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Resistance Training and 1,25$(OH)_2D_3$ Administration to Maintain Respiratory Muscle Function and Reduce Pneumonia Risk in Cancer Patients

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1.0 INTRODUCTION

Pneumonia as a Problem in Older Cancer Patients. Pneumonia is a major cause of mortality in both **older** patients and **cancer** patients. Rates of pneumonia triple among individuals who are 65 years of age and older, and billions of dollars go toward the treatment of this life-threatening complication. Although less research along these lines has been conducted in cancer patients, >30% of patients with cancer develop pneumonia, resulting in death under some circumstances; and, importantly, our group's published preliminary data, which show under-reporting of causes of morbidity and mortality in cancer patients, suggest this percentage is a gross underestimation. The fact that cancer is now a disease of older patients only heightens concerns for this increased risk of respiratory morbidity and mortality and only further underscores the need to intervene to reduce this risk. This proposal recognizes this double threat – older age and cancer – acknowledges that pneumonia is a major source of morbidity and mortality in older cancer patients, and, ultimately, aims to reduce this risk.

Importantly, work from the **Sieck laboratory shows that weakness of the diaphragm muscle (the major inspiratory muscle) due to wasting of more fatigable fast-twitch muscle fibers results in compromised coughing and sneezing**. These circumstances impair an individual's ability to clear his/her airway and place that person at greater risk for pneumonia. Such selective wasting and weakening of diaphragm muscle fibers can occur in a variety of conditions, but recently the Sieck laboratory showed that it also occurs with aging. In addition, multiple studies demonstrate that generalized **muscle wasting occurs in over 80% of patients with advanced cancer** and that this commonly observed clinical phenomenon is tightly associated with shortened survival. We contend that **muscle wasting from aging and muscle wasting from cancer** represent a double threat for older cancer patients and that mitigating the atrophy and weakening of diaphragm muscle fibers is a prime therapeutic target that will lead to a reduction in respiratory morbidity and mortality and thereby improve survival in older cancer patients.

Interventions that May Prevent Morbidity. Interestingly, data from our group and others suggest that, in the setting of cancer, two interventions appear to improve the strength of respiratory muscles and prevent this complication of pneumonia: inspiratory muscle resistance (strength) training and the administration of the vitamin D metabolite, 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$). First, over the years, inspiratory muscle resistance (strength) training to treat chronic obstructive pulmonary disease, obstructive sleep apnea, neuromuscular diseases, and other diseases has shown increasing promise. Second, our group observed that $1,25(OH)_2D_3$ exposure results in an increase in mitochondrial oxygen consumption rate and increased protein synthesis in human skeletal muscle cells; these changes that suggest $1,25(OH)_2D_3$ administration could ultimately lead to improved respiratory muscle strength and less respiratory morbidity and mortality in older cancer patients.

Hypothesis. This proposal is unique because: 1) the impact of inspiratory muscle resistance exercise for improving respiratory muscle strength in older cancer patients has not yet been investigated in a clinical setting and, 2) to our knowledge, no studies have tested the administration of $1,25(OH)_2D_3$ among older cancer patients -- or in cancer patients in general -- to maintain inspiratory muscle strength and to reduce respiratory morbidity.

The central hypothesis of this proposal is that inspiratory muscle resistance exercise and the administration of $1,25(OH)_2D_3$ result in an increase in inspiratory muscle strength in older cancer patients.

2.0 BACKGROUND:

Muscle Loss in Older Cancer Patients. Over 80% of patients with incurable cancer suffer weight loss [1]. This weight loss is derived largely from loss of lean tissue and is associated with early death and debility [2,3,4]. Emphasizing the vital role of lean tissue, Roubenoff and Kehayias provide evidence that loss of 45% or more lean tissue is incompatible with life [5]. Weight loss has been cited as the sole cause of death at autopsy in as many as 20% of cancer patients [1]. In a 1400-patient study, Martin and others observed that 53% of cancer patients had lost muscle, as determined by CT scan measurements at the L3 vertebral level, and that this muscle loss is an independent predictor of poor survival ($p < 0.001$) [4]. Because this same loss of muscle occurs as a direct result of aging – termed "sarcopenia" -- the development of **cancer** in an **older** individual creates, in effect, a double threat that places older cancer patients at greater risk for all the morbidity described above [5]. Finally, despite the testing of multiple interventions, to date, no intervention has been shown to augment lean tissue and improve survival.

What Do These Weight-/Muscle-Losing Cancer Patients Die From? To date, early death in older, weight-losing cancer patients has been clearly demonstrated but poorly characterized. What do weight-/muscle-losing cancer patients die from? **An estimated 30% are diagnosed with pneumonia, a cause of death that could be linked to muscle wasting [8-13]; however, our previously published work suggests this percentage is a gross underestimate [14].**

Importantly, the Sieck laboratory has shown that age-related muscle loss leads to compromised coughing and sneezing and an inability to clear the airway [15-18]. **The current proposal is unique in that it brings work from the Sieck laboratory into the clinic for the first time, begins to examine this work within the context of cancer, and further expounds upon – and proposes to break – these ostensible links between muscle wasting, incidence of pneumonia, and early death in older cancer patients.**

The Benefits of Exercise, Logistics, and Measuring Outcomes. For decades, inspiratory muscle resistance (strength) training has been tested in chronic obstructive pulmonary disease, obstructive sleep apnea, neuromuscular diseases, and other diseases with emerging success [19-24]. In cancer-associated weight loss, a meta-analysis described inconclusive findings [25], but, in multiple other cancer settings – including, for example, cancer-induced fatigue and cardiovascular morbidity in cancer survivors – exercise in general appears to improve clinical outcomes [26-29]. For inspiratory muscle strength, portable devices enable patients to participate in resistance exercise programs at home (https://www.usa.philips.com/healthcare/product/HCHS730010/treshold-inspiratory-muscle-trainer); we propose to use one of these devices here to begin to test **the hypothesis that the use of such devices can improve diaphragmatic strength and reduce pneumonia risk in older cancer patients.**

Respiratory muscle strength will be assessed by measuring the maximal inspiratory muscle strength (MIP or PImax) and maximal expiratory pressure (MEP or PEmax). In addition the SNIP test (sniff nasal inspiratory pressure) will also be performed by subjects to measure inspiratory muscle strength. It is particularly important in measuring muscle force exerting from the diaphragm. This test requires only that patients "sniff" forcefully through one nostril. . The best and worst of 10 measurements are recorded.

$1,25(OH)_2D_3$ and Its Potential Role in Treating Muscle Wasting. In preclinical data, our group has shown that $1,25(OH)_2D_3$ appear to mitigate cancer-associated muscle wasting. Exposure of human skeletal muscle cells to Lewis lung carcinoma cells led to changes in mitochondrial fusion/fission mediator proteins, mitochondrial fragmentation, and mitochondrial oxygen consumption rate -- all of which are consistent with and conducive to muscle fiber atrophy. However and importantly, the additional exposure of these cells to $1,25(OH)_2D_3$ abrogated these changes. Such preclinical findings give rise to **the hypothesis that the administration of $1,25(OH)_2D_3$ will reverse muscle wasting and its associated morbidity**, including the development of pneumonia, and will thereby decrease the morbidity and mortality of cancer-associated muscle wasting. In conjunction with exercise, as alluded to above, the possibility of reducing pneumonia risk and improving survival may be even greater. The above hypothesis becomes all the more interesting and imminently testable in view of the fact that a safe and often clinically used dose of $1,25(OH)_2D_3$ has already been determined. A dose of 0.25 micrograms per day is often prescribed safely to patients with renal osteodystrophy and, therefore, appears to be a reasonable dose to test in this proposal.

3.0 STUDY OBJECTIVES

3.1 To explore the effect of inspiratory muscle resistance training on inspiratory muscle strength.

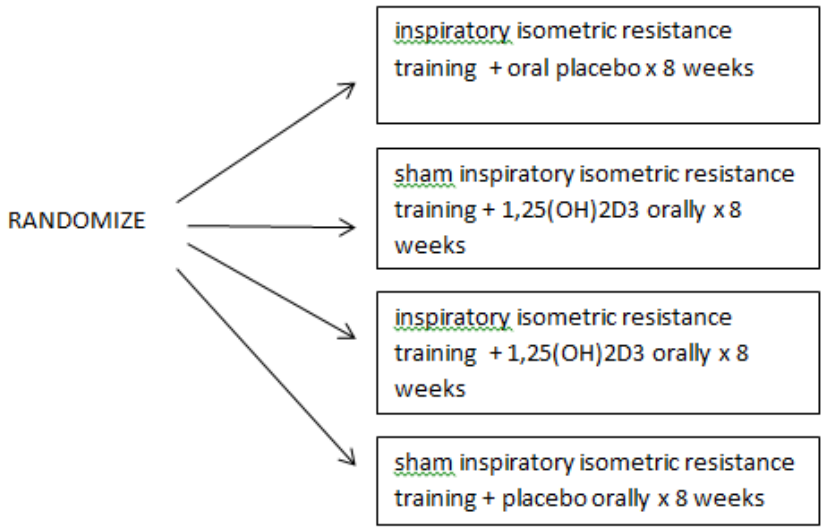
3.2 To explore the effect of $1,25(OH)_2D_3$ administration on inspiratory muscle strength.

3.3 To explore the combined effect of inspiratory muscle resistance training and 1,25(OH)2D3 administration on inspiratory muscle strength.

In short, this work is intended to provide point estimates and standard deviations for the effects of an 8-week interventions on the “sniff test” as described in the 4-arm study below.

4.0 STUDY DESIGN

This is a randomized, double-blinded dummy pilot study design (n=60 with 15 patients to be assigned to each study arm):



PRIMARY STUDY ENDPOINT: To acquire descriptive data on the SNIFF after 8 weeks of the above interventions.

SECONDARY STUDY ENDPOINT: To acquire data on the safety of inspiratory isometric resistance and $1,25(OH)_2D_3$

5.0 IDENTIFICATION OF SOURCE DATA

The following source data will be directly recorded on case report forms:

- Vital signs at baseline and at 8 weeks
- Bilirubin, creatinine, serum calcium and phosphorous at baseline
- SNIP TEST results at baseline, 2, 4 and 8 weeks
- MIP and MEP TEST results at baseline, 2, 4 and 8 weeks
- Serum calcium and phosphorous levels at 2,4, and 8 weeks
- Adverse events

6.0 PATIENT ELIGIBILITY [30-32]

Eligibility Criteria:

1) 18 year of age or older

2) diagnosis of cancer

3) renal and hepatic function (creatinine </= 2 x the institutional upper limit of normal; bilirubin </= 2 x the institutional upper limit of normal)

4) no contraindication to receive either of the planned interventions of inspiratory resistance training or $1,25(OH)_2D_3$ in the opinion of the healthcare provider

5) no difficulties with swallowing oral medications in the opinion of the enrolling physician (no documentation necessary in the medical record).

Contraindications:

1) Patient is taking calcium or vitamin D supplements and is unwilling to stop for 8 weeks

2) Severe chronic obstructive pulmonary disease (oxygen dependent or patient self-reports unable to walk one block without difficulty

3) Calcium or phosphorous level above the institutional upper limit of normal

Subject Recruitment:

Patients will be recruited from all the clinical facilities at the Mayo Clinic in Rochester, Minnesota. The study team will rely on referrals from healthcare providers.

Early Patient Withdrawal: Patients can withdraw from the study at any time based on their wishes. In the event that an intervention-related adverse event occurs, patients will be withdrawn from the study by the study team.

Patients who develop an increase in their calcium or phosphorous level above the institutional baseline will be taken off the study agent/placebo and referred to their primary healthcare provider. Patients will be given the option to continue on with the inspiratory resistance training to complete the eight week training period.

Human Subjects

1. Risks to the subjects

Human Subjects Involvement and Characteristics: All protocols and all techniques to be used will be approved by the Mayo Clinic Institutional Review Board prior to initiation of any studies. Subject characteristics and inclusion/exclusion criteria have been clearly specified above. Our plan is to complete the study on 60 participants with 15 in each group. We are anticipating a target accrual of 75 subjects to account for anticipated dropout. In order to have 60 participants complete the study.

Sources of Materials: Samples of blood, obtained during the study will be used exclusively for research purposes.

Potential Risks: The following are the potential risks for this study:

a) Blood will be withdrawn. The risks of drawing blood include, pain, bruising, lightheadedness, and/or fainting, or rarely, infection at the site of the needle stick.
b) Blood Pressure will be measured. The cuff can cause discomfort when pumped up and becomes tight. This is temporary discomfort.
c) Isometric resistance training. Participating in unaccustomed exercise may include the risk of chest wall soreness.

d) 1,25 $(OH)_2D_3$ agent intervention. Although rare, potential risks include: weakness, headache, nausea, vomiting, sleepiness, dry mouth, constipation, muscle pain, bone pain, or a metallic taste.

7.0 STUDY INTERVENTIONS

1) 1,25$(OH)_2D_3$. As per Drug Bank., this agent is used to treat vitamin D deficiency or insufficiency, refractory rickets (vitamin D resistant rickets), familial hypophosphatemia and hypoparathyroidism, and in the management of hypocalcemia and renal osteodystrophy in patients with chronic renal failure undergoing dialysis. This protocol will use doses that are identical to those used for these other clinical indications.

Also, as per Drug Bank, the first pathway involves 24-hydroxylase activity in the kidney; this enzyme is also present in many target tissues which possess the vitamin D receptor such as the intestine. The end product of this pathway is a side chain shortened metabolite, calcitroic acid. The second pathway involves the conversion of calcitriol via the stepwise hydroxylation of carbon-26 and carbon-23, and cyclization to yield ultimately 1a,25R$(OH)_2$-26,23S-lactone D_3. The lactone appears to be the major metabolite circulating in humans. Enterohepatic recycling and biliary excretion of calcitriol occur. The metabolites of calcitriol are excreted primarily in feces. Cumulative excretion of radioactivity on the sixth day following intravenous administration of radiolabeled calcitriol averaged 16% in urine and 49% in feces.

Patient instructions: Patients will be instructed to take 1 tablet/placebo once per day.

2) Inspiratory isometric resistance exercise. Patients will be provided with a power breath device and will be instructed on how to use it. Inspiratory muscle resistance training involves subjects being exposed to 10-15 minutes of training per day each day for 8 weeks using a commercially available inspiratory threshold-training device. Subjects will be asked to gradually increase training to 20-30 minutes per day or two 15 minute sessions. (https://www.usa.philips.com/healthcare/product/HCHS730010/treshold-inspiratory-muscle-trainer). The inspiratory muscle training groups will breathe against a resistance set to generate 30% of PI_{max} (as estimated by a "sniff" test). Patients in the sham group will train daily against a resistance set to only 15% PI_{max}.

Method for Assigning Subjects to Treatment Groups.
Patients will be randomly assigned to one of the 4 treatment arms with stratification based on the following:

1) sex: male versus female

2) patient-reported degree of weight loss in the preceding 3 months: >/=5% versus < 5% (or no weight loss).

3) patient reported history of pneumonia in the past five years: yes or no

Preparation and Administration of Study Drug.

The Mayo Clinic Pharmacy will generate 1,25$(OH)_2D_3$ tablets 0.25 micrograms along with identical placebo. Assignment will remain blinded to patients, healthcare providers, and members of the study team who have direct patient contact.

A member of the study team who has no patient contract will set the resistance on the inspiratory; the resistance gauge will then be effaced with rubbing alcohol.

Monitoring.

	Baseline (within 14 days of registration to study)	2 weeks (+/- 7 days)	4 weeks (+/- 7 days)	8 weeks from last visit (+/- 7 days)	Total blood volume
history and physical examination	X		X	X	
laboratory results (creatinine, bilirubin, CDHVD 1,25 Dihydroxy D2 and D3, transaminase, alkaline phosphatase)	X				5ml
SNIP, MIP and MEP tests	X	X	X	X	
Laboratory results Calcium and phosphorous	X	X	X	X	1ml each time point
Questionnaires*		X	X	X	

*adherence questionnaire and arm assignment questionnaire (see Appendix 1)

SAMPLE SIZE AND STATISTICS. A total of 15 patients per arm (60 total) will be included in this study. This sample size is based on precedent from other trials that were aimed at obtaining data on point estimates of efficacy and standard deviations. All data, including patient demographics and adherence data, will be presented descriptively with means, medians, percentages, ranges, standard deviations, and 95% confidence intervals, as appropriate. All data will nonetheless be generated and summarized with the goal of publication. In a highly exploratory manner, we will report the data described below within the context of study arm assignment; however, comparisons between arms will not be presented as primary outcome data but as highly exploratory, non-primary, non-secondary analyses.

Definition of Endpoints. All patients will undergo a sniff test at baseline, 2 weeks , 4 weeks and at 8 weeks. As described earlier, patients will be asked to perform the test 10 times; the best and worst measurements will be recorded.

1) Primary endpoint. These sniff test readings and the descriptive presentation of these data will be the primary endpoint of this trial.

2) Secondary endpoint. Patients will also be provided with an adherence questionnaire that they will be completed at the end of 8 weeks; this questionnaire has been used extensively by our group in prior studies and will serve as a secondary endpoint for this trial [30-32].

3) Exploratory secondary endpoint. In view of the fact that an identical placebo can result in clinical improvements in 30-40% of cancer patients, we will develop a questionnaire that queries patients about which study arm they believe they were assigned [32]. We will present the results from this questionnaire descriptively as a percentage with 95% confidence intervals. These exploratory findings will be of value as we plan for a larger, more definitive clinical trial; this questionnaire will potentially add preliminary validation to our choice of placebos.

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