OSTEOARTHRITIS AND FALLS AMONG OLDER ADULTS

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FACULTY OF MEDICINE
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ABSTRACT

Falls are major public health problem in older adults. Fall-related injuries have been reported as the leading causes of years lived with disability globally. While osteoarthritis, a common degenerative joint disorder, has been considered an established risk factor for falls. Our literature review has found limited evidence and conflicting results to support this assumption. This study was performed and analysed in a two-staged design: 1) a case-control comparison of characteristics related to OA among fallers and non-faller controls, 2) a pre-planned subgroup analysis of individuals with OA within a randomized controlled trial of multifaceted interventions in the secondary prevention of falls in older people. Cases consisted of 229 fallers; individuals aged 65 years and above with a history of two falls or one injurious fall in the past 12 months. 160 control participants were non-fallers, aged 65 and above without no history of falls.

Regardless of the definition used, OA was not associated with falls. However, different degrees of severity of OA symptoms in varying OA definitions showed an interesting relationship with falls. In individuals with radiological OA, mild symptoms appear protective of falls which was probably due to increase of anxiety while those with clinical OA and severe symptoms are at increased risk of falls compared to those with mild symptoms mediated by fear of falling. Thus, OA was not directly associated with falls, however, psychological problems secondary to OA might have a different impact on the risk of falls.

In a separate study of postural control (n=102), impaired postural balance found among fallers was not influenced by presence of OA. The poorer EPE observed in individuals with symptomatic OA appeared to have a protective effect against falls. An evaluation of the features of OA detected on MRI revealed that that presence of sub-chondral cysts and menisceal tears mediates in increase in postural sway among fallers.

Among our older participants with OA, fallers had higher serum TIMP2 level, indicating that falls among older adults with OA was associated with a higher degree of degeneration.

In the subgroup analysis of individuals with OA from the RCT on multifactorial intervention for falls, the modified Otago exercise improved postural control and reduced fear of falling in those with pre-existing impairments in gait and balance.

In essence, this study has contributed to existing knowledge on falls by contradicting previously unsubstantiated assumptions of the association between OA and falls. Instead, a sinusoidal relationship appears to exist between OA and falls, with mild OA being protective of falls and severe OA predisposing to falls. Falls risk appears to be influenced by psychological status, while impaired dynamic postural control associated with increased falls risk is not influenced by the presence of OA. However, the presence of sub-chondral cyst and menisceal tear detected by MRI did mediate the impaired postural control observed in our fallers. In our serological analysis, falls among older adults with OA were associated with a more active degenerative state. The improvement in postural control and falls efficacy observed among our OA fallers, suggest that the modified Otago is potentially benefical, and will serve as a pilot study for a larger randomized-controlled study for secondary falls prevention for individuals with OA.

ABSTRAK

Jatuh merupakan masalah kesihatan umum yang besar dalam kalangan warga emas. Kecederaan yang disebabkan jatuh telah menjadi penyebab yang utama bagi bilangan tahun hidup dalam kekurangan upaya global. Osteoarthritis merupakan degenerasi sendi yang lazim dan telah dianggap sebagai salah satu faktor risiko jatuh. Walaubagaimanapun, masih terdapat kekurangan bukti kajian dan kontradiksi literatur terhadap anggapan tersebut.

Kajian ini dijalankan dan dianalisis dalam 2 bentuk: (1) kes-kawalan dan (2)sub-analisis daripada dapatan kajian klinikal rambang (RCT). Kes adalah 229 "fallers" yang merupakan individu berumur 65 tahun dan ke atas dan mempunyai 2 peristiwa jatuh atau satu peristiwa jatuh yang mencederakan dalam masa 12 bulan yang lepas. Manakala 160 kawalan merupakan "non-fallers"; individu yang berumur 65 tahun ke atas dan tidak pernah jatuh. Hasil kajian (n=389) daripada MyFAIT menunjukkan bahawa OA tidak berkaitan dengan jatuh tidak kira definisi OA yang digunakan.

Walaubagaimanapun, perbezaan dalam keterukan symptom OA dalam definisi yang berbeza menunjukkan perhubungan yang menarik dan tersendiri dengan jatuh. Individu yang mempunyai radiological OA, simptom yang ringan menunjukkan risiko jatuh yang sangat rendah berbanding yang tidak mempunyai sebarang simptom yang mungkin disebabkan oleh perasaan risau. Manakala individu yang mempunyai klinikal OA dan mempunyai simptom yang sangat teruk mempunyai risiko jatuh yang tinggi di sebabkan oleh perasaan yang takut dengan jatuh.

Justeru, masalah psikologi yang disebabkan oleh OA mungkin mempunyai impak yang berbeza terhadap risiko jatuh. Dalam kajian yang berasingan tentang kawalan postur (n=102), masalah keseimbangan postur dikalangan "fallers" didapati tidak dipengaruhi oleh kehadiran OA. Kelemahan dalam EPE dikalangan individu yang mempunyai OA

yang bersimptom memungkinkan mereka untuk selamat dari jatuh. Kajian tentang kesan ciri-ciri OA yang dapat dilihat melalui MRI terhadap pertalian diantara jatuh dan tinggi kegoyangan postur pula menunjukkan bahawa kehadiran sub-chondral cyst dan menisceal tear memainkan peranan mereka sebagai pengantara. Kajian tentang penanda biologi OA yang berpotensi dikalangan "fallers" dan "non-fallers" yang didiagnoskan OA menunjukkan bahawa, terdapat kaitan diantara jatuh dan ketinggian paras TIMP2 dalam serum, menandakan bahawa jatuh merupakan keadaan yang disebabkan oleh kesan gabungan proses degenerasi yang tinggi. Manakala hasil analisis sub-grup menunjukkan bahawa, senaman OTAGO memberi manfaat kepada "fallers" dengan membaikpulih kawalan postur dan mengurangkan rasa takut jatuh.

Kesimpulannya, kajian ini telah memyumbang ke dalam ilmu pengetahuan bahawa OA yang ringan mengurangi kemungkinan jatuh manakala OA yang teruk meninggikan kemungkinan jatuh. Walaubagaimanapun, kelemahan psikologi disebabkan OA mungkin mempunyai impak yang tersendiri ke atas risiko jatuh. Tambahan pula, kelemahan kawalan postur dalam keseimbangan dinamik juga tidak dipengaruhi oleh kehadiran OA. Ketidakstabilan postur di kalangan warga emas yang mempunyai OA didapati disebabkan oleh kehadiran sub-chondral cyst dan menisceal tear yang hanya dapat dilihat melalui MRI. Analisa makmal ke atas serum menunjukkan bahawa jatuh adalah disebabkan gabungan ketinggian tahap keterukan OA, Kesan positif yang didapati daripada sub-grup dalam intervensi OTAGO mencadangkan bahawa dalam usaha mencegah kejatuhan sekunder dikalangan warga emas yang mempunyai OA kajian ini boleh menjadi kajian rintis untuk kajian yang lebih besar.

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LIST OF SYMBOLS AND ABBREVIATIONS

ACR	:	American College Rheumatology
AP	:	Antero-posterior
ARHP	:	Association of Rheumatology Health Professionals
BMI	:	Body mass index
BOS	:	Base of Support
CI	:	Confidence Interval
CINAHL	:	Cumulative Index to Nursing and Allied Health Literature
cm	:	Centimeter
COG	:	Centre of Gravity
DASS21	:	21-item Depression, Anxiety and Stress Scale
DCL	:	Directional Control
deg	:	degree
DLYs	:	Disability life years
DMOAD	:	Disease modifying therapy development in OA
ED	:	Emergency department
ELISA	:	Enzyme-linked immunosorbent analysis
EPE	:	End Point Excursion
EPOSA	:	European Project on Osteoarthritis
FDA	:	Food and Drug Administration
FES-I	:	Falls efficacy fear of falling test international
FoF	:	Fear of falling
FR	:	Functional reach
HR	:	Hazard Ratio
HRQoL	:	Health related Quality of life

I^2	:	I-square for heterogeneity test
ICD-10	:	International Statistical Classification of Diseases and Related Health Problems 10th Revision
IQR	:	Interquartile range
IL1	:	Interleukin 1
IL6	:	Interleukin 6
JSN	:	Joint space narrowing
kg	:	Kilogram
KL-	:	Kellgren-Lawrence
KOOS	:	Knee Injury and Osteoarthritis outcome score
LFC	:	Lateral femoral condyle
LOS	:	Limit of stability
mCTSIB	:	Modified Clinical Test of Sensory Interaction on Balance test
MetS	:	Metabolic Syndrome
MFC	:	Medial Femoral condyle
mL	:	Mililiter
mm	:	Milimetre
MMP	:	Matrix metalloproteinases
MMSE	:	Mini Mental State Examination
MRI	:	Magnetic Resonance Imaging
MyFAIT	:	Malaysian Falls Assessment and Intervention Trial
MXL	:	Maximal Excursion
NA	:	Not available
ND	:	Not described
NPY	:	Neuropeptide-Y
NS	:	Not significant

NSAIDS	:	Non-steroidal anti-inflammatory drugs
OA	:	Osteoarthritis
OARSI	:	Osteoarthritis Research Society International
OEP	:	Otago Exercise Programme
OR	:	Odds Ratio
PEDro	:	Physiotherapy Evidence Based
PICOS	:	Participants, interventions, comparisons, outcomes, and study design
PPA	:	Physiological Profile Assessment
QoL	:	Quality of life
RCT	:	Randomized Controlled trial
ref	:	Referrence
SD	:	Standard deviation
SMD	:	Standardized mean difference
SPSS	:	Statistical Package for the Social Science
STS	:	Sit to stand
TIMP	:	Tissue Inhibitor of Metalloproteinases
TNF-α	:	Tumor Necrosis Factor- alpha
TUG	:	Timed Up and Go
UM	:	University of Malaya
UMMC	:	University of Malaya Medical Centre
USA	:	United State of America
VAS	:	Visual Analog scale
WOMAC	:	Western Ontario and McMasters Universities Arthritis Index
XR	:	X-ray
χ^2 tests	:	Chi-squared test
6MWT	:	Six-Minute Walk Test

LIST OF APPENDICES

CHAPTER 1: GENERAL INTRODUCTION

1.1 General

Falls in the older adult is becoming an increasingly serious problem. Each year, one in every three adults age 65 and older, and almost 50% of those over 80, experience at least one fall (Burt, 1998). It is not just the higher incidence of falling in older adults that is a concern, but the combination of it's high incidence and the higher susceptibility of older adults to injury. It has been reported to be the major contributor for functional decline and healthcare utilization worldwide (Alamgir, Muazzam & Nasrullah, 2012; Murray et al., 2015; Rubenstein, 2006). In Malaysia, a longitudinal study conducted in Kuala Lumpur have reported that functional ability is significantly reduced at one year after an initial presentation to the ED with a fall and mortality is increased at one and three years in fallers who experience indoor falls (M. P. Tan et al., 2016).

Osteoarthritis (OA) is most prevalent type of arthritis and has significant impact on healthrelated quality of life (HRQoL) (Murray et al., 2015). Severe pain, the hall mark of the OA symptoms ia also a major predisposing factor for increased falls risk (Leveille et al., 2009). Pain from OA can lead to decreased functional ability, reduced social and recreational activities and increased fear of falls can lead to decreased quality of life and progression to frailty.

In spite of advancements in healthcare, effective treatment strategies are now available for primary and secondary prevention for falls. However, few such studies have addressed falls associated with OA. While OA have been traditionally considered an established a risk factor for falls, published studies so far have presented mixed results (Ng & Tan, 2013). Several barriers have prevented adequate evaluation of falls in OA: the lack of

homogeneity in OA diagnostic tools used and the heterogeneous nature of OA itself. Therefore, a holistic evaluation of OA and falls using analogous OA definitions to clinical practice is important.

1.2 Research question

The main research question of this study is, "How is OA associated with falls among older adults in terms of biochemical, physical, clinical, imaging and psychological aspects?" The specific research questions are:

1. Does the presence of OA increase the risk of falls among older adults?
2. What are the underlying mechanisms involved in the relationship between OA and falls?
3. How does the presence of OA symptoms affect dynamic postural control among older fallers?
4. How does Magnetic Resonance Imaging (MRI) detected OA features relate to high postural sway among older fallers with OA?
5. How do OA biomarker explain the underlying mechanism between OA and falls among older people with knee OA?
6. What is the effect of a modified Otago Exercise Programme (OEP) on postural control, fear of falling, and falls in older individuals with knee OA?

1.3 Objectives of the study

The overall objectives of this study is to evaluate the biochemical, physical, clinical, imaging and psychological aspects of the relationship between OA and falls. The specific objectives are:

1. To determine the association between OA and falls.
2. To explore the possible underlying factors associated with the OA-falls relationship in terms of gait and balance and other psychosocial factors.
3. To investigate the influence of OA in the association between poor dynamic postural control balance and falls in older people.
4. To study the relationship between MRI knee OA features and postural sway among older fallers with OA.
5. To explore the association between OA biomarkers and falls
6. To evaluate the effect of the Otago Exercise Programme (OEP) on postural balance, fear of falling, and falls in older fallers with knee OA and gait and balance problems.

1.4 Organization of thesis

The thesis is divided into 7 chapters, each of which is then subdivided into sections and subsections. The chapters are arranged in the following sequences:

Chapter 1 presents the background of the work undertaken and the objectives of the study.

Chapter 2 provides an overview of falls and OA among older people. The previous accepted wisdom on the OA-falls relationship and the mixed results from previous studies

are discussed. The existing evidence on interventions for prevention of falls among OA subjects is reviewed systematically.

In Chapter 3 the association of OA and falls is explored. The underlying mechanisms are studied, in terms of postural control, psychological factors and medications used.

Chapter 4 characterizes the postural control parameters among fallers and non-fallers and determines the influence of the presence of OA in the association found between impaired postural control and falls. The association of specific knee OA features from the MRI results and postural control parameters were determined.

In Chapter 5 describes the results of enzyme-linked immunosorbent (ELISA) assays used to test selected OA biomarkers for the detection of OA characteristics (inflammation, catabolism and symptoms) in subjects' sera.

Chapter 6 reports the postural control outcomes of the modified Otago Exercise Programme (OEP) intervention as well as the secondary outcomes of falls occurrence and fear of falling among fallers with OA. As part of an RCT this study provides unbiased results on falls intervention among OA subjects.

Chapter 7 concludes this thesis report and proves recommendations for the future studies.

CHAPTER 2: LITERATURE REVIEW

2.1 Falls in Older Adults

Falls in older people are major public health concerns. One in three adults aged 65 years and older experience at least one fall annually (Tromp et al., 2001). Fall-related costs have been estimated at 0.85% to 1.5% of total healthcare expenditure (Heinrich et al., 2010). Injuries due to falls are also the leading causes of years lost from disability (YLDs) (Murray et al., 2015) and can result in unintentional injuries with major sequelae such brain hematoma, hip fractures and mortality (M. P. Tan et al., 2016); (Alamgir, Muazzam & Nasrullah, 2012).

2.1.1 Defining fall and Near-Falls

A review of literature published from 1987 to 2005 identified 30 different definitions for falls (Zecevic et al., 2006). In another systematic review in 2006, they found that there was still no mutual consensus for the definition of falls. The most common definition used was the definition by the Kellogg group (Hauer et al., 2006) where a fall is defined as "an event which results in a person inadvertently coming to rest on the ground or other lower level and other than as a consequence of the following: sustaining a violent blow, loss of consciousness, sudden onset of paralysis as in a stroke, epileptic seizure". The available definitions are however are not yet fully comprehensive as falls can also occur due to blood pressure variability which result dizziness, syncope and cardiovascular abnormalities, these criteria should also be included as falls event. For the purpose of this study, we will be defining falls as "an event where the individual comes to rest on the ground or other lower level", without exclusion of external forces, haemodynamic disturbance or fits (World Health Organization, 2008).

2.1.2 Falls consequences

The consequences of falls vary from very mild soft tissue injury to severe consequences such as pain, hip fractures, hematoma, traumatic brain injuries and premature death for older adult (Alamgir, Muazzam & Nasrullah, 2012). Besides physical trauma, falls are also associated with future falls, and many deleterious psychological defects such fear-of falling, depression, and anxiety. Reduced activity and stiffness will eventually lower their quality of life due to social isolation. From a recent study in Malaysia, study showed that the rate of mortality is increased at one and three years in fallers who experienced indoor falls and attended the Emergency Department (M. P. Tan et al., 2016).

2.1.3 Falls risk factor

Falls are multifactorial events, with variable risk factors depending on the population, location, and environment studied. Falls risk factors have been reviewed within a published systematic review in 2010 (Tinetti & Kumar, 2010). This section provides an update on that work.

Table 2.1 summaries the risk factors for falls from selected prospective cohort studies which has established the standard for future risk factor studies. Systematic reviews and clinical reviews were also included. From the literature, the major risk factors for falls include previous falls, impaired gait and balance, muscles weakness, cognitive impairment, depression, diabetes, visual deficits, dizziness or ortho-stasis, disabilities and medication intake. There are other important factors that have gained attention lately, namely renal impairment, incontinent and pain. Arthritis has been described in the above systematic review as a significant risk factor for falls, but the issues and actual relationship are addressed in the next chapter, and therefore not included here.

The actual relationship between falls and risk factors are, however, often complex with mediators often accounting for existing associations. As example, depression is the mediator between joint pain and falls (Eggermont et al., 2012) and in another study, anxiety mediated the associations between dizziness and falls (Menant et al., 2013). In addition, medications are considered complex risk factors for falling. Medications prescribed for chronic diseases such antipsychotic, NSAIDs, and other to treat hypertension or heart failure may adversely affect the patients by increasing their unsteadiness, reduced alertness and dizziness. Falls management will be trickier as the culprit may be a combination of two or three risk factors. The presence of mediating effects from other risk factors may need a modified or 'snow-ball' method of falls intervention.

Therefore, it is essential to consider all existing risk factors for falls in individuals receiving screening for falls. A comprehensive model of risk of falls in individuals with a specific disease such people with diabetes, hypertension or osteoarthritis is needed in order to determine other factors' influence on falls which will suggest more effective therapeutic falls management.

Table 2.1: Published falls risk factors in community dwelling older people

Risk Factor	Source (SR=systematic review, R=review, C= cohort study, MA= meta-analysis)	Approximate measure of effect
Balance and postural control deficit	(Lord, Clark & Webster, 1991)C, (Piirtola & Era, 2006) R, (Pluijm et al., 2006)C, (Delbaere et al., 2006) C, (Stalenhoef et al., 2002) C, (Al-Aama, 2011) R, (Tinetti & Kumar, 2010) SR	Odds ratio ~ 4
Reduced mobility	(Morris et al., 2007) C, (Tiedemann et al., 2008) C	Odds ratio 3.7
Home hazards	(Lord, Menz & Sherrington, 2006) R, (Fletcher & Hirdes, 2002) C, (Pluijm et al., 2006)C, (van Bemmel et al., 2005) C	Relative risk 3.6
Muscle weakness	(Otaka, 2008) SR, (Moreland et al., 2004) SR, (Pluijm et al., 2006)C, (Stalenhoef et al., 2002) C, (Al-Aama, 2011) R, (Tinetti & Kumar, 2010) SR, (de Zwart et al., 2015) C	Odds ratio~3
History of falls	(Capon et al., 2007)C, (Morris et al., 2007) C, (Pluijm et al., 2006)C, (Papaioannou et al., 2004) C, (Stalenhoef et al., 2002)C, (Al-Aama, 2011)R, (Tinetti & Kumar, 2010) SR	Odds ratio ~ 3
Parkinson's disease	(Fink et al., 2005) C, (Fletcher & Hirdes, 2002) C	Odds ratio 3
Fear of falling	(Scheffer et al., 2008) C, (Pluijm et al., 2006) C, (Delbaere et al., 2006) C, (Delbaere et al., 2004) C, (S. L. Murphy et al., 2008) C	Odds ratio 3

Table 2.1: Continued

Risk Factor	Source (SR=systematic review, R=review, C= cohort study, MA= meta-analysis)	Approximate measure of effect
Use of an assistive device	(Nandy et al., 2004) R	Relative risk 2.6
Frailty	(Ensrud et al., 2008) C (Two of: weight loss, the subject's inability to rise from a chair 5 times without using her arms, and reduced energy level)	Odds ratio 2.4 (recurrent falls, frail vs. non-frail)
Cognitive impairment	(Assantachai et al., 2003) C, (Shaw, 2002) R, (Fletcher & Hirdes, 2002) C, (Papaioannou et al., 2004) C, (van Doorn et al., 2003) C, (van Schoor et al., 2002) SR (Tinetti & Kumar, 2010) SR, (Delbaere et al., 2012) C	Odds ratio ~2-4
Dizziness	(Menant et al., 2013) C, (Tinetti & Kumar, 2010) SR	Odds ratio 1.6-2.6
Impaired ADL	(Capon et al., 2007) C, (Reyes-Ortiz et al., 2004) C, (Assantachai et al., 2003) C, (Perracini & Ramos, 2002) C, (Pluijm et al., 2006) C, (Shumway-Cook et al., 2005)C, (Tinetti & Kumar, 2010) SR	Odds ratio 2
Depression	(Reyes-Ortiz et al., 2004) C, (Stalenhoef et al., 2002) C, (Tinetti & Kumar, 2010) SR (Eggermont et al., 2012) C	Odds ratio 2
Vitamin D deficiency	(Faulkner et al., 2006) C, (Bischoff-Ferrari et al., 2005) MA, (Latham, Anderson & Reid, 2003) SR, (Snijder et al., 2006) C, (Barr et al., 2010) C	Odds ratio 1.8

Table 2.1: Continued

Risk Factor	Source (SR=systematic review, R=review, C= cohort study, MA= meta-analysis)	Approximate measure of effect
Testosterone deficiency	(Orwoll et al., 2006) C, (Szulc et al., 2003) C	Relative risk 1.8
Anaemia	(Duh et al., 2008) C, (Penninx et al., 2005) C	Relative risk 1.7
Diabetes	(Reyes-Ortiz et al., 2004)C, (Schwartz et al., 2008)C (Tinetti & Kumar, 2010) SR	Odds ratio 2.8
Urinary incontinence	(Vaughan et al., 2010) C, (Abreu et al., 2014) C	Odds ratio 1.28-5.46
Medication	(Allain et al., 2005) R, (Hartikainen, Lonnroos & Louhivuori, 2007) SR, (Landi et al., 2005)C (Payne et al., 2013) C, (Carbone et al., 2010) C, (Huang et al., 2010) C, (Tinetti & Kumar, 2010) SR	Odds ratio 1.68 (mainly benzodiazepines antidepressants, antipsychotics) Odds ratio 1.62 (postmenopausal) Odds ratio 1.22 (diabetic)
Neuropathy	(Schwartz et al., 2008) C	Odds ratio 1.5 (diabetics)
Female gender	(Reyes-Ortiz et al., 2004) C, (Assantachai et al., 2003)C, (Fletcher & Hirdes, 2002) C (Tinetti & Kumar, 2010) SR	Odds ratio 2.1-3.9
Visual deficit	(Schwartz et al., 2008) C, (Coleman, 2007) C, (Assantachai et al., 2003) C, (Perracini & Ramos, 2002)C, (Lord, 2006) R, (Szabo et al., 2008) C, (McCarty, Fu & Taylor, 2002)C (Tinetti & Kumar, 2010) SR, (Dhital, Pey & Stanford, 2010) R	Odds ratio 1.4 (diabetics) 1.5-3.0 other populations

Table 2.1: Continued

Risk Factor	Source (SR=systematic review, R=review, C= cohort study, MA= meta-analysis)	Approximate measure of effect
Metabolic syndrome	(Liao et al., 2012) C	Odds ratio 2.56
Sleep disturbance	(Helbig et al., 2013) C	Odds ratio 1.2-1.6
Body weight	(Furuya et al., 2009) C (Tinetti & Kumar, 2010) SR	Odds ratio 1.05 (rheumatoid Arthritis)
Pain	(Tinetti & Kumar, 2010) SR, (Muraki, 2014) C	Odds ratio 1.6 (Knee Pain)

2.2 Osteoarthritis

2.2.1 Definitions of OA

According to an article by the Orthopedics Research Society (ORS), the consensus definition from American Academy Orthopedics Surgeons of OA is *a chronic joint disease that is a result of mechanical and biological events. Mechanical events uncouple the degradation and synthesis of cartilage and subchondral bone. Ultimately, morphologic, biochemical, molecular, and biomechanical changes occur with variable degrees of inflammation without systemic effects*.

Osteoarthritis as defined by Osteoarthritis Research Society International (OARSI) is *a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness* (Kraus et al., 2015).

Both definitions are comprehensive, however a more simple definition and high understood reliably by lay people is recommend for future research. None of the consensus provide the standardized OA definition for clinical setting. This could be supplemented by a further sub-classification of OA by symptoms severity and structural changes. A standardized definition according to diagnostic tools may also help in improving the definition.

2.2.2 Etiology and incidence of OA

The etiology and incidence of OA is remains poorly understood. However, it is believed that it has a multifactorial etiology. Osteoarthritis develop slowly and progresses over a long period of time. As people get older they will be more likely to get OA as their muscles and joints that may have become worn out. The risk factor of knee OA in the older population has been reported in a systematic review in which the main factors found included obesity (pooled OR 2.63, 95% CI 2.28-3.05), previous knee trauma (pooled OR 3.86, 95% CI 2.61-5.70), hand OA (pooled OR 1.49, 95% CI 1.05-2.10) and female gender (pooled OR 1.84, 95% CI 1.32-2.55) (Blagojevic et al., 2010). Age, gender and family history of OA were, however, non-modifiable risk factors and therefore their value in research is rather limited. Joint injury and being obese are, on the other hand, preventable. Being obese puts excess strain on weight bearing joints i.e. knees and hips, as a result, obese individuals have worse OA compared to the normal person.

During the past 7 years, metabolic Syndrome (MetS) which is co-occurrence of cardiovascular risk factors that include insulin resistance, obesity, atherogenic dyslipidaemia and hypertension have been found to be linked to OA. A previous study has reported that central obesity predicts higher total pain index and nearly doubles the risk of chronic pain among OA patients (Iannone & Lapadula, 2010). Activated white adipose tissue increases the synthesis of pro-inflammatory cytokines, such as interleukin (IL-6), (IL-1) and tumour necrosis factor (TNF-α), and of adipokines capable of promoting synovial inflammation.

The inflammation theory expands beyond MetS. Berenbaum proposed three immunological classifications for OA (secretory inflammatory phenotype), crystal OA (innate immunity), and posttraumatic OA (local inflammation) (Berenbaum, 2013). He

suggested that the mechanics and inflammation theory is actually a continuous process, any abnormal mechanical stress applied on a joint can be converted into activated intracellular signals in joint cells by mechanoreceptors which may eventually lead to over expression of inflammatory soluble mediators which result inflammation and pain.

2.2.3 Determination of OA

The diagnosis of OA can usually be made by self-reporting symptoms of OA such as pain with stiffness, joint crepitus, knobby swelling at the joint and physical function limitation of the joint. Tools like Western Ontario and McMasters Universities Arthritis Index (WOMAC) (Bellamy, 2012), Knee Injury and Osteoarthritis outcome score (KOOS) (Roos & Toksvig-Larsen, 2003), and American College Rheumatology (ACR) criteria for OA are tools which have been validated to assess the symptoms in a population aged over 50 years. Diagnosis is confirmed through physical examination and to a certain extent X-rays or imaging tests (MRI) will be useful to determine the severity of OA. Serologically, various biochemical markers has been tested to detect OA ranging from sera, synovial fluid to urine biomarkers, however, no biomarker is considered a surrogate measure for clinical outcomes in OA (McAlindon et al., 2015).

2.2.3.1 Imaging

Imaging evidence are considered crucial in obtaining the diagnosis and to quantify therapeutic effect in clinical trials involved with OA. Available imaging modalities ranged from a simple radiographic image, ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) (Y. Wang, Teichtahl & Cicuttini, 2016).

Traditionally in the clinical setting, radiographic evidence is used for establishing OA severity during screening to determine the patient eligibility, and for evaluating disease

progression under certain treatments (Eckstein et al., 2014). However, poor correlation between radiographic and symptoms have made radiographic evidence a suboptimal imaging biomarker (Bedson & Croft, 2008; Finan et al., 2013). Besides, limited information can be obtained by radiography which only shows the presence of osteophytes and joint space narrowing (JSN) limiting the study's ability in capturing the heterogeneous features of OA (Braun & Gold, 2012).

The MRI scanner is now increasingly used for the assessment of joint structures particularly in knee OA (Y. Wang, Teichtahl & Cicuttini, 2016). The ability of MRI to assess bone and cartilage in detail is helping to understand the nature of OA as a 'whole organ' disease. A previous study from Netherlands has suggested that the MRI definition for knee OA is more sensitive compared to radiography in detecting structural knee OA (Schiphof et al., 2014).

Other studies had however found that neither MRI nor radiography is able to discriminate between painful and painless joints (Javaid et al., 2012). It is rather controversial to conclude that MRI as just another sub-optimal imaging biomarker after radiography as we are all aware that the nature of 'pain' can be very subjective and might be influenced by other extrinsic factors such weather (Timmermans et al., 2015). Other imaging modalities are not as commonly as radiography and MRI. They are, however, still useful in diagnosing OA at particular sites including hand OA, ultrasound showed better performance in predicting hand OA progression (Mathiessen et al., 2015). Plain radiography, however, remains the 'gold standard' of OA imaging, since it is inexpensive, fast, and easily available (Bijlsma, Berenbaum & Lafeber, 2011).

2.2.3.2 Clinical diagnosis

Osteoarthritis symptoms such pain is the main reason for seeking medical treatment from their family doctor. Osteoarthritic patient also experiences joint stiffness particularly on the morning. Pain and stiffness are considered the two symptoms that are commonly reported by OA patients and are characterized in American College of Rheumatology (ACR) clinical criteria for osteoarthritis of the knee and hip (R. Altman et al., 1986). The performance of the ACR criteria as a diagnostic tool has however raised some doubt previously. A study on primary care setting showed that ACR clinical criteria seems to reflect later signs of advanced disease while inevitably missing out the early stages of disease, the study therefore suggested that new approaches are needed to identify early and mild OA (Peat et al., 2006).

Early OA however still remains poorly understood in terms of depth, morphologic appearance and physiological features. Findings from a recent study showed that in individuals without radiological OA, the development of incident of OA is associated with a prodromal pain, stiffness, and difficulties in performing physical activities after 4-year study period (Case et al., 2015). The first appearance of joint pain can be detected during weight bearing activities which involves bending such as climbing stairs (Hensor et al., 2015). Current findings and understanding on early OA may shape the new approach in clinically diagnosing OA. More specific characteristics such as which activity causes pain are recommend for the new tool.

2.2.3.3 Molecular methods

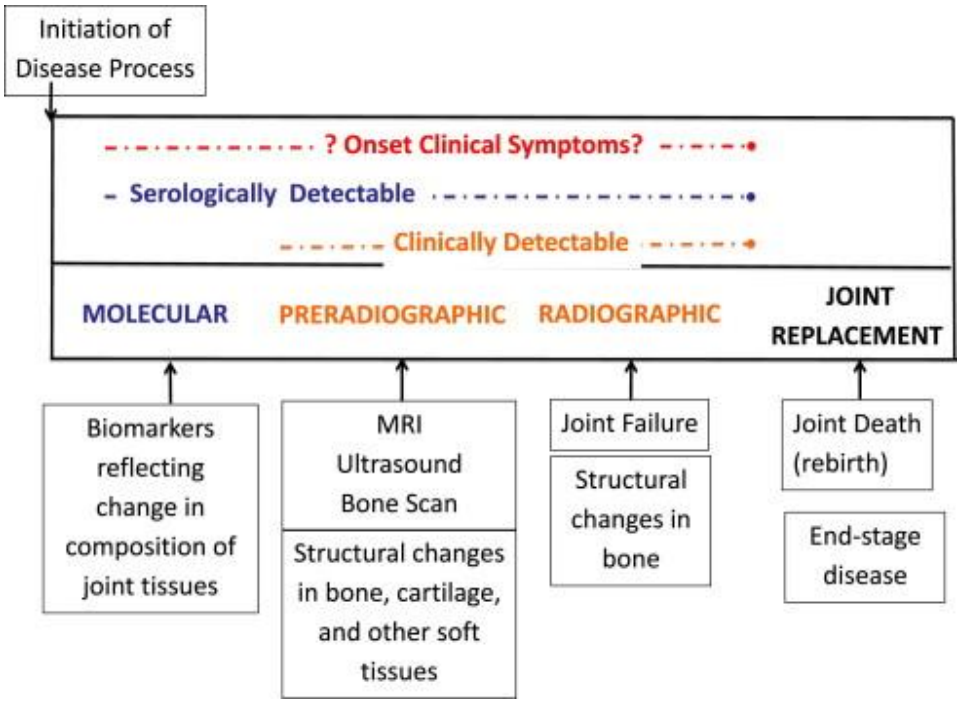


Figure 2.1: The natural history of OA and the purported roles of biomarkers during the disease process. Original attributed to V Kraus (originally presented at Osteoarthritis Research Society International (OARSI) Congress 2009).

Many hurdles and challenges in OA research currently limit the development of OA treatment. The absence of adequately sensitive biomarkers to quantify the efficacy of therapy reduces the probability of obtaining the elusive cure for OA . The draft regulatory (FDA) guidance and current gold standard for measuring clinical efficacy in disease modifying therapy development in OA (DMOAD) is radiographic joint space narrowing (JSN) ("Food and Drug Administration: Guidance for Industry. Clinical Development Programs for Drugs, Devices, and Biological Products Intended for the Treatment of Osteoarthritis (OA).", 1999). Radiography, however, has slow responsiveness to change, while alternatively, molecular biomarkers may provide a rapid indication of response to

a particular intervention and streamline the discovery of new therapeutic agents (Lotz et al., 2013).

Bauer and colleagues had proposed the BIPED classification (Table 2.2) in order to provide specific biomarker definitions with the goal of improving the ability to develop and analyze OA biomarkers (Bauer et al., 2006). In a latest systematic review, incidence and progression of OA might be associated with three different types of biomarkers: 1) biomarkers of matrix destruction e.g. uCTX-II, 2) biomarkers of systemic and local (synovial) inflammation eg. interleukin (IL 1,6,17) , and 3) biomarkers of matrix production and differentiation e.g. COMP (Hosnijeh et al., 2015). To date, none of the available biochemical markers of OA has been recognized as the most suitable biomarker for OA disease activity or severity. Majority of the biomarkers have been classified as investigative (I) and Burden of disease (B) or Burden of disease only (B) biomarkers according to the BIPED criteria (Bay-Jensen et al., 2016).

Table 2.2: Summary of "BIPEDS" biomarker classification for OA and comparison with FDA[1]

	Terms	Category
B	Burden of Disease	Biomarker associated with extent of severity of OA
I	Investigative	Biomarker not yet meeting criteria for another category
P	Prognostic	Predicts incidence or progression of disease (FDA prognostic biomarker) or likelihood of response to a treatment intervention (FDA predictive biomarker)
E	Efficacy of Intervention	Indicative of treatment efficacy (FDA pharmacodynamics or activity biomarker) and for which the magnitude of the change is considered pertinent to the response. Surrogates form a subset category of biomarkers intended to substitute for a clinical efficacy endpoint
D	Diagnostic	Differentiates diseased from non-diseased
S	Safety	Identify adverse effects and provide means of safety surveillance

NOTE: [1] V.B Kraus *et al*, 2015

2.2.4 Classifications of OA severity

Kellgren and Lawrence system are traditionally used to classify OA severity according to radiography (Kellgren & Lawrence, 1957). It measures the presence of typical features of osteoarthritis observed on a joint radiograph: Joint space narrowing, osteophytes or sclerosis. The grading system considers the following characteristics:

Table 2.3: Kellgren and Lawrence grading system[1]

Grade	Characteristic
Grade 1	Unlikely narrowing of the joint space, possible osteophytes
Grade 2	Identified small osteophytes, possible narrowing of the joint
Grade 3	Multiple, moderately sized osteophytes, definite joint space narrowing, some sclerotic areas, possible deformation of bone ends
Grade 4	Multiple large osteophytes, severe joint space narrowing, marked sclerosis and definite bony end deformity.

NOTE: [1] Kellgren & Lawrence, 1957

The KL-grading scale has been criticized on their emphasis on the osteophyte and the combination of osteophytes with joint space narrowing; it is because they could develop independently. In addition the overall grades in severity from normal to severe (0-3) are not equidistant from each other (Spector & Cooper, 1993), which have made the system relatively insensitive to change. This limits KL-grading scale to screen and for grading subjects with gross clinical severity. The Atlas was first introduced in 1995 as the alternative to KL-grading scale. In 2007, an updated version of Atlas has been published (R. D. Altman & Gold, 2007). This tool however is only used in clinical trials.

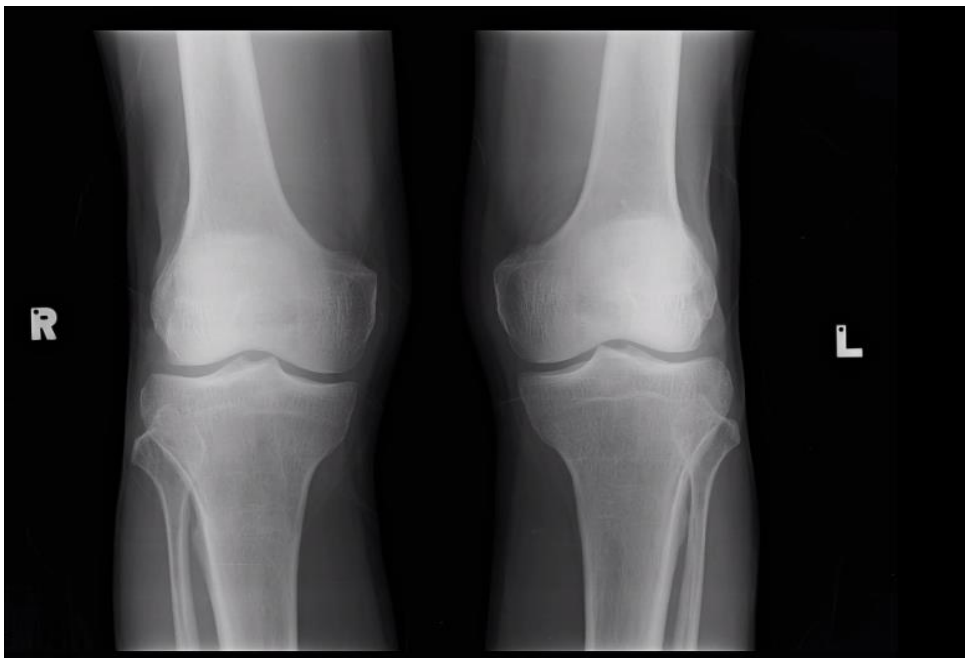


Figure 2.2: X-ray image for Normal knee

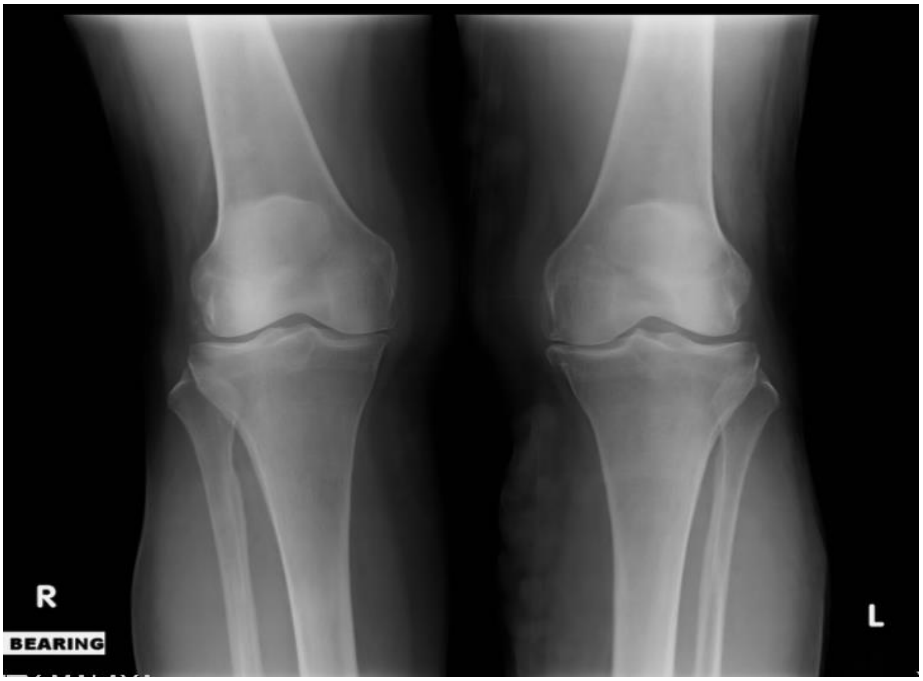


Figure 2.3: X-ray image for Knee OA KL-grade 1

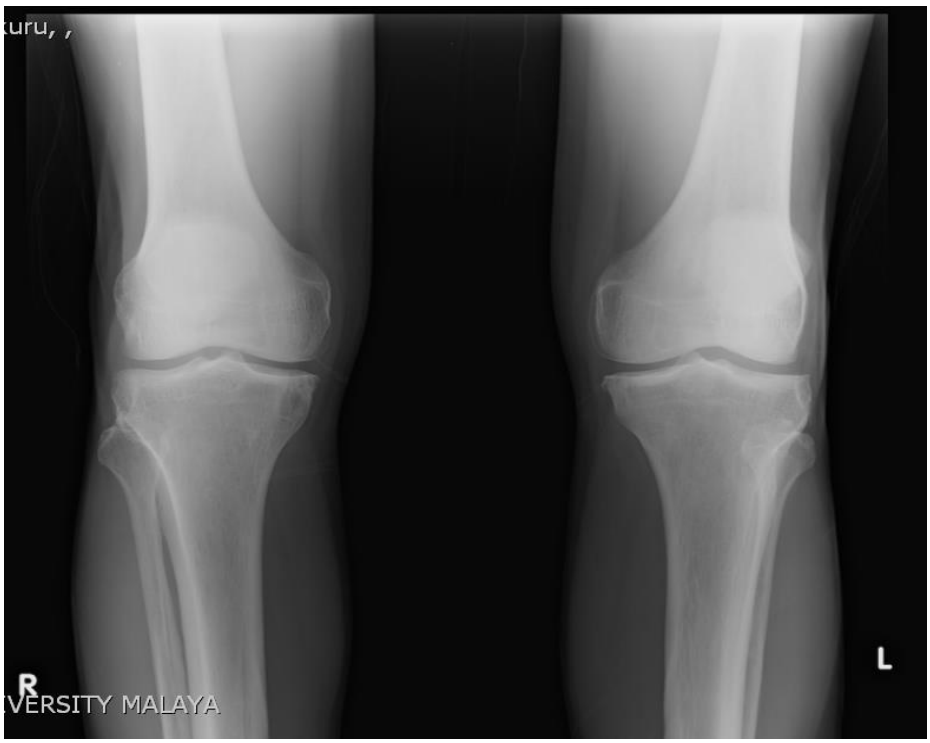


Figure 2.4: X-ray image for Knee OA KL-grade 2

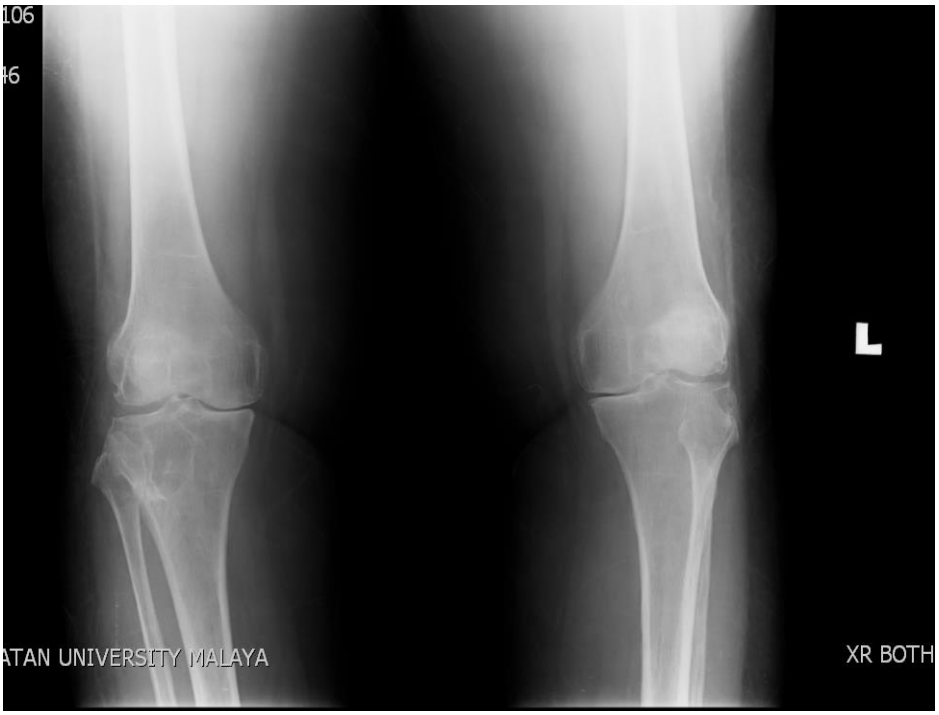


Figure 2.5: X-ray image for Knee OA KL-grade 3

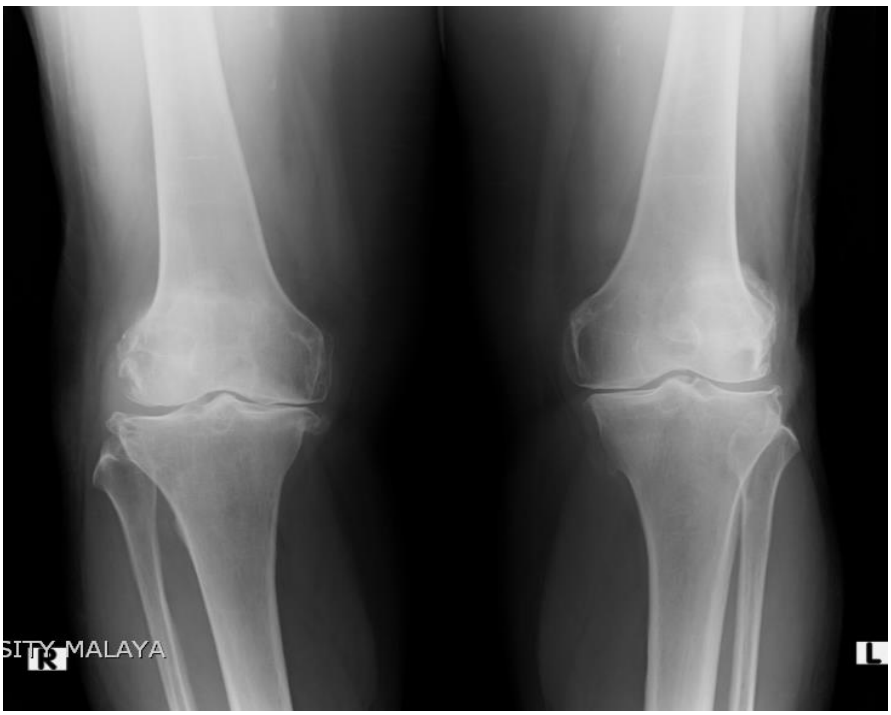


Figure 2.6: X-ray image for Knee OA KL-grade 4

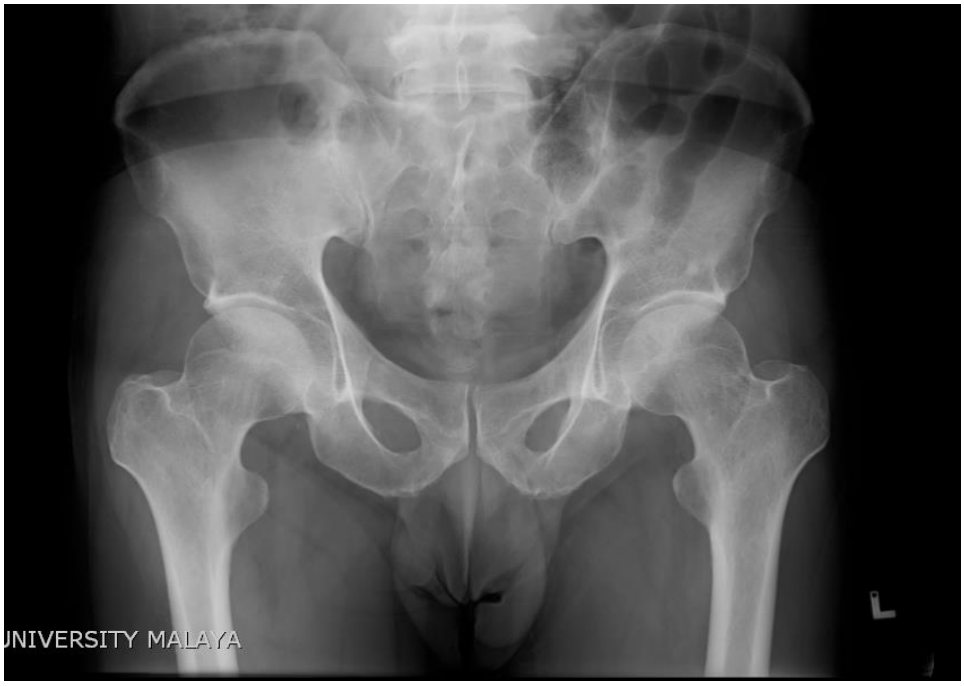


Figure 2.7: X-ray image for Normal Hip

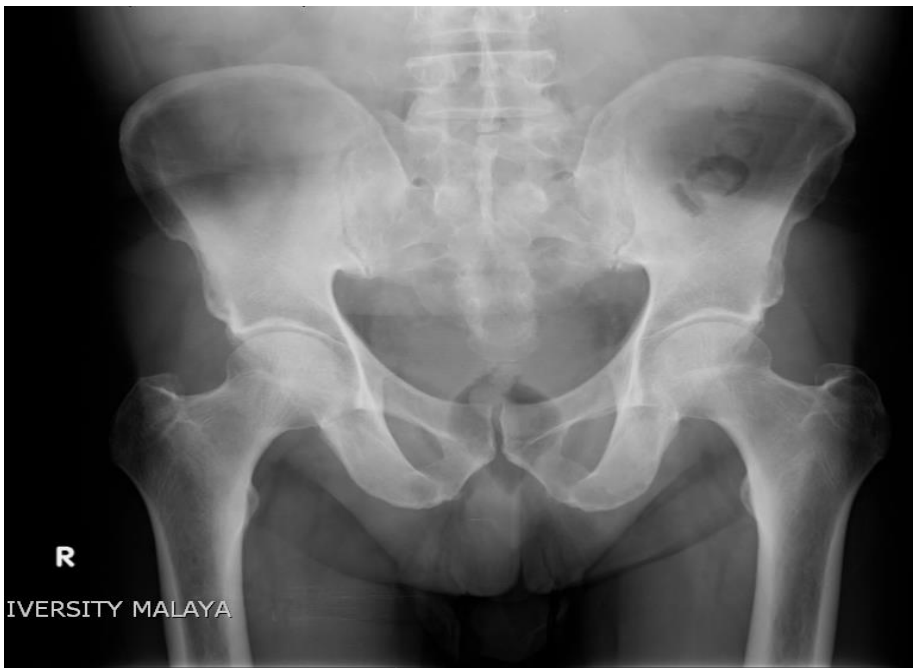


Figure 2.8: X-ray image for Hip OA KL-grade 1

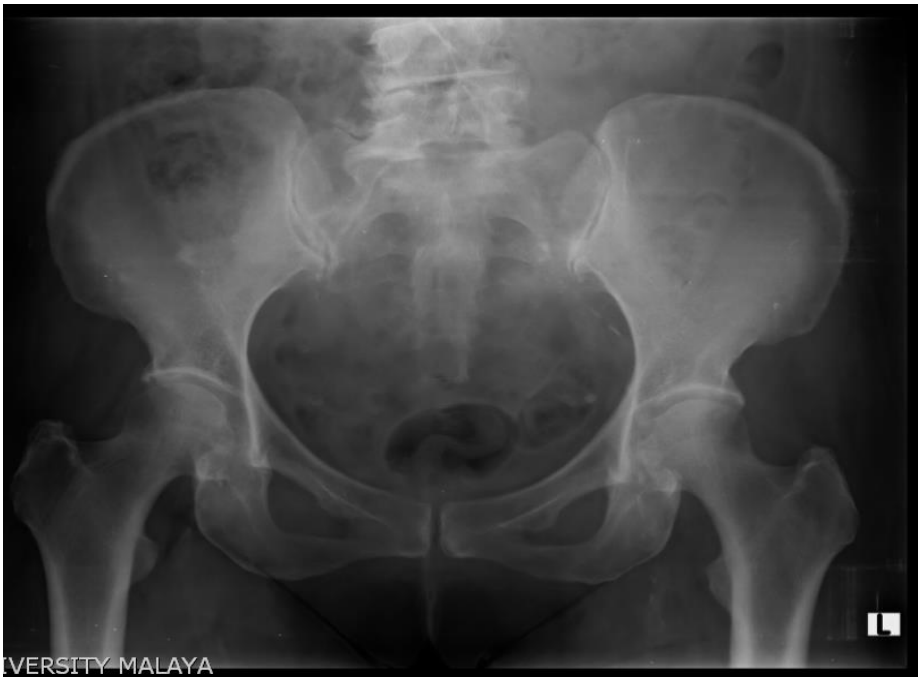


Figure 2.9: X-ray image for Hip OA KL-grade 2

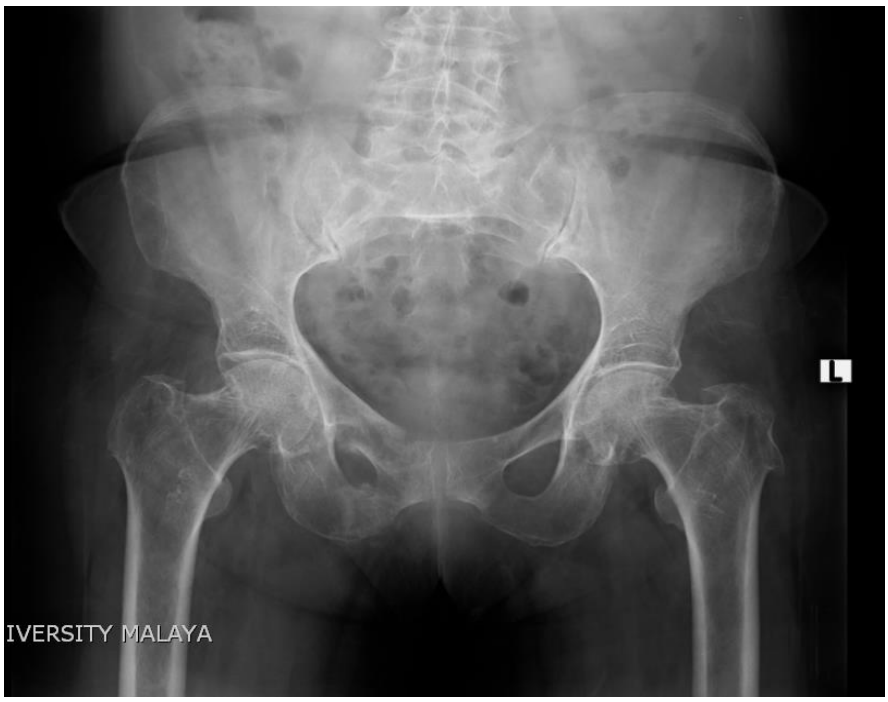


Figure 2.10: X-ray image for Hip OA KL-grade 3

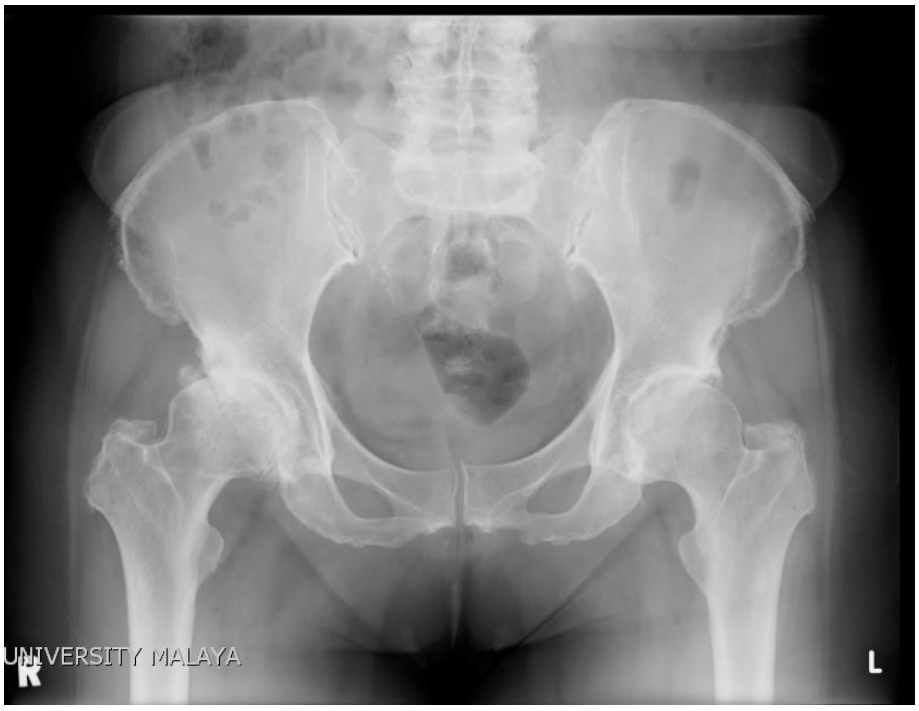


Figure 2.11: X-ray image for Hip OA KL-grade 4

To quantify symptoms severity, WOMAC (Bellamy, 2012) and KOOS (Roos et al., 1998) or HOOS were commonly used tools. KOOS and HOOS use exactly the same question as WOMAC but with additional of activity daily living, sports and quality of life measures. The problem with these tools is that, there is no published cut-off is currently available to classify disease severity. Standardized cut-offs according to ethnicity should be developed in order to explain the severity to the lay person.

The issues that have been identified (Emrani et al., 2008) have also been seen over the years in the clinical setting (Schiphof et al., 2014), demonstrating that the classification of OA has remained ambiguous in the general health and primary-care settings, but KL-grading is still widely use. New approaches are needed to counter this problem. The KL-grading scale should have an updated grading system by reconstructing the tools. A wider and equidistant scale for severity grade should be build according to specific characteristics, as an example one which separates joint space narrowing with osteophytes and grades them as individual features.

2.3 The Association of OA and Falls.

Osteoarthritis has been reported as a risk factor for falls (Tinetti & Kumar, 2010). Older individuals suffering from OA may have poorer balance, reduced quality of life as they restrict their daily activity which eventually increase the risk of falls. Table 2.4 summaries all the previous study on falls associated with osteoarthritis. This is the updated version from review article by (Ng & Tan, 2013), by using same search method, 7 studies were included. Six of the seven studies showed that, having joint symptoms and pain due to OA were associated with falls. While the findings from three studies which compared radiographic OA and symptomatic OA showed that radiographic OA was not

associated with falls (Table 2.4) (Arden et al., 1999) (Muraki et al., 2011) (Dore et al., 2015).

The authors of this review studies raised the issue that the actual relationship between OA and falls remains inconclusive and therefore represents a major gap in clinical knowledge (Ng & Tan, 2013). Findings of a weak association between radiographic evidence of OA and falls but not the symptoms have also added to this intriguing subject. It is rather puzzling that presence of structural changes in the joint did not necessarily affect subjects' balance or functional ability. There are also people with arthritic symptoms but no radiographic evidence of OA who are at a higher risk of falls. This may suggest that pain had more important role on falls rather than radiographic evidence of OA. A previous study, however, showed disparity between gender in the association between knee pain and falls where it is more common among women than men. Conflicting findings between published studies on OA and falls therefore persists.

It has been suggested that this has probably happened due to the varying definitions of OA used by the previous study (Leveille et al., 2009). In addition, there is an expanding awareness that radiographic often have poor correlation with symptoms (Bedson & Croft, 2008), contrary to the American College of Rheumatology (ACR) criteria, which are suggested to be more reflective of clinical practice (McAlindon, 1999). Alternatively, future studies should employ OA definitions which are analogous to clinical practice by using all three common tools; self-reported OA, radiographic OA and clinical OA, in evaluating the relationship between OA and falls. Research of OA and falls at the molecular level has also been suggested as a potentially useful tool to study the relationship in depth.

Table 2.4: Summary of Studies on Falls Associated with Osteoarthritis

Reference	Participants	Study design	OA criteria	Findings
(Nahit, Silman & Macfarlane, 1998)	111 cases, 229 controls	Retrospective study	Hip pain	↑ Falls in women, OR=3.6 (1.9–6.7) not men, OR= 0.8 (0.3–2.3)
(Arden et al., 1999)	5,552 women >65 year with physician diagnosed (n=3,366) and radiographic OA (n= 644)	Prospective, cohort study	Self-reported, physician diagnosed arthritis	↑ Recurrent falls, RR=1.4 (1.2–1.5)
			Radiographic OA	↓ Recurrent falls (≥2 in 12 months), RR=0.7 (0.5–0.95)
(Leveille et al., 2002)	1,002 women >60 years	3-year longitudinal cohort study	Pain-rating scale	↑ Falls with widespread musculoskeletal pain, OR=1.66 (1.25–2.21)
(Arden et al., 2006)	6,641 men and women ≥75 years participating in an RCT in VitD (2,186 cases)	Prospective cohort study	Self-reported knee pain and clinical diagnosed OA	↑ Falls Knee pain, HR=1.26 (1.17–1.36) OA, HR=1.12 (0.97–1.30)
(Muraki et al., 2011)	1,675 men and women, mean age=64.3 years	Retrospective study	Knee and lumbar back pain	↑ Multiple falls in women only: knee pain, OR=1.87 (1.06–3.28) lumbar back pain, 1.72 (1.01–2.88)
			Radiographic OA knee and lumbar spine	No longer significant after adjustment for confounders

Table 2.4: Continued

Reference	Participants	Study design	OA criteria	Findings
(Muraki, Akune, Ishimoto, et al., 2013)	745 men and 1,470 women, mean age= 68.5	Longitudinal Cohort study	Knee pain	↑Falls in women only Knee Pain, OR=1.38 (1.03–1.84)
(Dore et al., 2015)	1, 619 men and women, >60 years	Prospective cohort study	Symptomatic OA	↑ Falls with increasing number of symptomatic OA joint
			Radiographic OA	Not significant with radiological OA Hip OA, OR=1.60 (1.14–2.24) or knee OA, OR=1.39 (1.02–1.88) remained significant after controlling for covariates

Note: OA, osteoarthritis. Risks are presented as odds ratio (OR), risk ratio (RR) or hazard ratio (HR) with 95% confidence interval in parentheses

2.4 Physical Therapies for Improving Balance and Reducing Falls Risk in Osteoarthritis of the Knee (published in Age and Ageing, 2015)

The mainstay of therapeutic approach for OA is weight loss and exercise. Systematic reviews have demonstrated that regular physical activity and exercise are effective interventions for knee OA (Iwamoto, 2011). However, the primary outcomes in these reviews were pain and function. No previous systematic review article has addressed the effects of physical therapy on falls or fall-related measures in individuals with OA.

2.4.1 Objective

To systematically review eligible studies that included balance outcomes and falls risk following physical therapy in individuals with knee OA to determine whether physical therapy improves balance and falls risk in individuals with knee OA.

2.4.2 Methods

2.4.2.1 Criteria for studies selection

The study question was built on the PICOS (participants, interventions, comparisons, outcomes, and study design) framework. We included randomised controlled trials (RCTs) and quasi-randomized trials published in the English language. All studies involving individuals with knee OA in which the mean age of participants was 60 years and above were considered. Studies which included participants with co-existing hip or spine OA were excluded, as we were interested in the effects of physical therapy on knee OA alone.

Only studies that investigated or compared the physical therapy interventions were selected. Studies would be included if they evaluated physical therapy with other forms of therapy such as disease-modifying osteoarthritis drugs, analgesics and joint

injection. Studies that evaluated other forms of therapy without exercise or other physical interventions were excluded. The authors considered all interventions that involved an element of physical training such as walking, strength training, endurance training, and physiotherapy interventions as physical therapy. Studies that employed objective balance-related outcomes and/or falls risk were included. Balance outcomes used by these studies included timed up and go (TUG), Berg's balance scale (BSS), Step test, Sit to stand (STS), and gait speed. Falls outcome measures employed included falls risk assessment and fear of falling.

2.4.2.2 Search methods for identification of studies

We searched for RCTs from CINAHL (Cumulative Index to Nursing and Allied Health Literature) (up to June 2016), Cochrane Library, PubMed, and Web of Science by using the following keywords: (*aged OR elderly OR older adults*) *AND (knee osteoarthritis) AND (falls OR falls risk) AND (balance)*. We applied language restriction. In MEDLINE (OvidSP) subject-specific search terms were combined with the sensitivity-maximising version of the MEDLINE trial search strategy (Lefebvre 2008). The strategy was modified for use in CINAHL, Cochrane Library, PubMed, and Web of Science. We inspected reference lists of articles and reviewed the abstract of potentially relevant articles based on the title of references. The full articles were sourced from conference proceedings, back issues of relevant journals, bibliographies of retrieved publications, books and relevant websites.

2.4.2.3 Data collection and analysis

One review author screened the title, abstract and descriptors of identified studies for possible inclusion. From the full text, two authors independently assessed potentially eligible RCTs for inclusion and resolved any disagreement through discussion. We contacted the authors of full articles for additional information if necessary. The data were independently extracted by pairs of review authors using a pre-tested data extraction form. Disagreement was resolved by consensus or third-party adjudication.

To assess the quality of the methodology used in the studies, we used the PEDro scale that contains 11 items (Maher, 2003). We added six more items - rationale of the study, recruitment method, setting and location of the study, intervention, objective(s), defined outcome measure(s), and sample size determination to assess the quality of the included studies.

The meta-analyses that examined the effects of interventions on balance were performed using RevMan 5.2. No analysis was performed on falls risk due to absence of odd ratios or risk ratio of falls in the published studies. The difference in change score between intervention and control group for each outcome of interest was computed and divided by the pooled standard deviation using random effects model. All data mean differences were calculated using standard mean difference (SMD) with the associated 95% confidence interval. Heterogeneity across selected studies was tested using I^2 statistic. Adjustments were performed in some data by multiplied -1 or alternatively to ensure that all scale point in the same direction.

2.4.3 Results

The initial search yielded 130 relevant publications, 96 of which were excluded on the basis of titles, abstracts, duplicate studies and other reasons (reviews, non-randomized studies, or not relevant to our analysis) (Figure 2.14). Thirty-four potentially relevant studies were identified for full-text analysis. Four RCTs were excluded because they lacked control subjects (Gail D Deyle, 2005; Rogers, 2011; Teixeira, Piva & Fitzgerald, 2011; Tok et al., 2011). Seven RCTs were excluded because the outcome measures did not include balance measurement tools (TUG, STS, Step test, 6-minute walk test (6MWT), and gait velocity) or falls (Evcik & Sonel, 2002; A. Foley, 2003; Gaines, Metter & Talbot, 2004; Penninx et al., 2001; Teixeira, Piva & Fitzgerald, 2011; Tossige-Gomes et al., 2012; Trans et al., 2009). Two other RCTs were excluded because the study population included subjects with hip OA (Fransen, 2007; R. S. H. Hinman, S. E. Day, A. R., 2007). One study was excluded because the study population included participants with rheumatoid arthritis (Williams et al., 2010). Finally, 15 RCTs were selected for this systematic review, with the main characteristics summarised in Table 2.5.

2.4.3.1 Participants

A total of 1482 participants were included in the 15 studies. The included studies were RCTs and were published in 1997-2013. The mean age of participants in all 15 studies was ≥60 years. All participants had knee OA. The trials ranged in sample size of 32 (Sayers, 2012; Simao, 2012) to 437. The median sample size was 72 participants. The trials were carried out in nine countries: USA (Baker et al., 2001; Deyle et al., 2000; Ettinger et al., 1997; Wang et al., 2009), Taiwan (Hsieh, 2012; Jan, 2009; T.-J. Wang et al., 2011), South Korea (R. Song et al., 2003; R. R. Song, Beverly L. Lee, Eun-Ok Lam, Paul Bae, Sang-Cheol, 2010) , Brazil (Imoto et al., 2013; Simao, 2012), Japan (Hiyama,

2012) ,New Zealand (Hale, L. A.Waters & D. Herbison, 2012), Denmark (Lund et al., 2008), Columbia (Sayers, 2012) .

2.4.3.2 Intervention

The duration of intervention and follow-up ranged between two weeks and 18 months. The studies employed a large variety of physical therapy interventions. Tai Chi was used in three studies (R. L. Song, E. O. Lam, P. Bae, S. C., 2003; R. R. Song, Beverly L. Lee, Eun-Ok Lam, Paul Bae, Sang-Cheol, 2010; Wang et al., 2009), while the remaining employed water-based exercise (Hale, L. A.Waters & D. Herbison, 2012), walking programme (Hiyama, 2012), aerobic and resistance exercises (Ettinger et al., 1997), home-based progressive and manual physical therapy of strength training (Baker et al., 2001; Deyle et al., 2000), weight-bearing exercises(Jan, 2009), high-speed and slow-speed power training (Sayers, 2012), squat exercise with whole-body vibration (Simao, 2012), aquatic and land-based exercise (Lund et al., 2008; T.-J. Wang et al., 2011), neuromuscular electrical stimulation (NMSE) with strength training (Imoto et al., 2013) and light therapy (exposure to 890nm radiation). (Hsieh, 2012).

The common assessment tools (TUG, BBS, Walking speed, 6MWT, and STS) were employed in 12 out of 15 studies. Five studies used 6MWT, five studies used STS three studies used TUG test, three studies measured gait speed and two studies used BBS test. One study used a balance platform to measure standing balance, one study measure balance by standing on one foot with eye closed and another one study used Step test. One study measured falls risk using the Physiological Profile Assessment (PPA) and 11-item Korean version of the Survey of Activities and Fear of Falling in the Elderly.

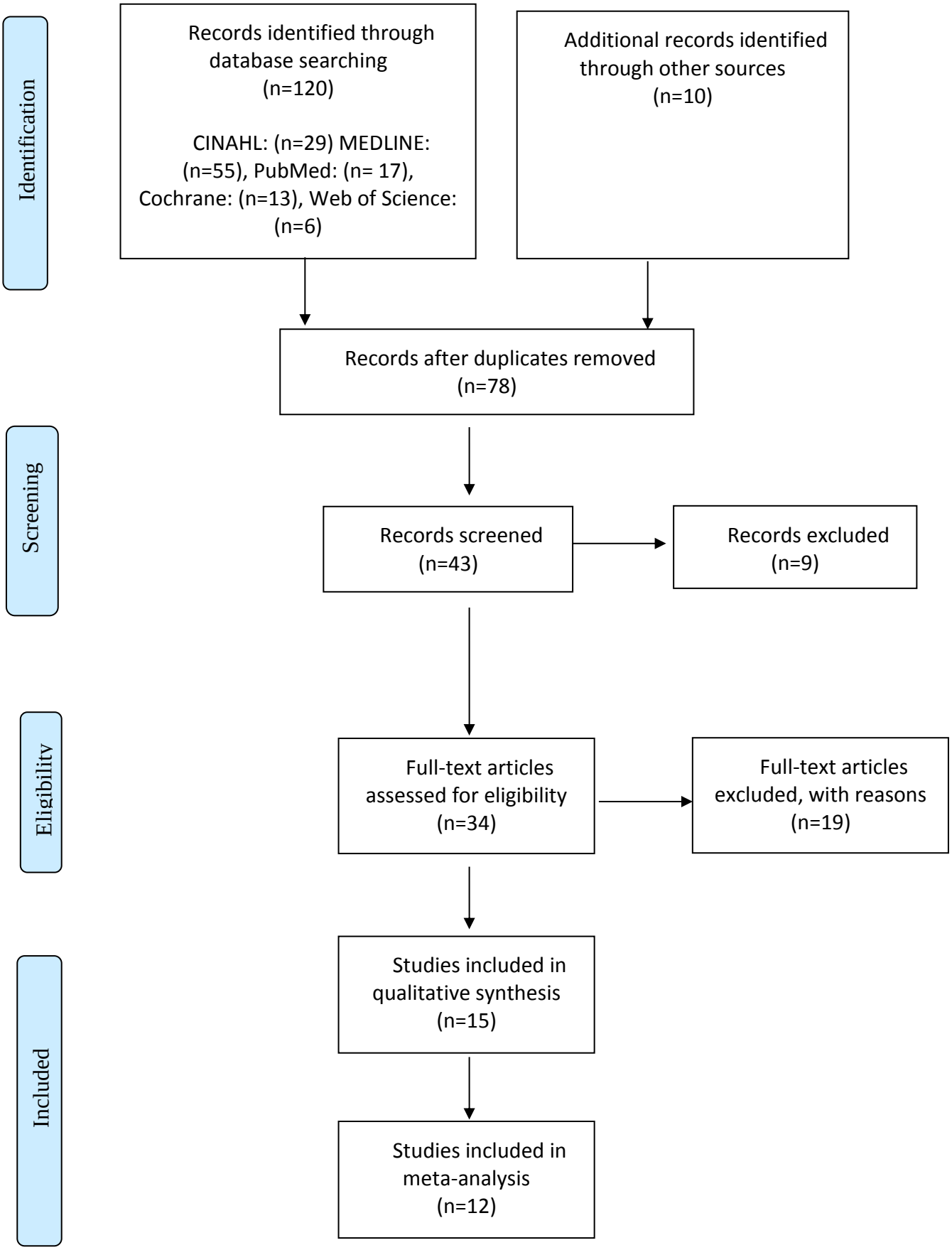


Figure 2.12: Search strategy of the systematic review

Table 2.5: Characteristics of all the included RCTs

Study, Year	Total Number of Subjects (M/F)	Age (Mean±SD), Years	Study Group (n)	Intervention Group					Control Group	Study Design
				Type of Intervention	Duration / Exercise time	Frequency	Outcomes Measures	Intergroup Difference		
Tai Chi										
Song, 2003	72(0/72)	(63±9.8)	Exercise (n=22) C(n=21)	Tai Chi	12 weeks / 20 minutes	3 times a week	Balance **(time for subject standing on one foot with eyes closed on floor pad)	Significant (p=.002)	None	Non-blinded
Wang, 2009*	40(10/30)	(65)	Tai Chi (n=20), Attention Control group (n=20)	Tai Chi	12 week / 60 minutes	Twice a week	STS	Significant (p<0.001)	Wellness education and stretching program	Non-blinded
							6MWT**	NS (p=.1)		
							Standing balance	NS (p=.7)		

Table 2.5: Continued

Study, Year	Total Number of Subjects (M/F)	Age (Mean±SD), Years	Study Group (n)	Intervention Group					Control Group	Study Design
				Type of Intervention	Duration / Exercise time	Frequency	Outcomes Measures	Intergroup Difference		
Tai Chi										
Song, 2010	65 (0/65)	Tai Chi (63.03±7.27) C (61.20±7.96)	Tai Chi (n=30), C (n=35)	Tai Chi	6 months / 2 hours	Twice a week for the 3 weeks, then once a week for 6 months	Fear of Falling	Significant (p=.01)	Self-help education program	Non-blinded
Strength Training (land-based)										
Etingger, 1997(a)*	437(129/308)	Resistance exercise (68±6) C (69±6)	Resistance exercise (n=146) C(n=149)	Resistance exercise	18 months / 1 hours	3 times per week	6MWT**	Significant (p=.02)	Received health education	Single-blinded

Table 2.5: Continued

Study, Year	Total Number of Subjects (M/F)	Age (Mean±SD), Years	Study Group (n)	Intervention Group					Control Group	Study Design
				Type of Intervention	Duration / Exercise time	Frequency	Outcomes Measures	Intergroup Difference		
Strength Training (land-based)										
Deyle GD, 2000	83 (34/49)	Treatment (60±11) Placebo (62±10)	Treatment (n=33) Placebo (n=36)	Manual Therapy of standardized knee exercise program	4 weeks / ND	Twice	6MWT**	Significant (p<.05)	Received sub-therapeutic ultrasound to the knee at an intensity of 0.1W/cm^2 with a 10% pulsed mode	Single-blinded
Baker, 2001*	46 (10/36)	Exercise (69±6), C (68±6)	Exercise (n=23), C(n=23)	Home-based progressive strength training	4 months	3 times per week	STS**	Significant (p=.03)	Nutrition education	Single-blinded

Table 2.5: Continued

Study, Year	Total Number of Subjects (M/F)	Age (Mean±SD), Years	Study Group (n)	Intervention Group					Control Group	Study Design
				Type of Intervention	Duration / Exercise time	Frequency	Outcomes Measures	Intergroup Difference		
Strength Training (land-based)										
Lund, 2008 (a)*	79 (17/64)	Land (68±9.5) C (70±9.9)	Land (n=25), C (n=25)	Land-based exercise	8 Weeks / 50 minutes	Twice	Standing balance using balance platform	NS (p>.05)	None	Single-blinded
Jan, 2009 (a) & (b)	160 (33/73)	(a) WBE (62.0±6.7) (b) NWBE (63.2±6.8) C (62.6±6.7)	WBE (n=36) NWBE (n=35), C (n=35)	Weight-bearing exercise	8 weeks / ND	Daily	Walking speed**	Significant (p<.008)	None	Observer blinded/
TJ Wang, 2011 (a)	84 (17,67)	(67.7±5.9)	Land (n=26) C (n=26)	Land-based exercise	12 weeks / 50 minutes	3 times per week	6MWT**	Significant (p=.015)	None	Single-blinded
Sayers, 2012 (a) & (b)	33 (8/25)	(a)HSPT (66.9±4.9) (b) SSST (65.9±8.3) C (68.4± 8.1)	HSPT (n=12) SSST (n=10), C (n=11)	High-speed power training	12 weeks / ND	3 times per week	STS**	NS (p>.05)	Stretching exercise	Single-blinded
							BBS	NS (p>.05)		

Table 2.5: Continued

Study, Year	Total Number of Subjects (M/F)	Age (Mean±SD), Years	Study Group (n)	Intervention Group					Control Group	Study Design
				Type of Intervention	Duration / Exercise time	Frequency	Outcomes Measures	Intergroup Difference		
Strength Training (land-based)										
Simao, 2012 (a)	32 (4/28)	Squat (69±3.7) C (71±5.3)	Squat group (n=11) C (n=12)	Squat exercise	12 weeks / ND	3 times per week	BBS,	NS (p>.05)	Instructed not to change their lifestyle during the study or engage in any new type of physical activity.	Observer blinded
							Gait Speed Test	NS (p>.05)		
							6MWT**	NS (p>.05)		
Strength training (water-based)										
Hale, 2012	39 (13/26)	(75±1.3)	I (n=23) C (n=16)	Water based Exercise	12 weeks / 20-60 minutes self-paced sessions	Twice weekly	Step test	NS (p>.05)	Community-based computer-skills training program	Observer-blinded/
							TUG	NS (p>.05)		
							Falls risk	NS (p>.05)		

Table 2.5: Continued

Study, Year	Total Number of Subjects (M/F)	Age (Mean±SD), Years	Study Group (n)	Intervention Group					Control Group	Study Design
				Type of Intervention	Duration / Exercise time	Frequency	Outcomes Measures	Intergroup Difference		
Strength training (water-based)										
Lund, 2008 (b)*	79 (17/64)	Aquatic (65±12.6) C (70±9.9)	Aquatic (n=27), C (n=25)	Aquatic	8 Weeks / 50 minutes	Twice	Standing balance using balance platform	NS (p>.05)	None	Single-blinded
TJ Wang, 2011 (b)	84 (17/67)	(67.7±5.9)	Aquatic (n=26) C (n=26)	Aquatic	12 weeks / 50 minutes	3 times per week	6MWT**	Significant (p=.015)	None	Single-blinded
Strength training other components										
Simao, 2012 (b)	32 (4/28)	Platform (75± 7.4) C (71±5.3)	Platform group (n=12) C (n=12)	Squat exercise with whole-body vibration	12 weeks / ND	3 times per week	BBS	Significant (p<.05)	Instructed not to change their lifestyle during the study or engage in any new type of physical activity.	Observer blinded
							Gait Speed test	Significant (p<.001)		
							6MWT**	Significant (p<.05)		

Table 2.5: Continued

Study, Year	Total Number of Subjects (M/F)	Age (Mean±SD), Years	Study Group (n)	Intervention Group					Control Group	Study Design
				Type of Intervention	Duration / Exercise time	Frequency	Outcomes Measures	Intergroup Difference		
Strength training other components										
Imoto, 2013	200 (14/286)	NMSE (60.60±6.72) C (58.78±9.60)	NMSEG (n=100) C (n=100)	Education, quadriceps strengthening exercises and NMES	3 to 12 weeks / 1½ hour	ND	TUG**	Significant (p=.05)	Educational guide	Double-blinded
Aerobics										
Etingger, 1997(b)*	437 (129/308)	Aerobic (69±6) C (69±6)	Aerobics (n=144) C (n=149)	Aerobics	18 months / 1 hours	3 times per week	6MWT**	Significant (p<.001)	Received health education	Single-blinded

Table 2.5: Continued

Study, Year	Total Number of Subjects (M/F)	Age (Mean±SD), Years	Study Group (n)	Intervention Group					Control Group	Study Design
				Type of Intervention	Duration / Exercise time	Frequency	Outcomes Measures	Intergroup Difference		
Aerobics										
Hiyama, 2012	40 (0/40)	I (71.9±5.2) C (73.8±5.7)	I (n=20) C (n=20)	Walking Programme	4 weeks / asked to increase their daily steps to 3000 more than their baseline	Daily	TUG	Significant (*p*=.002)	Physical therapy once a week. Ice therapy, range of exercise at home every day.	Observer-blinded
							Tandem gait**	Significant (*p*=.025)		
Other interventions										
Hsieh, 2012	72 (10/62)	Treatment (61.1±9.4) Placebo (61.3±12.0)	Treatment (n=37) C (n=35)	Short-term light therapy (890-nm radiation)	2 weeks / 40 minutes	3 times per week	Fast-speed walking time	NS (*p*=.284)	Power-off radiation treatment	Double-blinded
							STS	NS (*p*=.499)		

NOTE: M= Male, F= Female, I= Intervention, C, Control; 6MWT, 6-minute Walk Test; BBS, Berg's Balance Scale; STS, Sit to stand; WBE, Weight-bearing Exercise; NWBE, Non weight-bearing Exercise; HSPT, High-speed power training; SSST, Slow-speed strength training; NMSE, Neuromuscular electrical stimulation; TUG, Timed up and go; ND, Not described; NS, Not significant; *, outcome measure (balance/falls risk) used in the study was a secondary outcome; **, outcome results included in meta-analysis (Figure 2.13 and 2.14)

2.4.3.3 Methodological Quality Assessment

Table 2.6 summarises the quality component checklist and PEDro score for each study. The mean PEDro score for all studies was 7, indicating high quality RCTs were selected., high quality of trial design, with intention-to-treat analysis, and allocation concealment would improve the quality of the RCTs as well as reduce potential biases.

2.4.3.4 Intervention Effects

(a) ***Balance***

Only eleven out of 14 studies demonstrated that the selected interventions significantly improved the balance in subjects with knee OA. One of the studies that involved Tai Chi demonstrated benefits in balance improvement by reducing STS time, after 12 weeks with continued benefits at 48 weeks (Wang et al., 2009). Simao *et al* (Simao, 2012) showed squat exercise and whole-body vibration significantly improved the balance (BSS: $p<.05$) and gait performance (gait speed and 6MWT; $p<.05$ and $p<.001$, respectively). Interestingly, the gait speed in the platform group was faster than in the squat group ($p<.01$) after training. The weight-bearing exercise group from Jan *et al* (Jan, 2009) displayed significantly greater improvements in walking speed on the figure-of-8 and spongy surface as well as reposition error, when compared with the non-weight-bearing exercise and control groups ($p=0.008$). Two-way ANOVA analysis showed that the walking group had better performance in balance when compared to control group, in terms of TUG ($F(1,38) = 11.1$, $p=0.002$) and tandem gait ($F(1,38)=4.7$, $p=0.034$) (Hiyama, 2012). High-speed power training showed significant improvement in STS test after collapsing across the groups ($p<.05$) but no intergroup difference was found. Water-based exercises (Hale, L. A.Waters & D. Herbison, 2012) (Lund et al., 2008) and short-term light treatment (Hsieh, 2012) did not show intergroup difference. The group receiving NMSE showed significant improvement in the TUG test compared to its control

group (p=0.05). Compared to the control group, both aerobic and resistance exercise showed better performance in the 6MWT (p<.05) (Ettinger et al., 1997). There was an average improvement of 13.1% in 6MWT in the interventions group from this study (Deyle et al., 2000). Home-based strength exercise significantly improved STS performance compared to the control group (-1.03s is -0.18s, p<.05) (Baker et al., 2001).

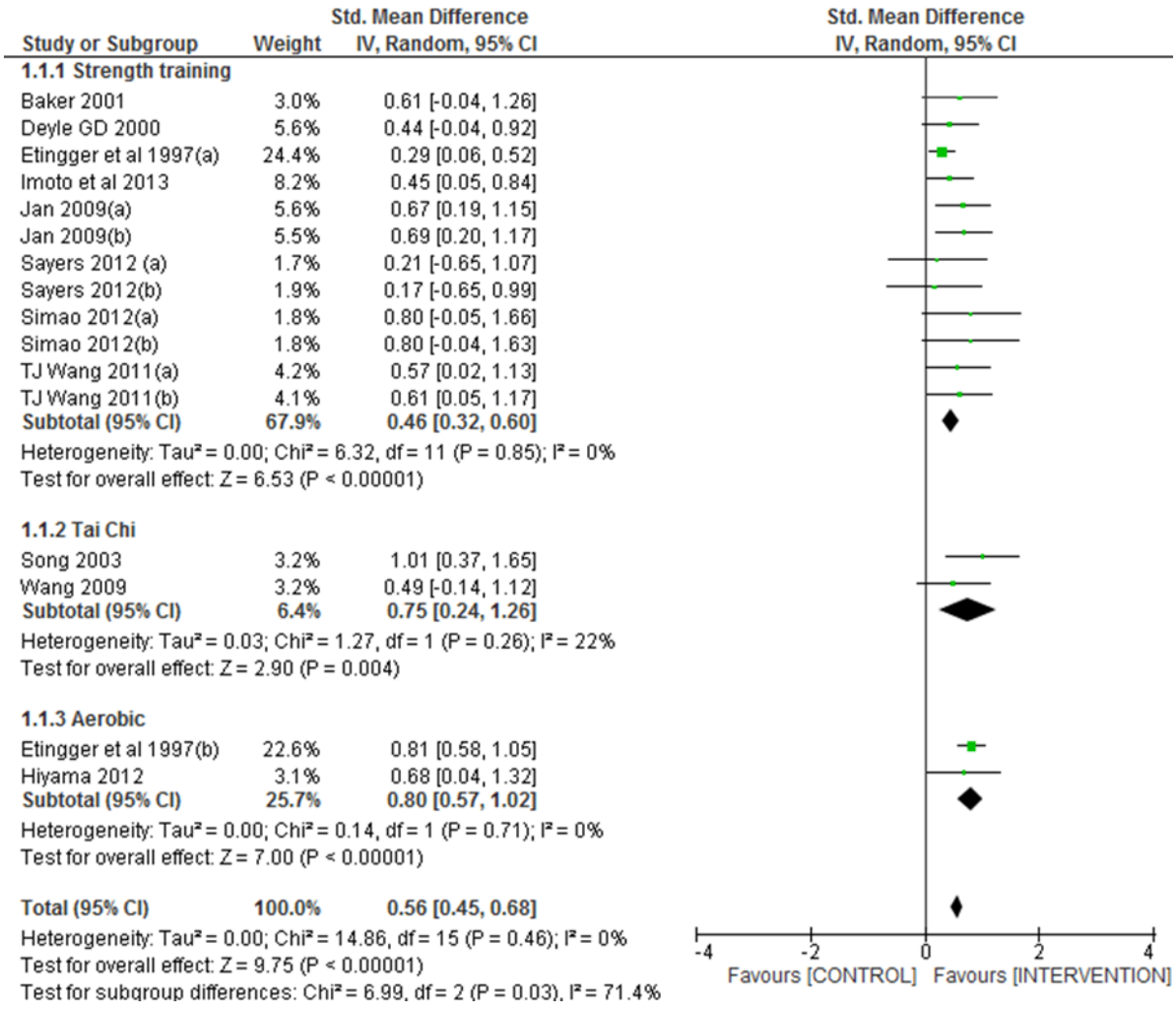
(b) ***Falls Risk***

Hale *et al* showed that water-based exercise did not reduce falls risk (Hale, L. A.Waters & D. Herbison, 2012) but interestingly showed that the reaction time (p<.03) and contrast sensitivity (p<.05) components of the PPA improved significantly in the control group post-intervention (Hale, L. A.Waters & D. Herbison, 2012). Song *et al* (R. Song et al., 2010) demonstrated a significant intergroup difference in fear of falling, with F=6.40 (p=.01), after Tai Chi. Fear of falling score decreased significantly in the Tai Chi group with mean change of -2.40(±5.54) after intervention and no changes found in the control group.

Table 2.6: Quality components checklist and quality evaluation

Contained in Study	Etinger 1997	Deyle GD, 2000	Baker, 2001	Song, 2003	Lund, 2008	Jan, 2009	Wang, 2009	Hiyama, 2012	TJ Wang, 2011	Hale, 2012	Sayers, 2012	Song, 2010	Simao,2012	Hsieh, 2012	Imoto, 2013
1. Rationale for Study	x	√	√	√	√	√	√	√	√	√	√	√	√	√	√
2. Eligibility Criteria*	√	√	√	√	√	x	√	√	√	√	x	√	x	√	√
3. Recruitment Method	√	√	√	√	√	x	√	x	√	√	x	x	x	√	√
4. Setting & Location of the Study	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
5. Intervention	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
6. Objective	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
7. Defined Outcome Measure	√	√	√	√	√	√	x	√	√	x	√	√	√	√	√
8. Baseline Comparability*	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
9. Sample Size Determination	√	√	√	√	√	x	√	x	√	√	x	√	√	√	√
10. Intention-To-Treat Analysis*	1	0	1	0	1	1	1	0	0	1	1	1	0	1	1
11. Allocation Concealment*	0	1	0	1	1	0	1	1	1	1	1	0	1	1	1
12. Random Allocation*	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
13. Blinding of Participant*	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0
14. Blinding of Therapies*	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

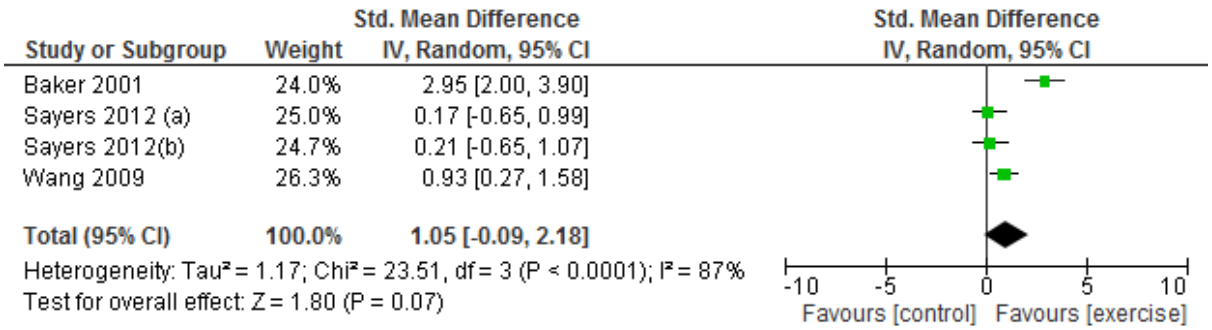
NOTE: *, accessed by PEDro; √, Present (not scored); x, absence; 1, Yes (scored); 0, No (scored).



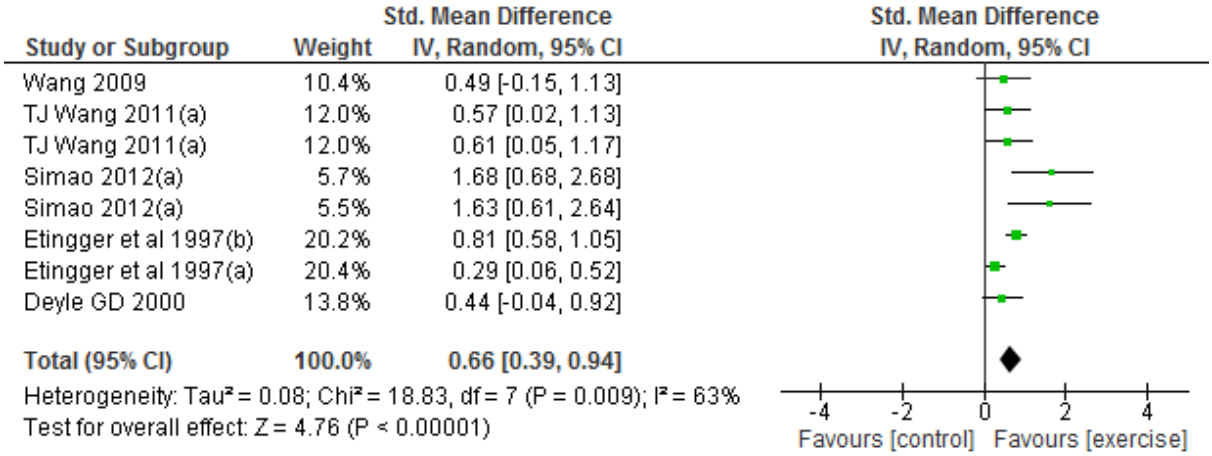
Etingger 1997(a), Resistance training; Etingger 1997(b), Aerobic; Jan 2009(a), Weight-bearing exercise; Jan 2009(b), Non-weight-bearing exercise; Sayers 2012(a), High-speed power training; Sayers 2012(b), Slow speed power training; Simao 2012(a), Squat exercise; Simao 2012(b), Squat exercise with whole-body vibration; TJ Wang 2011(a), land-based exercise; TJ Wang 2011(b)aquatic exercise,

Figure 2.13: A Forest plot of the meta-analysis of RCTs comparing various interventions with control groups for change in balance outcomes.

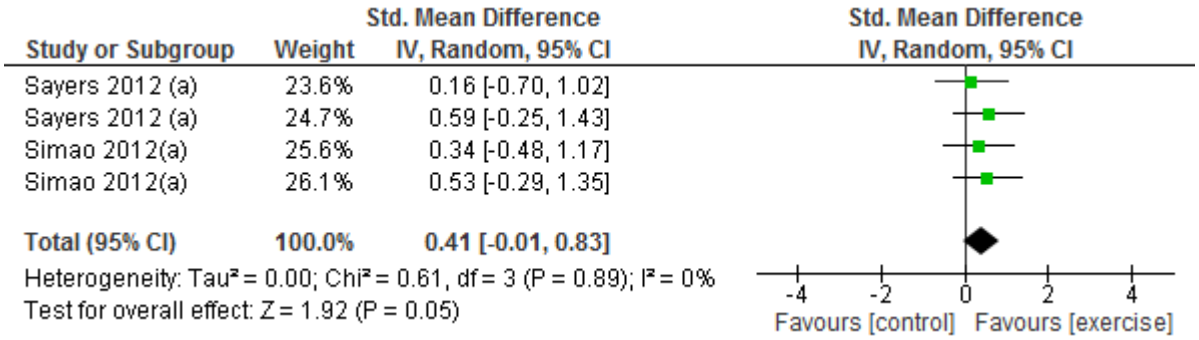
(a)


Std. Mean Difference
Study or Subgroup
Weight
IV, Random, 95% CI
Baker 2001 24.0% 2.95 [2.00, 3.90]
Sayers 2012 (a) 25.0% 0.17 [-0.65, 0.99]
Sayers 2012(b) 24.7% 0.21 [-0.65, 1.07]
Wang 2009 26.3% 0.93 [0.27, 1.58]
Total (95% CI) 100.0% 1.05 [-0.09, 2.18]
Heterogeneity: Tau² = 1.17; Chi² = 23.51, df = 3 (P < 0.0001); I² = 87%
Test for overall effect: Z = 1.80 (P = 0.07)
Std. Mean Difference
IV, Random, 95% CI
-10 -5 0 5 10
Favours [control] Favours [exercise]

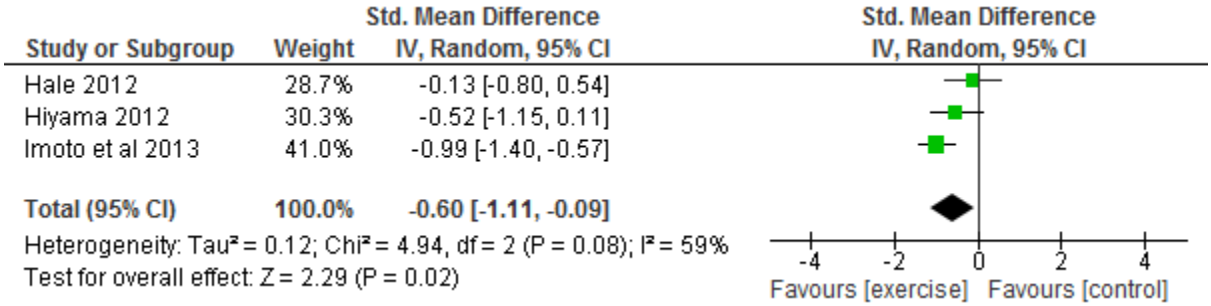
(b)


Std. Mean Difference
Study or Subgroup
Weight
IV, Random, 95% CI
Wang 2009 10.4% 0.49 [-0.15, 1.13]
TJ Wang 2011(a) 12.0% 0.57 [0.02, 1.13]
TJ Wang 2011(a) 12.0% 0.61 [0.05, 1.17]
Simao 2012(a) 5.7% 1.68 [0.68, 2.68]
Simao 2012(a) 5.5% 1.63 [0.61, 2.64]
Etingger et al 1997(b) 20.2% 0.81 [0.58, 1.05]
Etingger et al 1997(a) 20.4% 0.29 [0.06, 0.52]
Deyle GD 2000 13.8% 0.44 [-0.04, 0.92]
Total (95% CI) 100.0% 0.66 [0.39, 0.94]
Heterogeneity: Tau² = 0.08; Chi² = 18.83, df = 7 (P = 0.009); I² = 63%
Test for overall effect: Z = 4.76 (P < 0.00001)
Std. Mean Difference
IV, Random, 95% CI
-4 -2 0 2 4
Favours [control] Favours [exercise]

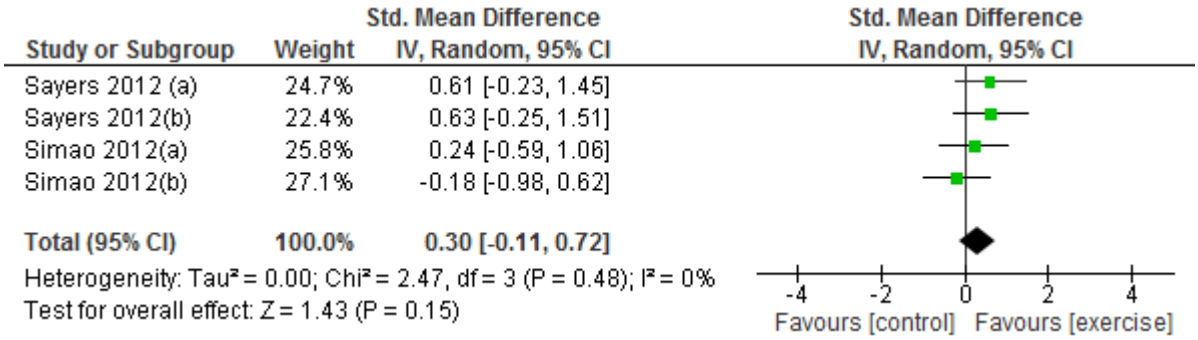
(c)


Std. Mean Difference
Study or Subgroup
Weight
IV, Random, 95% CI
Sayers 2012 (a) 23.6% 0.16 [-0.70, 1.02]
Sayers 2012 (a) 24.7% 0.59 [-0.25, 1.43]
Simao 2012(a) 25.6% 0.34 [-0.48, 1.17]
Simao 2012(a) 26.1% 0.53 [-0.29, 1.35]
Total (95% CI) 100.0% 0.41 [-0.01, 0.83]
Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 3 (P = 0.89); I² = 0%
Test for overall effect: Z = 1.92 (P = 0.05)
Std. Mean Difference
IV, Random, 95% CI
-4 -2 0 2 4
Favours [control] Favours [exercise]

(d)



(e)



Etingger 1997(a), Resistance training; Etingger 1997(b), Aerobic; Jan 2009(a), Weight-bearing exercise; Jan 2009(b), Non-weight-bearing exercise; Sayers 2012(a), High-speed power training; Sayers 2012(b), Slow speed power training; Simao 2012(a), Squat exercise; Simao 2012(b), Squat exercise with whole-body vibration; TJ Wang 2011(a), land-based exercise; TJ Wang 2011(b)aquatic exercise,

Figure 2.14: A Forest plot of the subgroup analyses of RCTs comparing results from various interventions with control groups according to different types of outcome measures. (a)STS, (b) 6MWT, (c) gait speed, (d) TUG, (e) BBS.

2.4.3.5 Meta-analysis of Outcome Measures

Meta-analyses of study outcomes were possible in 12 out of the 15 selected studies. Subgroup analyses were conducted according to three main types of intervention, namely strength training, Tai Chi, and aerobic exercises. The eight RCTs that involved strength training consisted 12 types of exercise and all showed significant improvement of balance in the aggregated result (SMD= 0.46, 95% CI 0.32-0.60, $p<0.00001$, p for

heterogeneity=0.85, I^2=0%) (Figure 2.15). Same trend was found in the pooled results of Tai Chi and aerobic exercises (SMD=0.75, 95% CI 0.30-1.20, *p*=0.004, *p* for heterogeneity=0.26, I^2=0%) and (SMD=0.80, 95% CI 0.57-1.02, *p*<0.00001, *p* for heterogeneity=0.71, I^2=0%, respectively). The pooled result for all 12 studies suggested that these three types of intervention significantly improve balance in subjects with knee OA.

In addition, we also performed a meta-analysis for common outcome measure used in included RCTs. Five studies reported on 6MWT showed significant intergroup difference with aggregated result (SMD= 0.66, 95% CI 0.39-0.94, *p*<0.00001, *p* for heterogeneity=0.009, I^2=63%) (Figure 2.16 (b)). For gait speed, the two studies which reported on this showed significant improvement in the exercise group compared to control group result (SMD= 0.41, 95% CI -0.01-0.83, *p*=0.05 *p* for heterogeneity=0.89, I^2=0%) (Figure 2.16 (c)). Three studies which reported on TUG showed significant intergroup differences which favours the exercise group results (SMD= -0.60, 95% CI -1.11- -0.09, *p*=0.02, *p* for heterogeneity=0.08, I^2=59%) (Figure 2.16 (d)). However, studies which reported on BBS, consisting of four types of interventions and three studies which reported STS showed non-significant in pooled result (SMD= 0.30, 95% CI -0.11-0.72, *p*=0.15, *p* for heterogeneity=0.48, I^2=0%) and (SMD= -0.95, 95% CI -1.35- -0.55, *p*=0.07, *p* for heterogeneity<0.00001, I^2=87%) respectively (Figure 2.16 (a)).

2.4.4 Discussion

Strength training exercises, Tai Chi and aerobics exercises significantly improved balance outcomes in 11 of the 15 studies. The addition of vibration or NMSE in strength training also benefited balance significantly. Water-based exercise was beneficial in only one out

of three studies. Light therapy did not improve balance outcome. In terms of difference in tools used for outcome measurements, STS and BBS did not showed significant intergroup difference in meta-analysis compared to gait speed, TUG and 6MWT.

Various types of physical therapies have been employed in previously published RCTs. In addition to strengthening exercises, aerobics and Tai Chi, there were also studies which added vibration or neuromuscular electrical stimulation to their exercise programmes. One study used light therapy alone as their intervention. The results were highly varied, with some studies demonstrated significant improvements with their interventions while others did not. Seven studies which involved strength training, two studies of aerobics training, and three studies of Tai Chi were classified as positive studies (Baker et al., 2001; Deyle et al., 2000; Ettinger et al., 1997; Hiyama, 2012; Imoto et al., 2013; Jan, 2009; Simao, 2012; R. R. Song, Beverly L. Lee, Eun-Ok Lam, Paul Bae, Sang-Cheol, 2010; Wang et al., 2009; T.-J. Wang et al., 2011). Three RCTs were classified as negative studies. Water-based exercises in two studies (Hale, L. A.Waters & D. Herbison, 2012; Lund et al., 2008) and short-term light treatment using radiation showed no significant improvement in balance and falls risk (Hsieh, 2012). One study was classified as both positive and negative study because high-speed power training as the intervention showed improvement but no more than slow speed training and control group (Sayers, 2012).

While the PEDro scores for individual RCTs were considered acceptable, none of the studies we selected used falls occurrence and frequency of falls as their outcome measures. The outcome measures employed for balance and falls risk used were heterogeneous which limited the applicability of the comparisons. The studies which

measured falls risk employed surrogate measures of falls like the PPA and fear of falling (Hale, L. A.Waters & D. Herbison, 2012; R. R. Song, Beverly L. Lee, Eun-Ok Lam, Paul Bae, Sang-Cheol, 2010). Hard outcome measures of falls require adequate periods of follow-up and usually involves the use of fall diaries (Ganz, Higashi & Rubenstein, 2005). In order to possess adequate statistical power to detect hard falls outcomes, much larger studies than the ones currently reported will be required.

Aerobics, resistance training, NMES with squat exercises, weight-bearing exercises, and squat exercises with vibration showed significant intergroup differences. The common factor among these exercises is likely to be lower limb girdle strength training. As quadriceps and limb girdle weakness is one of the factors related to progression of knee OA, strength training is vital in increasing muscle power (Lange, Vanwanseele & Fiatarone Singh, 2008). In addition, weight-bearing and aerobic exercises improved walking speed of the intervention group, possibly by optimizing neuromuscular control of the knee joint that lead to reduced falls risk (J. Takacs et al., 2013). The addition of whole body vibration and NMES in squat exercise improved balance by increasing muscle strength in the lower limbs (Imoto et al., 2013; Simao, 2012). Even though no significant intergroup differences were found in the study by Sayers et al, it is worth stating that high-speed power training, slow speed power training, and stretching (control) benefited patient with knee OA.

Tai Chi is a safe exercise that requires no special equipment, independent to weather, and can be administered at no cost (Jun-Hong Yan, 2013). The three Tai Chi studies (Song et al., 2003; R. R. Song, Beverly L. Lee, Eun-Ok Lam, Paul Bae, Sang-Cheol, 2010; Wang et al., 2009) showed significant improvement of balance and risk of

falls. Tai Chi exercises improved fear of falling and STS time in these studies (Jan, 2009; R. R. Song, Beverly L. Lee, Eun-Ok Lam, Paul Bae, Sang-Cheol, 2010). From discriminant analyses, STS identified 65% of subjects with balance dysfunction; thus, STS measurements are considered an acceptable measure of balance function (Whitney et al., 2005). As fear of falling is linked to future falls in older people (Kim Delbaere, 2010), decrease in fear of falling after Tai Chi suggested indirectly that Tai Chi could be a preventive exercise for falls.

Water-based exercises showed no significant improvement in balance and falls risk between groups for participant with knee OA. (Hale, L. A.Waters & D. Herbison, 2012; Hsieh, 2012; Lund et al., 2008). We postulated that it was due to lack of strength-based exercises. The study by Hale *et al* (Hale, L. A.Waters & D. Herbison, 2012) did not include any strength training while Lund *et al* (Lund et al., 2008), which compared aquatic and land-based exercises involved little resistance exercise in the aquatic exercise group. The exercise duration was inadequate in the study by Hale *et al* which might have led to the lack of improvement in their frail participants (Hale, L. A.Waters & D. Herbison, 2012). Therefore, future studies on water-based programmes should include strength training and longer duration (>12weeks) of intervention.

An overestimation of the treatment effect is possible because our systematic review only contained nine studies of limited sample sizes as only a few published studies fitted the inclusion criteria. Secondly, heterogeneity in the tools of assessment used made comparison of all the outcomes difficult. Next, we encountered difficulty in evaluating the studies that did not report allocation concealment in their trials. This may contribute

an element of bias. Finally, some studies only involved women as their participants, which contributed to gender bias.

In order to improve the empirical knowledge on this field, this systematic literature search conducted has highlighted certain areas of recommendation. Firstly, a more robust, adequately powered randomized controlled study should be conducted. In addition, falls occurrence and frequency should be used as hard primary outcomes in these RCTs that involved exercise interventions in the prevention of falls in individuals with OA. Secondly, we recommend a consensus on a standardized assessment tools in measuring balance and falls risk to enable structured comparisons be made between studies. Lastly, we also recommend that future studies should investigate the other types of intervention or add on more novel method of enhancing popular interventions like Tai Chi and water-based exercises.

2.4.5 Summary

Strength training, Tai Chi, and aerobics exercises improved balance and falls risk in older individuals with knee OA, while water-based exercises and light treatment did not significantly improve balance outcomes. However, none of the studies so far has evaluated exercise therapy in large enough samples to determine actual falls reduction. Larger RCTs with a longer duration of study are needed to reaffirm current findings to investigate the long-term effect of these interventions.

CHAPTER 3: THE RELATIONSHIP BETWEEN OSTEOARTHRITIS AND FALLS

3.1 Introduction

Falls risk in any individual increases with the cumulative presence of gait and balance disorder, foot problems, skeletal muscle weakness and culprit medications (Tinetti, Speechley & Ginter, 1988). Lower extremity osteoarthritis (OA) has traditionally been considered an established risk factor for falls (Panel on Prevention of Falls in Older Persons & British Geriatrics, 2011). However, there is limited evidence surrounding the role of OA on falls, with available studies having conflicting outcome (Ng & Tan, 2013). The main objective for this study was to explore the possible underlying factors associated with the OA-falls relationship in terms of gait and balance, medicine and other psychosocial factors.

3.2 Literature review

From our Literature review in Chapter 2, it is known that falls is a multifactorial condition. While OA has been considered as one of the risk factor, very little evidence that support the assumption and previous studies were presenting mixed result (Subtopic 2.3). Further study is still needed to evaluate the association and underlying mechanism involved.

3.3 Methodology

3.3.1 Ethics approval

The study was approved by the University Malaya Medical Centre Medical Ethics Committee (reference number: 925.4) and was compliant with the WMA Declaration of

Helsinki 2013 (World Medical, 2013). Written, informed consent was obtained from all participants.

3.3.2 Study Population

Subjects aged ≥65 years attending the Primary Care Clinics, Outpatient department, and the ED department at the UMMC were screened opportunistically for a history of recurrent falls. Fallers were those with two or more falls in the past one year. While the non-fallers were healthy volunteers with no history of falls recruited from voluntary organizations and senior citizens groups through word-of-mouth advertising. The exclusion criteria for both cases and controls were MMSE<24, Severe physical disabilities (unable to stand) major psychiatric illness or psychosis. A sample size of 389 participant was considered to provide 80% power to detect am effect size of 0.30 which is small to medium effect size (G*Power 3.1) (Faul et al., 2007). Written informed consent was obtained from all participants.

3.3.3 Study Design and protocol

This was a case-control, cross-sectional study in design from a larger randomized control trial, the Malaysia Falls Assessment and Intervention Trial (MyFAIT) (P. J. Tan et al., 2014). In this study, the subject's information was taken directly from the baseline measurements in their first appointment at the falls clinic. Osteoarthritis assessments, gait and balance measures, and psychological aspects were tested in all subjects; fallers and non-fallers.

3.3.4 Measurement and observations

3.3.4.1 Diagnosis of OA

(a) ***Self-reported OA***

Participants were defined as having self-reported OA if they answered 'yes' to the following question, "Have you ever been told by a doctor that you have or have had knee or hip osteoarthritis?" (Edwards et al., 2014).

(b) ***Clinical OA***

A rheumatologist blinded from clinical data, uses both history and physical examination to identify the presence of OA based on guidelines by the European Project on Osteoarthritis (EPOSA) (Edwards et al., 2014). EPOSA incorporated the use of the *Western Ontario and McMasters Universities Arthritis Index (WOMAC) (ARHP Research Committee, 2012, June 2012)* in their guidelines to identify presence of joint pain, stiffness and physical function limitation in separate subscales. Knee OA was characterised by knee pain (evaluated by the *WOMAC* 'pain' subscale), plus *any three* of the following symptoms: (i) age over 50 years, (ii) morning stiffness (evaluated by the *WOMAC* 'stiffness' subscale), (iii) crepitus on active motion in at least one side, (iv) bony tenderness in at least one side, (iv) bony enlargement in at least one side, and (v) no palpable warmth of synovia in both knees (Edwards et al., 2014). Hip OA was characterised by hip pain (evaluated by the *WOMAC* 'pain' subscale) and *all* of the following symptoms: (i) age over 50 years, (ii) morning stiffness (evaluated by the *WOMAC* 'stiffness' subscale). Presence of joint pain and stiffness was characterized by any score above zero in the *WOMAC* questionnaire on these subscales.

(c) ***Radiological OA***

Standard weight-bearing, anterior-posterior X-rays were taken from both sides of knees and hip for all consenting participants. A radiologist blinded from clinical data assessed the radiographic images for severity of knee and hip OA using the KL grading scale. KL grades 2-4 were defined in our study as 'presence of radiological OA', while grades 0 or 1 were considered 'no radiological evidence of OA'.

3.3.4.2 WOMAC Questionnaire for symptom severity evaluation

If OA was identified using any of the three diagnostic methods, the severity of OA symptoms (subscale and categorized) was determined using the WOMAC index. Three language versions (English, Malay and Chinese) of the WOMAC index were provided to cater for the different ethnic groups of Malaysia.

WOMAC is a tri-dimensional, disease-specific, patient-reported outcome (PRO) measure. It probes clinically-important criteria, patient-relevant symptoms that are pain, stiffness and physical function in OA patient. The index consists of three sub-scales titled: Pain, Stiffness, and Difficulty Performing Daily Activities which is 24 questions (5 pain, 2 stiffness, 17 physical function). It can be completed in less than 5 minutes. Visual Analogue (WOMAC VA3-series) scaling format was used in this study as it was slightly more sensitive than WOMAC LK3.0. The WOMAC Index is self-administered and does not require the presence of an interviewer. However, we did review the questionnaire to make sure the patient has completed all question and assisted patients who were unable to read.

(a) ***WOMAC Subscale Scores***

The maximum scores for each subscales are 500mm, 200mm and 1700mm respectively (ARHP Research Committee, 2012, June 2012). A maximum score indicates

the highest levels of joint pain, stiffness and function limitation when performing activities of daily living.

(b) ***Categorized Scores***

The total WOMAC Score is the summation scores of the three subscales. Using 25th, 50th and 75th percentile values as ordinal cut-offs, the total WOMAC Score was further categorized into 4 groups: no symptoms (0mm), mild symptoms (1-200mm), moderate symptoms (201-465mm) and severe symptoms (≥466mm).

3.3.5 Balance measurement

The Timed Up and Go (TUG) and Functional reach (FR) tests were selected to quantify reaction time, gait initiation, limb girdle strength, gait speed and dynamic balance from all the subjects.

3.3.5.1 Timed Up and Go test (TUG)

Timed Up and Go (TUG) test has been recommended and endorsed by the Osteoarthritis Research Society International (OARSI) as one of the performance-based tests of physical function in people with hip or knee OA (Kroman et al., 2014). Participants were asked to complete a continuous 3-meter walk from and back to a seated start position in normal pace, on a 46cm-high chair with arms. They were allowed to use a walking aid if needed. Time taken to complete the task was measured using a stopwatch and recorded in seconds (s).

3.3.5.2 Functional reach test (FR)

Functional reach was considered the maximal reach while standing without losing balance. Each participant was instructed to stand with his or her left shoulder closest to a wall, with the left arm raised to 90 degrees' forward flexion. A 1-metre ruler was placed

at shoulder (acromion) height, parallel to the patient's arm. The assessor measured the starting position of the participant's outstretched fingers at the fifth metacarpal head. Without touching the wall and feet together, the participant was instructed to "reach out as far as you can without moving your feet". The distance of furthest reach was measured at the fifth metacarpal head. The initial reading and the final reading after were recorded. The exact value measured for functional reach test was from the subtraction of final and initial reading. The measurements were recorded in centimetres (cm).

3.3.6 Psychological domain

Fear of falling and psychological status were the main focus in measuring psychological domain in this study.

3.3.6.1 Falls Efficacy of fear of falling (FES-I) short version

Fear of falling is measured using the seven-item short Falls Efficacy Scale-International (FES-I) (Kempen et al., 2008). The short FES-I enquires about concern for falling while performing various basic activities of daily living such as getting off a chair, showering or bathing, picking up objects, walking up or down slopes, going up or down stairs and going outdoors. The degree of concern is recorded with a four point Likert scale. The maximal score is 28, indicating extreme fear of falling, and the minimal score is 7, indicating no fear of falling.

3.3.6.2 21-item Depression, Anxiety and Stress Scale (DASS-21)

Depression, anxiety and stress were measured with the 21-item Depression, Anxiety and Stress Scale (DASS-21). This is a self-reported measure in which subjects rate the frequency and severity of the negative emotions of depression (e.g., loss of self-esteem/incentives and depressed mood), anxiety (e.g., fear and anticipation of negative events) and stress (e.g., persistent state of over arousal and low frustration tolerance) over

the previous week. Frequency or severity ratings are made on a series of 4-point scales, with 0 indicating “did not apply to me at all” and 3 indicating “applied to me very much, or most of the time” (Oei et al., 2013). The scores are calculated individually for the three components: depression, anxiety and stress. The minimal score for each component is 0 and the maximal score is 42. The DASS-21 a short version of DASS42 is available with 7 items per scale.

3.3.3 Statistical Analysis

SPSS 20.0 (IBM SPSS Statistics) statistical software package was used for statistical analysis. Significant differences between faller and non-faller groups were assessed using chi-squared test for categorical variables, and t-test and Mann-Whitney U tests for continuous variables. Mean (± standard deviation) or median (interquartile range) were expressed where appropriate and were indicated. Continuous data were then transformed into dichotomous variables to avoid linearity assumptions during analysis. Using percentile values as ordinal cut-offs, the total WOMAC score was further classified into categories: No symptoms= 0 mm, mild symptoms= 1-200 mm, moderate symptoms= 201-465 mm and severe symptoms ≥ 466 mm respectively. Binary logistic regression was used to determine the odds ratios for the occurrence of falls adjusted with significant demographic variables, and further adjustment of impaired physical performance, NSAIDs usage and psychological domain in separate models. The strength of this associations was presented in odds ratio (OR) and 95% confidence interval (CI).

3.4 Results

3.4.3 Subjects characteristic

A total of 389 participants (229 fallers, 160 non-fallers), with a mean age of 72.2±6.1 years old were included for analysis. Majority were females (67%). Fallers compared to

non-fallers, were significantly older, have poorer TUG and FR scores, and were more likely to have hypertension, diabetes and visual impairment. Fallers were also more depressed, stressed, and fear of falling compared to the non-fallers and significantly higher number in NSAIDs-user. No significant differences were observed between the two groups in terms of gender, ethnicity, body mass index (BMI), occurrence of OA, and type of OA diagnosis (self-reported, clinical and radiological) (Table 3.1).

Table 3.1: Subjects' characteristics according to occurrence of falls.

Characteristics	Fallers (n=229)	Non-Fallers (n=160)	p-value
Age (years), mean (SD)	75.11 (7.11)	71.08 (5.22)	**<0.001**
Female sex, n (%)	150 (65.5)	113 (70.6)	0.288
BMI (kg/m^2), mean (SD)	24.43 (3.83)	24.89 (4.15)	0.273
Comorbidities, n (%)			
Heart diseases	14 (6.1)	8 (5.0)	0.650
Hypertension	138 (60.3)	79 (49.7)	**0.039**
Diabetes	78 (34.1)	28 (17.6)	**<0.001**
Stroke	14 (6.1)	4 (2.5)	0.140
Atrial fibrillation	7 (3.1)	3 (1.9)	0.474
Visual impairment	74 (32.3)	33 (20.8)	**0.012**
Type of Osteoarthritis, n (%)			
Self-reported OA	88 (38.4)	51 (31.9)	0.184
Clinical OA	81 (35.4)	60 (37.5)	0.667
*Radiological OA**	106 (84.8)	65 (81.2)	0.505
Physical Function			
Timed-Up and Go (s), median (IQR)	14.1 (6.0-100.0)	10.4 (5.1-40.0)	**<0.001**
Functional Reach (cm), median (IQR)	24.4 (3.0-46.0)	28.9 (11.0-44.5)	**<0.001**
Impaired Physical Function, n (%)			
TUG ≥13.5s	122 (53.5)	32 (20.1)	**<0.001**
FR ≤18cm	63 (27.5)	15 (9.4)	**<0.001**
DASS-21			
Depression, median (IQR)	4 (0-12)	2 (0-6)	**<0.001**
Anxiety, median (IQR)	2 (0-6)	2 (0-6)	0.120
Stress, median (IQR)	6 (2-12)	4 (0-10)	**0.024**
Short FES-I, *median (IQR)*	12 (8-18)	8 (7-12)	**<0.001**
NSAIDs user, n (%)	22 (9.6)	4 (2.5)	**0.006**

NOTE: Bold font indicates Statistical Significance BMI=Body Mass Index. OA=Osteoarthritis. TUG=Timed Up and Go test. FR=Functional reach test. IQR=inter-quartile range. FES-I=Falls efficacy fear of falling test international. DASS-21=21-item Depression, Anxiety and Stress Scale. NSAIDs=Non-steroidal anti-inflammatory drugs.

*Not all participants agreed to a radiological examination or had pre-existing X-rays within the preceding 12 months.

Table 3.2 describes the associated factors for the occurrence of falls according to the type of OA diagnosis. For individuals with diabetes and with visual impairment there were increased risks of falls in those with self-reported OA.

Table 3.2: Baseline odds ratios for the occurrence of falls according to type of osteoarthritis diagnosis.

	Falls, Odds Ratio (95% CI)		
	Radiological OA	Clinical OA	Self-reported OA
Number	171	141	139
Age (y), mean difference	1.061 (0.982-1.146)	1.025 (0.947-1.108)	1.034 (0.963-1.111)
Gender, n (%)	0.726 (0.356-1.480)	0.698 (0.319-1.524)	0.606 (0.256-1.435)
BMI (kg/m^2), mean (SD)	1.044 (0.946-1.151)	0.995 (0.904-1.096)	0.928 (0.841-1.024)
Comorbidities, n (%)			
Heart diseases	1.918 (0.500-7.359)	1.301 (0.363-4.664)	0.762 (0.164-3.548)
Hypertension	1.061 (0.571-1.969)	1.620 (0.817-3.209)	1.328 (0.657-2.684)
Diabetes	1.730 (0.829-3.610)	1.673 (0.773-3.621)	**5.793 (2.093-16.029)**
Stroke	1.461 (0.364-5.862)	1.875 (0.351-10.014)	2.450 (0.500-12.011)
Atrial fibrillation	1.231 (0.109-13.849)	1.468 (0.130-16.583)	-
Visual impairment	1.595 (0.728-3.498)	1.119 (0.492-2.547)	**3.082 (1.334-7.117)**

NOTE*:* BMI = body mass index; OA = osteoarthritis; CI = confidence interval.

Table 3.3 summarized the results of WOMAC severity of symptoms scores (subscale and categorized) and the total WOMAC score between fallers and non-fallers with the different OA diagnostic criteria. In both radiological and clinical OA, fallers had significantly higher joint stiffness, function limitation and total WOMAC score (i.e. maximum score indicates most pain, stiffness and function). Only fallers with clinical OA had higher joint pain scores compared to non-fallers. There were no differences in scores between fallers and non-fallers with self-reported OA for joint pain, stiffness and function limitation. Differences between categorized severities of symptoms were present between fallers and non-fallers for all diagnosis of OA. A greater proportion of fallers compared to non-fallers had severe OA symptoms in all types of OA. Significantly more non-fallers had mild OA symptoms for all definitions of OA, whereas significantly more fallers had 'asymptomatic' OA (radiological evidence of OA with no symptoms).

Table 3.3: Comparison of WOMAC symptom severity scores between fallers and non-fallers according to osteoarthritis diagnosis.

	Radiological OA			Clinical OA			Self-reported OA		
	Fallers (n=106)	Non-fallers (n=65)	p-value	Fallers (n=81)	Non-fallers (n=60)	p-value	Fallers (n=88)	Non-fallers (n=51)	p-value
Severity of Symptom (Subscale Scores) (mm), median (IQR)									
Pain (5-item)	40.0 (0-435)	20.0 (0-310)	0.228	100.0 (5-450)	50 (5-310)	**0.003**	50 (0-450)	30 (0-350)	0.156
Stiffness (2-item)	7.5 (0-200)	0 (0-200)	**0.011**	45 (0-200)	12.5 (0-200)	**0.005**	15.5 (0-200)	10 (0-200)	0.495
Function Limitation (17-item)	182.5 (0-1700)	48.0 (0-945)	**0.010**	327 (0-1700)	179 (0-945)	**0.001**	278 (0-1504)	150 (0-945)	0.061
Total WOMAC Score (mm), median (IQR) *	295 (0-1930)	88 (0-1245)	**0.012**	480.0 (10-2100)	282.5 (5-1245)	**<0.001**	361.5 (0-2100)	240 (0-1245)	0.068
Severity of Symptoms, n (%) **									
No symptoms	27 (25.5)	16 (24.6)	**0.012**	0	0	**0.001**	15 (17.0)	7 (13.7)	**0.041**
Mild	19 (17.9)	28 (43.1)		18 (22.2)	25 (41.7)		17 (19.3)	18 (35.3)	
Moderate	25 (23.6)	13 (20.0)		21 (25.9)	22 (36.7)		17 (19.3)	14 (27.5)	
Severe	35 (33.0)	8 (12.3)		42 (51.9)	13 (21.7)		39 (44.3)	12 (23.5)	

NOTE: Bold font indicates Statistical Significance. OA = osteoarthritis; IQR = interquartile range; *, Total WOMAC Score is the summation of "Pain", "Stiffness" and "Function Limitation" scores.; **, Categorized using percentile cut-offs from Total WOMAC Score. "No symptoms": 0mm. "Mild": 1-200mm. "Moderate": 201-465mm. "Severe": ≥466mm.

3.4.4 Association between OA and falls

Table 3.4 explored the association between falls and severity of OA symptoms according to type of OA, before and after three consecutive adjustments for confounders. When comparing symptom severity among participants with radiological OA (using the asymptomatic group as the reference), 'Mild' OA symptoms were associated with reduced risk of falls. In participants with clinical OA (using 'mild' symptoms group as the reference), individuals with 'severe' symptoms were associated with increased risk of falls. The 'mild' symptom group was used as the reference as the minimum criteria for clinician diagnosed OA was joint pain. After adjustments for socio-demographic characteristics in Model 1, followed by additional adjustments of impaired TUG or FR (Model 2) and NSAIDs usage (Model 3), both associations remained significant. There were no significant associations observed between severity of symptoms and falls in self-reported OA.

Table 3.5 explored the mediating role of FoF and psychological domains on the association between symptoms severity and falls according to OA diagnosis. In Model 1, after the adjustment of confounding variable, subjects with radiological OA and mild symptoms had significantly reduced risk of fall compared to the asymptomatic groups, and subjects with clinical OA and had severe symptoms were higher risk of falls compared to those with mild clinical OA. After additional adjustment for anxiety, the association of reduced falls risk and mild symptoms in radiological OA was then attenuated (Model 4), while the association of severe symptoms in clinical OA and increased risk of falls was no longer significant after controlling for FoF in a separate model (Model 2)

Table 3.4 : Odds Ratio for Falls according to Severity of OA Symptoms in different diagnosis of OA

			Falls OR (95% CI)			
			Unadjusted	Model 1[a]	Model 2[b]	Model 3[c]
Radiological OA	171	*No symptoms (ref)* *	1			
		Mild	**0.402 (0.172-0.940)**	**0.382 (0.151-0.967)**	**0.369 (0.145-0.942)**	**0.388 (0.153-0.987)**
		Moderate	1.140 (0.458-2.836)	0.978 (0.351-2.725)	0.862 (0.301-2.469)	0.924 (0.334-2.554)
		Severe	2.593 (0.967-6.950)	2.466 (0.845-7.193)	2.199 (0.702-6.886)	2.256 (0.766-6.647)
Clinical OA	141	*No symptoms*	NA	NA	NA	NA
		Mild (ref) *	1			
		Moderate	1.326 (0.566-3.106)	1.210 (0.486-3.015)	1.154 (0.459-2.901)	1.225 (0.493-3.044)
		Severe	**4.487 (1.883-10.693)**	**3.685 (1.473-9.217)**	**3.345 (1.279-8.748)**	**3.598 (1.426-9.075)**
Self-reported OA	139	*No symptoms (ref)* *	1			
		Mild	0.441 (0.144-1.345)	0.603 (0.151-2.403)	0.603 (0.150-2.415)	0.639 (0.159-2.564)
		Moderate	0.567 (0.181-1.776)	0.484 (0.116-2.009)	0.458 (0.109-1.932)	0.410 (0.096-1.754)
		Severe	1.517 (0.502-4.584)	2.208 (0.549-8.875)	1.917 (0.466-8.240)	2.262 (0.562-9.107)

NOTE: Bold font indicates Statistical Significance. OA= Osteoarthritis, TU=, Timed Up and Go test, FR= Functional reach test, NSAIDs= Non-steroidal anti-inflammatory drugs. a= Adjusted for age, gender, ethnicity, comorbidities. b =Adjusted for age, gender, ethnicity, comorbidities and impaired TUG or FR, c= Adjusted for age, gender, ethnicity, comorbidities and NSAIDs usage. No symptoms= 0 mm, mild symptoms= 1-200 mm, moderate symptoms= 201-465 mm and severe symptoms ≥ 466 mm respectively

Table 3.5: Mediation of Fear of falling and psychological status in the association between symptoms severity and falls according to osteoarthritis diagnosis.

			Falls OR (95% CI)				
			Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]	Model 5[e]
Radiological OA	171	*No symptoms (ref) **					
		Mild	**0.382 (0.151-0.967)**	**0.330 (0.123-0.882)**	**0.387 (0.153-0.978)**	0.392 (0.153-1.005)	**0.387 (0.152-0.982)**
		Moderate	0.978 (0.351-2.725)	0.638 (0.208-1.953)	0.951 (0.342-2.650)	1.007 (0.355-2.854)	1.013 (0.361-2.842)
		Severe	2.466 (0.845-7.193)	1.220 (0.368-4.050)	2.624 (0.853-8.070)	2.959 (0.952-9.198)	2.658 (0.891-7.929)
Clinical OA	141	*No symptoms Mild (ref) **	NA	NA	NA	NA	NA
		Moderate	1.210 (0.486–3.015)	0.907 (0.343-2.397)	1.225 (0.493-3.044)	1.303 (0.509-3.340)	1.261 (0.497-3.200)
		Severe	**3.685 (1.473–9.217)**	2.385 (0.878-6.482)	**3.598 (1.426-9.075)**	**3.421 (1.311-8.925)**	**3.840 (1.492-9.884)**
Self-reported OA	139	*No symptoms (ref) **					
		Mild	0.603 (0.151-2.403)	0.597 (0.138-2.582)	0.759 (0.179-3.212)	0.639 (0.157-2.597)	0.625 (0.156-2.513)
		Moderate	0.484 (0.116-2.009)	0.301 (0.065-1.397)	0.767 (0.173-3.396)	0.449 (0.105-1.923)	0.475 (0.114-1.976)
		Severe	2.208 (0.549-8.875)	1.052 (0.227-4.877)	2.446 (0.578-10.350)	1.666 (0.402-6.898)	2.179 (0.542-8.764)

NOTE: Bold font indicates Statistical Significance. OA=Osteoarthritis. No symptoms= 0 mm, mild symptoms= 1-200 mm, moderate symptoms= 201-465 mm and severe symptoms ≥ 466 mm respectively, a=Adjusted for age, gender, ethnicity, comorbidities, b =Adjusted for age, gender, ethnicity, comorbidities and Fear of falling (short FES-I), c= Adjusted for age, gender, ethnicity, comorbidities and Depression. d= Adjusted for age, gender, ethnicity, comorbidities and Anxiety, e= Adjusted for age, gender, ethnicity, comorbidities and Stress

3.5 Discussion

This study provides evidence on the relationship between falls and symptom severity in individuals with clinical and radiological OA. Radiological OA participants with 'mild' OA symptoms had lower risk of falls compared to an individual without OA symptoms while clinical OA participants with 'severe' OA symptoms, have increased risk of falls compared to individuals with 'mild' symptoms. These associations remained consistently significant even after adjustments for potential confounders, impaired physical performance and NSAIDs. However, mild symptoms-lower risk of falls among radiological OA and severe symptoms-higher risk of falls relationship among clinical OA were attenuated when controlling for anxiety scored from DASS-21 and FoF respectively. This indicates that impaired physical function is not attributable to the association between osteoarthritis and falls and analgesics usage did not have any influence on the associations observed but subjects with radiographic evidence of OA with mild symptoms were protected from falls, with the level of protection mediated by their anxiety state. Fear of falling mediated the high risk of fall among clinical OA patients with severe symptoms.

As mentioned earlier, the evidence for increased risk of falls attributable to OA is conflicting (Ng & Tan, 2013). A review of previously published articles has found that radiological evidence of OA is not associated with increased risk of falls. This is unsurprising considering that it is well established that radiological evidence of OA correlated poorly with physical symptoms of OA. However, the conflicting results of previous studies were also partly due to the highly varied criteria employed to determine the presence of OA.

In our study, there was no significant difference in the proportion of individuals with either self-reported OA, clinical OA or radiological OA among fallers and non-fallers. However, when we considered the different degree of severity of OA symptoms, we managed to reveal new knowledge on the polemic of mixed results on OA and falls. In agreement with previous studies, increased of OA symptoms such pain, stiffness and physical function limitation were associated with falls (S. J. Foley et al., 2006). Such associations however can only be found among the clinical OA subjects but not in self-reported OA or radiological OA group. The likelihood of self-reported physician diagnosed OA is not a good measure of the presence of OA or OA severity in our study. While radiological OA showed contrasting result as the mild OA symptoms group significantly had less falls risk compared to the non-symptomatic.

The results of our study have therefore importantly highlighted that fallers are not more likely to experience OA, regardless of methods of detection, but different types of diagnosis showed different interactions with the associations of increased severity OA symptoms and risk of falls. However, our sample size is not adequately powered to detect smaller associations between OA and falls, and our convenience sample may not be representative of the general older population. The prevalence of self-reported physician diagnosed OA is nevertheless comparable to that reported in the USA population (Hootman & Helmick, 2006), while the prevalence of joint pain in our control population is similar to that of rheumatic complaints among individuals aged >65 years in a Malaysian survey (Veerapen, Wigley & Valkenburg, 2007).

Physical performance in older adults with OA has been commonly evaluated in a number of studies. However, these studies had rarely evaluated the specific relationship

between the reduction in physical performance due to OA and falls (Alencar et al., 2007; Muraki, Akune, Oka, et al., 2013). To the best of our knowledge, this was the first study to date trying to describe the influence of impaired physical performance in the association between increase OA symptoms and falls using three different detection methods. Alencar *et al* compared the functional mobility between osteoarthritic elderly women with and without a history of falls and found that fallers had significantly worse TUG scores (Alencar et al., 2007). Alencar *et al* however, has not evaluated the symptom burden of their study population with OA (Alencar et al., 2007). Nevertheless, our finding suggested that poorer physical performance does not influence the risk of falls among older adults with OA.

The attenuation of the mild OA symptoms-lower risk of falls relationships in radiological OA group after controlling for anxiety and confounding variables suggest that subjects with mild OA may have more anxiety and increased self-awareness which leads to increased vigilance against falls compared to the non-symptomatic OA. The reduction in falls among those with mild OA may also occur due to activity restriction (Nguyen et al., 2011; Trivedi, 2004). Similarly, among clinical OA subjects, the association of severe symptoms and increased risk of falls remained significant even after following adjustment of impaired physical function nor psychological status, indicating that the association was not necessarily mediated by deficits in physical performance. Neuromuscular and central mechanisms may still mediate this relationship, where symptoms might interfere with cognition or executive function as suggested by MOBILIZE study (Leveille et al., 2009).

Our finding that fear of falling mediated the higher risk of falls among clinical OA subjects with severe symptoms indicates that the psychological state plays a major role in falls. Fear of falling correlates with increasing of pain (Patel et al., 2014). As ours was a cross-sectional study, no causation could be assigned, and the sequence of event, whether severe OA led to reduced activity due to fear of falling, which consequent physical conditioning leading to falls, or whether the physical disability associated with severe OA led to falls which then led to increased fear-of-falling could not be differentiated (S. L. Murphy, Dubin & Gill, 2003; S. L. Murphy, Williams & Gill, 2002).

Similar to a previous study, we did not observe a lower rate of falls among analgesic user (Leveille et al., 2009). Analgesics use had adverse effects and contribute to falls (Rolita et al., 2013). In this study findings, however, NSAIDs usage was not considered a mediator in the severe symptoms-falls relationships. The usage of NSAIDs did not influence the relationship found between falls and OA.

This study reveals previously unexposed relationships between falls and OA. There are also very few OA studies on at-risk fallers. Recruiting fallers from a higher risk group can be invaluable as at-risk fallers may have different physiology and psychological states the effect of their recurrent falls. These findings should therefore be corroborated with larger, prospective studies as it will be a crucial step for falls management strategies among the older people. Future research should now be directed at understanding the differences in currently available OA diagnostic criteria and reported symptoms, as well as the reasons underlying the association between falls and joint symptoms but the lack of association with OA using currently employed diagnostic criteria. Future research should also determine the reasons behind the contradictory association between decreased

risks of falls among radiographic OA patients with mild OA symptoms. A better understanding of factors that influence falls risk in this context is very much required in order to develop more effective management strategies for OA associated falls.

3.6 Conclusion

Mild OA defined using clinical and radiological criteria appeared to have a protective effect against recurrent and injurious falls, while severe OA using clinical criteria was associated with increased risk of falls. Our findings also provide evidence the relationship between OA and falls is not explained by physical limitations but psychological domains, with anxiety accounting for the protective effect of mild OA, and fear of falling accounting for the increased risk associated with severe OA. This intriguing conundrum between the symptoms of OA and falls will need to be further evaluated in larger prospective studies.

CHAPTER 4: POSTUROGRAPHY, FALLS AND OSTEOARTHRITIS

4.1 Introduction

It has been suggested that neuromuscular changes seen in those with knee OA is related to falls as it affects postural control among the older adults (J. Takacs et al., 2015). OA affects knee function by means of increase muscle weakness, impaired proprioception and reduced knee range of motions (Hassan, Mockett & Doherty, 2001; Knoop et al., 2011). In addition, the loss of balance associated with OA has been attributed to the symptoms of pain and stiffness (R. S. Hinman et al., 2002; Truszczynska et al., 2014).

While it would appear likely that falls occur in older adults with OA as the result of loss of postural control attributed to the symptoms of OA, this hypothesis has, however, not been substantiated by published evidence. We, therefore, evaluated the role of osteoarthritis in deficiencies in postural control observed among fallers.

In addition, no previous study has attempted to evaluate the relationship between the mechanical changes with postural control in the context of falls in older adults and very few studies have used magnetic resonance imaging (MRI) to link OA related symptoms to underlying pathological changes. For this chapter, we therefore also had an additional objective of determining the relationship between MRI features of OA and postural control in older adults with and without a history of falls in the preceding year.

4.2 Literature review

The association between postural control and falls among older adult was first reported in 1977 by Overstall *et al* (Overstall et al., 1977). The definition of 'postural control' or 'postural stability' is the control of the body's position in space for the purposes of stability and orientation (Woollacott & Shumway-Cook, 2002). Losing balance due to postural control impairment has been traditionally accepted as a risk of falling (Tinetti, Speechley & Ginter, 1988). Numerous previous prospective or retrospective studies have now confirmed the irrefutable link between falls and increased postural sway (Fernie et al., 1982; Maki, Holliday & Topper, 1994; Melzer, Benjuya & Kaplanski, 2004; Overstall et al., 1977; Sohn & Kim, 2015). Factors which influence postural control include age, muscle weakness, cognitive function and diseases of the central nervous system (Lord et al., 1999; Maylor & Wing, 1996).

Osteoarthritis has also been thought to influence postural control due to joint incongruence which will lead to increased postural sway (Spirduso, 1995). Studies have reported that patients with knee OA have significantly higher sway with both eyes open and eyes closed (R. S. Hinman et al., 2002; Wegener, Kisner & Nichols, 1997). While poor proprioception due to OA has been suggested as the culprit of losing balance among older adult with OA (Bennell et al., 2003; Hassan, Mockett & Doherty, 2001; Jerosch, Prymka & Castro, 1996; Knoop et al., 2011), this assumption however is remains unclear. One contrasting study has shown that poor proprioception is not related to disease-related functionality in knee OA (Baert et al., 2013). In a recent study, individuals with symptomatic OA were found to have altered behaviour in postural control compared to normal subjects (Turcot et al., 2015).

While previous studies have evaluated the influence of OA on the association between impaired postural balance and falls, these studies were small studies involving only a handful of subjects. Petrella *et al* reported that, regardless of the presence of OA, fallers are more likely to have poor limit of stability (Petrella et al., 2012). This study however only involved female participants. Using a balance platform, Alencar *et al* has found that women with OA who has a history of falls had worse functional performance compared to women with OA who were non-fallers (Alencar et al., 2007). This study had not involved controls without OA. There is, therefore, a need to further study to evaluate in more detail, the role of postural control in determining the risk of falls among individual with OA.

4.3 Methodology

4.3.1 Ethics approval

The study was approved by the University Malaya Medical Centre Medical Ethics Committee (reference number: 925.4) and was compliant with the WMA Declaration of Helsinki 2013 (World Medical, 2013). Written, informed consent was obtained from all participants.

4.3.2 Participants

This was also a sub-study from a larger randomized control trial, the Malaysia Falls Assessment and Intervention Trial (MyFAIT), detailed description of case selection can be found in Section 3.3.1.

4.3.3 Dynamic Postural Balance Assessment

Participant was tested with two established groups of balance tests: limits of stability (LOS), modified Clinical Test for Sensory Interaction and Balance (mCTSIB) using a long-force plate balance platform (Neurocom® Balancemaster, USA). The balance platform utilizes a fixed 18"x60" dual force plate to measure the vertical forces exerted through the participant's feet. Individual task outcome was recorded and analysed with the standard software supplied with the equipment.

4.3.3.1 Limits of Stability

The LOS battery of tests documents the maximum distance a person can intentionally displace their centre of gravity (COG). Subjects were asked to lean their body in the forward, backward, lateral and intermediate directions without losing balance, stepping, or reaching for assistance. The directional control (DCL) (the amount of movement in the intended direction minus the amount of extraneous movement (off axis), expressed as a percentage), end point excursion (EPE) (the distance travelled by the COG on the primary attempt to reach target, expressed in percentage), and maximal excursion (MXE) (the furthest distance travelled by the COG) were measured through this test.

4.3.3.2 Modified Clinical Test for Sensory Interaction and Balance

The mCTSIB quantifies postural sway velocity in four different sensory conditions: - eyes opened on firm surface, eyes closed on firm surface, eyes opened on unstable foam surface, and eyes closed on unstable foam surface. Subjects were asked to stand upright and to attempt to hold their position for 10 seconds for each test condition. Each condition was tested for three times. Composite sway is quantified as the mean sway velocity averaged over the 12 measurements and expressed in degree/second (deg/s).

4.3.4 Magnetic Resonance Imaging

MRI of both knees were performed using 3.0 Tesla Signa® HDx MR Systems (GE Healthcare, Milwaukee, Wisconsin, USA) with a body coil and standard knee protocol. The protocol included these sequences: coronal proton density weighted sequence, sagittal and axial 3D FIESTA (fast imaging with steady state acquisition) sequences. An additional axial T2-weighted fat saturation sequence extended proximally to both thighs was carried out for thigh muscle atrophy detection. Cartilage integrity is scored per region using Modified Outer Bridge score, with scores ranging from 0 (normal) to 4 (severe abnormality). For joint effusion, one knee-specific score was used, ranging from 0 (physiological amount of effusion) to 3 (large effusion). Presence or absence of synovitis was assessed.

4.3.5 Classification of OA

Individuals with no radiological evidence of OA were considered the "non-OA" group. Those with radiological changes consistent with OA (KL-grade 2-4) but who had not reported any clinical symptoms of OA like pain or stiffness were considered the "asymptomatic OA" group. Individuals with both radiological OA and presence of pain or stiffness in their affected joint were included in the "symptomatic OA" group.

4.3.6 Statistical Analysis

The SPSS 20.0 (IBM SPSS statistics) statistical software package was used for statistical analysis. Normality of data distribution was checked using the normality test. Continuous variables were reported as mean with standard deviation (SD) for normally distributed variables or median with interquartile range (SD) for non-normally distributed variables. The differences between fallers and non-fallers were assessed using the

independent sample t-test for continuous data and Chi-squared test for categorical variables. Linear regression analyses were used to adjust for the potential confounders to determine the association between LOS parameters with falls and OA.

Comparisons with MRI changes were only made with the mCTSIB scores. To avoid repetition, the mCTSIB scores were only reported for the subgroup who agreed to and received MRI scans. Individual and total mCTSIB scores were dichotomized using median cut-offs. Any scores above the median were considered higher sway velocity; Eyes Open, Firm surface (>0.40 deg. s^{-1}), Eyes Closed, Firm surface (>0.60 deg. s^{-1}), Eyes Open, Foam surface (>1.10 deg. s^{-1}), Eyes Closed, Foam surface (>2.00 deg. s^{-1}), and total mCTSIB (>1.10 deg. s^{-1}) respectively.

The associations between increased in severity of cartilage lesion and presences of OA related features with higher postural sway velocity from computed mCTSIB >1.10 deg. s^{-1} in fallers and non-fallers sub-group was analysed using logistic regression with dummy variables for each grade of cartilage lesion severity and absence as the reference group. The Chi-square test was used in multiple sub-group analyses according to MRI determined OA severity to determine the odds ratio for having high postural sway among fallers compared to the non-fallers with same abnormalities. Logistic regression analyses were used to determine the association between MRI features and higher sway velocity in computed CTSIB scores in fallers and non-fallers, adjusted for confounding variables. The strength of the associations was presented in odds ratios (OR) and 95% confidence intervals (CI).

4.4 Results

4.4.1 The Role of Osteoarthritis in the Limits of Stability among Fallers and Non-Fallers

4.4.1.1 Participant Characteristics

Posturography was available for 102 participants, 60 fallers and 42 non-fallers. Fallers were significantly older than non-fallers, and significantly more likely to report diabetes. No significant difference was found between fallers and non-fallers in terms of presence of OA (Table 4.1). Fallers had a lower mean ± standard deviation in performance score on MXE compared to the non-fallers (65.02 ± 17.61 vs 72.62 ± 14.48; p=0.023) and DCL (57.27 ± 13.88 vs. 62.91 ± 11.09; p=0.031) but no difference in EPE (52.07 ± 13.44% vs 55.77 ± 13.70%; p=0.185) were observed between fallers and non-fallers.

Table 4.1: Baseline characteristics of participants

	Fallers (n=60)	Non-fallers (n=42)	p-value
Age, years	74.54 ±6.07	70.71±4.66	**<0.001**
Gender, female n (%)	46 (80.7)	31 (68.9)	0.246
Ethnicity, n (%)			0.081
Malay	10 (17.5)	18 (40.0)	
Chinese	35 (61.4)	21 (46.7)	
Indian	11 (19.3)	5 (11.1)	
Others	1 (1.8)	1 (2.2)	
BMI kg/m^2	24.75 ± 4.48	24.83 ± 3.48	0.926
Comorbidities, n (%)			
Heart disease	1 (1.7)	1 (2.4)	0.807
Hypertension	34 (57.6)	19 (45.2)	0.219
Diabetes Mellitus	25 (42.4)	6 (14.3)	**0.003**
Stroke	3 (5.1)	0 (0.0)	0.264
Radiological OA, n (%)	51 (85.0)	29 (69.0)	0.640
Groups, n (%)			
No OA	8 (13.3)	7 (16.7)	0.640
Symptomatic OA	42 (70.0)	27 (64.3)	0.544
Asymptomatic OA	10 (19.0)	8 (16.7)	0.756
Dynamic postural parameters mean (SD)			
End Point	51.03 (14.36)	55.38 (13.75)	0.129
Maximal Excursion	65.02 (17.61)	72.62 (14.48)	**0.023**
Directional control	57.27 (13.88)	62.91 (11.09)	**0.031**

NOTE: Bold font indicates Statistical Significance. OA= Osteoarthritis, BMI= Body-mass index, SD= standard deviation

4.4.1.2 Within Group Comparison of Postural Control According to Osteoarthritis Classes

Table 4.2 displays the EPE, MXE and DCL score between the three OA categories; symptomatic OA, asymptomatic OA, and no OA, within the two main groups of fallers and non-fallers. Among fallers, there was no significant difference in EPE, MXE or DCL during three way comparisons using ANOVA between the non-OA, asymptomatic OA and symptomatic OA groups. Among non-fallers, significant differences were present in all three parameters EPE, MXE, and DCL. During pairwise comparison using post-hoc LSD, EPE, MXE and DCL were significantly different between the symptomatic OA and

asymptomatic OA groups, as well as non-OA and symptomatic OA groups, but no significant difference found between non-fallers with asymptomatic OA and non-fallers without OA indicating that presence of OA without symptoms were not likely to affect postural control. Instead only subjects with OA-related symptoms show evidence impaired postural control (Table 4.2)

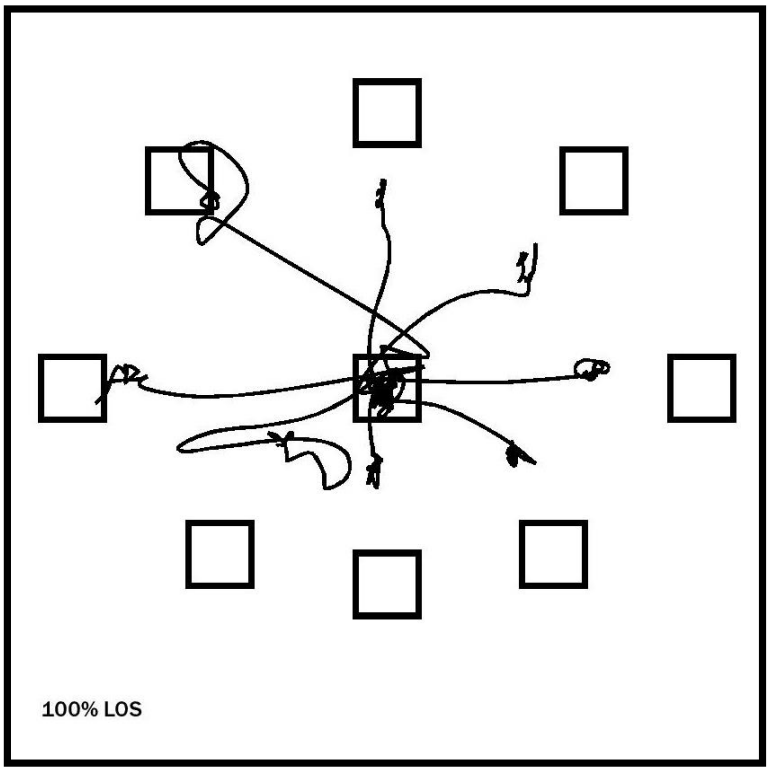


Figure 4.1: Good performance in LOS

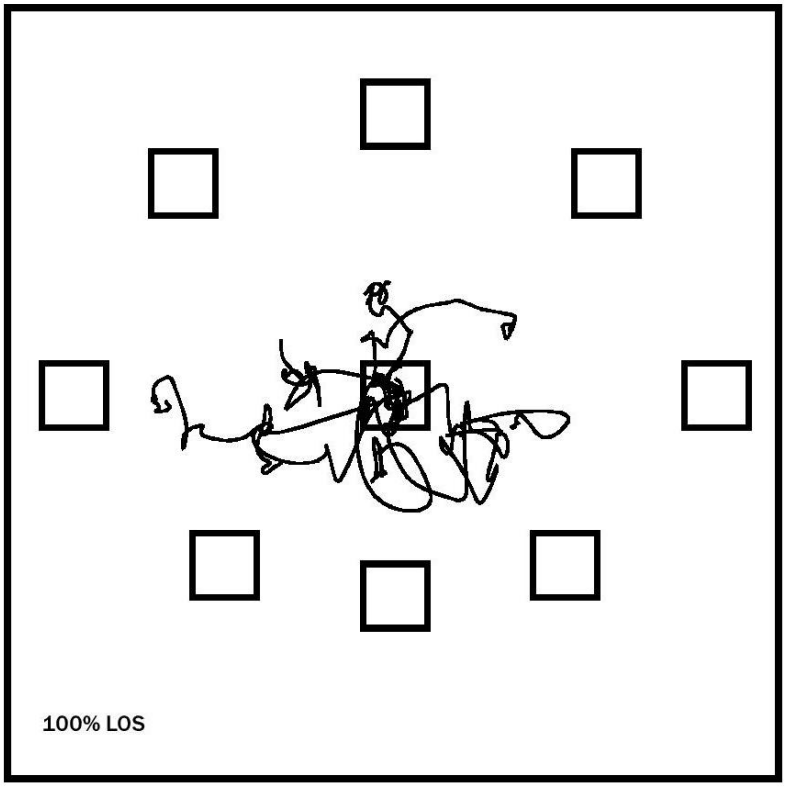


Figure 4.2 : Poor Performance in LOS

Table 4.2: Within Group Comparisons for Dynamic Postural Control Parameters

	Fallers (N=60)				Non-fallers (N=42)			
	No OA (N=8)	Asymptomatic OA (N=10)	Symptomatic OA (N=42)	P-value[a]	No OA (N=7)	Asymptomatic OA (N=8)	Symptomatic OA (N=27)	P-value[a]
End Point	55.25 (12.77)	49.40 (13.91)	50.62 (13.65)	0.660	64.29 (13.05) *	65.13 (13.52) ¥	50.19 (11.45) *¥	**0.003**
Maximal excursion	70.25 (13.61)	59.30 (14.58)	65.38 (18.83)	0.418	82.57 (10.64) *	78.50 (9.49) ¥	68.30 (14.96) *¥	**0.026**
Directional control	59.50 (16.04)	55.60 (14.91)	57.24 (13.52)	0.843	68.57 (10.52) *	68.38 (10.38) ¥	59.82 (10.56) *¥	**0.049**

NOTE: Bold font indicates Statistical Significance. Values are Mean (Standard deviation); OA= Osteoarthritis [a]P-value shows significance of One-way ANOVA analyses; *Significant ($p<0.05$) in pairwise comparison (Post-Hoc LSD) of No OA vs Symptomatic OA, ¥ Significant ($p<0.05$) in pairwise comparison (Post-Hoc LSD) of Symptomatic OA vs Asymptomatic

4.4.1.3 Mediators of Postural Control in Falls and Symptomatic OA

In order to evaluate the role of symptomatic OA in the loss dynamic postural control associated with falls, we ran separate linear regression models on all three LOS parameters as explained above. Models B and C were unadjusted models with MXE and DCL as dependent variables and a history of falls as the independent variable, which demonstrated significant associations between recurrent and injurious falls with lower MXE and DCL. These relationship, however, were no longer significant after controlling for age and diabetes (Model K and Model L), suggesting that the impaired postural stability observed among fallers was confounded by increasing age and comorbidities. The presence of symptomatic OA was significantly associated with lower EPE (Model D). The difference remained significant even after adjustment for age and comorbidities (Model M). When we then entered both falls and the symptomatic OA into the same linear regression equation in Model G, symptomatic OA was independently associated with poorer EPE regardless of the presence of falls, which remained significant after adjustment for confounders (Model P). The association between falls with worsening MXE (Model H) and DCL (Model I) on the other hand, was independent of the presence of symptomatic OA, but these associations were no longer significant after adjustments for age and diabetes in Model Q and Model R respectively (Table 4.3).

Table 4.3: Linear regression on the association of poor postural control, falls and symptomatic OA (N=102)

	End Point Excursion	Maximal Excursion	Directional Control
Unadjusted Models	Model A	Model B	Model C
Falls	-4.35 (-9.98-1.29)	**-7.60 (-14.15- -1.06)**	**-5.64 (-10.75- -0.53)**
	Model D	Model E	Model F
Symptomatic OA	**-7.34 (-13.16- -1.52)**	-5.02 (-12.02-1.97)	-4.15 (-9.59-1.30)
	Model G	Model H	Model I
Falls	-3.94 (-9.45-1.57)	**-7.34 (-13.88- -0.81)**	**-5.42 (-10.58- -0.32)**
Symptomatic OA	**-7.09 (-12.89- -1.29)**	-4.56 (-11.43-2.32)	-3.81 (-9.17-1.56)
*Adjusted Models**	Model J	Model K	Model L
Falls	0.828 (-4.91-6.57)	-3.17 (-10.11-3.78)	-0.51 (-5.59-4.56)
	Model M	Model N	Model O
Symptomatic OA	**-6.75 (-12.11- -1.40)**	-4.60 (-11.23-2.04)	-3.81 (-8.62-1.01)
	Model P	Model Q	Model R
Falls	1.14 (-4.46-6.74)	-2.96 (-9.88-3.97)	-0.34 (-5.38-4.74)
Symptomatic OA	**-6.80 (-12.14- -1.42)**	-4.47 (-11.12-2.19)	-3.79 (-8.64-1.05)

NOTE: Values are β-coefficient (95% Confidence Interval); OA= Osteoarthritis; * Adjusted for age and Diabetes Mellitus; Models A to F= unadjusted models with falls or symptomatic OA as independent variables.; Models G to I= unadjusted models with falls and symptomatic OA as independent variables; Models J to O=falls or symptomatic OA as independent variables adjusted for age and diabetes; Models P to R=falls and symptomatic OA as independent variables adjusted for age and diabetes. Significant relationships are indicated in bold.

4.4.2 Features of Osteoarthritis on Magnetic Resonance Imaging and Postural Stability

A total of 67 participants (33 fallers, 34 non-fallers) were investigated with both MRI and mCTSIB. Fallers showed poor performance in computed mCTSIB test after dichotomization (p-value=0.019) compared to the non-fallers. Proportion of tissue abnormalities detected by MRI findings were also similar between groups (Table 4.5).

Table 4.4: mCTSIB Features of Fallers and Non-Fallers.

	Fallers (n=33)	Non-Fallers (n=34)	p-value
Postural sway velocity, Median (IQR)			
Eyes Open, Firm surface	0.50 (0.40-0.60)	0.40 (0.38-0.50)	0.185
Eyes Closed, Firm surface	0.60 (0.45-0.75)	0.50 (0.40-0.70)	0.120
Eyes Open, Foam surface	1.20 (0.95-1.55)	1.10 (0.80-1.40)	0.168
Eyes Closed, Foam surface	2.10 (1.65-2.85)	2.00 (1.58-2.45)	0.250
Computed mCTSIB	1.20 (0.90-1.45)	1.10 (0.88-1.25)	0.089
High Postural sway velocity, n (%)			
Eyes Open, Firm surface (>0.40)	17 (51.5)	15 (44.1)	0.544
Eyes Closed, Firm surface (>0.60)	12 (36.4)	11 (32.4)	0.730
Eyes Open, Foam surface (>1.10)	17 (51.5)	13 (38.2)	0.274
Eyes Closed, Foam surface (>2.00)	18 (54.5)	15 (44.1)	0.393
Computed mCTSIB (>1.10)	18 (54.5)	9 (26.5)	**0.019**

NOTES*:* Bold font indicates Statistical Significance. BMI = body mass index; NA= not applicable, mCTSIB= the modified Clinical Test for Sensory Interaction and Balance

Table 4.5: Magnetic Resonance Imaging in Fallers and Non-fallers.

Characteristics	Fallers (n=33)	Non-Fallers (n=34)	p-value
Tissue abnormalities detected by MRI,			
Cartilage changes (0-4), n (%)			
Medial femoral condyle			
0	0 (0.0)	1 (2.9)	0.645
1	1 (3.4)	0 (0.0)	
2	13 (44.8)	17 (50.0)	
3	6 (20.7)	8 (23.5)	
4	9 (31.0)	8 (23.5)	
Lateral femoral condyle			
0	3 (10.3)	5 (14.7)	0.893
1	2 (6.9)	2 (5.9)	
2	18 (62.1)	18 (52.9)	
3	3 (10.3)	6 (17.6)	
4	3 (10.3)	3 (8.8)	
Medial patella facet			
0	1 (3.4)	1 (2.9)	0.523
1	0 (0.0)	1 (2.9)	
2	2 (6.9)	6 (17.6)	
3	5 (17.2)	3 (8.8)	
4	21 (72.4)	23 (67.6)	
Lateral patella facet			
0	1 (3.4)	3 (8.8)	0.869
1	1 (3.4)	1 (2.9)	
2	9 (31.0)	12 (35.3)	
3	10 (34.5)	9 (26.5)	
4	4 (13.8)	6 (17.6)	
Joint effusion (small & moderate), n (%)	26 (78.8)	29 (85.3)	0.539
Subchondral cyst, n (%)	16 (48.5)	22 (64.7)	0.222
Meniscal tears, n (%)	22 (68.8)	19 (55.9)	0.319
ACL tears, n (%)	9 (27.3)	7 (20.6)	0.576

NOTE: OA= Osteoarthritis, KL= Kellgren-lawrence, MRI= Magnetic Resonance Imaging, ACL=Anterior Cruciate Ligament

The sub-group analysis in Table 4.6 revealed that cartilaginous lesion severity and presence of tissue abnormalities in MRI were not significantly associated with impaired postural control in both group fallers and non-fallers (Table 4.6).

Table 4.6: Associations between increased in severity of cartilage lesion and presences of OA related features with higher postural sway velocity from computed mCTSIB >1.10 deg. s^{-1} in fallers and non-fallers sub-group

	Total mCTSIB >1.10 deg. s^{-1}, Odds Ratio (95%CI)	
	Fallers (n=33)	Non-fallers (n=34)
Cartilage changes (Grade 0-4)		
Medial femoral condyle		
Grade 0-2 (n=32) (reference)	1	1
Grade 3-4 (n=31)	1.50 (0.34-6.53)	0.87 (0.19-4.01)
Lateral femoral condyle		
Grade 0-2 (n=48) (reference)	1	1
Grade 3-4 (n=15)	5.46 (0.55-54.28)	0.27 (0.03-2.50)
Medial patella facet		
*Grade 0-3 (n=19) (reference)**	1	1
Grade 4 (n=44)	1.33 (0.26-6.83)	0.49 (0.10-2.36)
Lateral patella facet		
Grade 0-2 (n=34) (reference)	1	1
Grade 3-4 (n=29)	2.06 (0.46-9.14)	1.02 (0.22-4.72)
Joint effusion (n=55) **	1.82 (0.34-9.83)	0.48 (0.06-3.46)
Subchondral cyst (n=38) **	1.14 (0.29-5.41)	0.31 (0.06-1.51)
Meniscal tears (n=43) **	2.63 (0.57-12.18)	1.85 (0.38-9.08)
ACL tears (n=16) **	4.14 (0.71-24.16)	1.14 (0.18-7.28)

NOTE: * Grade 3 was included in reference group due to very small number, **the group with absence of the selected features was assigned as reference group, ACL= Anterior Cruciate Ligament, mCTSIB= the modified Clinical Test for Sensory Interaction and Balance.

Table 4.7 shows the logistic regression analysis to evaluate the association between falls and increased postural sway among older adults by testing the influence of OA features detected by MRI. In Model 1 after adjustment of diabetes mellitus, the associations remained statistically significant. The association remained unchanged with additional adjustment for grade 4 cartilaginous lesion in the medial patella facet (Model 2) and joint effusion (Model 3). However, the strong association between falls and high postural sway was attenuated in Model 4 and Model 5 with the additional adjustment for presence of sub-chondral cyst and menisceal tears respectively.

Table 4.7: Logistic regression models that examined the associations between high postural sway velocity from computed mCTSIB value (>1.10) and falls with adjustment of tissue abnormalities detected by MRI.

	Total mCTSIB >1.10 deg. s^{-1}, odds ratio (95% CI)	$R^{2\wedge}$
Falls		
Unadjusted Model	**3.33 (1.20-9.29)**	**0.108**
Adjusted Model 1[a]	**2.94 (1.02-8.47)**	**0.124**
Adjusted Model 2[b]	**3.05 (1.02-9.08)**	**0.136**
Adjusted Model 3[c]	**2.99 (1.00-8.91)**	**0.140**
Adjusted Model 4[d]	**2.96 (1.02-8.54)**	**0.125**
Adjusted Model 5[e]	2.82 (0.97-8.18)	0.134
Adjusted Model 6[f]	2.86 (0.97-8.45)	0.189

NOTES*:* Bold font indicates Statistical Significance. mCTSIB= The modified Clinical Test for Sensory Interaction and Balance, * Nagelkerke R^2. a = controlling for diabetes mellitus, b = controlling for diabetes mellitus + Grade 4 cartilage lesion in medial patella facet, c = controlling for diabetes mellitus and Grade 3 & 4 cartilage lesion in lateral patella facet, d controlling for diabetes mellitus + small or moderate joint effusion, e = controlling for diabetes mellitus + presence of subchondral cysts, f = controlling for diabetes Mellitus + presence of meniscal tears either in medial or lateral side or both sides

4.5 Discussion

4.5.1 OA in Falls Related Loss of Postural Control

Our study has demonstrated that while among older individuals with no known history of falls in the preceding year, postural control is influenced by the presence of symptomatic OA, this relationship does not exist among older individuals with a history of one injurious fall or two or more falls. While older fallers with OA does have significantly poorer postural control compared to non-fallers with no OA this relationship is confounded by increasing age and comorbidities but not OA symptoms. Furthermore, presence of symptomatic OA among older adults was found significantly associated with poorer end point excursion (EPE) which was not associated with falls. Our study therefore suggests rather controversially that, while OA does affect dynamic postural control in

older individuals, the impairments in dynamic postural control that exist among older fallers are not attributable to OA symptoms.

Postural stability is a complex and interactive system in the human body. With increasing age, the ability to maintain the body's centre of gravity (COG) over the base of support (BOS) in a given sensory environment reduces, and this usually occurs as a result of an accumulation of physical deficits (Sharma & Pai, 1997). Previous studies have shown that subjects with knee OA swayed significantly in standing balance more than control subjects in both lateral and antero-posterior directions (Hassan, Mockett & Doherty, 2001; R. S. Hinman et al., 2002; Khalaj et al., 2014; Pua et al., 2011). Few studies have, however, evaluated dynamic postural control among individuals with OA, or evaluated the effects of OA on dynamic control among older fallers (Khalaj et al., 2014).

We measured dynamic postural control on a balance platform which assesses directional control, end point excursion and maximal excursion. These measures are expected to reflect the individual's ability to maintain their stability while performing activities of daily living. The potential to effectively reach forward or upward for objects as part of an essential daily activity which requires dynamic balance is quantified in MXE performance, for instance. While impaired dynamic postural control is expected to increase the risk of falls, the actual occurrence of falls, however, is also dictated by the likelihood of the individual exceeding their limits of stability. This may not occur if the individual has good awareness of their limitations and is equipped with compensatory mechanisms to overcome their deficits.

Within the control group in our study, we were able to demonstrate distinct differences in dynamic postural control performance between those with symptomatic OA compared to those with asymptomatic OA as well as with no OA. This result is concordance with the previous findings that showed OA symptoms affected dynamic postural control (Edwards et al., 2014; R. S. Hinman et al., 2002; Khalaj et al., 2014; J. Takacs et al., 2015). Our result also had, however, shown that dynamic postural balance among non-fallers with asymptomatic OA were no different from those without OA suggesting that radiological OA in older adults is not likely affect their dynamic postural control unless they had OA symptoms. The relationship however attenuated after adjustment of age and comorbidities except EPE, suggesting that poor performance in MXE and DCL was due to old age and comorbidities but not EPE. Since EPE measures the distance travelled by the COG on the 'primary attempt' to reach target, the poorer EPE scores among the non-fallers with symptomatic OA can be related to their strategy in maintaining balance during LOS test. We postulate that this explains the lack of association with falls despite experiencing knee pain or stiffness, as these individuals had adapted by exercising an increased level of care by limiting their EPE. It is also possible that a fall may not necessarily occur despite the presence of dynamic postural instability should the older individual possess the ability to avoid activities which exceed their limits of stability.

Our cases were older individuals with a history of recurrent or injurious falls in the preceding year. While postural control was impaired in this faller group compared to non-faller controls, the presence of OA regardless of symptoms was not associated with any changes in the limits of stability among our fallers, despite there being similar numbers of fallers with radiological OA. This suggests the possibility that the presence of OA does not influence dynamic postural control among older individuals with

recurrent falls. Alternatively, as it is well established that falls occur due to the presence of multiple risk factors, therefore fallers universally have impaired dynamic control which may occur from numerous risk factors.

Our previous study has suggested that those with radiological evidence of OA with mild symptoms have lower risk of falls compared to those with asymptomatic OA (Mat, Tan, Ng, et al., 2015). Within our study, while non-fallers with asymptomatic OA had better dynamic postural control than non-fallers with symptomatic OA both in within and between group comparisons, this relationship was not observed among fallers. This would again support our previous hypothesis that individuals with radiological changes consistent with OA in the absence of clinical OA symptoms were more likely to take risks as they were unaware of their joint limitations. However, it is also possible that fallers with asymptomatic OA are falling from other risk factors.

In the multivariate analyses, the poorer dynamic postural control observed among fallers was not accounted for by symptomatic OA but was instead mediated by age and comorbidities. This indicates that the dynamic postural instability observed among fallers with symptomatic OA were not directly attributable to OA. Instead, individuals who are older with comorbidities such as diabetes also had an increased likelihood of having OA (Eymard et al., 2015; J Aging Phys ActLaiguillon et al., 2015). In essence, this challenges previous assumptions that OA symptoms was associated with increased risk of falls as a result in loss of dynamic postural control (Alencar et al., 2007; Petrella et al., 2012). In fact, as increasing age and the presence of comorbidities are also associated with other established falls risk factors including dementia and polypharmacy, which are not assessed in this study, it is possible that the loss of dynamic postural control associated in fallers only leads to falls in the presence of other established risk factors which have yet

to be elucidated. In other words, fallers have impaired dynamic postural control regardless of underlying pathology which include OA, but additional risk factors are required to convert a non-faller with impaired dynamic postural control into an actual faller.

4.5.2 MRI features of OA and Falls.

Our study was the first study to evaluate the effect of OA changes detected with MRI on postural sway and to relate it to recent falls. Fallers in our study had significantly greater postural sway compared to non-fallers in unadjusted analysis. There was no difference in MRI detected OA changes between fallers and non-fallers. Using multivariate analyses, the greater postural sway observed among fallers with OA was accounted for by the presence of subchondral cysts or meniscal tears.

Postural sway previously attributed to lack of proprioception acuity has been linked to falls among older adults (Fernie et al., 1982; Melzer, Benjuya & Kaplanski, 2004). The degradation of proprioception threshold and loss of sensitivity in the joints has been considered to be an effect of ageing leading to loss of appropriate proprioceptive feedback in response to any perturbation or changes in posture (Riemann & Lephart, 2002). Using well-established posturography techniques, the findings in our study were consistent with that of previous prospective studies which showed postural sway is a predictor and indicator of falls (Boulgarides et al., 2003; Fernie et al., 1982). Our study, however, challenges previous assumptions that the increased postural sway is attributed entirely to reduced proprioceptive accuracy with the demonstration that MRI structural changes accounted for the loss of postural control associated with falls.

Postural control is a complex neuromuscular task which requires delicate coordination of afferent and efferent peripheral nerve activity, accurate processing in the higher control centre, and adequate joint integrity and muscle strength to perform the

necessary postural adjustments. Therefore, the assumption that postural stability is affected by proprioceptive accuracy alone represents an oversimplification of a highly complicated mechanism, which sets the human species apart as the only permanent biped on planet earth. Ageing is associated with delayed anticipatory muscle activity measured with electromyography and subsequent larger compensatory muscle responses and hence postural sway is expected to increase with age (Kanekar & Aruin, 2014). Proprioceptive accuracy is also impaired in individuals with knee OA when compared to age-matched healthy controls, however the cause of such impairment remains unknown (Knoop et al., 2011). In a study evaluating proprioceptive ability among women with OA, proprioceptive accuracy was impaired in those with established OA but the impaired proprioception was not associated with postural control (Alencar et al., 2007). *Lyytinen* et al evaluated the relationship between postural control and thigh muscle activity among men with knee OA, and found no deficits in postural control, but evidence of increased activity in individuals with OA (Lyytinen et al., 2010) . A previous study on postural control among female fallers with knee OA in a controlled study had confirmed the presence of impaired postural control in this context (Alencar et al., 2007). The relationship between postural control, proprioceptive accuracy and muscle activation and the integration of these signals in higher processing centres therefore remains largely unexplored.

In this study, subjects with a history of falls had significantly higher postural sway compared to non-fallers with the same degree of severity and abnormalities in their knees. Using statistical methods, we were able to demonstrate that this loss of postural control among fallers is accounted for by visible structural changes using MRI techniques. Available evidence demonstrating intact postural control with increased muscle activity among those with OA, would suggest that non-fallers are able to adapt to challenges to

postural stability by increased postural adjustments through muscle activation which then protects the individual from falls. Shanahan et al had suggested that poor proprioception among OA subjects could be mediated by problems with mechanoreceptors, processing or relay of somatosensory input to higher centres, or joint-specific interference with cognitive processes by the chronic of knee pain (Shanahan et al., 2015). However, our study has actually clearly demonstrated differential structural changes between fallers and non-fallers with OA, suggesting that the presence of falls among those with OA is attributable to the underlying pathological process. While loss of postural control occurs as a direct result of the presence of subchondral cysts and meniscal tears.

Mechanoreceptors contained in the anterior and posterior knee meniscus play an important role in the regulation of postural control and proprioception (Aagaard & Verdonk, 1999; Brindle, Nyland & Johnson, 2001). A previous study has shown that meniscal tears are associated with clinically relevant impairment in balance and walking endurance (Lange et al., 2007). This study therefore provides the explanation needed for our observation, as we can deductively conclude that meniscal tears reduce proprioceptive ability, which may contribute to poor postural control and balance and consequently leading to falls. Subchondral cysts are formed during cartilaginous repair, and is only found in 30.6% of individuals with knee OA, compared to joint narrowing and osteophytes, which were ubiquitous in this population (Audrey, Abd Razak & Andrew, 2014). One previous study on hip OA had however suggested that presence of subchondral cyst is related to greater pain and disability (Kumar et al., 2013). The increased pain with likely upstream increases in inflammatory processes underlying the pain, as well as downstream consequences of reduced mobility and muscle wasting are likely to have a deleterious effect on postural control through loss of proprioception and reduced muscle strength.

4.5.2.1 Study limitation

We had inevitably excluded fallers who had difficulty performing the tests on the balance platform, which could lead to selection bias. However, we had specifically selected only individuals with injurious or recurrent falls, and excluded individuals with one fall without injury, as it is difficult to differentiate those who had purely accidental falls from those with increased risk of future falls in these individuals. We had therefore preselected cases who were at particularly high risk of future falls.

Our study was of cross-sectional design and therefore unable to establish a causal link between the MRI changes and falls outcome. Nevertheless, we have identified a positive relationship between structural changes observed on MRI with impaired postural stability associated with falls in older adults. This information will be invaluable in determining future strategies for falls prevention in the OA population. Future research should now seek to confirm prospectively the temporal relationship between postural instability from MRI structural changes with falls. The role of targeted therapies including pharmacological therapies to prevent and treat subchondral cysts as well as possible surgical and other novel therapies for meniscal repair to prevent falls in individual with knee OA should also be determined.

4.5.3 Conclusion

The pattern of loss of postural control observed among those with symptomatic OA represents a reduction in end-point excursion, while loss of maximal excursion and directional control were associated with increased risk of recurrent or injurious falls. Further, the impairment in postural control observed among fallers was not attenuated by the presence of symptomatic OA in multivariate analysis. Our findings therefore

challenge previous assumptions that OA is linked to falls via the mechanism of reduced dynamic postural control. It is likely that older individuals with recurrent and injurious falls developed impaired dynamic postural control from a variety of mechanisms including OA.

The increase in postural sway associated with falls in older adults is mediated by subchondral cysts and meniscal tears apparent on MRI. The underlying mechanisms by which structural changes affect postural stability has yet to be elucidation, but may be due to a combination of reduced somatosensory as well as motor response due to the inflammatory process and nociceptive stimuli linked to the pathological changes. This study has therefore identified potential therapeutic targets for the prevention of falls in individuals with OA, which is the commonest cause of disability world-wide. Subsequent research could now establish causal links and evaluate targeted therapeutic approaches based on our findings.

CHAPTER 5: ASSOCIATIONS OF OA BIOMARKERS AND FALLS AMONG OLDER ADULTS WITH KNEE OA

5.1 Introduction

A better understanding of the mechanisms underlying OA and its potential relationship with falls is of paramount concern because of the increasing prevalence of OA and falls with age, and the expectation of older adults to remain active. Existing tools of imaging to assess degenerative joint condition do not address symptoms and catabolic activities, and lacking of correlation between structural changes and symptoms in OA (Javaid et al., 2012). Innovations in biological therapy offer great promise in understanding the pathophysiology of 'heterogeneous' nature of OA in better way. Biochemical markers may provide more sensitive results as they may reflect anatomical and pathological changes in the earlier stage of OA development and throughout the course of disease. The objective of this study is therefore to identify potential biomarkers which would differentiate fallers from non-fallers among older adults with knee OA.

5.2 Literature review

In age-related OA, a low chondrocyte proliferation rate is observed with a resultant increase in matrix metalloproteinase markers (Aigner et al., 2007) . The Tissue Inhibitor of Metalloproteinases (TIMP1 and TIMP2) are expressed in fibroblasts, macrophages, and endothelial cells, and potently inhibits most matrix metalloproteinases (MMPs) (Vaalamo, Leivo & Saarialho-Kere, 1999). The presence of a high level of these biomarker in the blood stream therefore indicates the presence of cartilage degradation. On other hand, IL-6 which is a well-established marker for inflammation, pain and associated with knee cartilage loss in older people (Stannus et al., 2010). Neuropeptide

Y (NPY) is neurotransmitter that has been associated with pain and it suggested to be a putative regulator of pain transmission and perception in OA related pain (L. Wang et al., 2014).

We hypothesize that a higher level of each chosen biomarker would be associated with increased risk of falls. By comparing the levels of these candidate biomarkers among fallers and non-fallers, we will be able to better understand the mechanisms involved in the association between OA and falls.

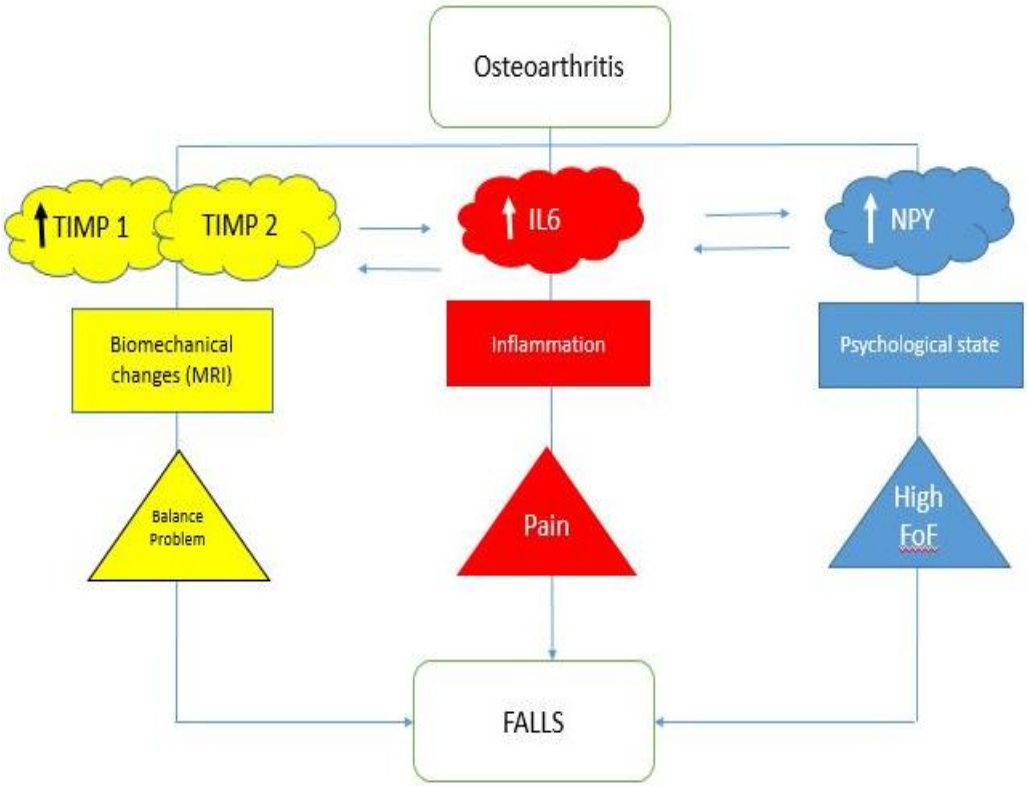


Figure 5.1: Theoretical framework on the association between OA biomarkers and falls

5.3 Methodology

5.3.1 Ethics approval

The study was approved by the University Malaya Medical Centre Medical Ethics Committee (reference number: 925.4) and was compliant with the WMA Declaration of Helsinki 2013 (World Medical, 2013). Written, informed consent was obtained from all participants.

5.3.2 Recruitment

Study participants consisted of older adults aged 65 years and above with at least two falls or one injurious falls over the preceding 12 months, while controls were volunteers with no falls over the past 12 months recruitment from the local community. Subjects were from our parent study, the Malaysia Falls Assessment and Intervention Trial (MyFAIT). Recruitment criteria for participants are described in section 3.3.1. Thirty participant who has agreed to donate their blood and undergone series of assessments (MRI, questionnaires and postural balance test) was included in this study.

5.3.3 Fear of falling

Fear of falling is measured using the seven-item short Falls Efficacy Scale-International (FES-I) (Kempen et al., 2008). The short FES-I enquires about concern for falling while performing various basic activities of daily living such as getting off a chair, showering or bathing, picking up objects, walking up or down slopes, going up or down stairs and going outdoors. The degree of concern is recorded with a four point Likert scale. The maximal score is 28, indicating extreme fear of falling, and the minimal score is 7, indicating no fear of falling.

5.3.4 Biomarker analysis

Single 7-ml blood samples were taken before the posturography assessments, and the serum was separated and frozen at -80^{o}C until analysed using enzyme-linked immunosorbent (ELISA). Samples were analysed in duplicate using commercially available ELISA kits specific to each biomarker:

- Biomarker related to matrix turnover: TIMP 1 and TIMP2 (R&D system)
- Biomarker related to inflammation: IL6 (Abcam)
- Biomarker related to symptoms: NPY (Abcam)

Determination of selected biomarkers concentration in serum were carried out using GraphPad Prism v5.0 (GraphPad Software, San Diego, CA, USA) software.

5.3.5 Postural Assessment

Postural control and stability were measured using the mCTSIB as described in section 4.3.3.

5.3.6 MRI imaging

A detailed description of the MRI protocol has been provided in Section 4.3.4.

5.3.7 Statistical analysis

The SPSS 20.0 (IBM SPSS Statistics) statistical software package was used for statistical analysis. Continuous data were expressed as mean (±standard deviation) or median (interquartile range). The independent t-test and Mann-Whitney U test were used as appropriate for comparisons. Categorical variables were expressed as frequencies with percentages in parentheses and analysed with the Chi-squared test. This study represents a proof of concept study to evaluate the possibility of explaining the hypotheses on the complex mechanisms underlying falls, and hence not powered to measure significant

associations. Instead, we conducted numerous exploratory analyses to identify potential trends in order to inform future larger studies. We examined distributions of biomarkers to assess the need for normalizing transformations and identify outlying values. Spearman correlations between all biomarkers, severity of cartilage lesion, WOMAC subscales, postural control, and fear falling with serum biomarker levels were calculated. We categorized the biomarkers into quartiles based on the distribution in the study population. Wilcoxon rank-sum and χ^2 tests for trend were used to test for differences in continuous and categorical baseline characteristics between quartiles of biomarkers. We evaluated the associations of the biomarkers with falls in 3 models, adjusting for confounders. Because of the expected heterogeneity of the lowest quartile group, we combined first and the second quartile group and assigned as reference group. Confounders were selected if the p-value associated with the variable was <0.10 in the models. Test of trend across quartiles of biomarkers were conducted by assigning a numerical value for each quartile and fitting this continuous variable in the model

5.4 Results

5.4.1 Demographic and clinical characteristic

Biomarkers were assessed for 30 participants (15 fallers, 15 non-fallers, mean age of 72.2±6.1 years, 67% females). After excluding haemolysed sample, the blood samples of 27 subjects were included for serum analysis. No difference was found in the baseline characteristics: age, gender distribution, ethnicity and body mass index (BMI) between the two groups Table 1. Fallers were reported to experience more stiffness. There was no difference in pain and physical function scores between fallers and non-fallers. No other difference was found in terms of comorbidities, MRI features, postural balance performance, and fear of falling (Table 5.1)

Table 5.1: Subjects' characteristic

	Fallers (n=13)	Non-fallers (n=14)	p-value
Age, years, *mean (SD)*	73.8 (5.1)	70.5 (4.0)	0.076
Gender, female n (%)	12 (92.3)	10 (71.4)	0.326
Ethnicity, n (%)			0.484
Malay	4 (30.8)	7 (50.0)	
Chinese	7 (53.8)	5 (35.7)	
Indian	1 (7.7)	2 (14.3)	
Others	1 (7.7)	0 (0)	
BMI, kgm^2, *mean (SD)*	25.9 (4.2)	24.4 (3.9)	0.324
Comorbidities, n (%)			
Diabetes Mellitus	4 (30.8)	3 (21.4)	0.678
Heart disease	0 (0)	0 (0)	NA
Hypertension	8 (61.5)	7 (50.0)	0.547
Stroke	0 (0)	0 (0)	NA
Visual Impairment	5 (35.5)	1 (7.1)	0.077
NSAIDs user, n (%)	0 (0.0)	2 (14.3)	0.481
WOMAC score, *median (IQR)*			
Pain	60 (0-150)	50 (0-150)	0.870
Stiffness	75 (0-100)	0 (0-50)	0.026
Physical function limitation	240 (111-555)	30 (0-350)	0.067
Grand total	350 (177-675)	70 (20-535)	0.126
MRI features (n=22)			
Cartilage Loss (Grade 4), n (%)			
Medial patella	11 (84.6)	10 (71.4)	0.187
Lateral patella	4 (30.8)	7 (50.0)	0.464
Medial femoral condyle	9 (69.2)	6 (42.9)	0.356
Lateral femoral condyle	3 (23.1)	2 (14.3)	0.270
Menisceal Tear, n (%)			
Medial	10 (76.9)	6 (42.9)	0.120
Lateral	4 (30.8)	3 (21.4)	0.678
Short FES-I score, Mean (SD)	14.31 (6.51)	11.71 (4.29)	0.230
Postural sway, Mean (SD)			
Standing balance	1.15 (0.33)	1.05 (0.31)	0.974

NOTE. BMI=Body Mass Index, NSAIDs= Non-steroidal anti-inflammatory drugs, WOMAC= Western Ontario and McMaster Universities, FES-l score= SD= Stander deviation, IQR= interquartile range, MRI=Magnetic Resonance Imaging

5.4.2 Anti-catabolic (TIMP1, 2), inflammatory (IL6) and symptoms-resiliency (NPY) biomarkers level in fallers and non-fallers

In Figure 5.1 fallers had elevated TIMP2 compared to the non-fallers (median (IQR), 94.74 (82.70-101.66) vs 80.38 (73.10-85.88), p-value= 0.017) respectively. There was no significant difference between groups for TIMP1, IL6, and NPY level.

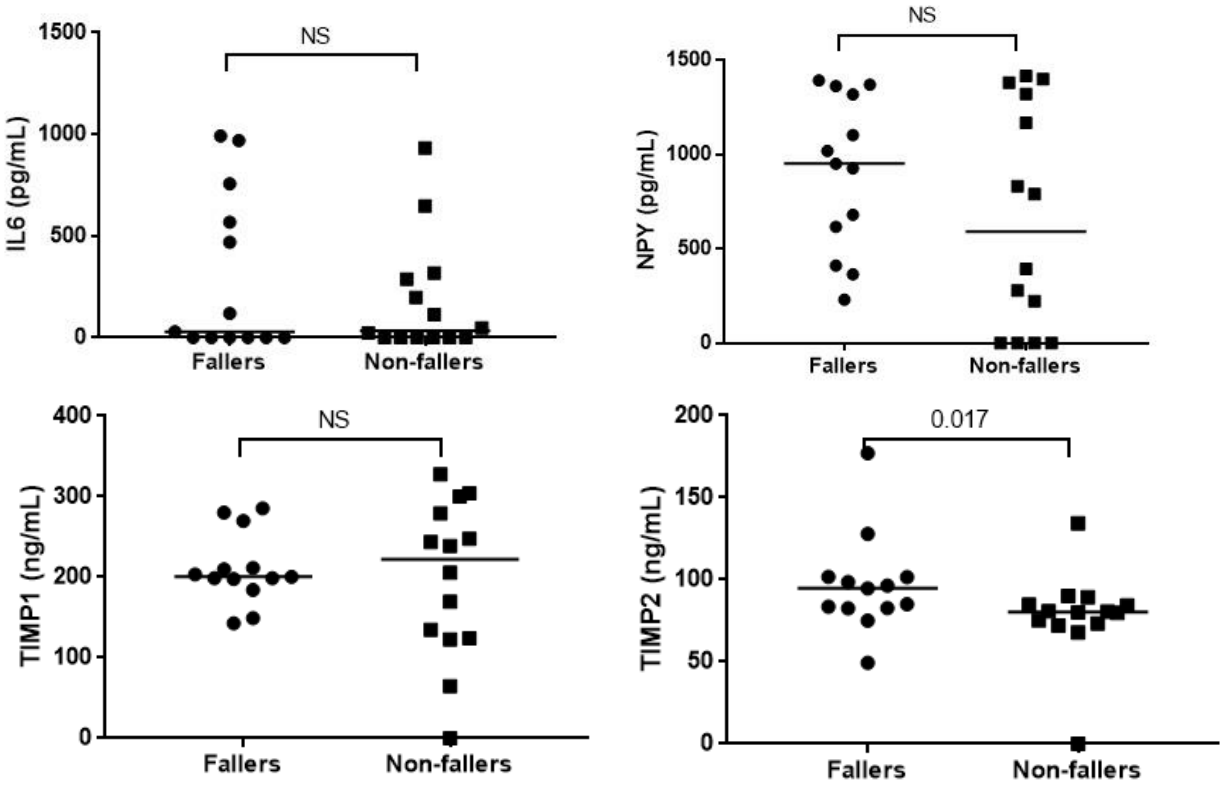


Figure 5.2: Anti-catabolic (TIMP1 and TIMP 2), inflammatory (IL6) and symptoms resilience (NPY) biomarkers values among fallers and non-fallers

5.4.3 Correlation between anti-catabolic (TIMP1, 2), inflammatory (IL6) and symptoms-resiliency (NPY) biomarkers

Table 5.2 documents the Spearman correlation (r_s) between all four biomarkers in faller and non-faller groups. Using the higher significance cut-off of $p<0.20$, among the non-fallers, TIMP2 was negatively correlated with IL6 and TIMP1, while in the faller group, TIMP1 showed negative correlation with NPY level.

Table 5.2: Correlations among biomarkers in fallers and non-fallers

		TIMP2	IL-6	NPY
Non-fallers (n=14)	TIMP1	-0.437 (0.118) *	0.144 (0.623)	-0.116 (0.694)
	TIMP2		-0.377 (0.183) *	-0.067 (0.821)
	IL6			0.025 (0.931)
Fallers (n=13)	TIMP1	-0.355 (0.234)	0.084 (0.785)	-0.462 (0.112) *
	TIMP2		0.286 (0.343)	0.275 (0.364)
	IL6			0.350 (0.242)

NOTE: Data in Table represent: Spearman's r (p-value), * indicate significance at $p<0.20$, TIMP1/2, tissue inhibitor of metalloproteinase, IL-6, Interleukin-6, NPY, Neuropeptide Y

5.4.4 Correlation between biomarkers and clinical characteristic

Table 5.3 demonstrated the correlation between increased in cartilage lesion severity and the concentration of all biomarkers. In non-fallers sub-group, increased in cartilage lesion severity on medial femoral condyle and lateral femoral condyle were significantly negatively correlated with NPY serum level. While in fallers sub-group, their NPY was significantly positively correlated with increased in cartilage lesion severity in medial patella site

To evaluate the association between severity of symptoms and function with biomarkers, Spearman correlation tests were performed. In the fallers group, WOMAC physical limitation and total WOMAC were positively correlated with TIMP 1. While TIMP2 was positively correlated with increased postural sway measured by mCTSIB. In the non-fallers group, the concentration of NPY was negatively correlated with WOMAC stiffness score, and IL6 was positively correlated with short FES-I scores (Table 5.4)

Table 5.3: Correlation Spearman R of concentration of biomarkers in fallers and non-fallers with increased in degrees of cartilage lesion.

	Increased in Cartilage lesion severity, Spearman rho			
	Medial Patella facet	Lateral Patella facet	Medial Femoral condyle	Lateral femoral condyle
Biomarkers				
Non-fallers (n=14)				
TIMP 1	-0.155	0.297	0.514	0.059
TIMP 2	-0.025	0.080	-0.243	0.359
NPY	-0.360	-0.284	-0.535*	-0.768**
IL6	0.084	0.201	0.531	-0.100
Fallers (n=13)				
TIMP 1	0.057	0.313	0.075	0.119
TIMP 2	0.057	0.040	0.311	-0.540
NPY	0.627*	0.195	0.285	-0.199
IL6	0.420	0.314	0.325	0.410

NOTE: TIMP1/2, tissue inhibitor of metalloproteinase, IL-6, Interleukin-6, NPY, Neuropeptide Y, * indicate significant at < 0.05, ** indicate significant at < 0.01

Table 5.4: Correlation Spearman R between Biomarkers and Symptom Severity, Fear of Falling and Postural Control

	WOMAC Pain	WOMAC Stiffness	WOMAC Physical function limitation	WOMAC grand total	Short FES-I	Postural Sway
Biomarkers						
Non-fallers (n=14)						
TIMP 1	0.224	0.156	0.229	0.145	0.052	0.129
TIMP 2	-0.173	-0.122	0.098	-0.029	0.074	0.120
NPY	-0.163	-0.577*	-0.181	-0.264	-0.113	0.295
IL6	0.215	0.339	0.280	0.244	0.591*	-0.111
Fallers (n=13)						
TIMP 1	0.064	0.279	0.598*	0.558*	-0.017	-0.085
TIMP 2	-0.083	-0.274	-0.281	-0.330	-0.080	0.579*
NPY	-0.006	0.365	-0.050	-0.121	0.476	-0.059
IL6	-0.317	0.029	-0.146	-0.165	0.240	0.311

NOTE: *indicate significance at $p<0.05$; FES-I, Short Falls efficacy fear of falling test international; TIMP1/2, tissue inhibitor of metalloproteinase, IL-6, Interleukin-6, NPY, Neuropeptide

5.4.5 Association between anti-catabolic, inflammatory, and symptom-resilience biomarkers with risk of falls

To study the association between biomarker levels and the risk of falls, we categorized data into 3 groups to identify potential trends, the data was first divided into quartile, and the first and second quartiles then merged to form one group, with the third and fourth quartiles making up the second and third groups respectively. In unadjusted linear model across quartiles, TIMP2 showed a significant association between increase TIMP2 in serum and falls risk. Specifically, a significant (P_{trend}=0.023) association was found for quartile comparison (Q4 versus (Q1-Q2 as the reference)). The association remained significant even after adjustment for potential confounding factor (age and visual impairment) (P_{trend}=0.036) in and further additional adjustment of symptom severity (P_{trend}=0.027). However, the association was no longer significant after the adjustment for cartilage lesion severity (P_{trend}=0.055). No significant association was identified for TIMP1, IL-6 and NPY biomarkers with fall risk (Table 5.5).

Table 5.5: Odds Ratios (OR) and 95 % Confidence Intervals (CI) of falls by quartiles of biomarkers

	Q1-Q2	Q3	Q4	P-trend
TIMP1				
No of cases/total (%)	6/12 (46.2)	2/6 (15.4)	5/9 (38.5)	
Unadjusted	1.0 (reference)	0.10 (0.01-1.54)	0.25 (0.02-3.10)	0.852
Multivariable[a]	1.0 (reference)	0.35 (0.03-3.90)	1.00 (0.14-7.43)	0.978
Multivariable[b]	1.0 (reference)	0.05 (0.0-2.18)	0.88 (0.10-7.43)	0.937
Multivariable[c]	1.0 (reference)	0.47 (0.04-6.11)	0.94 (0.12-7.57)	0.995
TIMP2				
No of cases/total (%)	4/13 (30.8)	3/7 (23.1)	6/7 (46.2)	
Unadjusted	1.0 (reference)	1.69 (0.25-11.34)	13.50 (1.20-152.21)	**0.023**
Multivariable[a]	1.0 (reference)	3.64 (0.25-53.41)	16.61 (1.14-241.68)	**0.036**
Multivariable[b]	1.0 (reference)	1.73 (0.06-48.58)	28.65 (1.62-505.38)	**0.027**
Multivariable[c]	1.0 (reference)	2.80 (0.29-26.95)	13.82 (0.89-214.17)	0.055
IL-6				
No of cases/total (%)	6/13 (46.2)	1/6 (7.7)	6/8 (46.2)	
Unadjusted	1.0 (reference)	0.23 (0.02-2.59)	3.50 (0.51-24.27)	0.539
Multivariable[a]	1.0 (reference)	0.28 (0.02-3.80)	3.03 (0.35-25.94)	0.622
Multivariable[b]	1.0 (reference)	0.26 (0.02-3.72)	2.87 (0.34-24.45)	0.526
Multivariable[c]	1.0 (reference)	0.67 (0.04-10.84)	3.31 (0.28-39.72)	0.743
NPY				
No of cases/total (%)	5/13 (38.5)	5/6 (38.5)	3/8 (23.1)	
Unadjusted	1.0 (reference)	8.00 (0.71-90.00)	0.96 (0.71-90.00)	0.454
Multivariable[a]	1.0 (reference)	6.39 (0.45-89.96)	1.48 (0.20-11.28)	0.553
Multivariable[b]	1.0 (reference)	8.32 (0.50-137.68)	1.79 (0.21-15.01)	0.547
Multivariable[c]	1.0 (reference)	5.00 (0.32-78.16)	2.03 (0.24-17.28)	0.424

NOTES: Bold font indicates Statistical Significance. a = adjusted for age, visual impairment, b = adjusted for age, visual impairment, and WOMAC Grand total, c = adjusted for age, visual impairment, increased in cartilage lesion severity, TIMP1/2, tissue inhibitor of metalloproteinase, IL-6, Interleukin-6, NPY, Neuropeptide

5.5 Discussion

To our knowledge, this is the first study to evaluate TIMPs, IL-6 and NPY as a prognostic biomarker for falls among older adult with osteoarthritis. We observed significant associations between increased risk of falls and elevated concentration of the anti-catabolic biomarkers (TIMP2). The associations were independent from increasing age, visual impairment and OA symptom severity but mediated by increased cartilage lesion severity. This study therefore suggests that TIMP2 may play a role as a putative regulator of falls or biomarker of falls among older adults with knee OA and may have the evaluating role for higher disease burden among fallers which could not be distinguished from anatomical changes through imaging modalities.

The tissue inhibitor metalloproteinase enzyme TIMP2 acts as an anti-catabolic protein that's regulate matrix metalloproteinases (MMPs)'s degradation activities in OA pathogenesis (Nagase, Visse & Murphy, 2006). It is one of the peptide proteins that is involved in degradation of the extracellular matrix. In addition to this inhibitory role against metalloproteinases, it plays critical role in the maintenance of tissue homeostasis (Bourboulia & Stetler-Stevenson, 2010). TIMP-2 inhibits the activity of all matrix metalloproteinases (MMPs), and its expression is constitutive, in contrast to the other TIMPs members which are inducible (G. Murphy & Nagase, 2008). Thus, the increase in TIMP2 among fallers with OA could indicate that there is excessive production of MMPs among those faller with OA. We suggested that the increased in protective biomarkers such TIMP2 as well as MMPs will indicate a more active degenerative state in fallers group compared to the non-fallers (Cattano et al., 2011). On other hand, a previous study had found that the increase in TIMP2 expression in the synovium of OA subjects represents an attempt to control proteolysis activity in the joint (Davidson et al., 2006).

The correlation analysis among biomarkers have been performed with in a targeted manner to facilitate further understanding of the expression of biomarkers among fallers and non-fallers. We found that there was a negative correlation between TIMP2 and TIMP1 among non-fallers. This finding is parallel to a genetic expression study among arthroplasty patients compared to non-OA control subjects. The investigators found increased TIMP2 expression in the synovial fluid, while TIMP1 was down regulated in infected cartilage (Kevorkian et al., 2004). That led us to assume that may be genetic polymorphisms may exist which leads to the differential expressed of those two enzymes among fallers and non-fallers.

Furthermore, among non-fallers the result of TIMP2 showed a negative correlation with IL6 that means the degree of inflammation plays a limited role in falls. An in-vitro study found that inhibition of IL6 in the synovial fluid caused decreased matrix production in OA explants (Tsuchida et al., 2012). Therefore, IL6 plays an anabolic role and the negative association with TIMP2 could be explained by the protective effect of IL6 from falls. Previous studies had, however, been done on few samples and further investigations on the effect of this biomarker should be done on larger sample to confirm our current finding.

There was a negative correlation between TIMP1 and NPY. NPY has multiple actions on cardiovascular performance, food intake (Pedrazzini, Pralong & Grouzmann, 2003), pain processing, inflammation and autoimmunity (Bedoui et al., 2003). Blood vessels around inflamed joint capsules have been increased NPY expression (Ichikawa et al., 1989). A case control study using radiographic OA grading found that NPY acts as a putative regulator of pain transmission and perception of pain in KOA patients. They also found a higher concentration of NPY in synovial fluid indicative of severity and

progression of Knee OA (L. Wang et al., 2014). Neuropeptide-Y plays important role in modulating individual variations in emotional and stress resilience (Heilig, 2004). In other word, this negative correlation may refer to individual differences in the response to OA symptoms. Alternatively the duration of OA could be the cause of this negative association (Gulec et al., 2010). The role of NPY in OA symptoms appears to be as key regulator of symptoms transmission and perception (L. Wang et al., 2014). The changes in NPY levels in the non-faller group suggested that non-fallers have greater adaptive ability. Adaptation to pain is an important strategy for accommodation of symptoms (McCracken & Eccleston, 2003).

Concentration of TIMP2 was positively correlated with increased in postural sway (standing) among fallers but not non-fallers. While no difference in postural control was observed between fallers and non-fallers there appears to be difference in TIMP2 expression in relation to postural control. To our knowledge, no previous clinical study has reported any association between balance and biomarker concentration. A previous animal study on OA had, however, found that deficiencies in TIMP2 was associated with motor deficits (Jaworski et al., 2006) and it has also been shown that reduced TIMP2 is associated with muscle weakness (Lluri et al., 2006). Both studies are however contrasting to our findings which may be explained by the presence of other comorbidities such diabetes or other metabolic disorders which were also present in our subjects.

When we correlated WOMAC scores with biomarkers we found that the physical limitation and overall OA severity were positively correlated with TIMP 1 among fallers. The increase in TIMP expression is also associated with decreased collagenase activity (Reichenstein et al., 2004). This result could indicate that increased TIMP1 production among fallers occurred in response to the high cartilage degradation. No previous reported

data has correlated TIMP1 with physical performance before. Only one previous report has been documented a negative correlation between TIMP2 6-minute walk performance among patients with heart failure (Bhalla et al., 2011).

The significant association of TIMP2 after adjustment for age and visual impairment, as well as age, visual impairment and WOMAC score confirmed that TIMP2 may have important role in determining the likelihood of falling since as it was not affected by other risk factors associated with falls in our population. The relationship was then attenuated by further adjustment for increased in cartilaginous lesion severity which indicates that the relationship between TIMP2 and falls is cartilage destruction, and therefore affirms the value of TIMP2 as a marker of cartilage degradation. The degree of cartilage degradation found by arthroscopy has been found to be strictly related to matrix metallopeptidase (MMP2 and MMP13) enzymic activity and the reducing inhibitory effect of MMP2 by TIMP2 (Marini et al., 2003). The gelatinase enzyme MMP2 plays an important role in extracellular matrix break down within the chondrocyte (Kinoshita et al., 1998) and is mostly expressed in high levels osteoarthritic cartilage cultures compared to normal cartilage cultures (Galasso et al., 2012). The attenuation after controlling for cartilage loss severity therefore strengthens our assumption that elevated TIMP2 indicates the more active degenerative state among fallers compared to non-fallers.

Our findings are unique as this was the first study to evaluate biomarker of falls among older adults with OA. However, because of the exploratory nature of this study, several limitations should be highlighted. First, control subjects without OA was not included. Although this was considered in the design of the MyFAIT study, the aim of the current pilot was to determine the contribution of OA serum candidate biomarkers to falls with the assistance of imaging technique, but not to determine specificity of the biomarkers

for diagnosing OA. The decision was therefore to focus on individuals with OA but varying in falls risk in order to identify the potential serum biomarkers to be used as a metric to monitor treatment for falls prevention. No firm conclusions should be drawn from this proof of concept study which has now confirmed the feasibility of using selected biomarkers as a means of mapping out complex mechanisms for the relationship between a multi-factorial disease as a risk factor to a multi-factorial outcome. Our preliminary results will now help justify the use of additional resources to perform such investigations.

5.6 Conclusion

Biomarkers are potentially important tools for the evaluation and diagnosis of morbidities associated with OA. The matrix turnover marker, TIMP2, was associated with increased risk falls among older persons with OA. The increased burden of disease represented by elevated anti-catabolic OA biomarkers revealed the underlying mechanism involved in the OA-falls relationship. Our findings have identified a preferred biomarker for future studies involving falls among OA patients. Further investigations should now be done to confirm the putative value of biomarker in understanding falling among OA patients.

CHAPTER 6: THE EFFECT OF OTAGO EXERCISE PROGRAMME (OEP) ON POSTURAL BALANCE, FEAR OF FALLING, AND FALLS RISK IN FALLERS WITH OSTEOARTHRITIS: A RANDOMIZED CONTROLLED TRIAL

6.1 Introduction

Falls prevention programmes in older people have been studied for decades with the most widely studied intervention being physical therapy (Gillespie et al., 2012). Considering the consequences of falls and the multifactorial nature of falls, the development of effective treatment strategies is important but require the cooperation of multiple agencies. As individuals with OA represent a specific group with disability, falls prevention programmes on this targeted population should take into account physical symptoms and barriers associated with OA. It has been suggested that physical therapy can benefit osteoarthritic older adults when it is of the correct form and intensity (Clyman, 2001), failing to meet the criteria may contribute to lack of success (Bennell, Buchbinder & Hinman, 2015). Furthermore, interventions which have a 'snowball effect' that could reduce multiple existing risk of falls in individuals simultaneously such as fear of falling, and gait and balance problems should be encouraged. Therefore, this study is conducted to evaluate the effect of the Otago exercise programme (OEP) on postural balance, fear of falling and falls risk in fallers with knee OA.

6.2 Literature review

Exercises which are characterized as mild to moderate are the most widely accepted treatment for OA. However, in falls prevention programmes the type of physical therapy involved are varied. Only adequately supervised exercise programmes have been found

to result in increased overall wellbeing and improvement in affected joints without acute flare of osteoarthritis (Rush, 2003).

In our earlier systematic review (Chapter 2, subtopic 2.4) on physical therapies in improving balance and reducing falls risk, Tai Chi, aerobic and strengthening exercise were found to have has benefited older adults with OA (Mat, Tan, Kamaruzzaman, et al., 2015). Existing published studies, however, have not used actual falls outcome (falls diaries), instead, surrogate outcome for falls such as balance and falls risk tools are employed. This is in contrast with the established studies in falls prevention programmes which had not been conducted exclusively among OA patients (Gillespie et al., 2012). Therefore, studies using actual falls outcomes should be conducted to evaluate the real effect of intervention in preventing falls among older adults with OA.

The Otago Exercise Programme (OEP) is effective in primary falls prevention (Gillespie et al., 2012). A Cochrane review on community-based interventions for falls prevention confirmed the effectiveness of OEP among older adults aged 75 years and above (Campbell et al., 1999a; Campbell et al., 1997; Gillespie et al., 2012; Robertson et al., 2001). The OEP, however, has not previously been tested among older fallers with OA. Our objective was, therefore, to evaluate the effects of a modified OEP delivered as part of a multifactorial intervention program on postural control and FoF in fallers who had knee OA and established gait and balance problems. In addition, fall recurrence and fall frequency were also considered to inform future larger studies.

6.3 Methodology

6.3.1 Ethics approval

The study was approved by the University Malaya Medical Centre Medical Ethics Committee (reference number: 925.4) and was compliant with the WMA Declaration of Helsinki 2013 (World Medical, 2013). Written, informed consent was obtained from all participants.

6.3.2 Study Design and Protocol

This represents a pre-planned subgroup analysis of the MyFAIT study with additional physical evaluation. Only the results of individuals with mild OA with gait and balance disorders were included in this sub study. The protocol of this study has been described elsewhere (P. J. Tan et al., 2014). Within the MyFAIT study, individuals aged 65 years or above with two or more falls or at least one injurious fall were recruited from primary care, hospital outpatient clinics and the emergency room. Eligible individuals received a multifaceted falls risk assessment and were then randomized to multifaceted falls intervention including gait and balance exercises, home hazards intervention, cardiovascular intervention, medications review, visual intervention and falls education, while control participants received health advice and conventional treatment. The criterion for gait and balance impairment was a TUG score of 13.5s. Therefore, individuals with radiological evidence of OA with a TUG score of 13.5s or above were included in this sub-study. Individuals randomized to the intervention arm of the MyFAIT study were considered the OA-falls intervention group, while the other fallers with radiological OA were who were randomized to the control intervention were considered as the OA-falls control group.

6.3.3 Severity of OA

Radiological and symptoms severity of OA was assessed with KL grading score and with the Knee Injury and Osteoarthritis Outcome score (KOOS). KOOS was a self-administered questionnaire which assesses all three domains of WOMAC (described earlier in 3.3.3.2 section) with the addition of sports and recreation function, and knee-related quality of life and has been found to be reliable, had better response to surgery and physical therapy and has been suggested to be used for short term and long-term follow up (Roos et al., 1998; Roos & Toksvig-Larsen, 2003). The KOOS scores were reassessed at six months to determine the effects of OEP intervention on OA symptoms.

6.3.4 Outcomes measures

The primary outcome measure for this study was time to first fall measured using a monthly fall diary. The diaries consisted of daily entries for the presence of absence of falls. The first diary was given to the patient upon randomization. Subsequent diaries were posted out to the participants monthly with a self-addressed, stamped envelope, and participants were reminded to return their diaries through telephone calls.

The secondary outcomes included falls recurrence, falls rate, fear of falling, and postural control. Postural control was assessed using posturography using a long force plate balance platform and the standard batteries mCTSIB and LOS which have been described in Section 4.3.3. Fear of falling was assessed with the short FES-I (Section 3.3.6.1). The latter two parameters were measured at baseline and six months. All measurements were conducted by the same trained assessor blinded to treatment allocation.

6.3.5 Modified Otago Exercise Programme (OEP)

The full-scale OEP starts with 5 minutes of flexibility exercises, followed by 17 strengthening and balance exercises - strengthening exercises for the knee extensors, knee flexors, hip abductors, ankle plantar flexors, and ankle dorsi flexors and; balance exercises such as knee bends, backwards walking, walking and turning around, sideways walking, tandem walking, tandem standing, one leg stand, heel walking, toe walking, heel toe walking backwards, sit-to-stand, and stair climbing (Campbell et al., 1999b). The original OEP included a walking component, which we have not included in this modified programme. All exercises (flexibility, strengthening, and balance) will take approximately 30 minutes to complete and is performed at least three times a week. Prior to the exercises, a baseline assessment was performed by an OEP-trained physiotherapist to prescribe individual exercise programs from the OEP manual. Each participant would receive an exercise manual which consists of large-print pictures and instructions of prescribed tailored exercises. They were also given a pair of ankle weight cuffs, weighing 0.5 to 1 kg for lower limb strengthening exercises. Each participant was invited to the hospital monthly for 6-months to be re-assessed by the physiotherapist, who made progressive adjustments according to the OEP exercise manual.

6.3.6 Adherence to the OEP

Intervention adherence was defined as the number of OEP days completed divided by the number of OEP days prescribed. This was monitored using a calendar given to the participants at the start of the OEP. Participants were advised to document the frequency and duration of exercises performed at home. The calendar was returned to the hospital monthly during hospital visit. If the calendar was not returned, the participants would be contacted by telephone.

6.3.7 Statistical analysis

As this was a sub-study of a larger randomized-controlled study, it was intended as a pilot study to inform a larger future randomized controlled study involving definitive falls outcomes, and hence not powered to detect a significant difference in its primary outcome of time to first fall. Power calculations were conducted using G*Power 3.1 (Faul et al., 2007). Assuming 50% of our sample without intervention will experience a further fall within six months, a sample size of 46 will provide 80% power to detect an 80% reduction in fall recurrence. Data were analysed using SPSS statistical software, version 21, using the intention-to-treat analysis. The outcome measures and mean differences between intervention and control groups were analysed using the independent t test. Within-group changes from pre- to post-exercise intervention were analysed by using paired Student's t tests. Between-group comparisons post-intervention were performed using analysis of covariance, with baseline measurements as the covariate. We used a Cox Proportional hazards model to analyse the time from randomisation to first fall and the significant difference between arms were tested using Log-rank. Mean time to first fall and 95% CI were calculated and time to fall were summarized graphically by Kaplan-Meier curve. Statistical analysis was performed using SPSS, version 20.0 with significance set at P-value <0.05.

6.4 Results

6.4.1 Demographic characteristic of subjects

A total of 41 subjects were included in this study, 24 were in control group and 17 were intervention. Demographic characteristic displayed in Table 6.1. Average age± SD of participants was 73.3 years±5.8 (range 69.5-78.0y) and 80.5% from them were women.

Table 6.1: Subjects' characteristic

Characteristics	Control (n=24)	Intervention (n=17)
Age	71.92 (5.06)	76.29 (5.86)
Sex, n (%)		
Male	5 (20.8)	3 (17.6)
Female	19 (79.2)	14 (82.4)
Ethnicity, n (%)		
Malay	4 (16.7)	3 (17.6)
Chinese	17 (70.8)	8 (47.1)
Indian	2 (8.3)	6 (35.3)
Others	1 (4.2)	0 (0.0)
BMI	24.19 (3.64)	25.85 (5.39)

NOTE: N=42 Values expressed as n (%), or mean±SD (range).

6.4.2 Osteoarthritis Symptoms Severity

Table 6.2 shows the within group analyses, and Table 6.3 shows the between group analyses for KOOS scores. Both within and between groups analyses did not show any significant differences in changes in OA symptoms at six-month follow-up.

6.4.3 Postural Control

Within group analyses are listed in Table 6.2. No differences in postural control parameters were observed after six months within the control group. For the intervention group, however, significant improvements in maximal excursion and directional control ($p<0.05$) and decreased postural sway in *Eyes Open, Foam surface* were observed after six months. Between group comparisons using analysis of co-variance adjusted for baseline measurements revealed significant improvements in directional control in the intervention group compared to the control group after six months (Table 6.3).

6.4.4 Fear-of-falling

Within group comparisons revealed no significant changes in short FES-I scores in the control group after six-months, but significant improvements in short FES-I scores in the intervention group after six months ($p<0.05$) (Table 6.2). Between groups comparisons, however, did not show any significant difference short FES-I at six months controlled for baseline scores (Table 6.3)

Table 6.2: Mean changes preceding 6-months in both groups

Group	Test	Mean difference (95% CI)	Significance
Control (n=24)	mCTSIB,		
	Eyes Open, Firm surface	0.03 (-0.05-0.11)	0.459
	Eyes Closed, Firm surface	-0.02 (-0.13-0.09)	0.701
	Eyes Open, Foam surface	-0.32 (-1.17-0.54)	0.451
	Eyes Closed, Foam surface	0.46 (-0.09-1.02)	0.097
	Computed mCTSIB	0.15 (-0.03-0.32)	0.096
	Limit of stability		
	End Point	-0.39 (-5.64-4.85)	0.878
	Maximal Excursion	-4.35 (-10.55-1.85)	0.160
	Directional control	-3.36 (-3.13-12.56)	0.111
	KOOS score		
	Symptoms	4.71 (-3.13-12.56)	0.227
	Pain	-0.29 (-8.40-7.82)	0.941
	Function	0.77 (-7.09-8.63)	0.842
	Sport	5.26 (-6.19-16.71)	0.352
	Quality of Life	8.38 (-2.14-18.89)	0.113
	Short FES-I score	3.42 (-1.64-8.47)	0.175
Intervention (n=17)	mCTSIB		
	Eyes Open, Firm surface	0.02 (-0.07-0.10)	0.668
	Eyes Closed, Firm surface	-0.07 (-0.20-0.07)	0.320
	Eyes Open, Foam surface	-0.86 (-1.65- -0.08)	**0.033**
	Eyes Closed, Foam surface	-0.79 (-1.89-0.31)	0.146
	Computed mCTSIB	-0.33 (-0.79-0.14)	0.161
	Limit of stability		
	End Point	3.63 (-1.21-8.46)	0.131
	Maximal Excursion	6.88 (0.69-13.06)	**0.032**
	Directional control	10.13 (2.55-17.70)	**0.012**
	KOOS score		
	Symptoms	9.83 (-1.52-21.17)	0.085
	Pain	7.89 (-3.08-18.85)	0.147
	Function	9.93 (-5.42-25.28)	0.189
	Sport	10.29 (-9.34-29.93)	0.283
	Quality of Life	14.99 (-1.54-31.51)	0.073
	Short FES-I score	-3.12 (-5.94- -0.30)	**0.032**

NOTE: Bold font indicates Statistical Significance. mCTSIB= modified Clinical Test for Sensory Interaction and Balance, KOOS = Knee Injury and Osteoarthritis outcome score, FES-I= Falls Efficacy International

Table 6.3: Baseline and after six months performance score

	Baseline		After 6 months*		
Variable	Control	Intervention	Control	Intervention	Adjusted differences†
Postural control					
mCTSIB					
Eyes Open, Firm surface	0.51 (0.18)	0.60 (0.26)	0.54 (0.17)	0.62 (0.25)	0.643
Eyes Closed, Firm surface	0.61 (0.30)	0.79 (0.43)	0.59 (0.22)	0.72 (0.28)	0.391
Eyes Open, Foam surface	1.70 (2.03)	2.03 (1.52)	1.38 (0.53)	1.16 (0.47)	0.163
Eyes Closed, Foam surface	2.46 (1.09)	3.06 (1.66)	2.93 (1.52)	2.26 (1.61)	0.077
Computed mCTSIB	1.23 (0.34)	1.64 (0.86)	1.38 (0.49)	1.32 (0.83)	0.206
Limit of stability					
End Point	56.83 (11.88)	44.44 (13.86)	56.43 (13.10)	48.06 (11.60)	0.824
Maximal Excursion	73.39 (14.99)	56.50 (13.61)	69.04 (13.26)	63.38 (11.12)	0.647
Directional control	64.82 (10.15)	53.38 (11.19)	61.45 (14.14)	63.50 (9.22)	**0.044**
OA symptoms					
KOOS score					
Symptoms	75.85 (18.84)	70.53 (17.95)	80.56 (13.83)	80.35 (18.80)	0.790
Pain	80.25 (17.65)	73.29 (20.12)	79.95 (15.38)	81.18 (22.12)	0.463
Function	79.67 (17.41)	65.07 (24.88)	80.44 (15.77)	75.00 (21.93)	0.751
Sport	57.08 (30.85)	33.82 (29.24)	62.34 (30.21)	44.12 (38.58)	0.616
Quality of Life	53.58 (26.63)	40.90 (27.80)	61.96 (26.10)	55.88 (31.85)	0.951
Fear of falling					
Short FES-I score	12.42 (5.04)	17.00 (5.55)	15.83 (11.20)	13.88 (4.91)	0.326

NOTE: Values expressed as mean (95% confidence interval). Bold font indicates Statistical Significance. mCTSIB = modified Clinical Test for Sensory Interaction and Balance, KOOS = Knee Injury and Osteoarthritis outcome score, FES-I = Falls Efficacy International, * indicate Intention-to-treat analysis., † indicate Analysis of covariance adjusted for baseline.

6.4.5 Falls Outcomes

A total of 18 falls were reported by participants from both groups, 8 by the intervention group and 10 by the control group. 47.1 % in the intervention group, and 41.7 % in the control group reported fall recurrence. The median number of falls, with interquartile ranges (IQR), experienced in six months were 1 (IQR 0-1) for the intervention group and 1 (IQR 0-1) for the control group. Figure 1 displays the Kaplan-Meier graph for time to first fall for both control and intervention groups. Our study showed no significant difference between groups for fall-free survival {control vs intervention, Estimates (95%CI): 133.3 days (108.7-157.7) vs 130.6 (101.3-159.9)} with a Hazard ratio (HR) of 1.063, 95% CI (0.571-1.980) (Figure 6.1).

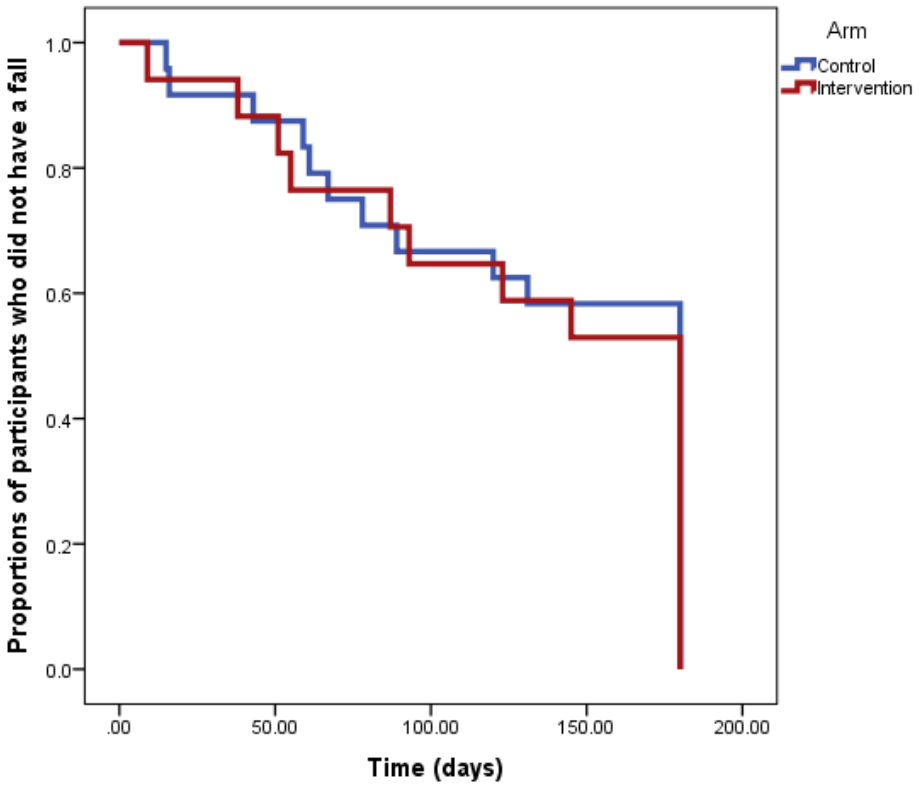


Figure 6.1: Kaplan Meier graph Time in days to first fall vs Proportion of participants in both arms

6.4.6 Adherence to the OEP

Seven participants (41%) in the intervention group completed the exercises of three or more times per week, eight participants (47%) completed the exercises two times per week, and one participant (12%) completed the exercises at least once per week.

6.5 Discussion

Our study showed that OA fallers with gait and balance problems were able to perform the modified OEP. Our pilot study was also able to demonstrate significant benefits in directional control on posturography in the intervention group compared to the control

group after six months. Paired analyses within groups demonstrated significant improvements in maximal excursion and directional control in the intervention group but not the control group. Within group comparisons also demonstrated a significant reduction in fear-of-falling at follow-up compared to baseline for the intervention group with no comparable changes in the control group.

Falls risk in our study was measured by using monthly falls diaries over 6-months. To our knowledge, this was the first study involving OA to measured falls risk by using a hard-falls outcome while most of the previous studies have been using surrogate falls risk measurements such balance tests (Mat, Tan, Kamaruzzaman, et al., 2015). In our study, there was no significance difference between groups for falls-free survival. As ours was a sub-study which was intended to be a pilot to inform future larger studies, our study was not powered to measure clinically significant differences in falls reduction. However, there does not appear to be any trend to significance, or any difference in outcome, which will limit any potential power calculations for future studies. In fact, as our initial case-control studies reported from Chapters 3 to 5 has highlighted the limited association between radiographically defined OA and falls in older adults, the lack of any trend for reduction in falls outcome for exercise interventions despite significant improvements in balance and falls efficacy outcomes is not entirely surprising. This further consolidates our previous hypothesis that there is no net increase in risk of falls individuals with OA. Therefore, while the presence of knee OA does lead to impairments in postural control which has now been found to be reversible with the OEP, the pattern of postural instability observed with OA is not related to falls.

Postural balance has been reported as one of the risk factor for falls among older persons with OA (Alencar et al., 2007). Our study has shown that a 6-month Otago programme benefited the intervention group by improving their directional control. Directional control is a component of the limits of stability test. It quantifies their postural control in the dynamic position (reaching to front, back, left and right). By improving the directional control, the possibility for older adults with OA to lose control on dynamic balance may also be reduced. As the OEP was designed to reduce the risk of falls by improving lower limb girdle strength, it may reduce postural sway which therefore improves their directional control (Liu-Ambrose et al., 2008; Meuleman et al., 2000; Suzuki et al., 2004).

Previous studies have found that home-based exercised programmes do help reduce FoF (Ratsepsoo et al., 2013). Fear of falling increases the risk of falls due to restriction of activity which eventually result in muscle weakness (Tinetti & Kumar, 2010). The OEP exercises therefore reduced fear of falling among older adults with OA. Larger RCT studies however are needed to evaluate the actual effect of the intervention.

Improvements in maximal excursion as well as directional control might also indicate improvements in cognitive function (Merlo et al., 2012; Polskaia et al., 2015; Tangen et al., 2014). Cognitive function is crucial in maintaining postural stability and preventing older adult from falls (Maylor & Wing, 1996; Melzer, Benjuya & Kaplanski, 2004). The figure of eight walking exercise contained in OEP has been expected to be correlated with measures of movement control and planning (i.e., tasks requiring timing and coordination to adapt muscle activation and movements to changes in the task or conditions for performance, the ability to smoothly alternate movement direction, and the

ability to recognize the demands of the task, such as gait variability and executive function (Capaday, 2002; Hess et al., 2010). We postulate that this specific exercise might has benefited the intervention group through improvements in their cognitive function and thus their postural control. Direct assessments of cognition were not performed in this study.

As it was just a sub-study of individual-tailored multifactorial intervention (MyFAIT), this analysis has not accounted for the effects of the other interventions in the intervention group such medication review, home hazard modification, and others. These interventions would have been most likely to affect the falls outcome, but there was no significance, and also fear of falling, but is unlikely to affect any physical outcomes that has been measured in this particular study.

Despite being underpowered and with a relative short length of follow-up, our study has yielded important results to inform future interventions. The likelihood of attaining falls risk reduction with exercise interventions for OA is questionable as the presence of loss postural control alone in our participants with OA does not necessary lead to increased falls risk. Future, adequately, powered studies should therefore consider alternative outcomes rather than falls risk reduction.

6.6 Conclusion

The Otago exercise programme benefited older adults with OA and gait and balance impairment by improving their postural control and reducing fear of falling. This study therefore will serve as a pilot study to inform appropriate design and power calculations for future research to evaluate the efficacy of exercise programmes in older individuals with gait and balance impairment and OA.

CHAPTER 7: CONCLUSION AND RECOMMENDATIONS

This chapter presents conclusions and recommendations based on the findings of the above series of investigations involving falls in OA. The conclusion is drawn concerning the issues raised, particularly on the conflicting literature on the relationship between OA and falls and prevention of falls among older individuals with OA.

The main findings of the case-control studies were that OA was not directly associated with falls among older adults. This was in spite of considering all the different available definitions. However, when we examined the symptom severity of those with the different available definitions, the presence of mild OA symptoms appears protective of falls compared to those with asymptomatic OA. Severe symptomatic OA was, however, associated with increased risk of falls in comparison to those with no symptoms or mild symptoms. However, psychological status rather than balance issues appears to influence the relationship between different OA severity and falls with anxiety accounting for the reduced falls among those with mild symptoms and radiological OA and fear-of-falling accounting for the increased risk of falls among those with severe OA clinically and radiologically. With posturography, the relationship between impaired dynamic postural balances which can increase the risk of falls did not change after adjustment for the presence of OA. Instead, the pattern of impaired postural stability and control associated with OA is different to the pattern of impairment in postural stability associated with falls, suggesting that OA related postural impairment bear no relation to falls outcomes. Instead age and the presence of comorbidities led to the postural stability associated with falls regardless of OA status. The MRI study, however, then revealed that the increased postural sway associated with falls were mediated to presence of sub-

chondral cysts and menisceal tears. This evidence of cartilaginous damage on MRI also accounted for the significant increase in TIMP2 among fallers with OA compared to OA non-fallers further supporting the findings that cartilaginous degradation accounts for the postural instability associated with falls. Summary of findings is depicted in Figure 7.1.

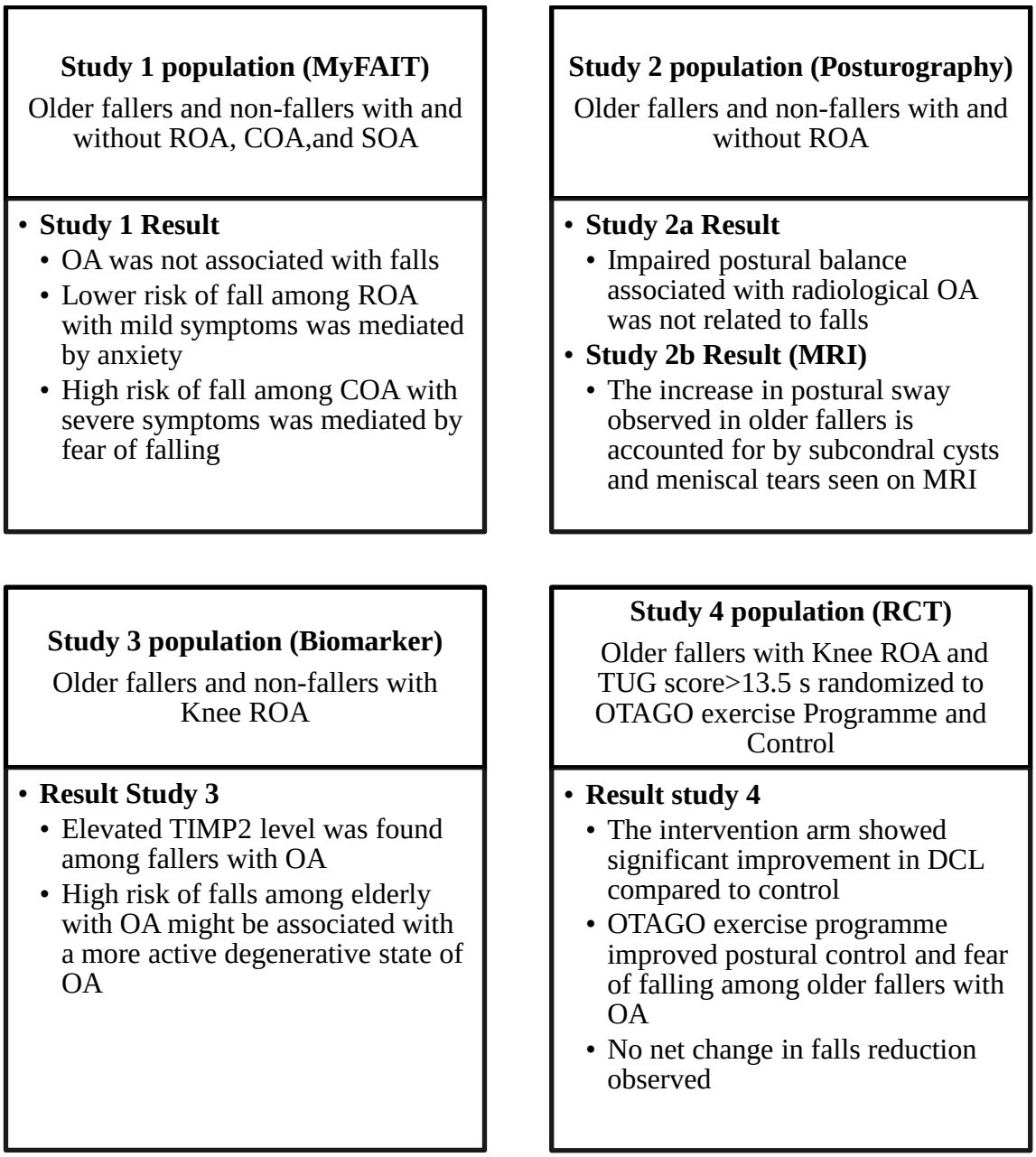


Figure 7.1 Summary of findings for studies 1 to 4

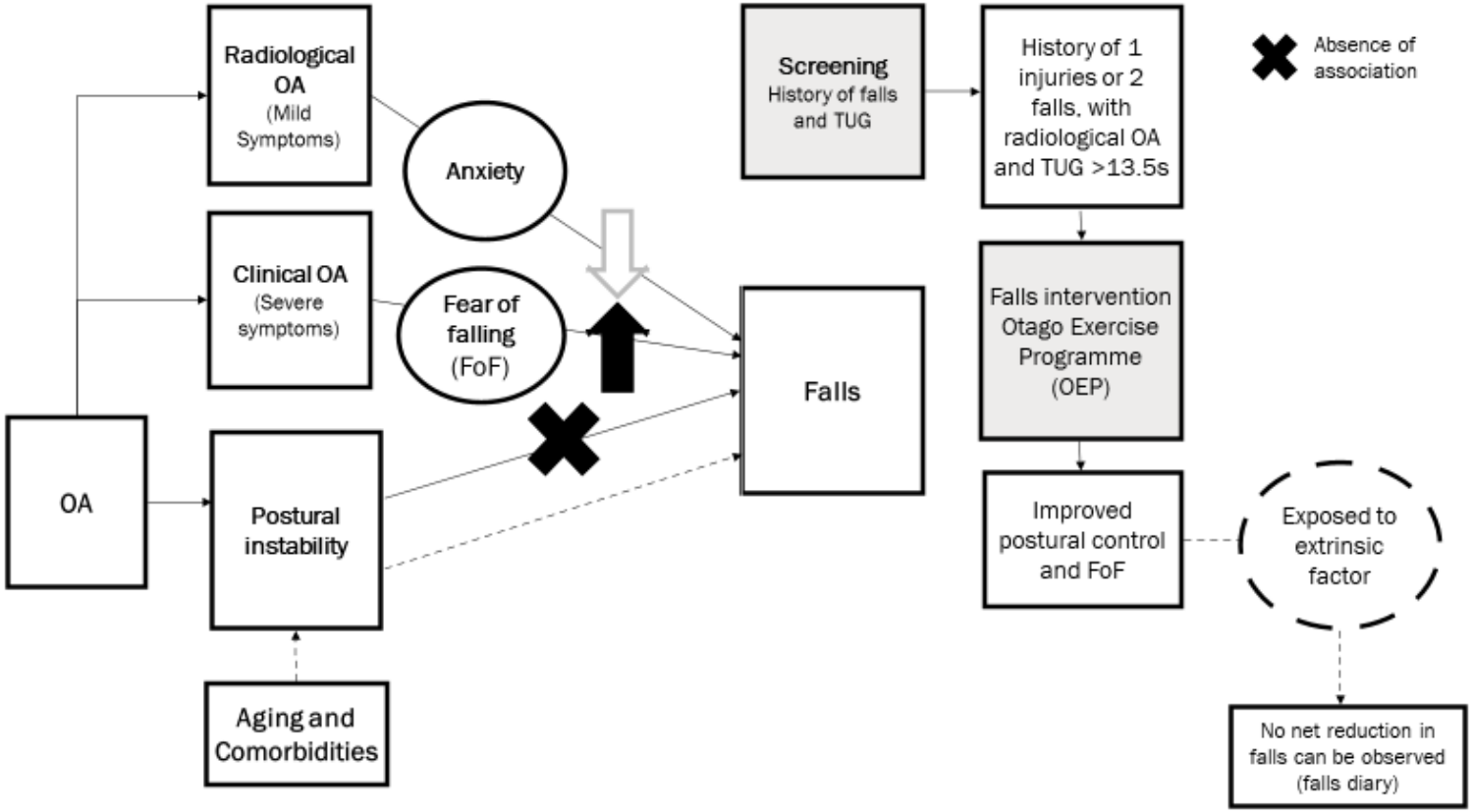


Figure 7.2 The relationship of OA and falls and Otago exercise programme for falls intervention among OA fallers.

Figure 7.2 depicted the relationships between all the main findings from this research study. This series of experiments has produced interesting findings that should help stimulate future research in this field. Since the presence of postural instability due to OA on its own does not necessary indicate increased risk of falls. Instead psychological factors do seem to play a role, as well as age and comorbidities which are relevant regardless of the presence or absence of underlying OA, should we now discount the relationship between OA and falls and ignore OA in falls assessments? Perhaps not, our research findings have suggested that meniscal tears and sub-chondral cyst are actually potentially reversible with surgical interventions, and may then be the answer for falls in OA participants.

In addition, we also know that in older patients with established OA, the ones with more severe OA are more likely to experience falls compared to those with no or mild OA, therefore when we compared OA and non-OA populations, the protective effect of mild OA may then mask the relationship between OA and non-OA in our study population. Intervention for falls in OA is therefore still deserves further evaluation. As our experiments were planned concurrently and such subgroups were not pre-planned, we had refrained from conducting subgroup analyses involving the severity of OA, which may have helped address this question. Larger studies powered for OA severity subgroups should now be conducted.

Our interventions reduced fear of falling and improved postural control, but no trends were observed for falls outcomes. We would like to suggest that there is a need to re-examine the selection of falls as an outcome for falls interventions, as reduction in fear of falling and improved balance control could improve physical activity, which

conversely then increases the exposure to extrinsic risk factors. Therefore, future falls prevention studies should also measure physical activity and quality of life as an outcome rather than falls reduction alone, which may not provide the true picture, since falls will not occur if the older person avoids all activities after their index fall, but this would have dire long-term health consequences and adversely affect the older person's quality of life. The extension of period of follow-up to include long term health and quality of life outcomes may also be beneficial, but not currently feasible under available funding structures.

This investigative strategy has therefore paved the way perfectly for a future larger longitudinal observational study, as well as an RCT evaluating OEP in fallers with OA, but this time using fear of falling, and quality of life as more suitable outcomes.

7.1 Future research recommendation

The findings in present study needs further confirmation in a large cohort study. As our case-control observational studies were of a cross-sectional design, cause-effect relationships could not be drawn. The larger prospective study should aim to differentiate the risk of falls between OA patient and controls. Further evaluation of biomarkers should consider the inclusion MMPs as a catabolic biomarker in order to evaluate the OA degenerative state, and should also include a control group (subjects without OA). In addition, our intervention study can serve as a pilot study for bigger falls interventions among older adults with OA using more robust measurements.

7.2 Clinical Implications

Our findings now question previous assumptions of the association between OA and falls. The doctor seeing the patient with the presence of OA and falls, should consider other risk factors rather than attribute the OA as the underlying pathology, particularly in those with mild and moderate symptoms. Severe symptomatic OA, however, does appear to be associated with increased risk of falls. The associated psychological symptoms among those presenting with falls and OA should also be considered, though effective strategies to tackle these remain limited. The encouraging findings from the sub-analysis of an ongoing RCT had suggested that the Otago exercise programme can be used in OA participants without any deleterious effects to OA symptoms. In the absence of any published studies in exercise therapy for secondary prevention of falls in OA participants, it may be advisable to prescribe OEP based on its efficacy demonstrated in the general older population. The distinct lack of a positive trend for falls outcomes, conversely suggest that Otago may not be effective in reducing falls, but does have beneficial effects on postural stability and psychological fear of falling, which may be used to guide patient expectations.

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LIST OF PUBLICATIONS AND PAPERS PRESENTED

1. Sumaiyah Mat, Maw Pin Tan, Shahrul Bahyah Kamaruzzaman, Chin Teck Ng: *Physical therapies for improving balance and reducing falls risk in osteoarthritis of the knee: a systematic review*. Age and Ageing 12/2014; 44(1). DOI:10.1093/ageing/afu112
2. Sumaiyah Mat, Pey June Tan, Chin Teck Ng, Farhana Fadzli, Faizatul I Rozalli, Ee Ming Khoo, Keith D Hill, Maw Pin Tan: *Mild Joint Symptoms Are Associated with Lower Risk of Falls than Asymptomatic Individuals with Radiological Evidence of Osteoarthritis*. PLoS ONE 10/2015; 10(10): e0141368. DOI: 10.1371/journal.pone.0141368
3. Sumaiyah Mat, Chin Teck Ng, Maw Pin Tan: *The Influence of Osteoarthritis on Dynamic Postural Control Parameters among Older Fallers*. Journal of Rehabilitation Medicine 3/2017: DOI: 10.2340/16501977-2202
4. Sumaiyah Mat, Naela A Alyousefi, Farhana Fadzli, Faizzatul Izza Rozzali, Chin Teck Ng, Maw Pin Tan: *Elevated Serum TIMP2 is observed among Older Fallers with Knee Osteoarthritis: a Pilot study.* (Under review)
5. Sumaiyah Mat, Chin Teck Ng, Farhana Fadzli, Faizzatul Izza Rozzali, Maw Pin Tan: *The Relationship between Osteoarthritis Changes on Magnetic Resonance Imaging and Postural Sway among Older Fallers.* (Under review)
6. Sumaiyah Mat, Chin Teck Ng, Maw Pin Tan*: Mediating Role of Psychological Domains on The Association between Osteoarthritis and Falls.* (Under review)
7. Sumaiyah Mat, Chin Teck Ng, Maw Pin Tan: *Effect of the Otago Exercises on Postural Balance and Fear of Falling among Older Fallers with Knee OA.* (To be submitted)

8. Sumaiyah Mat, Chin Teck Ng, Maw Pin Tan: *Effect of the Otago exercises on postural balance and fear of falling among older fallers with knee osteoarthritis*. Osteoarthritis and Cartilage 04/2016; 24:S66. DOI:10.1016/j.joca.2016.01.146 (Abstract)
9. Sumaiyah Mat, Chin Teck Ng, Maw Pin Tan: *Degenerative Menisceal Tears and Postural Control in Older Fallers: A Case-control Evaluation*. Osteoporosis International; 02/2015 (Abstract)
10. Sumaiyah Mat, Farhana Fadzli, Faizzatul Izza Rozzali, Maw Pin Tan, Chin Teck Ng: *The Relationship between Falls, Balance and Osteoarthritis in Older Residents in a Multi-racial Nation*. Australasian Journal on Ageing 06/2014; 33:38-38. (Abstract)

Presentations:

1. Oral presentation entitled “Radiographic Osteoarthritis is not associated with falls in older people” in World Congress of Geriatrics and Gerontology (WCGG) Dalian, China, October 2013.
2. Oral presentation entitled “The Relationship between Quality of Life and Falls in Older Individuals with Knee Osteoarthritis” in National Geriatric Conference, Ipoh, Malaysia, June 2014
3. Oral presentation entitled “The Relationship between analgesics and Osteoarthritis in Older fallers in a Multi-racial Nation,” in IAGG Asia/Oceania conference, Chiang Mai, Thailand, October 2015
4. Poster presentation entitled “Radiographic Osteoarthritis is not associated with falls” in National Geriatric Conference (NGC), Kuala Lumpur, September 2013
5. Poster presentation entitled “Assessment of Postural Stability with a Balance Platform among Fallers with Symptomatic Osteoarthritis in the MyFAIT study” IAGG, Dublin, Ireland, 2015