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Review

Loss of autonomic postural reflexes, Gait abnormalities and "freezing walk" in severe Parkinson's disease Patients contributes to falls and hip fractures

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Abstract

Since the average of life expectancy continues to ascend, the number of elderly people increases remarkably. Simultaneously, musculoskeletal diseases including PD and related disorders rise. Hip fractures, particularly in PD patients, should not be viewed as a routine public health concern that need orthopedic intervention only, but it is a challenge with consequences that override the orthopedic problem. The aim of this manuscript is to shed light and to try to identify the underlying causes of and circumstances surrounding the fall and hip fractures in Parkinson's disease (PD) patients, in order to find prevention strategies and choose appropriate therapy. We have analyzed, discussed and overviewed the latest updates of the medical literature concerning PD and the orthopedic complications. PD is a chronic neurodegenerative disorder characterized by rest tremor, rigidity, bradykinesia and loss of postural reflexes, leading to immobility and gait disturbance. The usual age of onset is between the sixth and eighth decades. Globally, the percentage of elderly aged 65 years and over was calculated to be 8 percent (521 million) in 2011 and it is expected to be 11 percent (939 million) of the total global population by 2030. Hip fractures are life-threatening and frustrated quandary that is usually seen among elderly people that requires high economic expenses. Plethora of factors contributes to falls and to increased risk of hip fractures in patients with PD. These factors include potential physiological aging changes and medical causes. One should try to identify the underlying causes of and circumstances surrounding the fall and hip fractures in PD patients specifically, in order to find prevention strategies and choose appropriate therapy by taking a multidisciplinary approach interventions that include neurologist, physiatrist, podiatrist, and family or caregivers the thing that will result in optimal outcomes for patients with PD.

Keywords: Parkinson' disease, Postural instability, Falls, Hip fractures, Prevention

INTRODUCTION

Parkinson's disease (PD) is a chronic and progressive neurodegenerative brain disorder, belongs to a group of neurological conditions called motor system disorders, which are the result of a degeneration of dopaminergic neurons in the substantia nigra of the midbrain located immediately dorsal to the cerebral peduncles. Roughly

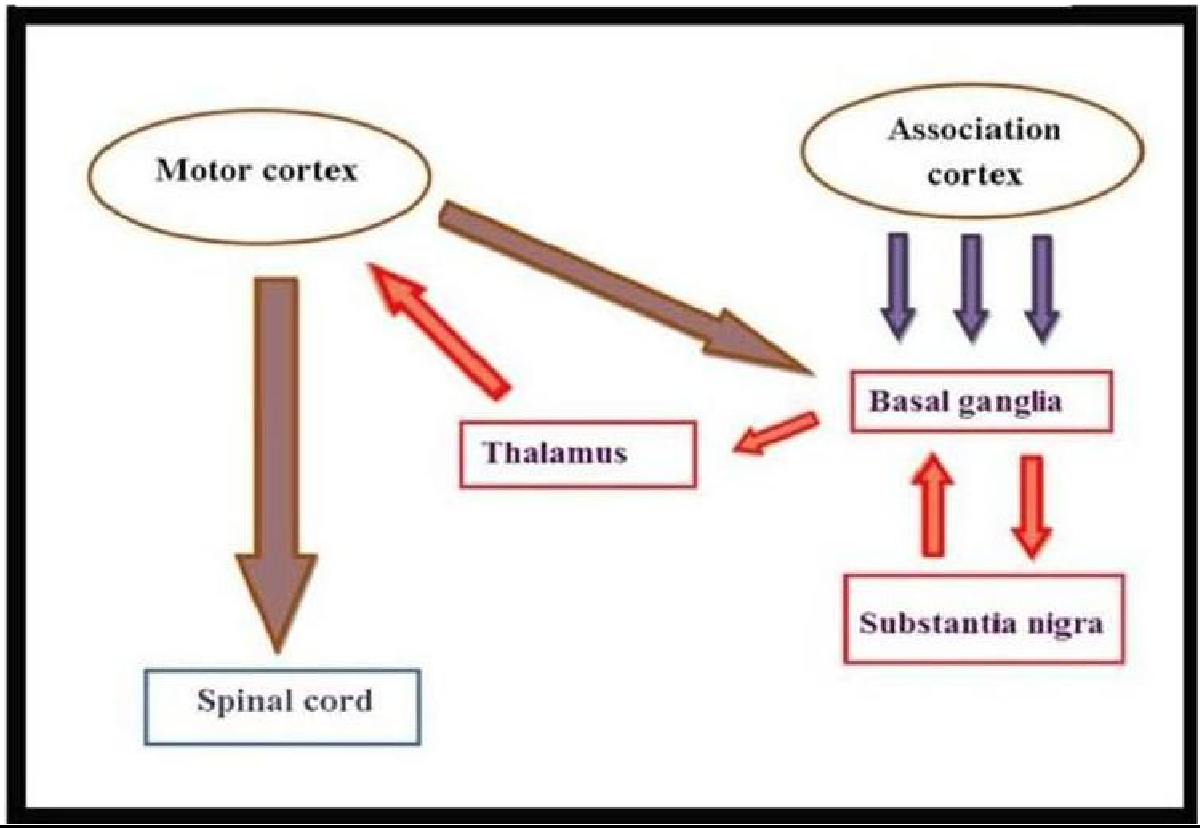

Figure 1. Describes the different projection from the basal ganglia (substantia nigra): The basal ganglia are a collection of nuclei found on both sides of the thalamus, outside and above the limbic system, but below the cingulate gyrus and within the temporal lobes. The basal ganglia receive inputs from multiple cortical areas, and then project to the motor cortex via the thalamus. The basal ganglia integrate these multiple inputs to modulate the output of the motor cortex.

95% of cases of PD are sporadic, and cannot be attributed to a specific environmental or genetic cause. However, approximately 5% of cases of PD disease are familiar, due to mutations in specific genes (Lachenmayer and Yue, 2012; Corti et al., 2011).

Epidemiologically, PD is the second most common neurological disorder, affecting more than one million individuals in the U.S and 50,000-60,000 new cases of PD are diagnosed each year, adding to the one million people who currently have PD. Worldwide, it is estimated that four to six million people suffer from the condition. The usual age of onset is between the sixth and eighth decades, and roughly 1% of the population over the age of 60 is affected, although 20% may be diagnosed under the age of 50. While PD itself is not fatal, the Center for Disease control rated complications from PD as the 14th leading cause of death in the United States.

Pathologically, PD is considered a disorder of the basal ganglia because the major projection from the substantia nigra is to nuclei of the basal ganglia. The basal ganglia are a collection of nuclei found on both sides of the thalamus, outside and above the limbic system, but below the cingulate gyrus and within the temporal lobes. The basal ganglia receive inputs from multiple cortical areas, and then project to the motor cortex via the thalamus. The basal ganglia integrate these multiple inputs to modulate the output of the motor cortex. Some of the connections are excitatory and some are inhibitory. The loss of the dopaminergic neurons input from the substantia nigra alters the balance of the output from the basal ganglia to the motor cortex, and this underlies the symptoms that are usually seen in PD. Researchers have also explored the thought that degeneration of dopaminergic neurons in other region of the brain and body contribute to PD. Scientists have discovered that the hallmark sign of PD — Intraneuronal inclusions comprised of a protein alpha-synuclein, which are also called Lewy Bodies — are identified not only in the mid-brain but throughout the nervous system, from brainstem to cortex (Figure 1).

Symptomologically, PD is a movement disorder characterized by rigidity, bradykinesia and loss of postural reflexes, leading to immobility and frequent falls. In addition, rest tremor is also an eminent symptom of the disease (Douglas et al., 1999; Koller et al., 1989). Early symptoms of PD are subtle and occur gradually often in no particular order. In some people the disease progresses more quickly than in others and affects patients in different manners with a miscellany of symptoms and responses to cure. It is unlikely for a patient to experience all or most of the symptoms known to be part of PD; the clinical presentation of the disease may be different. In addition to the four cardinal symptoms, other potential symptoms may be presented sooner or later such as: neuropsychiatric symptoms and autonomic dysfunctions. In the past PD was considered merely as a disorder of movement and motor impairment, but now it is known that PD includes initially autonomic nervous system dysfunction prior to motor impairment and cognitive dysfunction after motor impairment. The slowness of movement; stiffness of limbs and trunk, gait disturbances, impaired balance and coordination, stooped posture and slow, shuffling gait occupied a crucial space in this manuscript. These typical features of rigidity, bradykinesia and especially postural instability are seen as the disease progresses and become more severe leading PD patients to lose their natural sense of balance and equilibrium and can be the forerunners of falls and hip fractures. It has been reported that PD patients have a higher incidence of hip fractures than the general population (Johnell et al., 1992). In fact, because there are several categories of abnormalities that lead to immobility and falls among the elderly in general, one should try to identify the underlying causes of and circumstances surrounding the fall and hip fractures in PD patients specifically, in order to find prevention strategies and choose appropriate therapy.

Fall-related factors and risk of hip fracture among patients with Parkinson's disease

Plethora of factors contributes to falls and to increased risk of hip fractures in patients with Parkinson's disease. These factors include potential physiological aging changes and medical causes. Fractures, particularly of the femoral neck, are among the most devastating complications of falling in PD patients (Johnell et al., 1992; Hammer, 1991). Hip fractures, particularly in elderly people, should not be viewed as a routine public health concern that need orthopedic intervention only, but it is a challenge with consequences that override the orthopedic problem, with reflections in the areas of medicine, long time hospitalization, rehabilitation, psychiatry, caregivers, institutionalization and great economic resources (Fransen et al., 2002). Elderly population represents one of the highest growing segments of the worldwide population. Globally, the percentage of elderly aged 65 years and over was calculated to be 8 percent (521 million) in 2011 and it is expected to be 11 percent (939 million) of the total global population by 2030 (The World Bank Group: Word Population, 2011). In addition to the progressive increase percentage of elderly, the average of life expectancy also continues to ascend (National Institute of Aging and National Institute of Health, 2007). China is a shining example – per capita income has increased 21-fold over the last four decades and life expectancy has grown from 64 years in 1971 to 75 years in 2013 – with projections to 81 years by 2050. In Japan and Singapore, life expectancy in 2013 was already 84 years and is expected to increase by 10% to reach 92 years in 2050 (Haub, 2011). Regarding musculoskeletal and related disorders it is well known that the greatest challenge is the ageing of the population (United States Census Bureau 2013, Census. Gov, 2013). Demographic changes alone can be expected to cause the number of hip fractures to increase dramatically. In Asia, a 7.6-fold increase in the elderly people is predicted between the years 2000 and 2050 (James, 2002).

The high wave number of the elderly in Asian countries have seen a 2–3 fold increase in the incidence of hip fractures over the past 30 years (Kanis, 2007).

Globally the hip fractures have shown a plateau in incidence rates which doubles each decade after 50 years. The annual number of hip fractures is also projected to double by the year 2040 (Gullberg et al., 1997; Lau and Cooper, 1996; Cummings et al., 1985; Cummings et al., 1990). Approximately 1.6 million hip fractures occur worldwide each year; by 2050 this number could reach between 4.5 million (Zuckerman, 1996), and 6.3 million (Cooper et al., 1992).

It is also noted that hip fractures rate is 2-3 folds higher in women than in men. In fact, nearly 75% of all hip fractures occur in women (Jordan and Cooper, 2002). Each year, in the United States, more than 270,000 hip fractures occur, most of them in persons older than 60 years (Jeffrey et al., 2003).

The incidence of hip fracture varies considerably between different populations, on the top of the pyramid perched the Scandinavian populations who have the highest reported incidence of hip fracture worldwide (Kanis et al., 2002). Chen et al. reported that hip fracture developed in 10.4% of patients with PD and 4.1% of patients in the comparison cohort. The Cox proportional regression model showed an adjusted hazard ratio of 2.71 for PD patients (Chen et al., 2012). Melton et al. compared PD patients to an equal number of age- and sex-matched non-PD referent subjects from the community, PD patients were at a 2.2-fold increased risk of fractures generally and a 3.2-fold greater risk of hip fractures specifically (Melton et al., 2006).

New data from the Global Burden of Disease 2010 Study have shown that disability due to musculoskeletal disorders has increased by 45% from 1990 to 2010 compared with a 33% average across all other chronic, non-communicable disease areas. Musculoskeletal diseases are now the second greatest cause of disability worldwide and in most regions of the world (Horton, 2010).

Indeed, elderly PD patients as their counterpart are prone to hypovitaminosis D and K due to malnutrition or

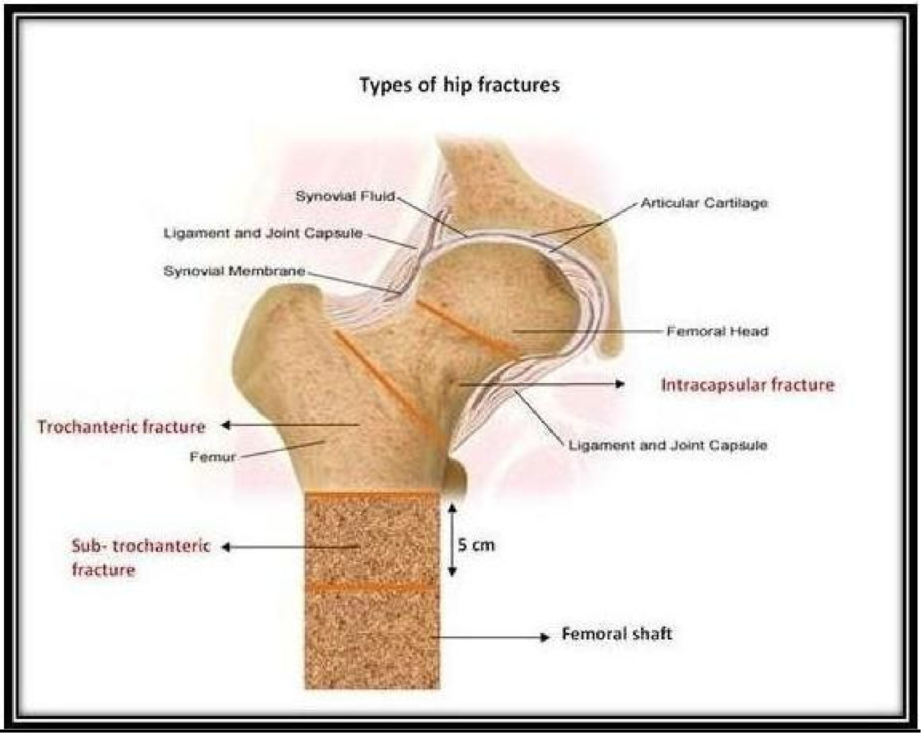

Figure 2. Describes the three types of Hip fractures. There are three broad categories of hip fractures based on the location of the fracture: femoral neck fractures, intertrochanteric fracture, and subtrochanteric fractures. The term pertrochanteric hip fracture may also be used in hip fracture literature and refers to a more inclusive set of extracapsular fractures, including intertrochanteric, subtrochanteric, and mixed fracture patterns.

sunlight deprivation, increased bone resorption due to immobilization, low bone mineral density, physical inactivity. In addition to all mentioned above, PD patients are even more at risk of hip fractures because of their background pathology and symptoms such as: Movement disorders with gait disturbances, imbalance, and short-stepped, shuffling and freezing walk.

Furthermore, poly-medications used to treat PD are powerful and have unwanted side effects. Indeed, Levodopa was associated with an increased overall fracture risk and an increased risk of hip fractures in high doses (Vestergaard et al., 2007). Hyperhomocysteinemia due to levodopa intake may be one additional risk factor for osteoporosis and fracture in PD patients (Lee et al., 2010). Tricyclic and selective serotonin reuptake inhibitor antidepressants are both associated with an independent increase in hip fracture incidence during the first weeks of treatment (Hubbard et al., 2003). Array of drugs such as: Antipsychotics, Antiemetic, Antihypertensives, Calcium channel blockers and Angiotensin converting enzyme inhibitor may be used by PD patients to treat other medical conditions. These medications not only exacerbate existing PD symptoms, but have the capability for inducing PD, leading to misdiagnosis. A complete drug history is important before making a diagnosis of sporadic PD. If the offending drug can be withdrawn, symptoms should resolve. Though most physicians know that the antipsychotics can cause a Parkinson-like condition, many are not aware that antiemetics such as metoclopramide have similar effects. PD-induced nausea should be treated with domperidone when associated with dopaminergic drugs.

Classification of Hip Fractures

Hip fractures occur in the proximal (upper) portion of the femur (Intra-articular or Exrta-articular of the hip joint). There are three broad categories of hip fractures based on the location of the fracture: femoral neck fractures, intertrochanteric fracture, and subtrochanteric fractures. The term pertrochanteric hip fracture may also be used in hip fracture literature and refers to a more inclusive set of extracapsular fractures, including intertrochanteric, subtrochanteric, and mixed fracture patterns (Zuckerman, 1996) (Figure 2).

The femoral neck fractures are the most common location for a hip fracture, accounting for 45% to 53% of hip fractures. Per 100,000 person years, approximately 27.7% of femoral neck fractures occur in men and 63.3% occur in women. (Michelson et al., 1995) found that the distribution of the types of hip fractures within the U.S.

population is 49% intertrochanteric, 37% femoral neck, and 14% subtrochanteric, and these estimates are relatively consistent across authors (Koval et al., 1996; Forte et al., 2008). The most commonly used classification system for femoral neck fractures is the Garden classification (Garden, 1961).

Garden classification for femoral neck fractures (Garden, 1961)

- Type 1 is an impaction fracture (Incomplete).
- Type 2 is a nondisplaced fracture (Complete).
- Type 3 involves various displacements of the femoral head.
- Type 4 involves complete loss of continuity between fragments.

A femoral neck fracture is intracapsular, that is within the hip joint and beneath the fibrous joint capsule (Figure 2, blue color area). Femoral neck fracture occurs in the narrowed section of the upper femur that lies between the femoral head and bony projections called trochanters. Indeed, most femoral neck fractures occur within the capsule that surrounds the hip joint and are therefore termed intracapsular. The blood supply to the femoral head is entirely dependent upon a series of arteries that pass through the femoral neck region. Therefore, fractures of the femoral neck can entirely disrupt the blood supply to the femoral head, resulting in increased rates of major healing complications such as fracture nonunion, osteonecrosis, or avascular necrosis and late osteoarthritis.

Intertrochanteric fracture

This fracture occurs between the neck of the femur and a lower bony prominence called the lesser trochanter (Figure 2, red color area). The trochanters are bony projections where major hip muscles attach. Intertrochanteric hip fractures occur outside of the joint capsule and are therefore extracapsular, and thus at lower risk for complications related to interruption of the blood supply through the femoral neck, but are at risk for displacement (Baumgaertner, 2013).

However, these fractures are complicated by the pull of the hip muscles on the bony muscle attachments, which can exert competing forces against fractured bone segments and pull them out of alignment. Thus, the healing complications for intertrochanteric fractures are often different from those of femoral neck fractures, and are more likely to include shortening of the length of the femur or healing of the fracture in a misaligned position (malunion). Intertrochanteric fractures may be further grouped into stable and unstable fractures, depending on the location, number, and size of the fractured bony segments. Femoral neck fractures and intertrochanteric hip fractures occur most often in elderly populations, who generally have other medical diagnoses. The fracture may have been due to a medically related problem such as a syncopal episode, dehydration, overmedication, or vertigo.

Subtrochanteric fracture

Occurs below the lesser trochanter, in a region that is between the lesser trochanter and an area approximately 6 cm below. Isolated subtrochanteric fractures occur in the area between the upper borders of the lesser trochanteric to 5 cm below it, toward the knee. Subtrochanteric fractures may include only a short linear section of the proximal femur or may be part of a larger fracture pattern that involves both the intertrochanteric and subtrochanteric sections of the femur. The blood supply to the bone of the subtrochanteric region is not as good as the blood supply to the bone of the intertrochanteric region and thus heals more slowly. Subtrochanteric fractures are also subject to competing forces exerted by muscular attachments on the femur that tend to pull the fractured fragments out of alignment.

Hip fractures and PD patients

Hip fractures among elderly are ones of the most life-threatening and frustrated quandary with high economic health burden for the patient and society (Burge et al., 2007; Melton, 1993). It is well known that hip fractures increase hazard of death over 10-fold in the first weeks after fracture (Melton et al., 1998). Generally, hip fracture, which increases exponentially with age cause the most morbidity with reported mortality rates up to 20-33% depending on age in the first year after experiencing a fracture (Graham et al., 1993; Raymakers and Duursma, 1992; Hannan et al., 2001; Leibson et al., 2002). It is worth to mention that PD patients have a two-fold increased risk of death over that of the general population (D'Amelio et al., 2006); furthermore, PD patients suffering hip fracture have reported mortality rate up to 31% in the first year of this serious event (Eventov et al., 1983). Overall, as one would expect PD patients with their characteristics movement disorder symptoms and after hip fracture are at increased risk of death within the first year after experiencing a fracture (Johnell et al., 1992; Melton et al., 2006; Genever et al., 2005). In fact, co-morbidities and pre-fracture functional status play a variable role in contributing to hip fracture risk and to mortality associated with fracture. Disorders known to contribute to hip fracture risk include diabetes, septicemia, pneumonia, and digestive disorders, cardiac and cerebrovascular or neoplastic diseases (Marks et al., 2003). Patient's health, of those who suffered fractures, are more likely to deteriorate, as such they showed increased subsequent hospital episode by (23%), with total number of in hospital care (21%) (Yassin et al., 2014). It also increased patients' difficulties in basic activities, house hold activities and advanced activities of daily living (ADL), and decrease total cognitive performance as well as increased upper body limitations (Wolinsky et al., 1997). In previous studies, it was calculated that 44% of patients developed one or more new permanent ADL limitations within 3 months after hip fracture (Cree et al., 2001).

Strategies for prevention of hip fracture in PD patients

Strategies to prevent fractures in elderly people in general and among PD patients in specific should be a main concern in the health systems, particularly, after the worldwide demographic changes and increase of the number of elderly which alone can be expected to cause the number of hip fractures to increase dramatically.

In the light of yearly increase in PD patients numbers, and since hip fracture in general is an important public health concern with serious health outcomes for PD patients in particular and their families, that requires high health care cost to governments, prevention strategies are highly needed to ameliorate its negative effects. Systematic reviews concluded that prevention of muscles weakness among elderly people could reduce several risk factors for hip fractures such as; low bone mineral content and bone loss; decreased effectiveness of protective reflexes; decreased soft tissue cushioning; and decreased mobility (Marks et al., 2003). In addition, prevention of falls and use of hip protectors could help prevent hip fractures (Marks et al., 2003; Sawka et al., 2007). Multifactorial intervention plan that included balance and strength training, adjusting the environment to the elders, vitamin D supplementation and educational activities, also showed decreased hip fracture within elders in long term care facilities, after 2 year follow up (Becker et al., 2011).

Recent studies have also found additional strategies specific to preventing hip fracture in PD patients. A prospective clinical trial involved women over 70 years old, showed that treatment with vitamin K2 and vitamin D2 helped increasing bone mineral density and consequently helped in the prevention of non-vertebral fractures (Sato et al., 2005; Iwamoto and Sato, 2013). Another scoping study that reviewed different interventions which were aimed to prevent hip fractures in elders (vitamin D, sunlight exposure, alendronate, fluoride, exercise or multimodal interventions, and hip protectors), found that the strongest evidence for hip fracture incidence reduction was attained by interventions with vitamin D supplementation (Sawka et al., 2010).

Another review of literature on the effectiveness of sunlight exposure, menatetrenone (vitamin K compound) (women), oral bisphosphonates (risedronate) with vitamin D supplementation (women) in preventing hip fracture in PD patients, found that the best evidence comes from the studies included in the review, that interventions with risedronate that inhibits osteoclastmediated bone resorption, improve hypercalcemia, increased cortical BMD and modulates bone metabolism plus vitamin D supplementation or risedronate plus menatetrenone can be candidate for intervention aimed to reduce falls within PD patients and possibly hip fracture, however the study highlights the lack of efficacy studies to determine the suitable intervention (Iwamoto and Sato, 2013; Iwamoto et al., 2012; McClung et al., 2001).

In addition, patients with PD may be affected with other conditions, and may be on poly-medications. Therefore, treatment must take a multidisciplinary approach. PD medications and other drugs used for possible other co-morbidities are powerful and have sometimes unwanted side effects. Avoidance of multi-medication and routinely review of drugs, as some may cause dizziness or drowsiness is extremely important to avoid unwanted consequences.

Moreover, physiotherapy to address gait dysfunction and strengthen muscles is a method to improve mobility and reduce bone loss. Getting the patient moving early can have a positive impact. Educating the patient, family members, and caregivers on PD and its consequences is vital. Dementia, depression, and the musculoskeletal manifestations of PD can all result in a prolonged and difficult recovery period. Patients with PD can also have a lot of falls; caring for them is a very physical ordeal. Taking a multidisciplinary approach—including a neurologist, physiatrist, podiatrist, and family or caregivers—will result in optimal outcomes for patients with PD.

DISCUSSION AND CONCLUSION

As the elderly population grows, the number of hip fractures continues to increase. Hip fractures rank in the top ten of all impairments worldwide in terms of loss in disability-adjusted years for elderly people (Johnell and Kanis, 2004). Worldwide, the total number of hip fractures is expected to surpass 6 million by the year 2050 (Kannus et al., 1996). The elderly have weaker bone and are more likely to fall due to poorer balance, medication side effects, and difficulty maneuvering around environmental hazards. Clinicians in many fields are involved in caring for patients with hip fractures and should be familiar with the basic assessment and management of these injuries. Consequences of hip fractures are significant in terms of lives lost and the associated negative impacts on hip fracture patients' functioning and quality of life (Richmond et al., 2003). This review aims to outline hip fracture as a major public health issue that confronts the senior population with PD. Hip fractures' outcomes might be serious for the patient, requiring surgery and hospitalization. For PD patients, these outcomes might be much more severe resulting in high dependence in managing their daily lives, health deterioration and may also cause higher death rates (2 fold) compared to non-PD subjects who experience hip fracture.

Studies that were conducted in different parts of the world, to examine the association between PD and hip fracture occurrence, consistently reported an increased risk of PD patients to sustain hip fractures compared to non-PD patients. These studies reported varying odds ratio ranging from 1.8 to 2.18, and hazard ratio varying between 1.8 and 3.2, Suggesting that PD patients are at least two fold at risk of suffering hip fracture than non-PD patients.

As an issue of great public health concern, different strategies were outlined to help prevent this injury or reduce its incidence. In addition to the strategies that were summarized in previous reviews (Marks et al., 2003; Becker et al., 2011), few prevention studies in PD subject have found that interventions with vitamin D supplements, treatment with vitamin K2 and with medications containing risedronate plus menatetrenone, exposure to sunlight may particularly benefit PD patient in hip fracture prevention, healing and reducing complications after surgery. However, evidence on efficacies of these strategies is still scarce and more studies are still needed.

Conflict of interest

Yassin Mustafa, Khatib Muhammad, Garti Avraham, Saffuri Husamm, and Prof. Dr. Bowirrat Abdalla declare that they have no conflict of interest.

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