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The orthopaedic quandary of hip fractures in patients with Alzheimer's disease require appropriate prevention strategy

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Abstract

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Elderly patients with Alzheimer's disease (AD) are subject to high incidence of hip fracture, especially in elderly female patients. The devastating and progressive consequences of AD are numerous and have unconstructive impacts in the whole body function; Psychological problems such as memory impairments; judgment deficiency; failure of the topographical orientation – characterized by the inability to orient oneself in one's surroundings as a result of dementia which lead to the disability or inability to make use of selective spatial information (e.g., environmental landmarks) or to orient by means of specific cognitive strategies such as the ability to form a mental representation of the environment (visuospatial dysgnosia) – other vital penalties are observed among AD patients such as the loss of activity of daily living, the failure of adequate motor function which cause together with other symptoms to movement instability (falls), orthopedic injuries and instigate a state of mental incapacity and motor unsteadiness among AD patients. Many other metabolic factors such as Hypovitaminosis D and K due to malnutrition or sunlight deprivation, increased bone reabsorption due to immobilization, and low bone mineral density (BMD) can increase the risk of falls and may contribute to an increase risk of hip fractures in patients with neurological diseases in general and especially AD patients. The purpose of this study is to shed light on this quandary, and to evaluate the risk of hip fracture in patients with AD by looking for prevention strategies capable to reduce the risk of hip fractures in patients with such neurological disease.

Keywords: Alzheimer's disease, Hip fracture, Risk factors, Prevention strategies.

INTRODUCTION

Neurodegenerative disorders, primarily, are multifactorial diseases characterized by chronic and progressive loss of neurons in discrete areas of the brain, causing debilitating symptoms and globally decreasing cognitive function such as dementia, loss of memory, decreased overall quality of life and well-being, sensory-motor disability, and eventually, premature death. For most

neurodegenerative diseases, there is little or no treatment; at best, treatments are symptomatic in nature and do not prevent or stop completely the progression of the disease.

Clinically, AD is the most frequent neurodegenerative disorder characterized by progressive memory deficits, impaired cognitive function, and altered and inappropriate

behavior. The crucial AD symptoms include: memory loss that disrupts daily life; challenges in planning or solving problems; difficulty completing familiar tasks at home, work or leisure; confusion with time or place; troubled understanding of visual images and spatial relationships; occurrence of new problems with words in speaking or writing; decreased or poor judgment; withdrawal from work or social activity; and changes in mood and personality (Mattson, 2004).

AD represents the most common form of dementia, which places a considerable and increasing burden on patients, caregivers, and society. Aging represents the most important risk factor and dementia has become one of the major challenges in our societies due to the universal phenomenon of population aging in the world. Brain regions involved in learning and memory processes, including the temporal and frontal lobes as well as the hippocampus, are shrunken in size in AD patients as the result of degeneration of synapses and death of neurons. AD is considered as a protein aggregation disorder, based on two key neuropathological hallmarks, namely the Hyper-phosphorylation of the tau protein resulting in the formation of Neurofibrillary tangles (NFTs), and the increased formation and aggregation of Amyloid-Beta peptide (A β) derived from Amyloid precursor protein (APP) (Haass et al., 2007). Although the exact underlying cause initiating the onset of AD is still unclear, an imbalance in oxidative and nitrosative stress (Sies., 1997; Klandorf and Van Dyke., 2012) intimately linked to mitochondrial dysfunction, characterizes already early stages of AD pathology (Bowirrat et al., 2012).

Neurological diseases, including AD, stroke, and Parkinson's disease have been reported to increase the risk for fractures. Fractures of the major bone in the hip joint, those of the femoral neck and trochanteric regions of the femur, are serious health care problems for the aging populations around the world in general and for AD patients in particular. The aims of this review are to clarify the risk factors for hip fracture in AD patients and highlight the available strategies to prevent and treat hip fracture or reduce its occurrence in AD patients.

World-wide epidemiology of AD and hip fractures

Hip Fracture in general is a continuously increasing global public health problem. In 2013, an estimated 5.2 million American has AD of all ages, of which 5 million are older than 65 years, with anticipated 13.8 million AD patients by 2050 (Hebert et al., 2013). 17% of American women who are elder than 71 have AD and other dementias compared with 11% of men (Plassman et al., 2007), with a yearly 270,000 hip fracture. In Canada, about 500,000 are with AD or related dementia (Larson., 2010; Rockwood and Keren., 2010) with 3,500 annual

hip fractures. In china, 5.69 million AD patients were estimated in 2010 with incidence of 6.25 per 1000 person years (Chan et al., 2013), with incidence rate of 88 per 100,000 in women and 97 in men (Liu et al., 1996). And From a comprehensive global literature review on incidence trend of hip fracture, the highest rate were found to be in Scandinavian countries and the lowest in Africa, noting variable rates in Asia with the highest in Iran and the lowest in mainland China (Cheng et al., 2011).

Classification of hip fractures

Hip fractures occur in the proximal (upper) portion of the femur (Intra-articular or Extra-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).

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 femoral neck fractures occur in men and 63.3 occur in women. Michelson et al., (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 1, 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

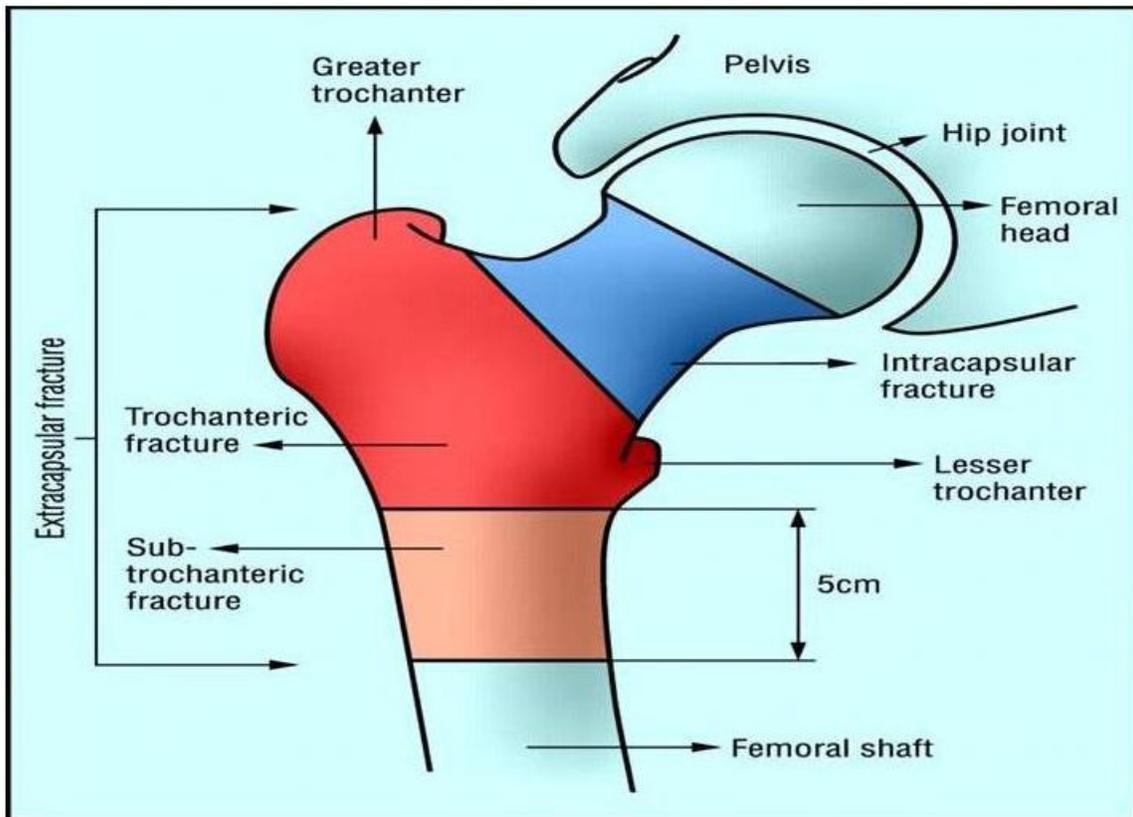


Figure 1. Classification of hip fractures: 1) femoral neck fractures – Intracapsular (blue); 2) Intertrochanteric fracture (red), and 3) Subtrochanteric fractures (brown).

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 1, 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, 2003).

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.

AD and risk factors for Hip Fracture

Risk factors for hip fracture in general, were investigated in several large studies and reviews (Marks, 2003) thus far, and are summarized as follow:

- 1) Falls: Hip fractures are one of the most serious consequences from falling. More than 95% of hip fractures are caused by a fall
- 2) Decreased mineral bone density and bone mass;
- 3) reduced muscular and bone strength (i.e., osteoporosis)
- 4) Reduction of soft tissue or fat covering the hip area. As a result, the hip's ability to withstand an impact with a hard floor surface and protect against a hip fracture is diminished
- 5) Physical inactivity
- 6) impaired perception, vision and cognition
- 7) Drugs induce and chronic diseases

Cause of hip fracture

Most hip fractures are due to ground-level falls while the patient/resident is standing or walking; up to 75% of hip fractures occur under these circumstances. In most cases, the immediate cause of hip fracture is a sideways fall with direct impact on the hip (i.e., the greater trochanter of the proximal femur). Falls to the side, in contrast to falls forward or onto the buttocks, increase the risk of hip fracture.

Association between AD and hip fracture

Many researches were conducted in different parts of the world to study hip fractures in AD patients in order to examine the association between AD and hip fracture. The following associations, summarized below (Table 1), were reported by these studies:

A notional UK study that aimed to examine AD as independent risk factor for hip fractures among elders, found that elders with AD have three folds the risk to suffer hip fracture, both in women and men, compared to non-AD elders (Baker et al., 2011). A more recent large cohort study in UK also, reported an increased hip fracture in AD patients compared to non-AD hospitalized subjects (RR=4.1) (Heun et al., 2013).

In a prospective cohort studies on women with AD, It

was found that women with lower bone mineral density (BMD), low concentrations of serum ionized calcium and serum 25-hydroxyvitamin (25-OHD) (mean 3.0 ng/ml) with compensatory hyperparathyroidism, have increased risk of hip fracture. Also, concentrations of serum pyridinoline cross-linked carboxyterminal telopeptide of type I collagen (ICTP) and bone Gla protein (BGP) were higher in the fracture group than in the non-fracture group. Elderly female AD patients with low BMD and 25-OHD concentrations < 5 ng/ml with secondary hyperparathyroidism have a high risk of hip fracture (Zhao et al., 2012).

A meta-analysis that was conducted by Zhao et al (2012) to explore the association between AD and hip fracture, showed OR of 1.8 (95%, CI 1.54-2.11), in AD patients compared to non-AD patients. This study also found that BMD acts as a strong predictor for hip fracture in AD subjects, compared to healthy ones (Zhao et al., 2012). A Canadian national population health survey explored the similar association and revealed an OR of 2.18, with AD as independent risk factor for hip fracture (Weller and Schatzker., 2004).

In Taiwan, a similar study was conducted on a Taiwanese cohort. AD was found to correlate with increased risk of experiencing hip fracture in older people. Incidence rate ratio for hip fracture in AD subjects was 2.4 fold greater than in non-AD old people. The reported incidence rates for hip fracture on a Taiwanese cohort with and without AD were: (27.8 and 11.7, respectively per 1,000 person years) (Lai et al., 2013).

The association between AD and all types of fracture was also examined in a large U.S. study on a cohort of elders between the years 2001-2004. The study found that the strongest correlation between AD and any fracture type was with hip fracture (HR= 1.8, 95% CI: 1.44-2.26) (Motsko and Jones., 2007). Another study from the USA of a retrospective analysis was performed on a historical cohort to compare fractures' rates in elders with AD, and those without AD between the years 2000 and 2006. The analysis revealed almost a twice the rate hip fractures in AD group compared to non-AD group (29.7% of AD patients suffered hip fracture, compared to 17.7% of elders without AD) (Malone et al., 2008)

Findings from a large representative, nation-wide cohort study in Finland, that was conducted to cover the period 2002-2009 (which included retrospective analysis for the period 2002-2005 and prospective analysis for the years 2006-2009). AD patients were found to have twice the risk to experience hip fracture compared to non-AD patients with (OR=2 95%, CI 1.8-2.2) calculated for the period 2002-2005. Latter the prospective analysis included 5 year follow up to determine the Hazard Ratio (HR) of incidence of hip fracture among the same population between the years 2005-2009, suggests also that AD patients have almost 2 fold the incidence rate of hip fracture. The same study also found that the

Table 1. Worldwide study of AD association with hip fractures

Study by/year	Country	Type of study	study population	Main findings
Nicole L. Baker et al. 2011	UK	Retrospective study, period 1988-2007	Compared hip fracture in AD patients and Non-AD patients	Risk in AD to suffer hip fracture is 3 fold the risk in non-AD
Heun et al. 2013	UK	Retrospective study, period 200-2007	Cohort study among hospitalized subjects	Increased hip fracture in AD subject RR= 4.1 compared to non- AD subjects
Sato et al. 2004	Japan	Prospective cohort study, 2 years follow up 1999-2000	Elderly female AD patients with average age 74	Increased risk for hip fracture within women with low BMD and with low concentration of serum ionized calcium and 25-OHD
Zhao et al. 2012		Meta-analysis Studies on association between AD and hip fracture published until 2012	Patients with AD compared with health controls	OR= 1.8 (95% CI 1.54-2.11) in AD patients compared to non-AD, BMD acts as strong predictor for hip fracture in AD patients
Weller et al. 2004	Canada	National population health survey 1994-1995	Elderly Canadians aged ≥ 65 .	OR= 2.18 for hip fracture within AD patients compared to non-AD patients
Lai et al. 2013	Taiwan	Cohort study 2000-2010	AD patients compared to non-AD patients	Incidence of hip fracture in AD patients is 2.4 fold the incidence in non-AD
Motsko et al. 2007	USA	Cohort/ 2001-2004	correlation between AD and any type of Fracture	Strongest correlations was found with hip fracture (HR= 1.8, 95% CI: 1.44-2.26)
Tolppanen, 2013	Finland	Nationwide study period 2002-2009/ Included retrospective period (2002-2005) and prospective period (2005-2009),	Hip fracture in AD patients compared to non-AD patients	Retrospective (OR=2 95%, CI 1.8-2.2) Prospective twice the incidence rate in AD after 4 years follow up (HR= 2.57, 95% CI 2.32-2.84)

associated risk of hip fracture in AD increased with age (Tolppanen et al., 2013).

Outcomes of hip fractures in ADs

In general hip fractures in elderly populations are followed with a high death rate (20%) among elders (>75 years) within the first year after experiencing a fracture (Davidson et al., 2001) with various groups at increased risk of death especially in patients with septicemia, pneumonia, digestive disorders, cardiac, 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%). It also increased patients' difficulties in basic activities, house hold activities and advanced activities of daily living as well as increased upper body limitations (Wolinsky et al., 1997). However, these consequences are

more severe in AD patients, as such; AD patients have higher mortality after undergoing hip fracture, with 1.5-fold increased mortality rate compared to non-AD patients, as reported by a nation- wide study in the UK (Nicole and Baker., 2011). Dementia was also seen as one of the factors that predicted a lowered functional recovery after hip fracture treatment according to a large systematic review (Marks et al., 2003)

Strategies for prevention of hip fracture in AD patients

In the light of yearly increase in AD numbers, and since hip fracture in general is an important public health concern with serious health outcomes for AD patients in particular and their families, that incurs 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 AD 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 et al., 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).

Acetylcholinesterase inhibitors (AChEIs) were also found to be associated with reduced hip fracture in AD patients with an adjusted OR of 0.42 (95% CI, 0.24-0.72) compared with patients who didn't use AChEIs (Tamimi et al., 2012). An additional prospective study on women with AD came to similar results, concluding that women with AD, who are under medications containing AChEIs may have improved recovery after hip fracture with forming better bone quality and reduced healing complications (Eimar et al., 2013).

Another review of literature on the effectiveness of sunlight exposure, menatetrenone and risedronate in preventing hip fracture in AD patients, found that the best evidence comes from the studies included in the review, that interventions with risedronate plus vitamin D supplementation or risedronate plus menatetrenone can be candidate for intervention aimed to reduce falls within AD patients and possibly hip fracture, however the study highlights the lack of efficacy studies to determine the suitable intervention (Iwamoto et al., 2013).

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 et al., 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 aimed to outline hip fracture as a major public health issue that confronts the senior population with AD. Hip fractures' outcomes might be serious for the patient, requiring surgery and hospitalization. For AD 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 (1.5 fold) compared to non-AD subjects who experience hip fracture.

Studies that were conducted in different parts of the world, to examine the association between AD and hip fracture occurrence, consistently reported an increased risk of AD patients to sustain hip fractures compared to non-AD 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 AD patients are at least two fold at risk of suffering hip fracture than non-AD 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 AD subject have found that interventions with vitamin D supplements, treatment with vitamin K2 and with medications containing AChEIs, exposure to sunlight may particularly benefit AD 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.

Competing interests

The authors declare that they have no competing interests.

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