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Review

Falls Incidence and Associated Risk Factors among People with Chronic Obstructive Pulmonary Disease (COPD)

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Abstract: Chronic obstructive pulmonary disease (COPD) is increasingly being recognized as a systemic disease rather than a mere disorder of the lungs. Central (respiratory) and peripheral (limb) muscle weakness are among the main pronounced systemic effects of COPD. While the disease primarily affects the lower limb muscles and contributes to gait impairment, COPD is also associated with an increasing risk of falls in patients (COPDp). Previous studies have reported higher rates of falls among COPDp (1.17 to 1.20 falls/person-year), amounting to four times higher than an age-matched healthy group. Potential fall risk factors include muscle weakness, impaired daily activities, cognitive dysfunction, and gait and balance impairment. Although COPDp often manifest many of these risk factors, there remains a gap in literature regarding falls during walking in this population. This study aimed to 1. analyze the literature to identify the risk factors of falling in COPDp, and 2. investigate the underlying mechanisms by which these risk factors can lead to increased prevalence of falling. The results suggest that in addition to the known risk factors of falling, low back pain and mental fatigue should also be considered as relevant risk factors in the treatment process of these patients. Moreover, respiratory problems, which are common in this population, have demonstrated pronounced effects on energy expenditure, gait, and other types of activities of daily living (ADLs), leading to reduced intensity, disrupted coordination of the trunk-pelvic structure with the lower limbs during gait, and altered motor control performance due to activation of muscles in an inefficient synergic manner. These problems potentially lead to the increased vulnerability of these patients to external disturbances and higher incidence risk of falls and injuries. Cognitive problems, which are typically due to reduced oxygen received by the brain, as well as general inflammation caused by COPD, also play a significant role in gait disruption and balance. Future research is warranted to determine the prevalence of falls in COPDp by examining the response of these patients to Medio-Lateral (ML) and Anterior-Posterior (AP) disturbances during gait in association with traditional and recommended fall risk factors.

Keywords: chronic obstructive pulmonary disease; COPD; fall risk factor; gait; balance; cognition; daily activity; muscle dysfunction

1. Introduction

There is little debate that the Corona virus, with its unprecedented scale and severity, has changed human life and redirected human priorities for decades to come. The impact of COVID-19 has extended far beyond a health crisis with devastating mortality/morbidity rates around the world to include unpredictable changes on the quality of social life and work environments, and unprecedented long-term global socioeconomic challenges. On the other hand, the pandemic has also created a test bed for the rapid emergence of disruptive innovations and technologies in many fields. Considering the potentially lethal effects of the virus on the lungs and the respiratory system, the field of rehabilitation has quickly evolved to define specific rehabilitation exercises tailored for Corona recovery (1), and to introduce novel physiological risk markers, such as the use of gait speed as a biomarker to assess the risk of contracting the virus (2). The impact of the Corona virus, as a severe lung disease, on the neuromuscular and cardiovascular systems among others, is an example of a cascade of systemic complications impacting several organ systems, suggesting the critical value of multifactorial comprehensive investigations.

COPD is a chronic lung disease, which also instigates systematic effects on other vital organs of the body, such as the neuromuscular system. Characterized by progressive and persistent expiratory air flow limitations (3), COPD results from long-term exposure to harmful gases and particles combined with individual factors, including events which influence childhood lung growth, such as severe asthma or bronchitis, and genetics (AAT deficiency). Unlike asthma, however, which is more common in children and adolescents, COPD is more common in the elderly (over 45 years) (4, 5). Prior to the recent pandemic, COPD was considered as the third cause of death in the world (6) with nearly 3.23 million deaths in 2019 (https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd)) and more than 300 million infections (50 million in Europe) (7-10). Environmental exposure to tobacco smoke, indoor air pollution and occupational dusts, fumes and chemicals are important risk factors for COPD, in addition to the increase in the phenomena of fine dusts and air pollution in big cities, as well as the aging of communities. Although COPD has traditionally been more prevalent among men (5), increasingly more women are being diagnosed with the disease in recent years, possibly due to the increasing number of women smokers around the world (11).

Moreover, while COPD is more typically associated with less developed countries, more than 16 million people (6.6% of adults) in the United States have been diagnosed with the disease, ensuing a huge financial burden of $72 billion a year (12). In the EU, the financial cost is estimated at $ 23.3 billion per year (10). For example, in Germany, the prevalence of COPD in people older than 18 is estimated at 5.8%, and increases to 18.1% for men older than 40 (13, 14). Therefore, although COPD has variable prevalence in different parts of the world, according to the geography, culture, economy, and environmental conditions, it is considered as a growing global health challenge, which is expected to continue to increase in prevalence and severity, along with global pandemics, the aging population and severe environmental changes associated with global warming (15).

The physical attributes of COPD include symptoms such as coughing, wheezing, and shortness of breath. COPD also leads to widespread inflammation throughout the body, which along with the challenges and frustration associated with chronic disease, could cause the reported cognitive problems presenting in these patients (16) (20). Moreover, COPDp often struggle with cardiovascular problems and other disabilities, as well as breathlessness or difficulty in breathing, which typically result in these patients leading a sedentary lifestyle (17) (18). This, in addition to sleeping difficulties (probably due to dyspnea), are among the main reasons for the increasing prevalence of depression and anxiety among COPDp and the increased intake of antidepressants or hypnotics (19). Constant health concerns, frustration/aggravation, lack of a definitive treatment and inability to perform many daily activities, all impact different aspects of the cognitive function of chronic patients. This is further exasperated in COPDp by the lack of proper oxygen delivery to the brain due to lung dysfunction and hence potential challenges at the brain level (21). This suggests that muscle problems in COPDp may not only be due to changes in muscle structure,(i.e. muscle atrophy), decreased oxygen uptake, as well as mass and CSA, but also due to an impaired neural drive (22), considering evidence that the problems of oxygen delivery to the prefrontal cortex reduce central motor drive (21).

Moreover, Vitamin D deficiency, which has been frequently reported in COPD patients, also has been known to exacerbate musculoskeletal problems in these patients (23).

Although COPD is known as an internal lung-related disease with respiratory complications, as previously mentioned, non-respiratory manifestations of COPD, such as musculoskeletal problems and motor disorders significantly impact the lives of these patients, and may disrupt the treatment process and aggravate the disease (25, 26). Specifically, increased prevalence of accidental falls in COPDp is one of the systematic challenges associated with the disease which negatively impacts the quality of life and life expediency of COPDp (27). Potential fall risk factors include muscle weakness, impaired daily activities, cognitive dysfunction, and gait and balance impairment. Due to the relevance of the topic, numerous researchers investigated these factors although there remains a gap in literature regarding falls during walking in this population. Furthermore, while numerous studies reported motor-balance problems in COPD patients and their association with the increased risk of falling, the underlying mechanism leading to falls in COPDp remains elusive. The question of how much is inactivity, energy expenditure, gait difficulties, and cognitive problems responsible for COPD patients falling remains an open area of research. This scoping review aimed to 1. analyze the literature to identify the risk factors of falling in COPDp, and 2. investigate the underlying mechanisms by which these risk factors can lead to increased prevalence of falling. The remainder of this review is organized as follows: Section 2 describes the methods used for the review including the study approach, strategy, criteria, and data extraction. Section 3 describes falls in COPDp, while section 4 details the main intrinsic and extrinsic fall risk factors, including muscle dysfunction, impaired activities, balance and gait deficits, and cognitive functioning. Section 5 presents the limitations and section 7 highlights the conclusions and future directions.

2. Methods

2.1. Study Approach

A literature review was conducted to identify/summarize the fall risk factors in people with COPD towards elucidating possible mechanisms underlying the increased risk of falls in these individuals. Intrinsic risk factors such as muscle weakness, gait and balance deficits, impaired daily activity, and cognitive problems are included in this review, as well as low back pain and mental fatigue as other potential risk factors.

Considering the nature and intent of this study, we opted for a scoping rather than a systematic review. Scoping reviews typically allow for a broader overview of the area of focus and can tackle a broader research question. As we aimed to address both research and clinical communities, a scoping review was more suitable expanding the range of readers and allowing for a more extensive inclusion criterion (24).

2.2. Search strategy

A comprehensive literature search was conducted within Google Scholar, ScienceDirect, and PubMed databases using a combination of keywords from the following groups: (1) “COPD” or “Chronic Obstructive Pulmonary Disease” (2) “Fall” or “Fall Incidence” or “Fall Risk Factor” (3) “Muscle” or “Gait” or “Balance” or “Daily Activity” or “Cognition” or “Mental Fatigue” or “Low Back Pain”. The search was limited to articles published in English before August 2022. The title and abstract of the search results were screened against the inclusion/exclusion criteria (next section). The full text of the relevant articles was reviewed and those meeting the study criteria were considered for further analysis. The references were checked to identify additional articles for possible inclusion in this study.

2.3. Study Selection Criteria

Articles were screened against the following inclusion/exclusion criteria. Articles for inclusion had to address (1) intrinsic and extrinsic fall risk factors in patients with COPD including muscle weakness, gait and balance deficit, impaired daily activity, and

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cognitive problems (2) underlying mechanisms for increased the fall incidence in these patients. Precipitating fall risk factors such as exacerbations and dyspnea are outside the scope of this study and not included in the review. These factors are acute episodes related to COPD. Articles analyzing the effects of medication, visual deficit, use of an assistive device and nutritional depletion and malnutrition, were also excluded. The articles meeting the inclusion and exclusion criteria were screened for value provided in fall risk assessment in COPD patients.

2.4. Data Extraction (fill the initials here)

Following the screening of the full-text articles based on the criteria, a primary reviewer (MD) performed the data extraction. A part of the data extraction was also carried out by additional reviewers (MM, SMS). The results were verified by (MP, KK). The clinical application and relevance were discussed and confirmed by our clinical collaborators (MM, MA, MR). The data extraction focused on two broad areas: well-known fall risk factors related to the physical and psychological status of the COPD patient and the potential risk factors related to the possible causes of falls in these patients.

3. Falls in COPD patients

Although COPD is known as an internal lung-related disease with respiratory manifestations, such as shortness of breath, chest tightness, dry cough and phlegm, as previously mentioned, non-respiratory manifestations of COPD, such as musculoskeletal problems and motor disorders significantly impact the lives of these patients, and may disrupt the treatment process and aggravate the disease (25, 26). Increased prevalence of accidental falls in COPDp is one of the systematic challenges associated with the disease which negatively impacts the quality of life and life expediency in these people (27).

In a review article, Riog et al. (27) examined the risk factors associated with falls in COPDp and classified them into two risk groups: intrinsic risk factors, such as gait and balance deficits, impaired activity of daily living, depression and cognitive problems, and medication and precipitating (acute) risk factors including exacerbation and dyspnea. Two years later in another study (28) they surveyed a population of 101 patients over 6 months using various questionnaires, such as Activities Balance Confidence (ABC) Scale and Physical Activity Scale for the Elderly (PASE), as well as structured forms for recording demographic data, current medications, co-morbidities, oxygen use, acute exacerbations of COPD, falls during the preceding 6 months and use of an assistive device. The results indicated that fall occurrence was relatively independent of the stage of COPD (25). Thirty-two participants (31.7%) reported at least one fall in the past six months, which was more than the number of fallers reported for an age-matched elderly group (27%). In addition, the incidence of falls in the COPD population was 1.2 falls per person-year, which is approximately 4 times the number reported for the healthy elderly (0.24 falls per person-year). Taking more medications (8 drugs vs. 5 drugs), age (75.5 years vs. 72.1 years), gender (60% among women), coronary heart disease, and dyspnea were recorded as the most important causes of falls.

Beauchamp et al. conducted three separate studies on the relationship between falls and COPD (29-31). Out of the 39 subjects who participated in their study, 46% reported falls at least once a year (29), which was higher than the findings reported by Riog et al. (28). Although the fallers were slightly older (71 vs. 69 years), there was no significant difference between the gender of fallers and non-fallers. Moreover, no significant difference was seen between the data of FEV1 (forced expiratory volume in the first second) obtained from spirometry between the two groups, while the use of supplemental oxygen was an important predictor in diagnosing fallers (29). Examining the balance status of these patients, revealed that compared to age- and sex- matched healthy people in all aspects of balance measured by Berg Balance Scale (BBS), the COPDp had a lower score (29, 31). They also compared the balance status of the faller and non-faller groups of COPD individuals, which indicated that patients with a history of fall had more balance problems (29). This study suggested that gait and balance impairments should be considered as risk factors for the fall incidence in these COPDp, and recommended that balance exercises should be prescribed during respiratory rehabilitation (31). This suggestion was the basis of a third study by the same group (30), in which they demonstrated that doing six weeks (three times a week) of balance exercises, along with breathing exercises, improved all the criteria of balance, lower body muscle strength and daily activity of patients as compared to the control group, who received only breathing exercises. This study confirmed that strengthening the lower body muscles and maintaining regular balance exercises are likely to reduce the risk of falling. This research group was the first to use a lean-and-release system to examine the differences between the response of COPDp and healthy individuals to unexpected perturbations (31). The importance of this work lies in the fact that falling in real life usually happens unexpectedly and is often triggered by external disturbances, such as slipping, stepping, or hitting an obstacle.

Simulating of such scenarios in a laboratory environment may help understand the governing mechanisms and underlying problems that lead to ineffective response leading to a fall. Beauchamp et al. (31) Reported on foot-contact times in response to delayed foot-off perturbations in COPD patients, indicating delayed response in unstable conditions, which is consistent with the longer anticipatory phase observed in these patients. In addition, although the onset of the lower body muscles of the COPD group was not significantly different from those of healthy individuals (except for the tibialis anterior muscle) in relation to the disturbance occurrence, the use of a dynamometer revealed that the torque produced by all lower torso muscles was significantly less than that in healthy individuals. This may explain not producing sufficient compensatory joint torque to restore balance in these patients, suggesting that the incorporation of balance exercises for patients with COPD should also include perturbation-based training (|28).

In a one-year study of 39 COPD patients in Australia, Oliveira et al. (32) reported a prevalence of 40% of fall incidence among these patients. They also identified the number of medications, comorbidities, and prior history of falls, as fall risk factors. Although smoking history (number of packs in a year) was an important risk factor among fallers, no correlation was found between lung function and fall incidence, which is also consistent with the findings of Riog et al. (28) regarding the independence of fall occurrence from the stage of COPD (obtained by spirometry). They cited the relationship between long-term smoking and balance performance among smokers to explain their work and suggested the relationship between balance problems and the occurrence of falls in COPD individuals as a probable mechanism. In their next study in 2017 (33), they reported 1.76 falls/person-year in COPD patients with acute exacerbation after hospital discharge, which was significantly higher as compared to the reported results for healthy elderly or COPD patients with stable conditions. This phenomenon was attributed to the deterioration of balance after discharge, accompanied by a decrease in quadriceps strength, increased dyspnea, as well as an increase in sway while standing. The Australian group's research has well demonstrated the importance of balance problems caused by COPD among people as a risk factor for falls. While the above studies showed the importance of falls as a common problem among COPD patients, most of these studies have included a limited number of patients (less than 100). Hakami et al. (34) used the UK primary care database to examine the incidence of falling among 44,400 COPD patients as compared with 175,545 healthy individuals. After adjusting for smoking status, age, gender and other confounding factors, patients with COPD were 47% more likely to have a record incidence of fall compared with non-COPD patients.

Interestingly, previous research has reported different results regarding the prevalence of falling in COPD individuals. A Swedish team in 2009 (35) investigated the fall occurrence in 80 COPD patients with an average age of 65, and reported 25 percent of the subjects had at least one fall per year. Another team from the University of KU Leuven in Belgium (36) studied a population of 44 people with COPD and reported a falling occurrence rate of 20%. They suggested that the occurrence of falling was seen only among very frail hospitalized patients, which is not comparable to other frail elderly patients. Indeed, they considered falling in COPD as an age-related issue, and not a component of the systemic effects of the disease, which contrasts with more. Recent results published by Riog, Beauchamp, and Oliveir and their groups (27-33). In particular, a study by Hakami et al. (34), which examined a large COPDp of these patients, found that the risk of falling was significantly higher in these patients as compared with healthy elderly of the same age group. The contrasting results obtained by the Swedish and Belgian groups may reflect disparity in healthcare around the world in association with economic, cultural, and social aspects. Countries with quality, accessible and affordable healthcare systems provide people, especially the elderly, with effective preventive medicine and better control and treatment options, highly relevant for systemic disease. The effect of socioeconomic variations in chronic obstructive pulmonary disease prevalence, diagnosis, and treatment has been extensively investigated, with the results reflecting that 90% of all reported deaths caused by COPD occurs in low-income countries (37).

4. Main fall risk factors in COPD patients

The multiplicity of risk factors for the occurrence of falls in COPD patients include typical the fall risk factors seen in the elderly, such as aging, female gender, history of falling and increasing comorbidities, in addition to COPD-specific factors, such as balance and gait disorders, muscle weakness, depression and cognitive disorders, increase in the number of medications, use of supplemental oxygen, increased 'fear of falling' and heavy smoking history. This is confirmed by data revealing that the probability of falling in this population is approximately 50% higher than age- and gender- matched older people.

Falls are considered as one of the principal causes of injury and hospitalization among the elderly and people with COPD. Statistics indicate that COPDp are among the top reasons for hospital referrals (38). Hip fracture is one of the main reasons for the loss of independence in the elderly, reducing the quality of life, and also is associated with increased mortality, with mortality rates of 26% and 37% for men and women (39), respectively, after one year post hip fracture. In 90% of the time, these fractures occur due to falls and incur high economic costs for the individual and the health care system (40). In COPDps, the prevalence of osteoarthritis is estimated at an average of 35.5% (41), which increases the risk of falls, and makes this group of patients more vulnerable to falls than other elderly. Huang et al. (42) examined 55,000 people and estimated the number of hip fracture incidences among COPDs at 649 per 100,000 person-years, which was more than two times the reported data for Non-COPD patients.

Generally speaking, the fall risk factors in individuals can be divided into two categories: patient-related (intrinsic) and environmental hazards (extrinsic) (27). The following section addresses these:

4.1. Intrinsic risk factors

4.1.1. Skeletal Muscle Dysfunction

COPD has a wide range of detrimental effects on muscle function over time, including muscle weakness, atrophy, shift in fiber type, poor oxidative capacity, and mitochondrial dysfunction (43). Many studies have reported a decrease in muscle volume, strength, endurance, and capillary density in these patients (44-46). These changes included quadriceps hamstrings and adductor muscle groups, with a decrease in CSA and mass for the lower torso muscles (18). For distal muscles, such as dorsi flexor and plantar flexor, EMG data also demonstrated weakness, as well as, higher fatigability in these individuals as compared to the control group (47). This problem (tendency to get tired and lose strength) could likely be related to decrease of muscle contractile and oxidative capacity due to impairments in gas exchange and $O2$ delivery in these patients (21). Lower limb muscle strength is an essential factor for having a proper response to recover from a fall (48), and hence the weakness of these muscles leads to the inability to produce sufficient muscle torque around the lower torso joints, especially at the ankle joint which requires synergistic cooperation and appropriate tendon stiffness (49). Atrophy, or deterioration in muscle mass, also causes decrease in the functional performance of muscles, which may lead to lack of proper response to external disturbances (50). Some of the muscle problems which occur in COPDp are related to aging and are common in the elderly. However, a study performed by Mathur et al., (51) revealed that the muscle volume, as well as, strength were 25% less in these individuals as compared to an age-gender-matched population. In addition, intramuscular fat amounted to 35% more in the COPDp, indicating a decrease in function and mobility in these patients as compared to their age-matched counterparts.

4.1.2. Impaired activities of daily living:

Numerous studies have shown a significant association between decreased daily activity and increased risk of falls in older adults (52-54). In COPD patients, due to shortness of breath, these patients usually get accustomed to a sedentary lifestyle, leading to a viscous cycle of exacerbation and further diminished activity. The shortness of breath naturally contributes to low levels of ADLs and leads to muscle deconditioning, and eventually, an excess lactate-CO2 production, which exacerbates shortness of breath over time (18). Multiple studies have also reported on the increased inactivity among these patients as compared to age-matched healthy individuals and even to patients with other chronic diseases (55-60). Both qualitative (Self-reported including questionnaires, diaries), as well as quantitative methods (wearable, pedometers, etc.) have been used to monitor the activity of COPDp during the day, revealing less walking time, movement intensity and steps/day.

In 2016, Iwakura et al. (61) examined the relationship between daily activity and various balance characteristics, including gait stability and anticipatory adjustments, quantitatively among COPDp for the first time. The results interestingly revealed that patients' balance was independent of possible confounding factors, such as the loss of muscle strength, and dyspnea, and was more associated with the number of steps per day. On average, these patients performed 4,546 steps, which was almost half of the control group, and less than the threshold of 5000 steps defined for a sedentary lifestyle. Therefore, it seems that balance problems (as a risk factor for fall) and inactivity can intensify each other.

Kawagoshi et al. (62) Examined the walking intensity of COPDp and found that they allocated less time to walk faster (faster than 2 km / h) or slower (at less than 2 km/h) during the day as compared to a healthy control. These patients also demonstrated lower frequency of standing up. They suggested that some of the daily activities, including sitting and standing up from a chair, going up and down stairs, walking at different speeds, were significantly reduced in these patients, which are necessary for proper stability during gait and typically increase anticipatory capabilities in the face of unexpected disturbances. Another study conducted on faller COPDp, stated that the experience of falling leads to a decrease in balance confidence and daily activity (63), yet another factor contributing to the risk of fall. Oliviera et al. (33) also cited balance problems after exacerbation as the reason for the increased incidence of COPD falls, which may be related to inactivity following exacerbation, also reported by Alahmari et al. (64, 65).

4.1.3. Balance deficits

The ability to maintain stability and balance to prevent falls in the elderly is critical. It is not surprising that many studies have identified lower back muscle weakness and balance problems (66, 67) as the most important risk factors for falls (68). Furthermore, in COPD patients, the relationship between different components of balance and falling has been well investigated (29-31). Due to diaphragmatic muscle dysfunction and increased respiratory demand in COPD patients, trunk muscles (EO, IO, and ES) are required to be more active in their secondary role to aid respiration (69). This over-activation increases the stiffness of the trunk, and thus reduces its contribution to maintaining balance (70-72). In a study by Smith et al. (70-72) on post-balance and sway during standing using COP and EMG data, COPDp exhibited decreased trunk maneuverability (and core segments in general) which was reported as their main cause of balance problems in the ML direction. On the other hand, although increasing respiratory frequency could have caused AP disturbance to their posture, COPD patients overcame this by increasing the hip AP angular motion as a compensatory strategy, and hence the sway value was not significantly different from the control group in the AP direction. ML balance problems in the elderly have been associated with increased fall risk (73). By comparing proprioceptive control strategies between COPDp and a control group, Janssens et al. (74) found that these patients were more likely to rely on the ankle joint (muscle proprioceptive signals), decreasing their reliance on the back during balance control, due to an impaired postural contribution of the inspiratory muscles to trunk stability.

Using the ankle-steered strategy, makes these patients vulnerable to falls, especially during unstable conditions, such as standing on foam. Weakness of the diaphragm, and its impact on trunk and pelvic muscles, cause postural alignment changes in these patients leading to further balance difficulties. Thoracic kyphosis, anterior pelvic tilt and forward head posture are known as the general features of posture in these patients (75-79), which biomechanically causes the displacement of the center of mass and the occurrence of balance problems.

4.1.4. Gait deficit

Gait or walking is reported as the main pre-fall activity leading to hospitalization (80). Poor gait function is considered as a major fall risk factor in COPD patients (27). Several studies have reported slower walking speed in these patients, as compared to healthy individuals (81-83), which may be in part due to weakness of the lower torso muscles, as well as limited daily activity resulting in the reduction of quantity and quality in both soft and hard musculoskeletal tissue compromising the function of gait. In several studies, Yentes et al. (79, 84-86) examined the biomechanical effects of COPD on the gait of these patients. The results showed a decrease in step width and step length and cadence, as well as, an increase in stride time and double support as compared to control. Decreasing the step width reduces the base of support, and thus increases the risk of falls.

Lahousse et al. (87) reported rhythm problems during the gait of 196 COPD patients as compared to healthy individuals regardless of age, sex, exacerbation and dyspnoea. Fallers with COPD had worse rhythm than non-fallers, which is consistent with other studies which reported an association between variables such as rhythm, variability and cognitive decline and risk of falls (88). This group proposed the *gait Rhythm* variable, a novel spatiotemporal gait variable, as a clinical criterion for assessing the risk of falls in patients with respiratory problems, as well as *gait variability*, which reflects system flexibility. Using an accelerometer, Annegarn et al. (89) observed that ML variability in trunk acceleration was higher in COPD patients than controls. They suggested that these individuals may use an active control strategy to compensate for balance disturbances and maintain stability in the AP direction, and therefore have less control over the ML direction, which in turn leads to increased ML variability and increases the risk of falling.

Yentes's et al. (90), further studied he control strategy of COPDp by attempting to answer the important question of why do these patients opt for balance control in the AP direction considering that control in the ML direction increases their risk of falling. By simultaneously examining the dynamic stability (margin of stability (MOS)) and energy expenditure during gait, this study showed that an increase in metabolic power was associated with a decrease in MOS in the AP direction; however, there was no significance correlation with the mean standard deviation or variability in ML direction. Therefore, because these patients are normally at the maximum level of energy consumption due to their increased effort to breathe adequately, it seems that their control system selects a strategy to maintain stability in the AP direction during gait at a normal level, but eventually, their balance problems in the ML direction are shown by increasing the mean and variability of MOS_ML. This study highlights the potential for energy expenditure to be used as as an effective measure/determinant for gait problems in COPDp. The results of

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the investigation by Smith et al. investigation (70), confirmed these results by examining the sway of COPDp, which reduced trunk involvement in maintaining stability and led to balance problems in the ML direction due to increased muscle stiffness.

The kinematics and kinetics of gait in COPDp have been thoroughly investigated. Yentes et al. (79) examined the lower joints' kinematics and kinetics of gait in COPD patients, as compared to a control group. They found no significant differences, except for the lack of increase in peak dorsiflexion moment in fatigue conditions, as well as a larger ankle joint peak power absorption at mid-stance, which was attributed to weakness of the anterior tibialis. These results reflect that variability in gait spatiotemporal variables is not always sufficiently discriminative between healthy and COPD patients. Other dynamic variables, such as sample entropy and local divergence exponent (91), were therefore used to quantify joint movement patterns in this population. The results demonstrated more restricted (decreased variability of fluctuation, increased predictability) and less consistent organization (decreased local dynamic stability) of lower limb joint movement patterns in COPDp during gait. Lack of sample entropy may indicate that the system was too rigid or too irregular, and consequently has less ability to adapt (such as experiencing an unexpected disturbance). An increased local divergence exponent has already been reported in the elderly in association with the history of falls (92). The study further revealed any changes of speed from self-selected, lead to increased problems of consistency in the organization of the movement patterns of the lower torso joints. They concluded that in general COPDp are unable to respond appropriately when faced with alterations in task demands or environmental disturbances which predispose them to fall.

In addition to kinematics, it is important to consider the kinetics of movement in COPDp, particularly in response to external disturbances. Lower body muscles need to produce enough compensatory torque across the various joints to maintain the COM within the base of support and protect an individual from falling. In COPDp, muscle weakness and motor disorders cause impairment in joint torque production against environmental perturbation, which leads to abnormal fall response and related injuries. Yentes et al. (79) reported a lack of a peak in the dorsiflexion moment only after heel-strike in COPDp gait, and suggested that this abnormality results due weakness in the tibialis anterior. Up to date, and to the best of our knowledge, there are no other investigations on COPDp gait kinetics in other planes aside from the sagittal plane and in response to a sudden perturbation. As falls in the real world are multidirectional, hip muscles need to produce enough joint adductor/abductor moments in the frontal plane to protect from falling in response to perturbation in the medio-lateral direction, this emphasizes the need and importance of 3D kinetics analysis in COPDp. Whether a traditional gait lab with motion capture systems and force plates are used, or novel wearable technology such as sensors and IMUs in conjunction with musculoskeletal models (for example, AnyBody from Aalborg Denmark), such information is significant for a comprehensive 3-D biomechanical analysis which bridges the gap in literature.

4.1.5. Cognitive functioning

4.1.5.1. Cognitive impairment

The brain, which has the highest demand for oxygen than any other organ in the body, can also be vulnerable to the systemic effects of COPD, where cognitive problems are reported in approximately 36% of these patients, or 3 times more than healthy individuals (93). Cognition is the mental ability through which human behavior can be adapted to new situations and/or preference changes (94). Executive functions, language, visuospatial and motor function, memory, attention and social emotions are all domains of human cognition (88).

Major involvement of associative cortical areas, in integration of sensory and executive tasks, explain the link between reduced cognitive capacity and increased risk for falls (27). The prefrontal cortex (PFC) is involved in attentional control and executive functions, including memory, planning, and decision making (95). In COPDp, the structural changes of PFC that usually occur with aging, are more pronounced than those in the same age group (93). Lower reaction time, delayed memory, and slower information processing speed are among the main problems observed in this group of patients (93). Different studies (96, 97) have reported an increase in the number of road accidents in COPD patients as compared to other elderly groups, which may be attributed to the cognitive disabilities. In addition, other structural changes such as reduced brain perfusion in both the anterior and sub-cortical areas, reduced motor cortex activity, and alterations in the neural structures (white matter lesion, brain atrophy), have also been identified in these patients (98).

In COPDp, researchers have observed a decrease in the ability to perform multiple complex tasks, such as driving or visuo-guided muscle contractions, which require the simultaneous use of cognitive ability and vestibular or visual systems. They suggested that the capacity to perform several simultaneous tasks is impaired due to frontal lobe dysfunction and an associated decrease in attentional capacity (99).

This disorder, which is called Dual-Tasking (Cognitive-Motor) Interference (DTI), also impacts the gait and activity of COPDp. When a person's cognitive ability decreases, the ability of appropriate response (e.g., in the face of obstacles during walking) also decreases, resulting in falls. In COPDp, research has shown that it took longer to perform a functional test with a cognitive task (100). Moreover, delay in responding to task changes has been reported in these individuals, and hence in the face of unexpected environmental disturbances during walking, such as uneven surfaces, slipping or tripping, cognitive and DTI challenges interfere with the needed reaction to maintain balance. In healthy people, even those with cognitive problems, it is possible to partially compensate for delayed responses by increasing muscle activity and producing sufficient joint torque. Muscle weakness, along with delayed reaction and difficulty in selecting the appropriate control strategy in COPDp increases their risk of falling (99).

Research on COPD gait in dual tasking revealed an increase in gait variability along with a decrease in the speed of gait. Both are measures of gait stability impairment, which is closely associated with the increased risk of falls. Furthermore, structural changes in the brain due to the reduced oxygen delivery caused by COPD, in addition to the cognitive impairment, also manifests itself in the form of neural drive to muscle problems. Alexandre et al. (101) showed that knee extensors cannot be optimally driven by the brain while receiving torque control visual feedback (dual task) in COPDp. Therefore, in addition to muscle weakness, higher DTI during muscle force production also increases the risk of falling in these patients, so that both the reaction time and the mental strength/capacity of these patients to external disturbances are disturbed due to problems in the brain caused by COPD.

4.1.5.2. Mental (cognitive) fatigue

Mental fatigue can be defined as a temporary as the temporary inability to maintain optimal cognitive performance resulting from hard mental or physical (102). Almost fifty to seventy percent of COPDp experience mental fatigue in their lives, which disrupts ADLs, reduces the quality of life and may even lead to temporary or permanent hospitalization of these patients (103). Fatigue generally falls into two categories: peripheral (performance) and central (perceived). Peripheral fatigue is identified as changes in objective measures of performance over a defined period of time, i.e. decline in the peak force generated during maximum voluntary muscle contraction, while central fatigue is a progressive failure to voluntarily activate muscles, which can originate at the spinal or supraspinal levels, and one of its components is mental or cognitive (104). This form of fatigue is considered as a psychobiological state, which is typically triggered by prolonged periods of demanding cognitive activities. Research has shown that mental fatigue is associated with changes in the activation of the prefrontal cortex, which is the part of the brain,involved with executive function, and is most likely damaged in COPDp. Therefore, it can be assumed that the mental fatigue most likely has a substantial impact on functional impairment in COPDp (105).

Behrens et al. (106) hypothesized that cognitive fatigue among older adults may lead to changes in gait and postural control, both of which require cognitive processes. In this study, the effect of mental fatigue on gait performance under single- and dual-task conditions was investigated in young and old participants. Questionnaires were used to review cognitive functioning (MMSE), Fall (FES-I)), Fatigue level (MFIS), wakefulness and mood (MDMQ) among the subjects. Variables such as psychophysiological workload, heart rate variability, as well as gait variability were evaluated during the experiment. Their results indicated that mental fatigue causes impaired gait performance (increased variability) during dual-task walking in old adults, and it should therefore be considered as a potential risk factor for the occurrence of falls in the elderly.

Up to date, the effect of mental fatigue on the gait of COPDp has not been studied, although Yentes et al. (79) reported minimal significant differences (only in the ankle joint power and peak moment) under REST and No-rest conditions among these patients. They asked patients to walk on a treadmill at their desired speed until they felt tired in the legs or shortness of breath, and then to perform 5 trips of 10 meters in a row without resting. Although they used this experiment to investigate the effect of fatigue on the gait biomechanics of COPDp, the results did not clearly show the complex relationship between fatigue, gait disorders and falling in this population.

In COPDp, impaired O2 delivery to both the pre-frontal cortex and the active limb muscles contributes significantly to a reduced central motor drive and the development of accelerated peripheral muscle fatigue, respectively (21). Thus, although mental and peripheral fatigues are manifested by separate mechanisms, they are systematically related and can exacerbate each other's effects. Impairment in gas exchange (e.g., decreased arterial O2 pressure) in COPDp due to fatigue, causes decreased cardiac output (21). Although the blood flow is reduced, the breathing effort is increased due to diaphragmatic disorders and absorbs more blood volume, resulting in reduced blood supply to the lower extremities and fatigue-induced movement problems. On the other hand, the simultaneous increase of afferent information from the respiratory/peripheral muscles, along with the decrease of brain capacity due to impaired cerebral oxygenation, constitute the mechanism of central fatigue in COPD individuals. As mentioned, after the manifestation of peripheral fatigue, aggravation of disease or strenuous daily activity (such as high-speed walking, climbing stairs, etc.), even if intermittent, could likely lead to centralized fatigue due to exacerbating respiratory needs and sending increased nerve signals to the brain. During dual tasking, when part of the brain's capacity is already involved, the effects of this form of fatigue will be more severe. In COPDp who are quite vulnerable to mental fatigue incidence, there is likely to be a significant association between gait and falling disorders with this form of fatigue. Examination of mental fatigue in people with COPD can highlight the importance of this phenomenon as a risk factor for falling, which can also disrupt the daily lives of these patients.

Table 1. literature review summary of fall risk factors in COPD patients.

author	risk factor	objective	observation
Gosker et al. (50) 2007	Skeletal muscle dysfunction	determining whether vastus lateralis muscle fibre type proportions are associated with COPD disease severity	the relationship was found between skeletal muscle abnormalities and important hallmarks of the disease in severe COPD
Mathur et al. (51) 2008	Skeletal muscle dysfunction	examining the relationship between muscle cross-sectional area (CSA) and volume by use of MRI in healthy and COPD individuals	muscle volume and strength were 25% less in COPDp as compared to an age-gender-matched healthy population
Iwakura et al. (61) 2016	Impaired activities of daily living	investigating the association between balance and physical activity measured by an activity monitor in elderly COPD patients	Impairments in balance and reductions in physical activity were observed in the COPD group
Kawagoshi et al. (62) 2013	Impaired activities of daily living	quantifying the walking time and frequency of postural changes in daily life in patients with COPD	the COPD patients' different walking times in daily life are significantly correlated with exercise capacity and dyspnea
Smith et al. (70) 2016	Balance deficits	determining whether recovery of balance from postural perturbations and trunk muscle activity differs in people with and without COPD before and/or after exercise	severe COPD is associated with impaired ability to recover balance and greater trunk muscle activity during postural challenges
Janssens et al. (74) 2013	Balance deficits	Determine the specific proprioceptive control strategy during postural balance in individuals with COPD and healthy controls	COPDp were more likely to rely on the ankle joint (muscle proprioceptive signals), decreasing their reliance on the back during balance control
Lahousse et al. (87) 2015	Gait deficit	investigating associations of COPD with various gait domains and explored a potential link with falling.	Persons with COPD exhibit worse Rhythm, especially fallers with COPD.
Fallahtafti et al. (90) 2020	Gait deficit	Is dynamic stability different between COPD patients and controls?	Patients with COPD operate at the upper limit of their metabolic reserve due to an increased cost of breathing
Hassan et al. (98) 2019	Cognitive impairment	comparing changes in dorsolateral prefrontal cortex (DLPFC) oxygenated hemoglobin ($\Delta O2Hb$), accuracy of backwards spelling, and decrements in gait velocity during single and dual tasks in patients with COPD and healthy younger and older adults	Decrements in performance during dual tasking highlight the impact of increased cognitive load and need of cognitive-motor interventions to improve cognition and physical function
Heraud et al (99) 2018	Cognitive impairment	Assessing the cognitive and motor performances of patients with COPD and healthy controls with in a dual task walking paradigm	providing evidence of insufficient attentional resources to successfully deal with DT in patients with COPD, and this was expressed through an exaggerated increase in gait variability in DT walking
Paneroni et al. (105) 2020	Mental (cognitive) fatigue	evaluating the impact of exercise training on fatigue, compared with normal care in patients with COPD	No study evaluating performance fatigue was found
Behrens et al. (106) 2018	Mental (cognitive) fatigue	cognitive fatigue among older adults may lead to changes in gait and postural control, both of which require cognitive processes	mental fatigue, induced by sustained cognitive activity, can impair gait performance during dual-task walking in old adults

4.2. Extrinsic risk factors

Slipping and tripping during walking are the most common causes of falls in the aging population and in patients with increased fall risk (80). Their inability to predictively (before the perturbation) or reactively (after the perturbation) adapt to changes and challenges in the environment causes increased risk of falling in these people. There is a need to physically prepare patients' perspective of falling for situations where unexpected mechanical disturbances to gait/balance could occur. While General exercise interventions (muscle-strengthening + balance exercises) moderately improve falls risk (14–17%), training reactive recovery responses following sudden perturbations (compensatory stepping, counter rotation or grasping actions) during walking may be more task-specific for falls prevention (80). The comparison of balance responses to external perturbations between COPD and healthy people reveals an association between COPD and fall risk factors. Gait perturbation can be simulated by methods such as: moveable floor platforms, ground surface compliance changes and belt accelerations or decelerations (AP perturbation), and/or moving the treadmill surface to the left and right (ML perturbation) during treadmill walking. The treadmill has advantages over the two other methods, including providing a feasible and less predictable platform (more difficult for participants to anticipate perturbations), in addition to the capacity of applying perturbations in both AP-ML directions and simulating continuous gait (80).

McCrum et al. (80), in their pilot study on 12 COPD patients, find no significant deficits in stability following sudden treadmill-based perturbations in the AP direction in this group. While previous studies demonstrated that COPDp suffer from balance problems in the ML direction (70-72, 90), this study only focused on AP perturbations, in addition to the limited number of subjects. Moreover, the effects of parameters, such as mental and physical fatigue, cognition, medication, history of falling, as well as the other well-known COPD related fall risk factors, were not investigated. The subjects had a FEV1/FVC < 0.70 and were able to complete a six-minute walking test, however, the severity disease of the subjects was not described. It is likely that all these patients were in a relatively good health condition (FEV1/FVC close to 0.7), whereas by subgrouping them based on the GOLD standard (or other methods such as the BODE index), the relationship between the severity of the disease and individuals' ability to maintain stability can be better defined. Further investigations are required to study how COPD affects balance responses to sudden perturbations in the COPDp population in comparison to age-matched healthy controls.

4.3. Hypotheses: Possible causes underlying the *increased risk of falls in COPD patients*

All the above-mentioned studies have reported serious motor-balance problems in COPD patients and their association with an increased risk of falling in this population. On the other hand, there remains a need to pinpoint the underlying mechanism(s) leading to falls in COPDp and examine the importance of different risk factors, their interrelationships, and association with patients' response to balance after a fall. The question of how much are inactivity, energy expenditure, gait difficulties, and cognitive problems responsible for COPD patients falling remains an open area of research. The following section delineates several of the possible hypotheses based on the literature:

H1- To keep energy expenditure at a normal level, patients with COPD are likely to reduce the intensity of their daily physical activity. Moderate- and vigorous-intensity physical activity requires anticipatory adjustments, gait stability, and transitions. There is a significant relationship between the level of daily life activity intensity and ability of COPDs to regain balance after a sudden external perturbation: As mentioned earlier, the gait of COPDp is typically adapted to maintain stability in the AP direction, albeit at the cost of instability in the ML direction due to the importance of energy expenditure control for COPD patients, which consequently, leads to an increased risk of falling (90). Therefore, this hypothesis assumes that such reduction in energy consumption can cause gait deficits and hence increase the risk of falling. When Hugli et al. (107) monitored the daily activities of COPDp and measured total energy expenditure, they found that, patients with stable COPD had normal daily energy expenditure. It seems that in addition to changes in the amount of daily activity of these patients, the intensity of the activity was also altered to control daily energy expenditure at a normal level. These changes, on the other hand, resulted in a weak response to external disturbances and hence in frequent fall incidence. This hypothesis is consistent with the results of Kawagoshi et al. (62). They found that the lack of activities with high/low intensities, such as fast/slow walking, going up/down the stairs, and sitting/getting up from a chair in COPDs' daily activities, to be an important problem which reduced the ability of the patients to provide an appropriate postural response when faced with a challenging or unexpected situation. Therefore, controlling (and reducing) energy consumption as an important constraint causes changes in various aspects of movement, as well as, the amount and quality of physical activity of COPDp.

H2- An appropriate modular organization of muscle Synergies is required to maintain postural control under challenging balance conditions. Physical inactivity in COPDp can result in differences in modular control of muscle coordination patterns during walking in this population as compared to healthy individuals. COPD decreases motor control performance in response to an unexpected gait perturbation by affecting the modular organization of muscle activity patterns in these patients: Inactivity affects the status of COPD patients via different mechanisms, such as the well-known cycle of "shortness of breath-inactivity-muscle deconditioning-increased carbon dioxide-shortness of breath". Therefore, a sedentary lifestyle can exacerbate the disease and possibly lead to increased risk of fall and injuries due to the patients' compromised musculoskeletal condition. Several studies have also identified balance deficits as an important risk factor for COPD falls. It can be therefore hypothesized that inactivity weakens the lower body muscles, such as the quadriceps, which synergistically along with the pelvic and abdominal muscles, contribute to postural stability. This leads to an increased trunk stiffness and decreases the trunk's contribution in maintaining balance, which consequently increases the risk of fall and/or the disruption in response to external disturbances.

H3- COPD patients suffer from cognitive impairment. Cognitive function is associated with falls and gait deficits in older adults. There is an association between domain-specific cognitive impairment in COPDp and their gait performance and response to external perturbation: Among all the variables reported by Lahousse et al. (87) regarding the gait of COPDp, only the "rhythm" indicated a significant difference between patient and control groups, as well as fallers and non-fallers. It has already been demonstrated that there is a relationship between memory and gait rhythm (88). Considering that COPD patients are at high risk of cognitive impairment, the relationship between different cognitive domains and gait impairments reported in this population is not studied yet. It can be hypothesized that COPD causes gait rhythm impairment by affecting cognitive ability, in particular memory, which increases the risk of falling in these patients. In addition, the correlation between brain structure/function and performance of gait and balance recovery responses to external perturbations in COPD patients remain controversial and equivocal.

H4- "Mental fatigue" is a risk factor for falling in COPDp and results increased gait variability and instability during dual-tasking: It has been reported that there is a close association between emotional status and movement alteration (108). In COPDp because of decreased cerebral gray matter (109), a potential increase in the risk of depression and anxiety is expected, which in turn, may cause movement alterations/deficits, especially during gait, as well as a higher risk of falling. Furthermore, since proprioceptive afferents emerging from muscles and connective tissue are unable to be adequately processed by the cerebellum in COPDp, iImpaired proprioception is another culprit behind control problems during movement and increased fall incidence in COPDp. Cognitive overloading due to the patients' chronic condition, when their cognitive functioning with aging and reduced oxygen supply to brain are already impaired, further increases the vulnerability of COPDp and their susceptibility to mental fatigue as compared to a normal elderly group, especially during dual-tasking.

H5- COPD patients have different "trunk coordination" relative to lower-body segments while walking and after perturbation, which should be considered as a fall risk factor: Most of reviewed studies considered gait disorders as key to understanding the relationship between the systematic effects of disease and falling in COPDp. Using 3D motion analysis, Yentes et al. (79) studied the characteristics of gait in COPDp focusing on the kinetics and kinematics of the lower-limb joint (ankle-knee-hip) in the sagittal plane. On the other hand, COPD is mainly an upper-limb disease based on the location of lungs and the pelvis and trunk play an important role in the manifestation of the disease. Moreover, while studies, including this one, focused only on the sagittal plane, hip adductor weakness reported in COPD patients confirms the importance of the incorporation of the frontal plane and the need for a full 3-D biomechanical approach. Although different studies (85, 91) investigated the variability of spatial-temporal parameters of the gait (i.e. step width, step length, cadence, etc.) of COPDp , the majority of these studies focused on end-point variability (the variability of the results of a movement, i.e. step width, length, etc.) and not the working point variability (the variability of segments and joints of a movement). Segmental coordination and coordinative variability are advanced mathematical methods that can be used to analyze a segment (such as the trunk) kinematics relative to other segments (pelvic, shank, etc.) in different anatomical planes (sagittal, frontal, transverse). "Segmental coordination" can help understand the effect of COPD on motor control and how to respond properly to perturbations and prevent injuries during the loss of balance and falls (110). However, we can hypothesize that coordination exercises, such as Tai Chi, can regulate breathing, strengthen upper and lower body musculature, and improve COPDs' trunk coordination, hence improving overall postural stability.

H6- COPD patients with "low back pain" (LBP) have different balance strategies to regain stability after unexpected perturbations, as compated to LBP-free and healthy age-matched controls, because they rely more on ankle rather than back muscles: Diaphragm dysfunction is a major cause of non-specific LBP among COPD individuals (75), where the prevalence is estimated between 41.2 and 69 percent (75). In addition to causing pain and reduced quality of life, LBP is a potential risk factor for falls. Researchers have shown that elderly people with LBP are almost three times more likely to fall as compared with healthy elderly, in addition to exhibiting greater postural sway, longer reaction time, and lower quadriceps strength (78, 111). As previously mentioned, in addition to its respiratory role, the diaphragm also helps the back muscles in maintaining spinal stabilization, and hence its dysfunction causes instability of the vertebrae and leads to LBP over time (69, 75). In a closed biomechanical chain, a decrease in diaphragm efficiency due to weakness, deformation, or fatigue causes the spine to rotate around the T8 level, which in turn causes the pelvic muscles to be stretched, exacerbating the pelvic tilt. Synergistically, the hip joint will rotate in the opposite direction, resulting in a rotation of the femoral-tibial coupling, followed by ankle pronation. Therefore, a diaphragm problem, along with this biomechanical chain of disorders, typically manifest at the ankle joint level, as confirmed by other studies (79). If not treated with proper rehabilitation, this will aggravate the diaphragm problem and further worsen the associated lung disease.

5. Limitations

Roig et.al (26) divided the risk factors of COPDp in two groups of intrinsic and precipitating factors. Intrinsic factors are associated with the physical and psychological status of patients, such as muscle weakness, gait and balance problems, cognitive disorders, etc., while precipitating factors, such as exacerbations and dyspnea, are health-related factors. Extrinsic factors can be added as third group and are associated with environmental factors, such as weak light and slippery conditions, but are not affected directly by the disease. Although both extrinsic and intrinsic factors were discussed in this study, some aspects pertaining to intrinsic risk factors, such as visual deficits and use of an assistive device, were left out due to the lack of sufficient related articles. Furthermore, Roig et al. introduced medication and central nervous system medications (e.g. antidepressants and narcotics) as potential risk factors in these COPDp. High usage of some medications (e.g. antidepressants and narcotics) and sedatives (benzodiazepines), as well as corticosteroids, in these patients can cause some side effects, such as impaired postural control, slowed postural reflexes, muscle weakness and also can increase the risk of fracture (26). All the

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aforementioned factors can potentially increase the risk for falling in COPDp. Although, the relationship between the type and number of medications with the risk of falling was not addressed in this study, it is recommended that future research investigate the mechanisms that explain this relationship.

6. Conclusions and Future Directions

This study aimed to 1. analyze the literature to identify and summarize the risk factors of falling in COPDp populations, and 2. investigate the underlying mechanisms by which these risk factors can lead to an increased prevalence of falling. The results confirm that the risk of falling in COPDp is substantially higher, as compared with age-matched healthy individuals, due to well known risk factors, including gait and balance problems, cognitive disorders and reduced daily activity. However, the precise underlying mechanism(s) which lead to increased falls in these patients remain unclear. Based on the literature reviewed here, this study also suggests that low back pain and mental fatigue should be added to the list of potential fall risk factors. This study importantly explored the possibility of a direct correlation between the improvement in performance of COPDp in response to unexpected disturbances and the intensity of daily activities, confirming that the probability of falling may likely decrease by performing daily activities or sports at low and high speeds according to the age and the disease level of these patients. Although up to date no significant differences have been reported in most of the kinetic-kinematic gait variables reported in the literature for COPDp as compared to healthy individuals, this study recommends analyzing the segmental coordination and intramuscular muscle synergy as means to understand the association between the gait challenges associated with the disease and subsequent fall mechanics. Future work is warranted towards understanding the underlying mechanisms leading to falls in COPDp by evaluating the responses to unexpected disturbances during walking in both ML and AP directions and by examining the impact of each of these risk factors on improving these responses.

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