muscle functions (Dodson et al., 2011; Van Roie et al., 2013). Muscular failure occurs when motor units have fatigued and cannot produce force to continue exercising (Willardson, 2007). The principle state that motor units are recruited based on force requirements, where economical slow twitch muscle fibers are activated prior to fast twitch muscle fibers (Mendell, 2005). Diverse explanations have been proposed for the role of motor units in increasing muscle strength and hypertrophy. Some have proposed that exercising until muscular failure is essential for recruitment of fast twitch muscle fibers, and that it is independent of the exterior load lifted (B. J. Schoenfeld, 2013). Others have suggested that a certain percentage of 1RM is needed to recruit fast twitch muscle fibers (Willardson, 2007). In addition, it has been speculated if motor unit recruitment is more essential during muscular adaptations, rather than acting as a mechanism (Hakkinen, Pakarinen, & Kallinen, 1992; B. Schoenfeld et al., 2014; B. J. Schoenfeld et al., 2015). Moreover, performing resistance training until muscular failure over a prolonged period of time will increase the risk of overtraining and training-related injuries. This do not only apply to individuals with diverse diseases like cardiovascular conditions and musculoskeletal injuries, but also to trained individuals (Willardson, 2007).

Training status influences the magnitude of strength gain and hypertrophy (Ratamess et al., 2009). During the introduction phase to training, the similar improvements observed between LL and HL on muscle functions, are likely due to high responsiveness in novices (Ratamess et al., 2009). The rapid increase in muscle strength without substantial signs of increased muscle thickness (Blazevich, Gill, Deans, & Zhou, 2007; Hakkinen et al., 1992) are influenced by neurological changes that alters the way the central nervous system controls muscles, together with alterations within the muscle itself (Hakkinen et al., 1992; P. Aagaard, 2003). To prohibit neurological changes from impairing the association between strength gain and muscle growth, a familiarization period prior to training is essential (Sampson, McAndrew, Donohoe, Jenkins, & Groeller, 2013). When mastering the general principles of resistance training, increasing the exterior load and varying training modalities are essential for muscular improvements and to avoid ceiling-effects (Radaelli et al., 2013; Ratamess et al., 2009). The modification should be based on training status, age, injury, current and previous diseases (Ratamess et al., 2009).

4 General effects of resistance training on muscle functions

Muscle strength and hypertrophy are triggered by resistance training through multiple mechanisms, acting in a complex manner. Suggested underlying mechanisms include mechanical tension, metabolic stress and hormones (B. J. Schoenfeld, 2010), that leads to changes in muscle phenotypes (Scott, Stevens, & Binder-Macleod, 2001). High mechanical tension is caused by performing resistance training with high exterior load. This damages the structure of muscle cells and in turn, change the activity of various intracellular signaling pathways leading to release of local growth factors regulating satellite cell proliferation and differentiation (B. J. Schoenfeld, 2010), by adding novel myonuclei to existing myofibrils. These cascades of events eventually leads to hypertrophy (B. J. Schoenfeld, 2010). However, mechanical tension is unlikely the solely mechanism for hypertrophy and strength gain. Exercise-induced metabolic stress caused by numerous repetitions with limited rest, is proposed to induce hypertrophy in a primary or secondary manner through alteration of free-radical production, hormone levels and cell swelling (B. J. Schoenfeld, 2010). Within the cell, metabolic stress may stimulate increased amount of mitochondria improving oxidative capacity of muscle fibers (Scott et al., 2001). A release of testosterone, insulin-like growth factors (IGF-1) and growth hormones (GH) is suggested to increase hypertrophy by inhibiting myostatin, increase protein synthesis, activate satellite cell proliferation and differentiation (B. J. Schoenfeld, 2010). Previous studies have however indicated that hormones may not be essential *per se* for muscle growth (Hakkinen et al., 1992; Holm et al., 2008; Morton et al., 2016). A less elucidated mechanism for hypertrophy and strength gain is hyperplasia which is well-known in animals but uncertain in human beings (B. J. Schoenfeld, 2010).

Prolonged periods of resistance training leads to increased muscle strength by altering the aspects of the muscle phenotypes, leading to enlargement of individual muscle fibers and shifting muscle fiber composition in a more functional direction (e.g. IIX →IIA) (Scott et al., 2001). This leads to an alteration in force production with faster contraction time. The natural ability of a muscle to produce force depends on factors such as cross-section area and the proportion of muscle fiber types (I, IIA and IIX) (Per Aagaard et al., 2001), where the proportion is affected by inactivity and age (E. Strasser, Draskovits, Praschak, Quittan, & Graf, 2013). The ability to produce force rapidly is important for the elderly population for prevention of falls and for performing weight-bearing tasks (Hunter et al., 2004). Because of vague training guidelines for increasing muscle strength and hypertrophy for the general population, it suggests the effectiveness of several resistance-training protocols.

Variable response to resistance training protocols have been observed. In a previous study of the elbow flexors, 12 weeks with progressive resistance training showed a range in 1RM strength from zero to 250% increase, with muscle size ranging from -2 to 59% increase (Hubal et al., 2005). The “low-responders” and “high-responders” to training may be influenced by genetic predispositions (Mattsson et al., 2016). A familiarization period prior to training interventions is proposed as essential for identifying variable responders (Sampson et al., 2013). Overall, basic training requirements of training volume and intensity tend to generate a positive response to training for the general population (Ratamess et al., 2009).

5 COPD and resistance training

COPD patients are encouraged to include both resistance- and endurance exercises into their pulmonary rehabilitation program (Spruit et al., 2013). Generally, programs have focused on endurance training even though resistance training improves muscle strength and mass to a higher degree (Iepsen et al., 2015; Liao et al., 2015; O'Shea, Taylor, & Paratz, 2009; Vonbank et al., 2012). The advantages of resistance training for COPD patients includes its simplicity and reduce ventilatory demands which, when perform continuously, improves muscle function, performance of daily tasks (O'Shea et al., 2009) and quality of life (Vonbank et al., 2012). Resistance training with heavy exterior loading is furthermore considered safe to perform in all GOLD stages, even during exacerbations (Troosters et al., 2010).

What resistance training modalities that benefits COPD for improving hypertrophy and strength gain are uncertain. Previous literature has shown positive effects of resistance training with high exterior load (Burtin et al., 2012; Hoff et al., 2007) despite a lower muscle strength, mass (Menon et al., 2012; Shrikrishna et al., 2012) and endurance compared to healthy controls (Janaudis-Ferreira et al., 2006). Even though several studies have compared muscular dysfunction between COPD and healthy, few have compared the effects of resistance training on muscle strength and hypertrophy. On the basis of previous findings, it is likely that COPD and healthy respond to resistance training in a similar degree. Furthermore, as LL and HL tend to increase muscle strength and hypertrophy in both young and old individuals, makes COPD likely to respond in a similar degree. Exercising with low exterior load is an important alternative to HL for individuals suffering from ventilatory limitations, metabolic disease, cardiovascular diseases and osteoporosis (GOLD, 2017). The idea of similar increase in muscle strength and hypertrophy between COPD and healthy after diverse training modalities is intriguing, and central for further resistance training guidelines.

Resistance training is often performed in a bilateral manner (two-legs at a time), and can be difficult to perform in patients with COPD. As resistance training elevates the ventilatory demands, that characterizes COPD, makes the idea of unilateral protocols (one-leg) an exciting alternative. By putting less stress on the ventilatory system and reducing dyspnea, enables COPD to exercise longer with a higher workload compared to bilateral exercises (Nyberg, Saey, Martin, & Maltais, 2016). In the study by Nyberg et al., (2016) healthy subjects had no additional advantage of performing exercises unilaterally. In an experimental setting, unilateral training is associated with neurological effects that affects the efficacy of motor pathways, giving rise to the inter-limb phenomenon of “cross-education” (Cirer-Sastre, Beltran-Garrido, & Corbi, 2017). The phenomenon can be problematic in contralateral protocols as muscle strength increase in the untrained limb (Lee & Carroll, 2007). In one previous meta-analysis with mostly young individuals, the untrained limb increased muscle strength by approximately 8% (Munn, Herbert, & Gandevia, 2004). Several paradigms to explain the mechanisms have been proposed, including a re-organization of motor pathways and motor-learning, where the opposite hemisphere in control of movements, trigger neurological changes in the contralateral limb (Lee & Carroll, 2007). To prevent cross-education from providing inaccuracies to contralateral data sets, it is essential to include familiarization periods to training protocols prior to interventions (Carroll, Herbert, Munn, Lee, & Gandevia, 2006; Cirer-Sastre et al., 2017; McCurdy, Langford, Doscher, Wiley, & Mallard, 2005), thereby reducing the impact of the initial neuronal adaptations.

The aim of this study was therefore to test the hypothesis of a similar increase on muscle functions in COPD and healthy after unilateral training.

6 Methodology

The master thesis is based on data originating from a large intervention administered by PhD-candidate Knut Sindre Mølmen, examining the effects of vitamin D3 supplementation on functional and biological effects of 10 weeks of resistance training in COPD patients (COPD) and healthy controls (HEALTHY). The intervention is performed at Inland University of Applied Sciences (INUAS), campus Lillehammer.

The aim of the master thesis was to evaluate effects of 10 weeks of unilateral resistance training (30RM and 10RM) on 1RM leg strength, repetitions to exhaustion at 50% of 1RM and quadriceps thickness in COPD and HEALTHY. The resistance training intervention was preceded by 3 weeks of unilateral familiarization to training protocols. The thesis is presented in the form of a scientific article, prepared for publication in Medicine and Science in Sports and Exercise. In addition to the article, the thesis includes a comprehensive theory and methodology section, according to guidelines from Norwegian School of Sport Sciences.

The study was approved by The regional committees for medical and health research ethics (REK) (reference number 2013/1094), registered at clinicaltrials.gov (NCT02598830) and carried out in accordance to the Declaration of Helsinki. Written and oral informed consent was obtained from all participants prior to initiation.

6.1 Study design and subjects

Ten patients with COPD and 26 HEALTHY controls participated in the randomized controlled study. The intervention was conducted from January to June 2017. Baseline characteristics of those who completed the intervention are shown in Table 1. Enrolment took place in Oppland county, Norway, where participants were recruited from Granheim Lung Hospital, advertisements in local and social medias and at the INUAS homepage. The following criteria for patient selection were used: above 45 years, stable COPD at GOLD stage II or III and novices to resistance training. Exclusion criteria were suffering from unstable cardiovascular diseases, chronic granulomatous disease, physically disabling musculoskeletal diseases, exacerbations the last four weeks, serious psychiatric comorbidity, known active malignant disease within the last five years, use of peroral steroids within the last two months or failing to understand Norwegian literary or verbally.

During the intervention, five participants were excluded from the data set. Three participants dropped out (personal reasons = 2 HEALTHY; injury = 1 COPD) and two (HEALTHY) did not perform training in according to the intervention. Leg injuries prior to intervention can have contributed to drop outs. Nine COPD (men = 5; female = 4) with mean age of 69 ± 4 years, and 22 HEALTHY (men = 9; female = 13) with mean age of 67 ± 5 years, completed the intervention. Participants with COPD had severe airflow obstruction (forced expiratory volume in 1 s of % predicted value) defining GOLD stage II and higher average pack years than HEALTHY ($p < 0.05$).

Table 1. Baseline characteristics

	COPD (n= 9)	HEALTHY (n= 22)
Sex (M:F)	5:4	9:13
Age (years)	69 ± 4	67 ± 5
Height (cm)	168.8 ± 10.6	170.2 ± 10.4
Body Weight (kg)	71.2 ± 21.6	76.4 ± 14.5
FEV_1 (L)	1.5 ± 0.3	2.9 ± 0.7
FEV_1 % pred.	57.0 ± 5.9	107.9 ± 13.3
FVC (L)	3.0 ± 0.8	3.9 ± 1.0
FVC % pred.	93.2 ± 13.3	117.2 ± 15.4
FEV_1/FVC (%)	49.6 ± 6.2	76.6 ± 5.3
PEF (L)	4.7 ± 1.4	7.9 ± 2.0
Pack years	28.7 ± 14.4	6.1 ± 9.5

Data are mean and SD. FEV_1, forced expiratory volume in one second expressed in litre (L); FEV_1% pred., percent of forced expiratory volume in one second of predicted value; FVC, forced vital capacity in one second (L); FVC % pred., percent of forced vital capacity of predicted value; FEV_1/FVC, ratio of FEV_1 to FVC (%); PEF, peak expiratory flow (L); pack years, packs of smoke per year

6.2 Intervention

In short, participants performed unilateral resistance training consisting of 30 repetitions (30RM) and 10 repetitions (10RM) until muscular failure two times/week for 10 weeks. See Table 2 for detailed information concerning the study design. Participants legs were randomly admitted to 30RM and 10RM by coin flip. Measurements of 1RM strength, repetitions to exhaustion at 50% of 1RM and quadriceps thickness (Q_t) was performed at baseline (-3 weeks; prior to familiarization to training protocols), prior to the intervention (0 weeks) and after 10 weeks of resistance training (10 weeks). Q_t was measured at -3 weeks and 10 weeks.

Table 2. Timeline over the experimental design

Muscle strength	↓		↓		↓
Muscle thickness	↓				↓
	Baseline tests	Familiarization	Test	Training	Post Test
Weeks	-3		0		13

6.2.1 Spirometry

Forced expiratory volume in one second (FEV_1), percent of forced expiratory volume in one second of predicted value (FEV_1% pred.), forced vital capacity (FVC), percent of forced vital capacity of predicted value (FVC % pred.), ratio of FEV_1 to FVC (FEV_1/FVC) and expiratory peak flow (PEF) were measured in all subjects using Oxycon (number SN 808808) at inclusion as described by Miller et al,. (2005). Reversibility tests were performed on subjects with abnormal lung functions (< 80% FEV_1 (pred.), using 2.5ml Ventoline (5mg salbutamol (GlaxoSmithKline AS, Oslo, Norge MTnr: 7488) and 1ml Atrovent (0.5mg ipratropiumbromid (Boehringer Ingelheim International GmbH, Ingelheim, Germany MTnr: 98-1432 NO), that were inhaled for approximately eight minutes using a neublizer (Philips Respironics Porta-neb). Reversibility tests were repeated 15 and 45 minutes after inhalation. Subjects performing the reversibility tests performed a clinical examination prior to inclusion. Participants were diagnosed with COPD according to GOLD guidelines, with post bronchodilator FEV_1/FVC < 0.7 (GOLD, 2017). Severity of the disease was defined by level of FEV_1% pred. (GOLD, 2017). A qualified nurse from Granheim Lung Hospital completed all tests. Calibration of devices were performed daily.

6.2.2 Resistance training

Unilateral resistance training was performed two times/week until volitional failure for 10 weeks. Prior to training, a familiarization period lasting three weeks was used to reduce effects of learning and cross-education on outcome measures (Lee & Carroll, 2007; Sampson et al., 2013). To avoid systematic differences, the dominant leg was first trained in the initial session and non-dominant leg first in the subsequent session. The procedure was repeated for the remaining weeks. Training consisted of leg press, knee extension, leg curl, chest press, pulldown and grip strength. The lower body performed three sets with two minutes' rest between sets and working legs. Exterior load was progressively increased when participants exceeded 35 repetitions of 30RM and 12 repetitions of 10RM. Upper body exercises consisted of two sets of 10RM, where the exterior load increased when exceeded 12RM. All sessions started with a five-minute warm-up on a stationary bicycle at low intensity. To ensure sufficiently protein intake, half of an energy bar containing approximately 15g protein was consumed after ended sessions. Each session was supervised by a qualified trainer. A doctor was available throughout the study for medical advises.

6.2.3 Maximal strength and endurance performance

1RM strength was assessed at -3 weeks, 0 weeks and 10 weeks in in knee extension and seated leg press (Technogym, Italy). Individual seating positions was noted at -3 weeks and utilized during all tests with full range of motion. Prior to the 1RM test, three specific warm-up sets with 10 repetitions at approximately 40% of 1RM, six repetitions at 70% of 1RM and three repetitions at 85% of 1RM were performed. Participants were given one minute rest between warm-up sets and were given two minutes rest between the last warm-up set and between consecutive 1RM tests. 1RM was found by increasing the weight by 1.25kg until failing to lift with full range of motion. The right and left leg completed an exercise before another was initiated. Dominant legs were first measured. 1RM tests were assessed by a qualified trainer.

Muscular endurance tests were measured in knee extension (Technogym, Italy) by performing repetitions to exhaustion at 50% of 1RM. When failing to continue an exercise with full range of motion or failing to maintain a dynamic movement, the test was ended. Values from baseline tests were used for measuring endurance improvements. The number of repetitions were counted by the test leader. Finger-stick lactate concentration [La-] was measured after one minute (Biosen C-Line Glucose and Lactate Analysers, United Kingdom) and a three minutes break were given before the other leg was tested.

6.2.4 Ultrasound to measure muscle thickness

A portable ultrasound apparatus (Echo Wave II, SmartUS EXT-1M, Telemed, Lithuania), with a linear array transductor (field of view 59 mm and 12 MHz scanning frequency; Lithuania), was used to assess quadriceps thickness (Q_t). Measurements were performed at -3 weeks and 10 weeks. The scanning site was located 60% of the length from the greater trochanter to the femur lateral epicondyle as previously described (Helland et al., 2017). During examination, subjects lay in a supine position with a rectangular box placed between the ankle joints to relax the upper thigh. Sufficient contact gel was applied to the transductor and minimal pressure was used to minimize distortion of underlying tissue. At -3 weeks, scanning location with individual characteristic landmarks was drawn onto a flexible, plastic sheet to ensure reproducibility in repeated scannings. To obtain muscle thickness of Q_t, the ultrasound probe was placed perpendicular to the long axis of the thigh on its superior aspect to visualize rectus femoris and femur. Q_t was defined as the distance between the upper aponeuroses of rectus femoris and the upper point of femur. At each time point, three images were obtained. All images were analysed after the intervention using the software ImageJ (Rasband WS. ImageJ, US. National Institute of Health, Bethesda, Maryland, USA, 1997-2012) in a randomized and blinded manner. The operators performing ultrasound measurements had no previous experience, but completed a familiarisation period before assessing muscle thickness in the project. High accuracy has been identified when a clinical without experience performed ultrasound assessments (Seymour et al., 2009). To avoid exercise-induced muscle swelling from affecting the measurements, ultrasound was performed prior to, or at least 12 hours after exercising. Assessing muscle thickness in lower limbs has proven to be reliable

(Bemben, 2002; English, Fisher, & Thoirs, 2012), valid (Reeves, Maganaris, & Narici, 2004) and having high reproducibility in sarcopenic quadriceps muscles (E. Strasser et al., 2013).

7. Statistics

All analyses were performed with IBM SPSS Version 24 and Excel (2016). Descriptive statistics are presented in the text and table as mean ± SD unless stated otherwise. Data were analysed for normality using Shapiro-Wilk Tests. Whenever data were not normally distributed, non-parametric statistics were used. To compare COPD and HEALTHY at -3 weeks, 0 weeks and 10 weeks, independent sample t-test or Mann-Whitney U Test was used. To compare the effects of strength modalities (30RM vs 10RM) and muscle thickness of Q_t (30RM vs 10RM) on groups of participants at -3 weeks, 0 weeks and 10 weeks, paired sample t-test or Wilcoxon signed rank test were used. To detect an effect of time on strength variables, repeated measures ANOVA with Bonferroni were used. To test for an interaction between COPD and HEALTHY, a two-way ANOVA with independent variable as condition (COPD/HEALTHY) and time (-3 weeks/0 weeks/10 weeks) on dependent variables (strength parameters, endurance performance and Q_t) was performed. Pearson correlation was performed between strength parameters and muscle thickness. All statistical tests were two-tailed and the threshold of statistical significance was set as p value of < 0.05.

8 Other measurements

In the main intervention, several other outcome measurements were included, such as biopsy samples from vastus lateralis, dual-energy X-ray absorptiometry, assessment of isokinetic and isometric strength with dynamometer at diverse angles and velocities, one-leg and two-leg VO_2 max tests and measurements of functional performance with sit-to-stand test and step test. Physical activity was utilized by physical activity questionnaires such as International Physical Activity Questionnaire (IPAQ) and COPD Assessment Test (CAT). These tests will not be mentioned any further.

9 Main authors practical participation in the study

The main author collaborated with PhD-candidate Knut Sindre Mølmen on logistics in the intervention. Execution of 1RM tests, repetitions to exhaustion at 50% of 1RM and measurements of muscle thickness tests was a collaboration between the main author, Knut Sindre Mølmen and the following bachelor students: Jan Kristian Fjelltun, Håvard Berge Bredesen, Nicolai Blindheim Jacobsen, Karoline Michalsen, Karin Heggeli Moen, Håkon Fure Jerpseth, Karianne Pedersen, Katarina Alsvik, Anette Gårderløkken, Anniken Braaten, Joachim Skjeseth Fjeller, Mads-Henrik Hafsmo, Malene Wilhelmsen, Vemund Lien and Vetle Olsen.

Analyzes of ultrasound images was performed by the main author and Knut Sindre Mølmen. Beyond this, the author assisted during biopsies, measured muscle function in dynamometer and performed one-leg and two-legged VO_2 max tests.

10 Economy

Inland University of Applied Sciences (INUAS), campus Lillehammer and Sykehuset Innladet, Norway provided research founding for conducting the intervention.

11 Literature research

To obtain an overview of the literature on the scientific field is PubMed and Web of Science used with the following keywords; Chronic obstructive pulmonary disease, elderly, resistance training (OR strength training OR weight training), quadriceps and volitional failure.

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Article

Similar increases on muscle functions in COPD and healthy after unilateral training

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Word limit: approximately 20 pages

Abstract

The aim of this study was to investigate the effects of 10 weeks of lower body unilateral resistance training on maximal muscle strength (1RM), muscular endurance performance (repetitions to exhaustion at 50% of 1RM) and muscle thickness (Q_t) between chronic obstructive pulmonary disease patients (COPD) and healthy individuals (HEALTHY). Nine COPD (69 ± 4 years) and 22 HEALTHY (67 ± 5 years) performed 30RM and 10RM training in a contralateral manner for 10 weeks, preceded by three weeks of familiarization to training protocols. 1RM and repetitions to exhaustion at 50% of 1RM was measured at baseline (-3 weeks), after familiarization (0 weeks) and after 10 weeks of training (10 weeks). Q_t was measured at -3 weeks and 10 weeks. At -3 weeks, COPD and HEALTHY showed similar 1RM strength, repetitions to exhaustion at 50% of 1RM and Q_t (p = 0.20 to 0.95). After 10 weeks of training, COPD and HEALTHY exerted similar increases in 1RM strength, repetitions to exhaustion at 50% of 1RM and Q_t (p = 0.33 to 0.96). Overall, there were no differences between 30RM- and 10RM-training on any of the variables.

In conclusion, 10 weeks of unilateral 30RM and 10RM resistance training led to similar increases in muscle strength, endurance performance and muscle thickness in COPD and HEALTHY. The intervention has clinical implications for prevention and rehabilitation of muscle waste, where diverse exterior load can be individualized according to health status and simultaneously improve muscle strength and thickness to similar degree.

Keywords

Chronic obstructive pulmonary disease, elderly, resistance training, quadriceps, volitional failure

Introduction

Chronic obstructive pulmonary disease (COPD) is a common, but life-threatening disease, characterized by chronic airflow limitations (1) and reduced skeletal muscle strength and mass (2, 3) that exceeds age-related sarcopenia (4).

Progressive physical training for maintaining muscle functions in COPD and elderly has been considered important not only for improving muscle mass and strength (5, 6), but also for improving functional health and quality of life (7-9). But what training modality that benefits COPD the most, is still a matter of debate. Generally, pulmonary rehabilitation programs for COPD have focused on endurance training even though resistance training improves muscle strength and mass to a higher degree (8-11). As resistance training performed bilaterally (two-legs at the same time) elevates the ventilatory demands, training can be difficult to performed in some COPD. A unilateral (one-leg) protocol have proven to be a beneficial alternative (12). It is likely that performing resistance training unilaterally, increase strength related outcomes to similar degree as healthy. Furthermore, recent literature has demonstrated that performing resistance training with low exterior load (LL) is equivalent to resistance training with high exterior load (HL), which can be beneficial for fragile individuals' due to less stress on tendons and bones (13).

The aim of this study was to assess the hypothesis that COPD exert similar effects on 1RM strength, muscular endurance performance (repetitions to exhaustion at 50% of 1RM) and muscle thickness (Q_t) as HEALTHY and secondly, to compare the effects of LL and HL.

Methods

Subjects

Ten individuals with COPD and 26 HEALTHY controls participated in the randomized controlled study. Participants were recruited from Granheim Lung Hospital, and advertisements in local and social medias and at the Inland University of Applied Sciences (INUAS) homepage. The following criteria for patient selection were used: above 45 years, stable COPD at GOLD stage II or III and novices to resistance training. Exclusion criteria were suffering from unstable cardiovascular diseases, chronic granulomatous disease, physically disabling musculoskeletal diseases, exacerbations the last four weeks, serious psychiatric comorbidity, known active malignant disease within the last five years, use of peroral steroids within the last two months or failing to understand Norwegian literary or verbally. During the intervention, three participants dropped out (personal reasons = 2 HEALTHY; injury = 1 COPD) and two (HEALTHY) did not perform training in according to the intervention. Leg injuries prior to intervention can have contributed to drop outs. Nine COPD and 22 HEALTHY completed the intervention. Baseline characteristics are shown in Table 1. Participants with COPD had severe airflow obstruction (forced expiratory volume in 1 s of % predicted value) defining GOLD stage II and higher average pack years than HEALTHY ($p < 0.05$). The study was approved by Regional Committees for Medical and Health Research Ethics (REK) and carried out in accordance to the Declaration of Helsinki prior to initiation. Written informed consent was obtained from all participants prior to initiation.

Experimental design

The randomized controlled study was part of a larger intervention involving vitamin D3 substitute (ClinicalTrials.gov: Identifier: NCT02598830). Participants performed unilateral resistance training consisting of 30 repetitions (30RM) and 10 repetitions (10RM) until volitional failure two times/week for 10 weeks. Participants legs were randomly admitted to 30RM and 10RM by coin flip. Measurements of 1RM strength, repetitions to exhaustion at 50% of 1RM and quadriceps thickness (Q_t) was performed at baseline (-3 weeks; prior to familiarization to training protocols), prior to intervention

(0 weeks) and after 10 weeks of resistance training (10 weeks). Q_t was measured at -3 weeks and 10 weeks.

Spirometry and reversibility

Spirometry was performed at inclusion with Oxycon (number SN 808808) as described by Miller et al,. (14). Reversibility tests were performed on subjects with abnormal lung functions (< 80% FEV_1 (pred.) using 2.5ml Ventoline (5 mg salbutamol (GlaxoSmithKline AS, Oslo, Norge MTnr: 7488) and 1ml Atrovent (0.5mg ipratropiumbromid (Boehringer Ingelheim International GmbH, Ingelheim, Germany MTnr: 98-1432 NO) that were inhaled for eight minutes using a neublizer (Philips Respironics Porta-neb). Reversibility tests were repeated 15 and 45 minutes after inhalation. Subjects performing the reversibility tests performed a clinical examination prior to inclusion. COPD was estimated according to GOLD guidelines as post-bronchodilator FEV_1/FVC of < 0.7. Severity was defined by levels of FEV_1 as percentage of predicted value (1). A qualified nurse completed all tests. Calibration were performed daily.

Table 1. Baseline characteristics

	COPD (n= 9)	HEALTHY (n= 22)
Sex (M:F)	5:4	9:13
Age (years)	69 ± 4	67 ± 5
Height (cm)	168.8 ± 10.6	170.2 ± 10.4
Body Weight (kg)	71.2 ± 21.6	76.4 ± 14.5
FEV_1 (L)	1.5 ± 0.3	2.9 ± 0.7
FEV_1 % pred.	57.0 ± 5.9	107.9 ± 13.3
FVC (L)	3.0 ± 0.8	3.9 ± 1.0
FVC % pred.	93.2 ± 13.3	117.2 ± 15.4
FEV_1/FVC (%)	49.6 ± 6.2	76.6 ± 5.3
PEF (L)	4.7 ± 1.4	7.9 ± 2.0
Pack years	28.7 ± 14.4	6.1 ± 9.5

Data are mean and SD. FEV_1, forced expiratory volume in one second expressed in litre (L); FEV_1% pred., percent of forced expiratory volume in one second of predicted value; FVC, forced vital capacity in one second (L); FVC % pred., percent of forced vital capacity of predicted value; FEV_1/FVC, ratio of FEV_1 to FVC (%); PEF, peak expiratory flow (L); pack years, packs of smoke per year

Resistance training

Unilateral training until volitional failure were performed two times/week for 13 weeks (three weeks familiarization and 10 weeks training) with 30RM and 10RM. To avoid systematic differences, dominant leg was first trained in the initial session and non-dominant leg first in subsequent session. The procedure was repeated for remaining weeks. Training consisted of leg press, knee extension, leg curl, chest press, pulldown and grip strength. The lower body performed three sets with two minutes' rest between sets and working legs. External load was increased progressively when exceeded 35 and 12 repetitions. Upper body exercises consisted of two sets of 10RM and were exceeded when performing 12RM. All sessions started with a five-minute warm-up on a stationary bicycle at low intensity. To ensure sufficiently protein intake, half energy bar containing approximately 15g protein was consumed after ended sessions. Each session was supervised by a qualified trainer.

Maximal strength and endurance performance

1RM strength was assessed at -3 weeks, 0 weeks and 10 weeks in knee extension and seated leg press (Technogym, Italy). Seating positions was noted at -3 weeks and utilized during all tests with full range of motion. Prior to 1RM test, three specific warm-up sets with 10 repetitions at approximately 40% of 1RM, six repetitions at 70% of 1RM and three repetitions at 85% of 1RM were performed. Participants were given one minute rest between warm-up sets and two minutes rest between the last warm-up set and between 1RM attempts. 1RM was found by increasing the weight by 1.25kg until failing to lift with full range of motion. Dominant legs were first measured. Right and left leg completed an exercise before another was initiated. 1RM tests were assessed by a qualified trainer.

Muscular endurance tests were measured in knee extension (Technogym, Italy) by performing repetitions to exhaustion at 50% of 1RM. When failing to continue an exercise with full range of motion or to maintain a dynamic movement, the test was ended. Values from baseline tests were used for measuring improvements. The number of repetitions were counted by the test leader. A three minutes break were given before the other leg was tested.

Muscle thickness

Portable ultrasound (Echo Wave II, SmartUS EXT-1M, Telemed, Lithuania) with a linear array transductor (12 MHz scanning frequency; Lithuania) assessed quadriceps thickness (Q_t) at -3 weeks and 10 weeks. The scanning site was located 60% from the greater trochanter to the femur lateral epicondyle as previously described (15). During examination, subjects lay in a supine position. Sufficient contact gel was applied to the transductor and minimal pressure was used to minimize distortion of tissue. At -3 weeks, scanning location with individual characteristic landmarks was drawn onto a flexible, plastic sheet to ensure reproducibility in repeated scannings. Q_t was defined as the distance between the upper aponeuroses of rectus femoris and upper point of femur. At each time point, three images were obtained. All images were analysed after the intervention using the software ImageJ (Rasband WS. ImageJ, US. National Institute of Health, Bethesda, Maryland, USA, 1997-2012) in a randomized and blinded manner. Assessing muscle thickness is reliable (16, 17), valid (18) and have high reproducibility (19) and accuracy (4). Difficulty of identifying individual landmarks within the muscles left seven COPD and 17 HEALTHY for data analysis.

Statistics

Descriptive statistics are presented in the text and table as mean ± SD unless stated otherwise. Data were initially analysed for normality with Shapiro-Wilk Tests. For non-normally distributed data, non-parametric tests were used. To compare patient groups at -3 weeks, 0 weeks and 10 weeks, independent sample t-test or Mann-Whitney U Test were used. To compare the effects of strength modalities (30RM vs 10RM) and muscle thickness of Q_t (30RM vs 10RM) on groups of participants at -3 weeks, 0 weeks and 10 weeks, paired sample t-test or Wilcoxon signed rank test were used. To detect an effect of time on strength variables, repeated measures ANOVA with Bonferroni were used. To test for an interaction between COPD and HEALTHY, a two-way ANOVA with independent variable as condition (COPD/HEALTHY) and time (-3 weeks/0 weeks/10 weeks) on dependent variables (strength parameters, endurance performance and Q_t) was performed. Pearson correlation was performed between strength parameters and muscle thickness. All statistical tests were two-tailed and the threshold of statistical significance was set as p value of < 0.05. All analyses were performed with IBM SPSS Version 24 and Excel (2016).

Results

Baseline values

At -3 weeks COPD and HEALTHY displayed similar 1RM strength (Fig.1A-D), 50% of 1RM performance (Fig.1E-F) and Q_t ($p = 0.20$ to 0.95; Fig. 2A-B). Neither COPD nor HEALTHY displayed differences between legs in 1RM strength ($p = 0.13$ to 0.73; Fig.1A-D) nor in Q_t ($p = 0.50$ and 0.16; Fig.2A-B). COPD displayed greater 50% of 1RM performance in 30RM- than 10RM leg ($p < 005$; Fig.1E). In COPD, three weeks of familiarization to 30RM and 10RM training protocols led to increased 1RM knee extension ($14 \pm 17\%$ and $30 \pm 28\%$; $p < 0.05$; Fig.1C), with no effects being apparent in 1RM leg press (Fig. 1A) and repetitions to exhaustion at 50% of 1RM knee extension (Fig. 1E). In HEALTHY, three weeks of familiarization to 10RM training protocols led to increased 1RM leg press ($10 \pm 11\%$, $p < 0.05$; Fig.1B), 1RM knee extension ($5 \pm 8\%$, $p < 0.05$; Fig.1D) and 50% of 1RM ($25 \pm 33\%$, $p < 0.05$; Fig.1F). 30RM-training protocol led to increased 50% of 1RM ($25 \pm 30\%$, $p < 0.05$; Fig.1F), with no effects being apparent in 1RM leg press and 1RM knee extension.

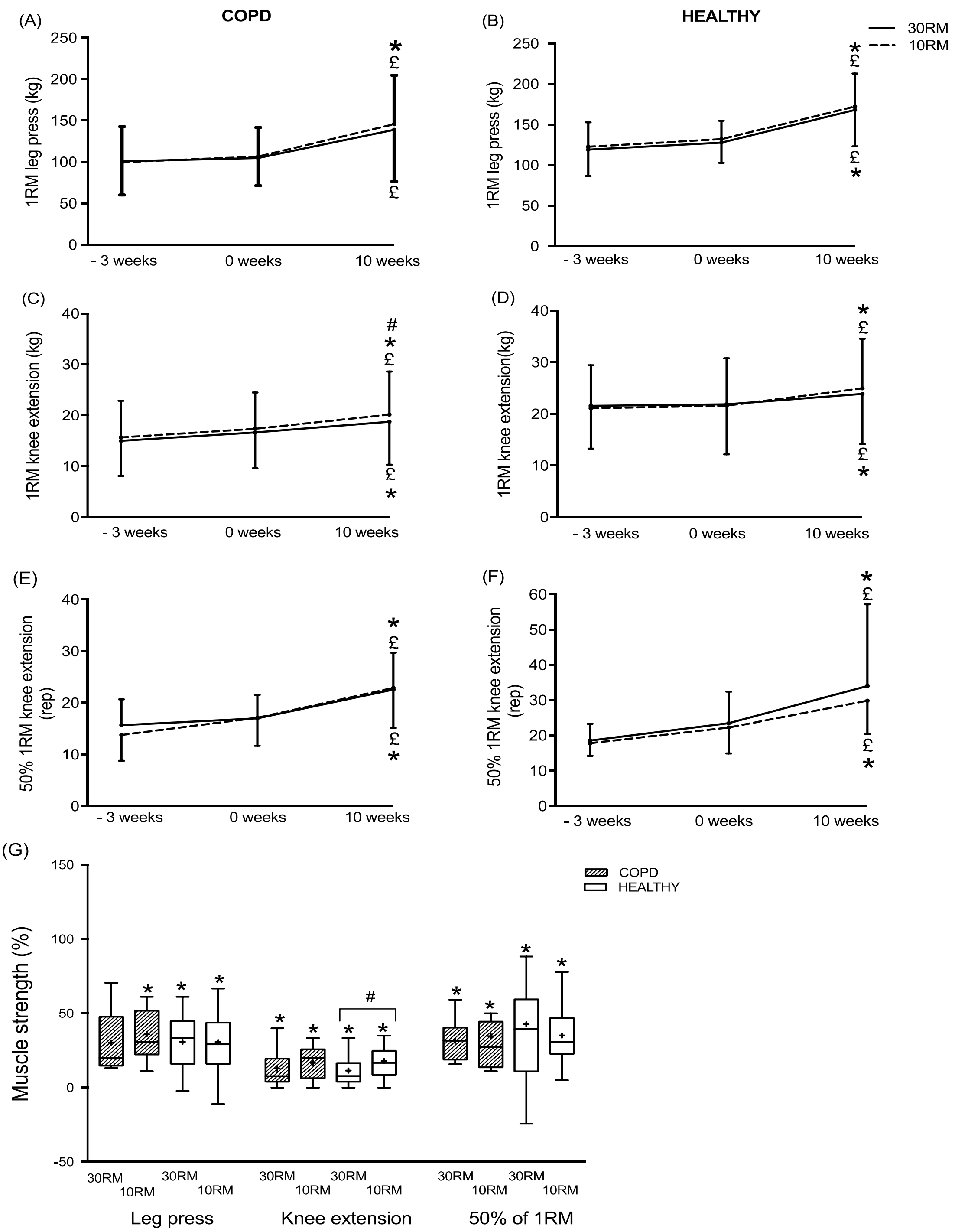

Figure 1. (A-F) Muscle strength and endurance at baseline (-3 weeks), after 3 weeks of familiarization to 30RM- and 10RM resistance training (0 weeks) and after 10 weeks of progressive 30RM- (solid line) and 10RM- (dotted line) resistance training in COPD and HEALTHY. £ indicates significant difference from -3 weeks to 10 weeks ($p < 0.05$), * significant difference from 0 weeks to 10 weeks ($p < 0.05$) and # indicates difference between 30RM and 10RM ($p < 0.05$). (A-B) 1RM leg press (kg). (C-D) 1RM knee extension (kg). (E-F) Repetitions to exhaustion at 50% of 1RM knee extension (rep). (G) Changes in muscle strength (%) (leg press and knee extension) and endurance (repetitions to exhaustion in knee extension) from 0 weeks to 10 weeks of 30RM- and 10RM-training in COPD (shaded symbols) and HEALTHY (open symbols). Boxplots are represented with interquartile range marking the boxes, central line marking the data sets median and + representing the mean

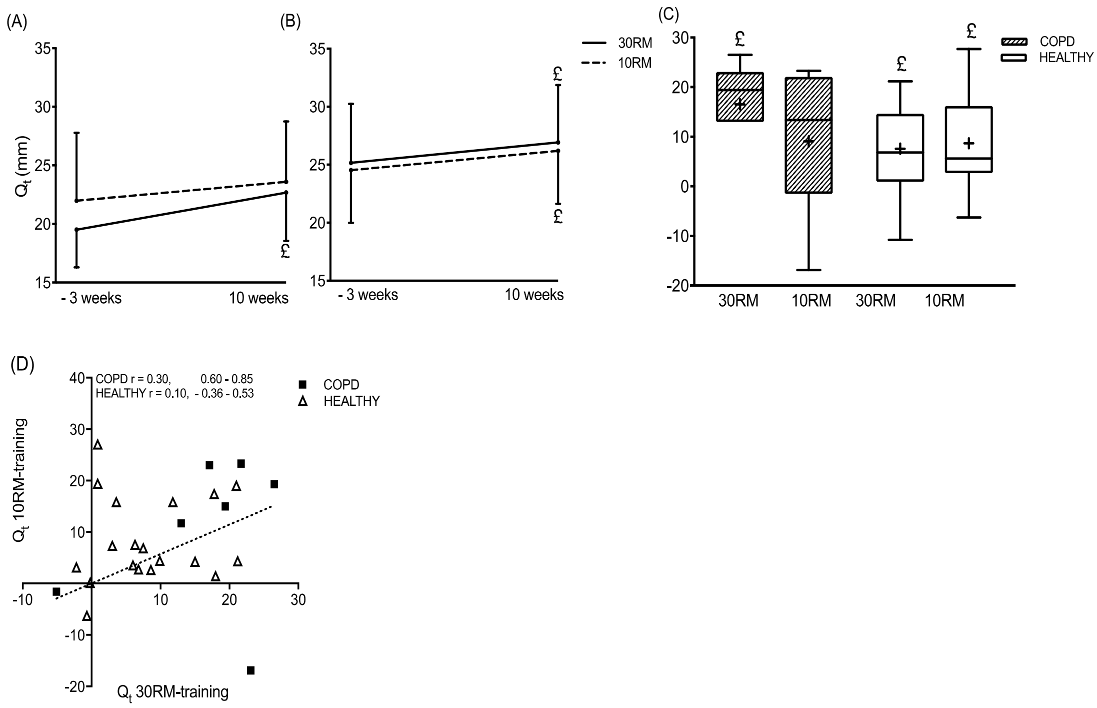

Figure 2. (A-B) Thickness of m. quadriceps femoris and intermedius before (-3 weeks) and after 10 weeks (10 weeks) of 30RM- (solid line) and 10RM training (dotted line) for COPD (A) and HEALTHY (B), where £ indicates significant difference from -3 weeks to 10 weeks ($p < 0.05$). Data are mean ± SD. (C) Changes in Q_t in response to 30RM- and 10RM training in COPD (shaded symbols) and HEALTHY (open symbols) (%). Boxplots are represented with interquartile range marking the boxes, central line marking the data sets median and + representing the mean. (D) Correlation between changes in Q_t in response to 30RM- and 10RM training in COPD (square) and HEALTHY (triangle). The dotted line represents a perfect 1:1 relationship. r denotes Pearson correlation and 95% confidence intervals

Training volume

In general, COPD and HEALTHY displayed similar training volume ($p = 0.50$ to 0.99; Fig.3). Overall, 30RM-training led to a higher training volume than 10RM-training in leg press ($p < 0.01$; Fig.3A, B) and knee extension ($p < 0.01$; Fig.3C, D). In COPD, 30RM and 10RM training volume increased from 0 weeks to 10 weeks in leg press (41 ± 22%; $p < 0.01$ and 28 ± 37%; $p = 0.32$), with a difference between legs ($p < 0.01$; Fig3.A) and in knee extension (30 ± 15%; $p < 0.01$ and 24 ± 24; $p = 0.09$), with no difference between legs ($p = 0.21$; Fig3.C). Combined leg press and knee extension displayed similar training volume between 30RM and 10RM at 0 weeks ($p < 0.01$) and 10 weeks ($p < 0.05$; Fig.3E). In HEALTHY, 30RM and 10RM increased in leg press (37 ± 30% and 47 ± 53%; $p < 0.01$), with a difference between legs ($p < 0.01$; Fig.3B) and in knee extension (57 ± 38% and 23 ± 37; $p < 0.01$), with a difference between legs (p < 0.01; Fig.3D). Combined leg press and knee extension displayed similar training volume between 30RM and 10RM at -3 weeks, 0 weeks and 10 weeks (p < 0.01; Fig.3E).

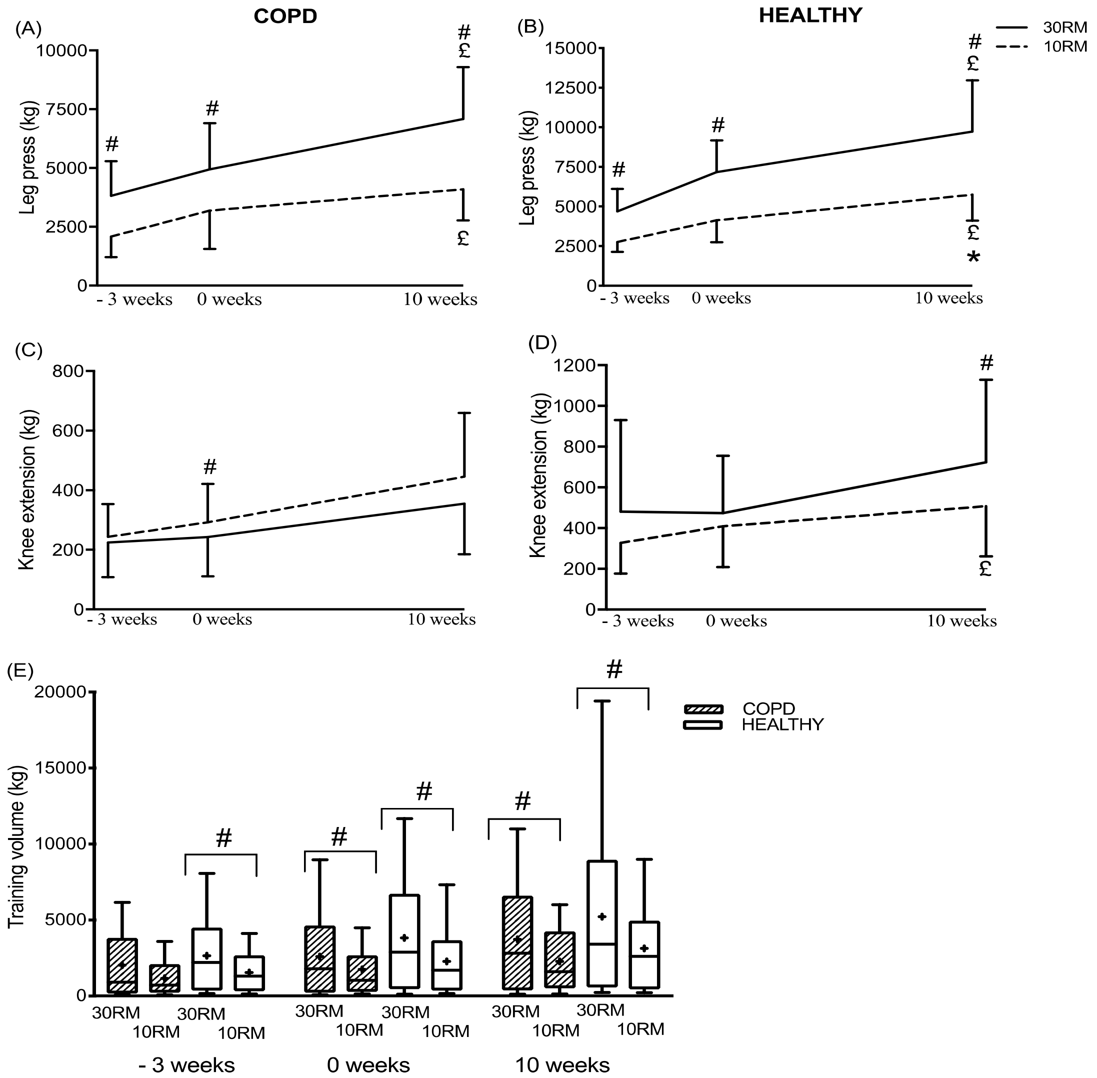

Figure 3. (A-D) Training volume at baseline (-3 weeks), after 3 weeks of familiarization to 30RM and 10RM resistance training (0 weeks) and after 10 weeks of progressive 30RM- (solid line) and 10RM (dotted line) resistance training in COPD and HEALTHY. £ indicates significant difference from -3 weeks to 10 weeks (p < 0.05) and # indicates difference between 30RM and 10RM (p < 0.05). (A-B) training volume leg press (kg). (C-D) training volume knee extension (kg). (E) overall training volume (leg press and knee extension combined) for 30RM- and 10RM training at -3 weeks, 0 weeks and 10 weeks in COPD (shaded symbols) and HEALTHY (open symbols). Boxplots are represented with interquartile range marking the boxes, central line marking the data sets median and + representing the mean

1RM strength and 50% of 1RM after 10 weeks of training

COPD and HEALTHY displayed similar increases in 1RM strength in leg press and knee extension in response to 30RM- and 10RM training ($p = 0.40$ to 0.69; Fig.1). In COPD, 10 weeks of resistance training of 30RM- and 10RM-training led to increased 1RM leg press (30 ± 21%; $p = 0.05$ and 36 ± 17%; $p < 0.05$; Fig.1G), with no difference between legs ($p = 0.13$; Fig.1A) and 1RM knee extension (13 ± 13% and 17 ± 12%; $p < 0.05$; Fig.1G), with the 10RM-leg exhibiting greater increase ($p = 0.01$; Fig.1C). In HEALTHY, 30RM- and 10RM-training led to increased 1RM leg press (31 ± 17% and 31 ± 20%; $p < 0.01$; Fig.1G), with no difference between legs ($p = 0.19$; Fig.1B) and 1RM knee extension (11 ± 12% and 18 ± 14%; $p < 0.01$; Fig.1G), with no difference between legs ($p = 0.54$; Fig.1D). COPD and HEALTHY displayed low correlation between 30RM- and 10RM-leg strength (Fig.4).

COPD and HEALTHY displayed similar increases in repetitions to exhaustion at 50% of 1RM in response to 30RM- and 10RM training ($p = 0.33$ and 0.78; Fig.1E-F). In COPD, 30RM- and 10RM training led to increased endurance performance (32 ± 14% and 35 ± 28%; $p < 0.05$; Fig.1G), with no difference between legs ($p = 0.82$; Fig.1E). In HEALTHY 30RM- and 10RM training led increased endurance performance (43 ± 43% and 35 ± 19%; $p < 0.01$; Fig.1G), with no differences between legs ($p = 0.38$; Fig.1F).

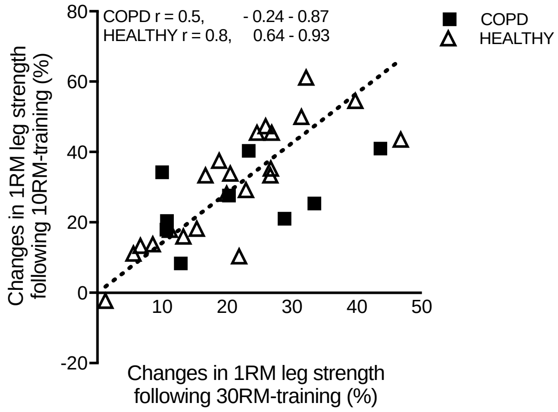

Figure 4. Correlation between changes in 1RM leg strength following 10 weeks of 30RM- and 10RM-training in COPD (solid squares) and HEALTHY (open triangles). The dotted line represents a perfect 1:1 relationship. r denotes Pearson correlation and 95% confidence intervals

Muscle thickness after 10 weeks of training

COPD and HEALTHY displayed similar increases in Q_t in response to 30RM- and 10RM- training ($p = 0.38$ and 0.96; Fig.2). In COPD, 30RM- and 10RM training led to increased Q_t (17 ± 11%; $p < 0.01$ and 9 ± 14%; $p = 0.17$; Fig.2C), with no difference between legs ($p = 0.62$; Fig.2A). In HEALTHY, 30RM- and 10RM training led to increased Q_t (8 ± 8%; $p < 0.01$ and 9 ± 9%; $p < 0.05$; Fig.2C), with no difference between legs ($p = 0.96$; Fig.2B). No correlations were found between changes in Q_t following 30RM- and 10RM-training (Fig.2D), between Q_t and 1RM muscle strength (Fig.5A) or between Q_t and repetitions to exhaustion at 50% of 1RM (Fig.5B).

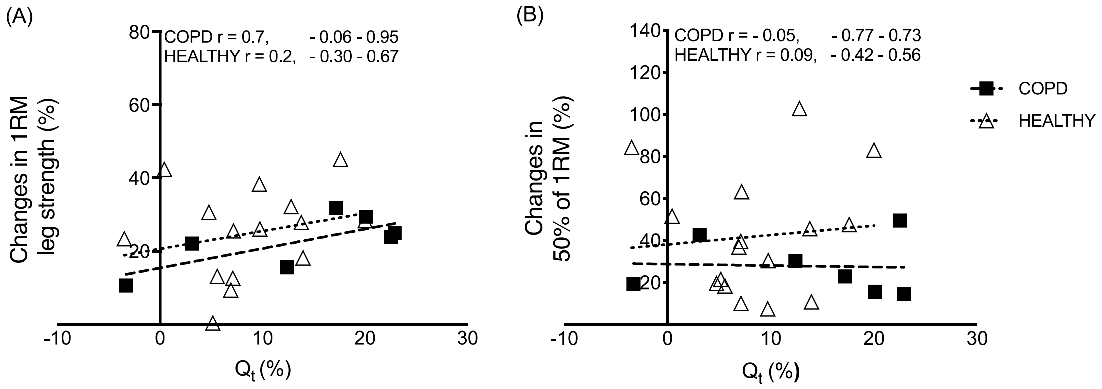

Figure 5. Correlation between changes in Q_t in response to 30RM- and 10RM training and increases in 1RM leg strength in COPD (square) and HEALTHY (triangle). Leg strength is represented as a combination of leg press and knee extension for training modalities. Data are individual values. The dotted line represents a perfect 1:1 relationship. r denotes Pearson correlation and 95% confidence intervals

Discussion

The present data showed that COPD and HEALTHY exhibited similar increases in 1RM strength, muscle-endurance performance (at 50% 1RM) and muscle thickness (Q_t) in response to 10 weeks of progressive resistance training. Similar findings have previously been observed with COPD and healthy elderly (3, 20, 21).Overall, 30RM- and 10RM-protocol exhibited similar effects on muscle characteristics in both populations when using a unilateral protocol, which corresponds with recent finding on LL and HL (22).

COPD and HEALTHY

Maximal strength and muscle thickness

The results show that resistance training leads to similar increases on maximal muscle strength (1RM) and muscles thickness (Q_t) in COPD and HEALTHY. This adds to the growing body of evidence that COPD and HEALTHY are highly responsive to resistance training and emphasize the importance of training to maintain and restore 1RM leg strength. Overall, it is evident that elderly are highly responsive to HL for improving muscle strength (23). Furthermore, Constantin et al. (20) and Menon et al. (3) have demonstrated similar increases on muscle strength and mass between COPD and healthy, when using multiple repetitions and sets. Other studies using other protocols have not detected such findings, and is possibly due to insufficient stimulus (12, 21).

The similar responses to training in COPD and HEALTHY in the present study, may be related to aspects of the study protocol, such as its unilateral design, status of COPD and the inclusion of a familiarization period prior to intervention. As for the first, previous studies have typically been performed using bilateral protocols (3, 20, 22). As resistance training often is performed bilaterally in practice, it reduces the generalizability in the present study. However, the unilateral design made it possible to compare differences in muscle strength and thickness in the same participant, without being affected by exercise adaptability (24). The unilteral design is likely to have reduced the ventilatory demands and consequently improved exercise capacity through available oxygen for working skeletal muscles (1). In previous studies with COPD, unilateral excersies improved aerobic capacity and work load more than bilateral excercieses (12, 25).

The similar baseline values between participant groups and the positive response to training, strengthens the explanation of lower levels of inflammation within skeletal muscles of the included COPD (26). As inflammation negatively affects satellite cell fusing and proliferation, lower levels may have given the muscle-cell the ability to recover rapidly (26). Contrastingly, as COPD is accompanied by reduced muscle strength (2-4, 20) and as training interventions generally show similar increases as healthy (3, 20), makes this explanation dubious. The similar baseline values indicate inclusion of generally healthy individuals with COPD, who possibly were more recreational active than the general COPD population. As previous studies with more fragile participants have showed higher increases in muscle mass and strength (3, 20) it supports this notion. Previous data can further be explained by diverse measurements of muscle strength and by the lack of inclusion of a familiarization period.

The familiarization period prior to intervention is likely to have avoided contralateral effects between 30RM- and 10RM-leg. During the introduction phase to resistance training, several neurological changes takes place, that impact strength adaptations causing increased force production (27, 28). A four weeks familiarization period in the upper limbs of healthy, have demonstrated to reduce these effects (29), however contralateral effects may be different in individuals (29), muscle groups and across populations. In the present study, COPD and HEALTHY demonstrated similar improvements from -3 weeks to 0 weeks, indicating a low impact of the familiarization period.

Suprisingly, a low to moderate association between Q_t and muscle strength and between Q_t and endurance performance was noted in both COPD and HEALTHY. While such a lack of relationship is supported by a previous study in COPD patients (Menon et al. (3), it conflicts the general perceptions of a strong relationship in healthy (6). A possible explanation for this discrepancy can be methodological issues connected with ultrasound images, which is operator-dependent (3). High accuracy during measurements has been shown with unskilled in previous literature (4). It is possible that measures of rectus femoris CSA which are more closely related to hypertrophy and force characteristics, could have detected a stronger relationship (17). However, if there is a low association between the change in muscle strength and thickness, this shows the essentials of neurological adaptations (30).

Endurance performance

The similar increases in endurance performance between COPD and HEALTHY are interesting. Compared to a previous study with COPD (21) the present results demonstrated higher improvements. In the study by Franssen et al. (21), dynamic strength training programs were individualized according to experienced functional impairments that may have caused the low increase. The improvement in this study can possibly be explained by alterations of fiber type distribution, away from type IIX fibers, towards I or IIA fibers (31), where the latter is a well-known result of resistance training. As type IIA are more prone to fatigue, the result may indicate increased amount of mitochondria (31).

30RM and 10RM

Maximal strength and muscle thickness

The observed similar increase after 30RM- and 10RM training is in accordance with previous interventions of LL and HL on muscle strength (22) and size (32, 33). The results lend further support in the notion that diverse exterior loading can improve muscle strength and muscle thickness in the lower body, which has important clinical implications for those incapable of performing HL. Most studies however favours HL for improving muscle strength and size in young and old individuals (34-37). Even though studies have favoured HL for strength gain, some has demonstrating similar findings of LL and HL on muscle size (32, 33). A higher increase in Q_t was noted in the present study compared to previous observations (32, 33). This can be explained by a close follow-up during training to ensure volitional failure and by diverse methods for utilizing muscle size.

The mechanisms for the similar findings between 30RM- and 10RM training is a matter of debate. The present study may suggest that age, the unilateral protocol and high training volume combined with performing exercises until volitional failure were essential. Overall, 30RM-protocol demonstrated a higher training volume than 10RM-protocol. This correlates well with previous studies comparing LL and HL (35). The low training volume during 30RM knee extension for COPD in the present study was surprising, but can explain the difference between 30RM and 10RM on 1RM knee extension. The difference in training volume indicates the importance of high training volume during LL to improve muscle strength. The similar increase after 30RM and 10RM on Q_t and muscle strength can be explained by a high metabolic and mechanic stimuli (38). Another possible explanation to the similar responses is the unilateral design that may have led to cross-education (39). However, due to a three-weeks familiarization period, which corresponds with the time window which these effects generally occur (39), makes this explanation unlikely.

Endurance performance

In the current data set, 30RM and 10RM exerted similar effects on endurance performance. This conflicts with current training guidelines recommending numerous repetitions (>15) for improving endurance performance (6). Conceivable explanations for the similar increase between the two modalities are unclear, but one possibility is that cross-education lasted longer than three weeks. This is in accordance with a recent study, suggesting that exercising with 80% of 1RM stimulates a higher neural adaptation than exercising with 30% of 1RM (30). Other explanations are the aforementioned alteration in fiber type distribution towards more glycolytic fibers with higher oxidative capacity (31).

Limitations

We recognise that observations are limited to few participants with stable COPD. The strict inclusion criteria are likely to have excluded fragile COPD in need of resistance training, however have excluded patients with frequently occurring exacerbations and other comorbidities. Even though muscle thickness was measured at -3 weeks, measurements at 0 weeks would have been preferable. Unfortunately, this was impossible due to a limited time frame. However, five weeks of training has been shown not to improve muscle thickness significantly (40).

Conclusion

Ten weeks of unilateral 30RM and 10RM resistance training led to similar increases in muscle strength, endurance performance and muscle thickness in COPD and HEALTHY. These finding suggests that diverse exterior loading is a potent way of increasing muscular functions in individuals with COPD and healthy elderly. Therefore, this intervention has clinical implications for rehabilitation and prevention of muscle waste, where the exterior load can be individualized according to health status and simultaneously improve muscle strength and thickness to similar degree. It would be of interest to reproduce the present findings in larger samples, in other diseases, and over a longer time span, allowing to examine differences between groups (e.g. based on gender and age). More studies on the advantage of performing exercises unilaterally in COPD are needed to confirm the present findings.

The intervention was founded by Inland University of Applied Sciences (INUAS), campus Lillehammer and Sykehuset Innlandet, Lillehammer Norway.

Inland University of Applied Sciences (INUAS), campus Lillehammer and Sykehuset Innladet, Norway provided research founding for conducting the intervention.

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Attachments

Informasjon og forespørsel om deltakelse i forskningsprosjekt om KOLS, tilskudd av vitamin D og styrketrening

Kronisk obstruktiv lungesykdom (KOLS) oppleves som et stort problem for mange mennesker. I dag er trening det viktigste du kan foreta deg for å sikre en best mulig hverdag. Dette vil hjelpe deg å ivareta lungekapasitet og muskelstyrke, samt gi deg det generelle velvære som typisk følger med fysisk aktivitet. Det er likevel en kjensgjerning at vi ikke har tilstrekkelig kunnskap om sykdommen til å kunne gi tilfredsstillende behandling og lindring av alle symptomer.

Det viser seg at mange som har KOLS ikke oppnår samme treningseffekt som personer uten lungeplager. Hos slike individer vil verken oksygenopptak eller muskelstyrke øke nevneverdig etter uker med trening. Det har blitt spekulert i at dette henger sammen med lave vitamin D-konsentrasjoner i blodet. Dette vitaminet spiller en rolle for oppbygging av muskler og personer med KOLS har ofte lave nivåer.

Det er mange måter å trene på og om du velger styrketrening *eller* kondisjonstrening, harde og korte økter *eller* lange og lette økter, vil det påvirke utbytte i forhold til både kondisjon og styrke. Den manglende treningseffekten man ser hos mange personer med KOLS kan også skyldes at de trener feil. Kanskje bør personer med KOLS trene på en annen måte enn den øvrige befolkningen?

Vi ønsker å undersøke om tilskudd av vitamin D og to ulike styrketreningsformer kan føre til forbedringer i styrke og kondisjon, og sykdomslindring hos personer med KOLS.

Hva går forskningsprosjektet ut på?

Prosjektet vil ledes av forskere ved Granheim lungesykehus, Sykehuset Innlandet HF Lillehammer og Høgskolen i Lillehammer. Hovedformålet er å identifisere den beste rehabiliteringsformen for personer med KOLS (>45 år). Kan vi gjennom små justeringer i praksis oppnå økt treningsutbytte, økt velvære og bedring i sykdomstilstand?

Studien skal utføres på ~50 KOLS-pasienter og ~50 friske individer. Disse skal deles tilfeldig i to grupper; den ene gruppen skal delta i et strukturert styrketreningsprogram i ca. fire måneder og innta vitamin D i ca. syv måneder. Den andre gruppen skal gjøre akkurat det samme, men skal innta «juksevitaminer» (placebo). Alle forsøkspersoner skal følge det samme treningsprogrammet. For underkroppen innebærer dette trening på to ulike måter; med stor motstand og få repetisjoner, og med liten motstand og mange repetisjoner. Den ene treningsmetoden skal utføres av det ene beinet og den andre skal utføres av det andre beinet. Du skal altså trene en fot om gangen. Dette for å unngå at du blir tungpustet. Når det gjelder overkroppen skal du gjennomføre ordinær tohånds styrketrening med stor motstand og få repetisjoner.

Forskerne skal måle effekten av treningen på forskjellige måter; ved å måle muskelstyrke og utholdenhet, gjennom blodprøver, samt gjennom små vevsprøver av lårmuskulatur (biopsi; for å se etter endringer i muskelcellenes egenskaper). Innsamlet biologisk material (inklusiv bl.a. blod og muskelvev) vil bli analysert etter avsluttet intervensjonen, tidligst høsten 2017. I tillegg vil vi innhente nødvendig bakgrunnsinformasjon, blant annet knyttet til helsetilstand, trening og kosthold. Alle dataene vil bli sammenlignet med tilsvarende data innhentet fra personer som ikke er rammet av KOLS. Dataene vil også inngå analyser som inneholder data fra både KOLS-rammede og friske for å kartlegge betydningen av vitamin D uavhengig av helsetilstand. Kontrollpersonene skal gjennomføre en tilsvarende syv måneders periode med supplement og styrketrening.

Vitamin D-tilskuddet vil bli inntatt som kapsler, og tilsvarer 10.000 internasjonale enheter (IE) *per* dag de første fjorten dagene, for deretter å reduseres til 2.000 IE/dag. Samlet sett vil dette gi gjennomsnittlig daglig inntak tilsvarende ~2.500 IE/dag, som ligger noe over veiledende anbefalinger fra norske myndigheter for personer med lave vitamin D-nivåer (2.000 IE/dag), men godt under øvre grense for inntak satt av European Food Safety Authority (EFSA) (4.000 IE/dag). Vitamin D-tilskudd så høyt som 10.000 IE/dag ser ikke ut til å være forbundet med helserisiko (EFSA).

Dersom du ikke er vant med styrketrening, vil den i en overgangsperiode kunne oppleves som ubehagelig og slitsom. Dette vil endre seg etter hvert som muskulaturen venner seg til treningen. Deretter blir det mer moro!

All trening vil, så langt det lar seg gjøre, foregå under veiledning på Høgskolen i Lillehammer eller Granheim lungesykehus, eller ved alternativ lokasjon.

Hvilken fordeler og ulemper vil du ha av å delta?

I perioden med trening vil vi anstrenge oss for å legge trenings- og testtidspunkt til rette for deg. Du vil bli en del av en velorganisert treningsgruppe og prosjektet vil således bli utbytterikt, både gjennom at du får kunnskap om styrketrening og effekter av styrketrening, og gjennom at det blir sosialt. Du vil få mulighet til å gjennomføre en del tester som du ellers ikke ville fått tilgang til og du vil også få tilbud om videre treningsprogram og råd angående vitamin D-inntak.

Treningsarbeidet vil mest sannsynlig være positivt for helsen din. Treningsrelaterte skader vil likevel kunne oppstå, både akutt og som følge av slitasje. For å redusere risikoen for skader vil du få gradvis tilvenning til treningsprotokollen. Du vil også få tett oppfølging av treningskyndig personell gjennom hele treningsperioden. Disse vil, så langt det lar seg gjøre, være tilstede på samtlige treningsøkter. Skulle vi oppdage avvik fra det vi forventer og/eller få mistanke om ukjente helseproblemer vil det bli tatt initiativ til videre medisinsk oppfølging. Du kan innta inntil 400 IE vitamin D per dag utover det prosjektspesifikke tilskuddet, noe som tilsvarer én *teskje* tran.

Noen synes biopsitaking er ubehagelig. Man vil typisk bli litt støl i muskelen 1-2 dager i etterkant. I svært få tilfeller vil biopsitaking kunne føre til at følelsen i huden forsvinner for en lengre periode, eller gi tydelig arrdannelse. Biopsitaking er også forbundet med en viss infeksjonsfare. Risikoen for disse komplikasjonene er svært liten ved bruk av prosedyrene som benyttes i dette prosjektet.

Erklæring om informert samtykke

Det er helt frivillig om du vil være med i dette studiet og du kan når som helst trekke deg fra forsøket uten at du trenger å oppgi noen grunn til det. Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg og få korrigert eventuelle feil som oppdages.
Om du trekker deg fra forsøket, vil innsamlet materiale og data om deg bli slettet, med mindre opplysningene allerede inngår i analyser eller er brukt i vitenskapelige publikasjoner.

Personvern

Opplysninger som registreres om deg er fødselsår, kjønn, høyde, vekt, data om medisinforbruk og sykdomshistorikk med spesielt fokus på lungefunksjon, data fra prestasjonstester, data om lungefunksjon, data om kroppssammensetning, data fra blod- og vevsanalyser, data om livsstil og data om selvopplevd livskvalitet. Dataene dine vil bli oppbevart Listene som forbinder identifikasjonsnummer og personnavn vil til enhver tid bli oppbevart på låst kontor og i passord-beskyttet tilstand, i etterkant av digitalisering. Høgskolen i Lillehammer ved administrerende direktør er databehandlingsansvarlig.

Biobank

Alle blod- og vevsprøver, samt øvrig informasjon som innhentes i prosjektet, inklusiv informasjon som blir utledet fra det biologiske materialet, vil frem til 31/12-2029 bli lagret i kodet tilstand i en forskningsbiobank tilknyttet prosjektet og vil deretter bli overført til den generelle biobanken «The TrainsOME – humane cellers tilpasning til trening og miljø» (REK-id: 2013/2041), situert ved Høgskolen i Lillehammer/Sykehuset Innlandet. TrainsOME-prosjektet er igangsatt for å avdekke sammenhenger mellom individers tilpasningsevne til trening, også kalt trenbarhet, og kroppslige/cellulære særtrekk. Gjennom den generelle biobanken og tilstøtende prosjekt skal prøvene analyseres sammen med prøver fra en rekke andre prosjekter, hvor den overordnete målsettingen er å studere faktorer som er bestemmende for generell trenbarhet. Dette innebærer generell analyse av cellebiologiske og genetiske trekk som for eksempel cellers form og utseende, arvematerialets sammensetning (inklusiv DNA-sekvens og epigenetisk modifisering), proteinforekomst og -funksjon, RNA-uttrykk og -regulering, hormonforekomst, og mange flere. Hvis du sier ja til å delta i studien, gir du samtidig samtykke til at det biologiske materialet og tilhørende data inngår i denne biobanken. Prøvematerialet vil bli oppbevart i låsbar fryser på låsbart lagerrom. Deler av muskelvevet vil bli analysert i utlandet, blant annet i Sverige og Danmark. Disse prøvene vil være merket med identifikasjonsnummer (og ikke med navn) under transport og vil bli returnert til Lillehammer i etterkant av analysearbeidet. For ytterligere informasjon angående den generelle forskningsbiobanken, se eget informasjonsskriv eller ta kontakt med hovedansvarshavende/prosjektleder Stian Ellefsen. I etterkant av KOLS-prosjektets avslutning i 2029 (31/12) vil forskningsdata utledet fra det biologiske materialet bli anonymisert og oppbevart på sikker server på ubestemt tid, sammen med øvrige data fra prosjektet. Disse dataene vil kunne inngå i analyser fra andre prosjekter som oppbevares i Trainsome-biobanken.

Økonomi
Studien og biobanken er finansiert gjennom forskningsmidler fra Høgskolen i Lillehammer og Sykehuset Innlandet. Det finnes i utgangspunktet ingen økonomiske egeninteresser. På sikt vil det kunne bli aktuelt å tilby treningsdiagnostikk, dvs anbefaling av konkrete individuelle treningsprogram basert på individuelle særtrekk, via en kommersiell plattform.

Forsikring
Forsøkspersoner er forsikret via Pasientskadeloven, jmf Helseforskningsloven § 50.

Informasjon om utfallet av studien

Du vil få tilgang til dine resultater ved å kontakte oss. Utfallet av studien vil bli publisert som offentlig tilgjengelige forskningsartikler og vil danne grunnlag for utforming av nye retningslinjer for styrketrening generelt, og for rehabilitering av KOLS-pasienter spesielt. På sikt vil det kunne bli aktuelt å tilby treningsdiagnostikk via en kommersiell plattform. Prosjektet er godkjent av Regional komitè for medisinsk forskningsetikk (REK sør-øst).

Prosjektmedarbeiderne kan kontaktes når som helst i arbeidstiden (tlf, epost):

Knut Sindre Mølmen (prosjektleder, PhD-stipendiat, Høgskolen i Lillehammer), 94860805, knut.sindre.molmen@hil.no

Stian Ellefsen (prosjektleder, Høgskolen i Lillehammer), 61288103, stian.ellefsen@hil.no

Bent Rønnestad (prosjektkoordinator, Høgskolen i Lillehammer), 61288193, bent.ronnestad@hil.no

Gunnar Slettaløkken (prosjektkoordinator, Høgskolen i Lillehammer), 61288182, gunnar.slettalokken@hil.no

Atle Lie Eriksen (prosjektkoordinator, Granheim lungesykehus), 61117300, atle.lie.eriksen@sykehuset-innlandet.no

Kontakt PhD-stipendiat Knut Sindre Mølmen dersom du ønsker ytterligere informasjon om studien.

Jeg bekrefter å ha lest og forstått samtykkeskrivet og er villig til å delta i prosjektet «KOLS, vitamin D-supplement og styrketrening». Jeg er klar over at det er frivillig å delta i prosjektet og at jeg når som helst kan trekke meg fra prosjektet, uten å oppgi grunn og uten at det gir noen som helst form for konsekvenser.

Sted:……………………….. Underskrift:

………………………………………..

Dato: …../…. 201..

Region:

REK sør-øst

Saksbehandler:

Anette Solli Karlsen

Telefon:

22845522

Vår dato:

28.10.2016

Deres dato:

11.10.2016

Vår referanse:

2013/1094/REK sør-øst A

Deres referanse:

Stian Ellefsen Høgskolen i Lillehammer

2013/1094 KOLS, vitamin D-supplement og styrketrening Forskningsansvarlig: Høgskolen i Lillehammer

Prosjektleder: Stian Ellefsen Vi viser til søknad om prosjektendring datert 11.10.2016 for ovennevnte forskningsprosjekt. Søknaden er

behandlet av leder for REK sør-øst på fullmakt, med hjemmel i helseforskningsloven § 11.

Vurdering

REK har vurdert følgende endringer i prosjektet: -Endringer i medarbeidere. Daniel Buck utgår fra prosjektet, og Knut Sindre Mølmen, Anne cecilie Lian, Håvard Nygaard, Roger Lien og Bjørn Sveensgaard knyttes til prosjektet som medarbeidere. -Endringer knyttet til prøvetaking i prosjektet. Antall muskelbiopsier som skal tas fra den enkelte deltaker reduseres fra 5 til 4. -Endringer i oppbevaringstiden av opplysninger utledet av innsamlet biologisk materiale. Det søkes om å oppbevare anonymiserte opplysninger utledet av det biologiske materialet som innsamles på ubestemt tid, på lik linje med andre opplysninger som er utledet av det biologiske materialet i den generelle biobanken "TrainsOME" (REK sør-øst saksnummer 2013/2041). -Endringer i antall forsøksdeltakere. Antall deltakere søkes redusert fra 65 KOLS-pasienter+ 65 friske kontroller til 50 KOLS-pasienter+ 50 friske kontroller. Antallet deltakere i vitamin D pilotprosjektet søkes endret fra 60 til 70 deltakere. -Endringer i prosjektets design i forhold til hvilke tester som skal gjennomføres før oppstart. -Endring i inklusjons- og eksklusjonskriterier. -Revidert informasjonsskriv. Informasjonsskrivet er revidert med tanke på potensiell risiko forbundet med deltakelse, forsikring av deltakere samt presiseringer av forhold rundt biobank.

Komiteens leder har vurdert søknaden og har ingen innvendinger til de endringer som er beskrevet.

Det forutsettes at det biologiske materialet og utledede opplysninger oppbevares i tråd med den godkjenning som til enhver tid er gjeldende for biobanken.

Vedtak

Komiteen godkjenner med hjemmel i helseforskningsloven § 11 annet ledd at prosjektet videreføres i samsvar med det som fremgår av søknaden om prosjektendring og i samsvar med de bestemmelser som følger av helseforskningsloven med forskrifter.

Dersom det skal gjøres ytterligere endringer i prosjektet i forhold til de opplysninger som er gitt i søknaden,

må prosjektleder sende ny endringsmelding til REK.

Av dokumentasjonshensyn skal opplysningene oppbevares i 5 år etter prosjektslutt. Opplysningene skal oppbevares avidentifisert, dvs. atskilt i en nøkkel- og en datafil. Opplysningene skal deretter slettes eller anonymiseres, senest innen et halvt år fra denne dato. Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren».

Prosjektet skal sende sluttmelding til REK, se helseforskningsloven § 12, senest 6 måneder etter at prosjektet er avsluttet.

Klageadgang

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jf. helseforskningsloven § 10 tredje ledd og forvaltningsloven § 28. En eventuell klage sendes til REK sør-øst A. Klagefristen er tre uker fra mottak av dette brevet, jf. forvaltningsloven § 29.

Med vennlig hilsen

Knut Engedal Professor dr. med. Leder

Kopi til: *geir.bergkastet@hil.no; post@hil.no*

Anette Solli Karlsen Komitesekretær