AN ASSESSMENT OF OSTEOPOROSIS CONDITION AND KNOWLEDGE AMONG WARFARIN USERS AT A HOSPITAL IN THE NORTHERN REGION OF PENINSULAR MALAYSIA

by

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LIST OF ABBREVIATIONS

AF	Atrial fibrillation
AOS	Asian Osteoporosis Study
BGP	Blood glutamic protein
BMD	Bone mineral density
BMI	Body mass index
DVT	Deep venous thrombosis
DXA	Dual-energy X-ray absorptiometry
EU	European Union
HPP	Hospital Pulau Pinang
HR	Hazard ratios
HRT	Hormone replacement therapy
INR	International normalized ratio
ISCD	International Society for Clinical Densitometry
MOKT	Malaysian Osteoporosis Knowledge Tool
NORA	National Osteoporosis Risk Assessment
OKT	Osteoporosis Knoweledge Test
OP	Osteotorosis
OR	Odds ratio
PE	Pulmonary Embolism
PLOS	Public Library of Science
QUS	Quantitative Ultrasound Scan
RM	Ringgit Malaysia
SD	Standard Deviation

SOS	Speed of Sound
SERM	Selective Estrogen Receptor Modulators
TIA	Transient Ischemic Attack
ucOC	Undercarboxylated Osteocalcin
USA	United States of America
USM	Universiti Sains Malaysia
VKA	Vitamin K Antagonists
WHO	World Health Organization

SUATU PENILAIAN KEADAAN DAN PENGETAHUAN OSTEOPOROSIS DALAM KALANGAN PENGGUNA WARFARIN DI HOSPITAL DI WILAYAH UTARA, SEMENANJUNG MALAYSIA

ABSTRAK

Osteoporosis ialah penyakit kronik yang mempunyai hubungan kompleks dengan pesakit yang menggunakan warfarin. Dalam usaha menyediakan pengurusan osteoporosis yang optima, nasihat untuk pesakit yang menggunakan warfarin adalah amat diperlukan. Sebahagian dari data klinikal yang terlibat dalam kajian kawalan kes dengan menggunakan kaedah persampelan mudah dengan 270 subjek (kumpulan kawalan dan pesakit) telah diambil untuk menilai status kesihatan tulang dengan mengukur ketumpatan mineral tulang (BMD) menggunakan imbasan ultrasound kuantitatif (QUS) untuk menilai juga pengetahuan osteoporosis (OKT). Keputusan QUS menunjukkan bahawa kelaziman BMD yang normal, osteopenia, dan osteoporosis ialah 23.3%, 53.7% dan 23%. Masing-masing kajian ini menunjukkan bahawa lebih tiga perempat kumpulan pesakit (82%) mempunyai risiko tinggi dalam ketumpatan mineral tulang (BMD) yang tidak normal. Pengguna warfarin menunjukkan kebarangkalian dua kali ganda lebih tinggi untuk mengalami osteoporosis berbanding dengan kumpulan kawalan. Tambahan pula, BMD mempunyai hubungan negatif dengan umur, tetapi mempunya hubungan positif dengan indeks jisim badan (BMI). Pesakit menunjukkan hubungan negatif dengan pengambilan warfarin pada dos yang tinggi. Selain itu, nisbah ganjil dalam kalangan wanita yang menggunakan warfarin mendapat skor insiden osteoporosis yang lebih

tinggi iaitu 2.4 kali ganda berbanding wanita yang tidak menggunakan warfarin. Berhubung perkara ini, wanita berbangsa Cina (berumur lebih daripada 50 tahun), di bawah terapi warfarin selama lebih daripada setahun, adalah lebih terkesan dalam pengurangan BMD jika dibandingkan dengan wanita Melayu atau India. Konklusinya, pesakit yang menggunakan warfarin mempunyai risiko yang lebih tinggi untuk menghidap osteoporosis berbanding dengan kumpulan kawalan. Bangsa, sejarah keluarga dalam tulang patah dan umur boleh dianggap sebagai faktor risiko osteoporosis yang signifikan ketika terapi warfarin yang kronik. Keputusan menunjukkan kumpulan kawalan, 69.3% daripada mereka mempunyai risiko tinggi untuk BMD yang tidak normal berdasarkan klasifikasi yang ditetapkan WHO. Ukuran QUS menujunkkan bahawa 35% daripada bangsa Cina, 33% daripada bangsa India dan 32% daripada bangsa Melayu mempunyai risiko yang tinggi untuk mengalami osteoporosis. Kajian juga menunjukkan pengurangan parameter QUS (T-score, BUA, SOS dan SI) dengan mengambil kira umur. Nilai purata untuk lelaki (pengguna dan bukan pengguna) adalah lebih tinggi.Untuk tahap pengetahuan osteoporosis, kajian menunjukkan subjek (kawalan dan pesakit) mempunyai tahap pengetahuan osteoporosis yang rendah. Terdapat perkaitan yang siginifikan antara kumpulan (pengguna dan bukan pengguna warfarin) dan tahap pengetahuan mengenai osteoporosis (tinggi atau rendah). Kajian menyatakan majority daripada responden (82.4%) mempunyai pengetahuan yang rendah bmengenai osteoporosis (hanya 15.8% sampel kajian didapati mempunyai OKT yang tinggi). Terdapat perbezaan yang ketara dalam kedudukan min antara pembolehubah yang mempengaruhi skor OKT. Untuk bangsa pula, bangsa Cina mencatatkan kedudukan min OKT yang lebih tinggi berbanding orang Melayu dan India. Untuk pendapatan

bulanan, peserta kajian yang memperoleh pendapatan lebih daripada RM2000 mencatatkan kedudukan yang tinggi untuk pengetahuan osteoporosis. Selain itu, berdasarkan pekerjaan pula, peserta kajian yang bekerja mempunyai tahap pengetahuan yang lebih tinggi. Peserta yang tinggal di bandar mempunyai pengetahuan yang lebih, di mana pesakit mempunyai pengetahuan lebih daripada kumpulan kawalan (nisbah ganjil [OR]=4.1, 95% CI: 1.90- 8.69). Dapatan kajian ini menunjukkan bahawa kebanyakan orang mempunyai pengetahuan yang sedikit mengenai osteoporosis. Pegawai kesihatan sepatutnya memainkan peranan yang penting dalam menjelaskan faktor-faktor risiko osteoporosis terhadap pesakit dan komuniti.

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AN ASSESSMENT OF OSTEOPOROSIS CONDITION AND KNOWLEDGE AMONG WARFARIN USERS AT A HOSPITAL IN THE NORTHERN REGION OF PENINSULAR MALAYSIA

ABSTRACT

Osteoporosis is a chronic disease that has a complex relation with patients using warfarin. In order to provide optimal management of osteoporosis, there is a need to advice patients about the usage of warfarin. A clinical part involved case-control study of a convenient sample of 270 subjects (controls and patients) recruited to assess the bone health status by measuring the bone mineral density (BMD) using quantitative ultrasound scan (QUS) as well as to evaluate their osteoporosis knowledge (OKT). The result of QUS showed that the prevalence of normal BMD, osteopenia, and osteoporosis were 23.3%, 53.7%, 23% respectively. This study showed that more than three-quarter patients group (82%) were at high risk of abnormal body mass density (BMD). The warfarin users were two times more likely to have a higher osteoporosis risk compared to control group. Moreover, BMD has a negative correlation with age, but has a positive correlation with body mass index (BMI). Patients showed a negative correlation with a higher dose of warfarin intake. In addition, odd ratio of females using warfarin scored higher incidence of osteoporosis by 2.4 times more than females who did not use warfarin. In this regard, Chinese females (more than 50 years old), under warfarin therapy for more than one year, were more affected for the reduction in BMD as compared to Malay or Indian females. In conclusion, patients who used warfarin are at a higher risk of

osteoporosis than the controls. Race,family history fracture, and age were considered as significant risk factors of osteoporosis during chronic therapy of warfarin. The result showed the control subjects, 69.3% of subjects had a high risk of abnormal BMD based on WHO classification . The QUS measurement showed that 35% of Chinese, 33% of Indians, and 32% of Malays had high- risk OP. A study illistered decrease in all QUS parameters (T- score, BUA, SOS, and SI) with regard to age. The average value for men (users and non-users) was higher than the one for. As for the knowledge of osteoporosis, the study revealed that the subjects (controls and patients) had a low level of osteoporosis knowledge. A significant association was found between groups (users and non- users warfarin) and level of osteoporosis knowledge (high or low). This study indicated that the majority of the respondents (84.2%) have a low knowledge score of osteoporosis (Only 15.8% of study sample was found to have high OKT). There was a significant difference in mean ranks between variables affecting OKT score. With regard to race, Chinese recorded higher mean rank of OKT than Malays and Indians. As for monthly income, participants who earned more than RM 2000 recorded higher rank for knowledge . With regard to occupation, participants who work for any reasons got higher rank knowledge. Urban participants had more knowledge, Patients had more knowledge than controls (odds ratio [OR] =4.1, 95% CI: 1.90- 8.69). The findings of this study revealed that most people have inadequate knowledge about osteoporosis. The heath care professional should play an active role in educating their patients and community about the risk factors of osteoporosis.

CHAPTER 1

INTRODUCTION

1.1 Overview

Osteoporosis is a silent disease that constitutes a great socio-economic problem, with a negative impact on both morbidity and mortality (Hadjidakis et al., 2005; Reyes & Moreno, 2005). It is not symptomatic (painless weakening of the bones) and may not be detected until a fracture occurs due to increased skeletal fragility and micro architectural deterioration of the bone tissue, thus a decrease in Bone Mineral Density (BMD), bone quality and strength (Cooper & Melton, 1992; Nicodemus & Folsom, 2001). The true occurrence of osteoporosis may be significantly underestimated because many women who suffer minimal trauma fractures are still not being evaluated for osteoporosis (Siris et al., 2006). Osteoporosis can result in height loss, severe back pain, deformity, or impairment of a person's ability to walk, disability, and even death (Heinemann & Donna, 2000; Salkeld et al., 2000). Caucasian and Asian women are at the highest risk of developing osteoporosis. However, Black and Hispanic women are also at significant risk. The point of identifying and evaluating populations at increased risk of developing osteoporosis is critical to disease prevention and management (Aloia et al., 1996; Luckey et al., 1996; National Institutes of Health (NIH), 2001).

The burden of osteoporosis is expressed not only in the economic costs companying (Lindsay, 1995; Ray et al., 1997), but also in its psychological and social consequences. The physical complications of the disease may be serious and includes pain, functional limitation and increased morbidity and mortality (Wolf et

al., 2000). Social and psychological effects include loss of independence, inability to work, isolation, decreased quality of life and diminished self-esteem and depression (Gold et al., 1998; Lips et al., 1999).

The prevalence of osteoporosis in Malaysia was reported as 24.1% in 2005, predominantly affecting the hip (Loh & Shong, 2007). Meanwhile, the rates of hip fracture are twofold higher in Hong Kong (Gullberg et al., 1997). In contrast, the prevalence of osteoporosis was found much lower in Thailand (12.6%), China (16.1%) and Taiwan (10.08%) (Lau et al., 2001). The overall prevalence of osteoporosis in the Asian population is higher than the western countries due to the fact that the Asian population has lower body mass index and shorter height (Loh & Shong, 2007).

The World Health Organization (WHO) has formed a working group in 1994 to define osteoporosis. Osteoporosis is defined as "a progressive systemic skeletal disease characterized by low bone mass and micro architectural deterioration of bone tissue, below the young adult mean with the presence of one or more fragility fracture (Kanis et al., 1994).

Osteoporosis is a clinical syndrome characterized by the failure of osteoclasts to resorb bone. Consequently, bone modelling and remodelling are impaired. The defect in bone turnover characteristically results in skeletal fragility despite increased bone mass, and it may also cause hematopoietic insufficiency, disturbed tooth eruption, nerve entrapment syndromes, and growth impairment. Although human osteoporosis is a heterogeneous disorder encompassing different molecular lesions and a range of clinical features, all forms share a single pathogenic nexus in the

osteoclast (Stark & Savarirayan, 2009). Osteoporosis was first described in 1904, by German radiologist, Albers-Schönberg (Cleiren et al., 2001).

1.2 Diagnosis of Osteoporosis

Most patients are asymptomatic and diagnosis is made only after a fracture. Common clinical presentations include:

1. Increased dorsal kyphosis (Dowager's hump)
2. Low-trauma fracture
3. Loss of height
4. Back pain

The diagnosis of primary osteoporosis can be detected after excluding secondary causes of bone loss. A clinical evaluation, which includes a careful history, physical examination and appropriate laboratory investigations, is mandatory. Although multiple risk factor assessment does not predict bone mass with sufficient precision (Slemenda et al., 1990), it remains the mainstay in decision making to identify the 'at-risk' patient requiring further investigation.

The prevalence of osteoporosis related fractures has increased in many countries around the world and this trend is expected to continue as the population ages. Although the majority of osteoporotic fractures currently occur in European countries, by the year 2050, over half of all hip fractures are predicted to occur in Asian countries (Cooper et al., 1992). In addition, osteoporosis is more common in Caucasian women but is a growing concern for men and other ethnicities (Tung & Lee, 2006). It is estimated that ten million individuals have osteoporosis and another thirty-four million suffer from low bone density. By 2020, approximately sixty-one

million individuals will have osteoporosis or low bone density (Heinemann & Donna, 2000). As bone strength decreases, the risk of fractures increases. The increased risk of fractures has led to increased morbidity and mortality of individuals living in the US (Woolf & Åkesson, 2003). In Malaysia, hip fractures as a result of osteoporosis affected 218 women per 100,000 (Lau et al., 2001), with a direct hospitalization cost of RM 22 million (US $6.5 million) (Yeap et al., 2013). Study on improving the management of osteoporosis in Malaysia is limited. However, with the increasing population of the elderly worldwide as well as in Malaysia, the prevalence of osteoporosis is expected to escalate. In 1997, the incidence of hip fracture in Malaysia among individuals above 50 years of age was 90 per 100,000. There was a marked increase in the incidence among the older age group. The incidence of hip fracture is consistently higher in women. In the Malaysian population, hip fractures commonly occurred among the Chinese compared to the Malays and Indians with 44.8% of hip fractures in Chinese women (Lee J.K. & Khir, 2007). Females were twice as commonly affected as compared to males. Race and sex-specific incidence data showed that the incidence was highest among Chinese females (220 per 100 000), followed by Indian females (200 per 100 000).

The age-specific incidence was 500 per 100 000 for patients above 75 years, compared to 10 per 100 000 in those between 50 and 54 years (Lee J.K. & Khir, 2007). The percentage of the Malaysian population aged above 65 years grows annually at a rate of 3% and it is projected that by the year 2020, there will be 7.3% or 2 million elderly people in the country (Noor & Ismail, 2002). In Malaysia, there has been a shift towards a more ‘‘affluent’’ diet and lifestyle, and increased prevalence of chronic disease over the past three decades (Tee, 1999). Therefore,

osteoporosis may be expected to pose an increasing public health problem if appropriate intervention is not taken. Referring to the incidence of nine million fractures, 39% occur in men (Johnell & Kanis, 2006). Although men suffer fewer fractures than women, they have a significantly higher morbidity and mortality rate (Johnell & Kanis, 2006). It is projected that by 2050, 50% of hip fractures will occur in Asia, with the majority occurring in China (Cooper et al., 1992).

The WHO diagnostic classification (Table1.1) (World Health Organization (WHO) & Food and Agriculture Organization of the United Nations, 1994) is made by BMD testing with Dual-energy X-ray Absorptiometry (DXA) using the T-score, calculated by subtracting the mean BMD (in g/cm2) of a young adult reference population from the patient's BMD and divided by the standard deviation (Gold et al., 1998; Lips et al., 1999) of the young adult reference population. The International Society for Clinical Densitometry recommends that BMD be measured at the lumbar spine (L_1L_4), total hip, and femoral neck, with the 33% radius (1/3 radius) being measured when the lumbar spine and/or hip cannot be measured (e.g., obese patient who exceeds weight) or is invalid (e.g., patient with lumbar laminectomy) (Schousboe et al., 2013). Osteoporosis cannot be diagnosed by BMD measurement at skeletal sites other than lumbar spine, total hip, femoral neck, and 33% radius or with technologies other than DXA. The quality of DXA instrument maintenance, acquisition, analysis, interpretation, and reporting is important in obtaining valid results that can be used for making appropriate clinical decisions. For a patient with a fragility fracture, a clinical diagnosis of osteoporosis may be considered independently of BMD results, assuming that other causes of skeletal

fragility (e.g., osteomalacia) are not responsible for the fracture. Establishing a diagnosis of osteoporosis is clinically useful because it facilitates communication among healthcare providers and patients concerning a disease with potentially serious consequences. In some countries, such as the United States, a diagnosis is necessary in order to select a numerical code for submission of insurance claims for reimbursement for medical services (Lewiecki et al., 2006; Schousboe et al., 2013).

The US National Bone Health Alliance (Siris et al., 2014), has recommended for osteoporosis to be diagnosed in postmenopausal women and men over the age of 50 years. (When following circumstances occur, T-score ≤ -2.5 at the lumbar spine or hip, low-trauma hip fracture, osteopenia by BMD with a low-trauma vertebral proximal Humerus pelvis, or, in some cases, distal forearm fracture, and when a Fracture Risk Assessment Tool (FRAX™) shows, high fracture risk (10-year probability of major osteoporotic fracture $\geq$ 20% or 10-year probability of hip fracture $\geq$ 3%) This sentence needs paraphrasing because it is long and confusing. In general, FRAX will not be used if the person is already receiving treatment with osteoporosis prescription drugs. The online FRAX tool can be used to estimate the 10-year probability of fracture risk for overall major osteoporotic fractures (i.e., spine, forearm, hip, and shoulder) and hip fracture for women and men aged 40-90. In general, a 10-year overall fracture risk of less than 10% is considered low risk; 10% to 20% is considered moderate risk; and greater than 20% is considered as high risk. The only drug-induced osteoporosis drugs evaluated with this tool are glucocorticoids, nicotine, and alcohol and may be used with patients taking warfarin.

Table 1.1: World Health Organization criteria for classification of patients with bone mineral density measured by dual-energy X-ray absorptiometry

Classification	**T-score**
Normal	-1.0 or greater
Low bone mass (osteopenia)	Between - 1.0 and - 2.5
Osteoporosis	-2.5 and below
Severe osteoporosis	-2.5 and below + fragility fracture

However, Hans study, reported that low calcaneus ultrasonographic variables were able to predict an increased risk of hip fracture, with similar accuracy to low femoral BMD obtained by dual photon x-ray absorptiometry (Hans & Krieg, 2009). Moreover, QUS has substantial advantages compared with DXA in terms of safety, cost, potential portability and its use has been extended to children. The calcaneus is the most common skeletal site for QUS assessment because it has a high percentage of trabecular bone that is replaced more often than cortical bone, providing early evidence of metabolic change. In addition, the calcaneus is fairly flat and parallel, reducing repositioning errors. The method can be applied to children, neonates, and preterm infants, just as well as to adults. Once micro imaging tools to examine specific aspects of bone quality are developed, it is expected that QUS will be increasingly used in clinical practice (Guglielmi & Scalzo, 2010).

1.3 Fracture Risk Assessment

There is an active correlation between BMD and fracture risk with approximately a two-fold increase in fracture risk for every 1 SD decrease in BMD (Marshall et al., 1996). However, many or most patients with a hip fracture have a T-score better than -2.5 (Wainwright et al., 2005). Although fracture risk is higher in patients with very low BMD, there are numerically many patients with, a T-score better than -2.5, with a T-score of -2.5 or worse. Therefore, there are numerically more fractures in those with higher T-scores. The presence of Clinical Risk Factors (CRFs) that are independent of BMD, particularly age and prior fracture, can help identify patients at high risk for fracture by providing information on fracture risk that is complementary to BMD. The National Osteoporosis Foundation (NOF) has provided an extensive list of CRFs in Table 1.2, for osteoporosis and fractures. Since most fractures occur because of a fall (Cosman et al., 2014).

Table1.2: Diseases and medications that cause or contribute to osteoporosis and fractures (Cosman et al., 2014).

Lifestyle factors	Low calcium intake, Vitamin D insufficiency, Excess of vitamin A, High caffeine intake, High salt intake Aluminium (in antacids), Alcohol (3 or more drinks/d) Inadequate physical activity, Immobilization Smoking (active or passive), Falling, Thinness
Genetic factors	Cystic Fibrosis, Homocystinuria, Osteogenesis Imperfecta Ehlers-Danlos Syndrome, Hypophosphatasia Parental history of hip fracture, Gaucher Disease Idiopathic Hypercalciuria, Porphyria, Glycogen Storage D Marfan Syndrome, Riley-Day Syndrome, Hemochromatosis Menkes Steely Hair Syndrome, Hypogonadal States Androgen insensitivity, Hyperprolactinemia Turner & Klinefelter Syndromes Anorexia Nervosa and Bulimia, Panhypopituitarism Athletic Amenorrhea, Premature ovarian failure
Endocrine disorders	Adrenal insufficiency, Diabetes Mellitus, Thyrotoxicosis Cushing Syndrome, Hyperparathyroidism
Gastrointestinal disorders	Celiac Disease, Inflammatory Bowel Disease. Primary Biliary Cirrhosis, Gastric BypassMalabsorption. GI Surgery Pancreatic Disease
Hematologic disorders	HemophiliaMultiple Myeloma, Systemic Mastocytosis Leukemia and Lymphomas, Sickle Cell Disease, Thalassemia
Rhumatic and Autoimmune D	Ankylosing Spondylitis, Lupus, Rheumatoid Arthritis
Miscellaneous conditions and Disease	Alcoholism, Emphysema, Muscular Dystrophy, Amyloidosis End stage renal disease, Parenteral nutrition Chronic metabolic acidosis, Epilepsy Post-transplant bone disease, Congestive heart failure Idiopathic Scoliosis, Prior fracture as an adult, Depression Multiple Sclerosis, Sarcoidosis
Medications	Anticoagulants (warfarin, heparin), cancer chemotherapeutic drugs, gonadotropin releasing hormone agonists. Anticonvulsants, cyclosporine A and Tacrolimus, lithium. aromatase inhibitors, depo-medroxyprogesterone barbiturates glucocorticoids (≥ 5 mg/d of prednisone or equivalent for ≥ 3 mg)

1.3.1 Warfarin as risk factor

Coumadin-based oral anticoagulants, referred to as oral anticoagulants, are indicated for the prevention and treatment of arterial and venous thromboembolic diseases. In the elderly, their main indication is the prevention of ischemic stroke, secondary to atrial fibrillation, which has a prevalence of 15% in that population and is an independent risk factor for ischemic stroke. The risk of ischemic stroke (5% per year) has been reduced with the use of oral anticoagulant which exerts their effect by interfering with the action of vitamin K in the process of activation of coagulation factors II, VII, IX and X. These drugs can alter bone metabolism by interfering with the activation of osteocalcin, a protein of the bone matrix, which depends on vitamin K. Even if the exact role of this protein has not been demonstrated, an increased concentration of inactivated osteocalcin associated with vitamin K deficiency or antagonism caused by the use of oral anticoagulants, has been associated with a decrease in hip bone mineral density and a high tended risk of hip fracture (Szulc et al., 1994).

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Warfarin is clinically utilized as an anticoagulant due to its antagonism of vitamin K, essential co-factor role in conferring functionality to blood coagulation proteins through the process of gamma carboxylation (Rubinacci, 2009). Specifically, the uncarboxylated (non-functional) proteins are converted to their carboxylated (functional) forms by vitamin K's actions. Through the same process, vitamin K also confers functionality to skeletal bone Gla proteins, including osteocalcin, which plays an important role in bone mineralization (Lam & Cheung, 2012). Low vitamin K serum concentration and nutritional intake from food

frequency questionnaires have been associated with low bone mineral density (Klein et al., 2009; You et al., 2005). It has resulted in increased risk of fractures in some studies which may be related to the functionality of skeletal bone Gla proteins such as osteocalcin (Alan et al., 2008; You et al., 2005)). In the carboxylated form, osteocalcin binds calcium to the hydroxyapatite (crystal) in bone matrix (Gage. & Lesko, 2008; Lindh et al., 2009; Loebstein et al., 2001).). Indeed, higher levels of undercarboxylated osteocalcin and lower levels of carboxylated osteocalcin have been associated with fractures, particularly hip fractures, in older adults (Caldwell et al., 2008; McDonald et al., 2009). Furthermore, serum concentrations of undercarboxylated osteocalcin have been shown to decrease with vitamin K supplementation (Sagrieya et al., 2010), and increase with warfarin (Carlquist et al., 2010).

Thus, as an inhibitor of vitamin-K-dependent gamma carboxylation of Gla proteins (Cen et al., 2010), warfarin may lead to bone effects similar to that seen with low serum vitamin K levels or high undercarboxylated osteocalcin levels.

A common anticoagulant commonly used for preventing and treating thromboembolic events in patients with deep vein thrombosis, pulmonary embolism, atrial fibrillation and prosthetic heart valves is warfarin. It is a mix of S-warfarin and R-warfarin with the former as the more active isomer, thus greater therapeutic effect. Various cytochrome P450 enzymes metabolized the enantiomers, specifically the cytochrome P450 1A2 (CYP1A2), CYP2C19 and CYP3A4 for the R-warfarin and CYP2C9 for the S-warfarin. It affects the activity of vitamin K epoxide reductase complex 1 (VKORC1), hence slowing the activation of clotting factors II, VII, IX and, X.Warfarin has a narrow therapeutic window and posed deadly consequences if

consumed in a wrong dose. Thus, the consumption of warfarin needs to be monitored continuously based on the international normalized ratio (Manning et al., 2008), Apart from that, the varying response to its dose adds to the difficulty of prescribing the right dose for warfarin. Generally, 4–6 weeks of frequent clinic visits, blood tests and correct adjustment of dosage are involved in the early stage of warfarin dosing. The factors influencing warfarin dosing are patients' clinical characteristics. (Loebstein et al., 2001) and genetic variations.

1.3.2 Vitamin K deficiency as risk factor

In the past decade, it has become evident that vitamin K has a significant role to play in human health that is beyond its well-established function in blood clotting. There is a consistent line of evidence in human epidemiologic and intervention studies to show that vitamin K can improve bone health. The human intervention studies have demonstrated that vitamin K can not only increase bone mineral density in osteoporotic people but also actually reduce fracture rates. Furthermore, it is evident in human intervention studies that vitamins K and D, a classic in bone metabolism, work synergistically on bone density. Most of these studies employed vitamin K2 at rather high doses but it has been criticized as a shortcoming of these studies. However, there is an emerging evidence in human intervention studies that vitamin K1 at a much lower dose may also benefit bone health, in particular when co-administered with vitamin D. Several mechanisms are suggested by which vitamin K can modulate bone metabolism. Beside the γ-carboxylation of osteocalcin, it is assumed that a protein is involved in bone mineralization. There is an increasing evidence that vitamin K also positively affects calcium balance, a key mineral in

bone metabolism. The Institute of Medicine is part of the United States National Library of Medicine, has increased the dietary reference intakes of vitamin K to 90 μg/d for females and 120 μg/d for males, which is an increase of approximately 50% from previous recommendations (Weber, 2001). It is recognized that vitamin K insufficiency increases the risk of osteoporosis and hip fractures (Booth et al., 2000). As women age, the undercarboxylated osteocalcin increases but not necessarily corresponding to decreased vitamin K levels (Plantalech et al., 1991). The non-carboxylated osteocalcin level was in a range similar to that seen in warfarin-treated patients (Plantalech et al., 1991). Those with elevated undercarboxylated osteocalcin have decreased bone density and increased risk of hip fracture (Vergnaug et al., 1997). The optional daily intake of phylloquinone K1 is 1000 μg to maintain maximal serum osteocalcin -y- carboxylation (Binkley et al., 2002).

1.3.3 Prevention of osteoporosis

In the prevention of osteoporosis, sufficient nutrition especially calcium and vitamin D intake, is important for bone health. Calcium intake corresponds positively to bone mass for individuals of all ages. High and continuous calcium intake since young until adolescence produces higher peak bone mass, hence lowering the risk of osteoporosis. Other than that, higher calcium intake increased the effectiveness of other treatments of osteoporosis such as vitamin D and hormone replacement therapy (HRT). Currently, Malaysians consume between 300–400 mg of calcium daily (Chee et al., 1997). When the diet is calcium deficient, calcium may be given in the form of supplements. The absorption of calcium supplements is highly variable ranging from 20-40% depending on the formulation. Vitamin D Active individuals who are

exposed to sufficient sunlight (> 15 minutes a day) should have adequate vitamin D levels. Elderly who are institutionalised, immobile, lack outdoor activities and have a poor diet will benefit from 800 IU vitamin D supplementation daily. There is a concern that excessive intake of calcium and/or vitamin D supplementation may encourage the formation of renal stone disease. All those who are on such supplementation should consume adequate fluids. Body weight low and excessive dieting is associated with low bone mineral status and increased fracture risk. Maintenance of a body mass index of not less than 19 kg/m2 is recommended for prevention of osteoporosis. Nutritional status maintenance of an adequate protein and energy intake is important especially in children and the elderly. Regular physical activities, in particular weight-bearing exercise is encouraged in all age groups in order to maximize peak bone mass, decrease age-related bone loss, and maintain muscle strength and balance. The individual's health status should be taken into consideration when recommending an exercise programmed.

Pharmacological agents HRT, Selective Estrogen Receptor Modulators (SERMs) and bisphosphonates have shown to be effective in the prevention of osteoporosis. Prevention of the most osteoporosis-related fractures especially in the elderly are a consequence of decreased BMD and falls. Variety of factors may lead to a fall such as poor balance, reduced muscle strength, poor vision, disease of nervous and musculoskeletal systems, excessive alcohol consumption, certain medications (e.g. sedatives, anti-hypertensives) and hazards at home (e.g. steps, inadequate lighting, slippery floors). Appropriate assessment and correction of risk factors for falls should be undertaken as well as protection of the hip by wearing hip protectors (Clinical Practice Guidelines on Management of Osteoporosis in Canada in2010).

1.4 Knowledge of Osteoporosis

The way people manage their health care is influenced their knowledge of and attitude towards certain diseases (Andersen, 1995). Knowledge is the basics of understanding and reacting towards health issues. In terms of disease prevention – in this case, osteoporosis – knowledge of patients is integral in the preventing and reducing risk of fractures. The knowledge involved those on suitable physical activities, sufficient dietary requirement of calcium and vitamin D, fall prevention and osteoporosis test (Yeap et al., 2013).

The main focus of osteoporosis prevention is the identification of non-osteoporotoc individuals who have high risk of developing osteoporosis. The second focus is early detection and prevention of future fractures. Generally, both involve osteoporosis-preventing behaviours (Lundy & Janes, 2009). Davis (2007) found that the sooner osteoporosis is detected, the lower chances of hospital admission due to osteoporotic fractures. Hence, this also stressed the importance of educating patients on the benefits of early screening and prevention.(Davis et al., 2007).

While patient's knowledge and osteoporosis preventive behaviour may be increased with the help of physicians (Cranney A. et al., 2008), and screening programs (Jensen et al., 2013; Yuksel et al., 2010), have found that patient's education is the most effective way. However, this finding is contradicted by findings of other scholars such as study by Etemadifar in 2013, who used different methodologies in their studies. The varying methods involving both qualitative and quantitative methods further add to the difficulty of reaching a consensus (Burke-Doe et al., 2008; Etemadifar et al., 2013) The difference in the results also suggest

that knowledge is not the only component that affects behavioral changes. Beliefs, attitudes and values may also be a barrier to implement osteoporosis preventive efforts (Andersen, 1995). The Development and Validation of the Osteoporosis Prevention and Awareness Tool (OPAAT) in Malaysia can be used to identify individuals in need of osteoporosis educational intervention (Toh et al., 2015).

1.5 Treatment of Osteoporosis

The prevention of osteoporosis consists of three types: primary, secondary and tertiary prevention. Primary prevention involves general management that includes the assessment of the risk of falls and their prevention to avert the onset of disease (Chang J.T. et al., 2004). It includes encouraging adequate calcium and vitamin D intake and exercise (Body et al., 2011; Yeap et al., 2013). Secondary prevention includes early detection and treatment, fall prevention and use of anabolic agents while tertiary prevention focuses on treatment. At the stage of tertiary prevention, healthcare professionals are involved in the retraining and rehabilitation of the patients (National Institutes of Health (NIH), 2001; Yeap et al., 2013).

1.5.1 Pharmacological treatment of osteoporosis

Every effort to increase BMD is important to delay the onset or slow the progression of osteoporosis complications (Maclean et al., 2008; National Osteoporosis Foundation, 2013). Many types of medications are used for the treatment of osteoporosis, based on an individualised assessment of the patient's risk factors and preferences. The goal of osteoporosis treatment is to improve BMD and reduce future fractures (Braddon & Phillips, 2004; Yeap et al., 2013). There are two

categories of osteoporosis medications: antiresorptive (anticatabolic) medications which either reduce bone resorption or inhibit bone turnover (by acting on osteoclasts); and anabolic medications which stimulate and increase the rate of new bone formation (by targeting osteoblasts) (National Osteoporosis Foundation, 2013; Rahmani & Morin, 2009; Yeap et al., 2013). Table 1.3 lists the commonly used medication in the treatment of osteoporosis.

Although these medications improve bone mass, the level of compliance and adherence is still poor. This, in turn, affects the effectiveness of the treatments (Gass & Dawson-Hughes, 2006; Kanis et al., 2008 b), and increases mortality and morbidity (Bolland et al., 2010). The major pharmacological Interventions available in Malaysia are the bisphosphonates, strontium ranelate, denosumab, teriparatide, raloxifene, and hormone therapy. All of them increase BMD and reduce fractures when given with calcium and vitamin (Yeap et al., 2013).

Table1.3: Medications used for the treatment of osteoporosis (Koda-Kimble et al., 2013; National Osteoporosis Foundation, 2013; Yeap et al., 2013).

Classification/ Medication	Mechanism	Therapeutic note
1-Antiresorptive medications		
Bisphosphonates Alendronate Etidronate Ibandronate pamidronate Riscdronate Zoiedronic acid	Inhibit osteoclast activity, reduce bone turnover, reduces bone loss, increases bone density and reduces the risk of spine, hip and other broken bones.	• Taken in the morning on an empty stomach with 6 to 8 ounces of plain water, at least 30 minutes before having anything to eat or drink. • Patients must remain upright (sitting, standing or walking) during this 30-minute period. Should be used in patients taking corticosteroids to protect from developing OP.
Estrogen therapy	Reduce bone turnover, increase bone density in both the spine and hip, and reduce the risk of hip, spine and other fractures.	• Can increase women risk of developing endometrial cancer, breast cancer, vascular thrombosis, cardiovascular risks, and heart disease. • Physicians usually prescribe hormone progesterone in combination with estrogen. It can cause vaginal bleeding, blood clots, breast tenderness and gallbladder disease.
Selective estrogen Receptor modulators Raloxifene ,Tamoxifen, Testosterone	Increases bone density and reduce the risk of spine and hip fractures.	Side effects are not common; but it can cause hot flashes, leg cramps and deep vein thrombosis (blood clots). Raloxifene is not used in patients at increased risk for stroke, atrial fibrillation or uncontrolled hypertension (high blood pressure). It can reduce the risk of some types of breast cancer and endometrial cancer, as well as, reduce lipid profile.

Continued..	**2-Anabolic medications**	
Synthetic Parathyroid hormone (PTH) Teriparatide	Increases the rate of bone formation, improve skeletal architecture and lower the risk of breaking bones and fracture in spine and throughout the skeleton.	Can cause, leg cramps and dizziness, modest elevations in serum and urine calcium. It is not to be given to people with metabolic bone diseases such as hyperparathyroidism and those with cancer that has spread to the bone. Bisphosphonates must be discontinued prior to treatment with Teriparatide.
3-Vitamins and minerals		
Calcium Vitamin D	Regulation of calcium absorption, muscle performance, balance, fall prevention, and bone health.	Should be given in combination for optimal results. Vitamin D is available from sunlight, some foods and supplements.

1.6 Statement of the Problem

Osteoporosis management is a lifelong process that requires effort from healthcare providers and patients. Patients are the key to a successful management. However, many complications can occur from a poor management. Patients must be proficient to successfully manage, maintain lifestyle changes, and make daily decisions for better healthcare. In addition, healthcare professionals must help patients to make a right decision and cope with the difficulties and barriers through education, support and advice (Funnell & Anderson, 2004; Levine, 2011).

Osteoporosis is a growing health problem in Malaysia with a high cost in terms of economics and disability. It is estimated that 27000 people have a broken hip every year because of osteoporosis in Malaysia. It is worthwhile to note that hip fractures in females is double compared to males (Lau et al., 2001). Compared to other Asian countries, Malaysia showed high prevalence of osteoporosis (24.1%) in 2005 (Loh & Shong, 2007). This may be due to rapid socio-economic growth, enormous urbanization and changes in dietary habits.

Although numerous measures have been taken to improve bone health and osteoporosis management through published Malaysian guideline (Yeap et al., 2013), there is a lack of good bone health management. It is important to explore patients' knowledge and awareness toward osteoporosis by identifying the source of information. Lack of awareness is the main reason for high prevalence of low bone mass (Doheny et al., 2007). Therefore, education is necessary to increase the level of Knowledge of patients who are culturally sensitive.

1.7 Significance of the Study

The proportion of low bone mineral density is high among the general population in Penang. The incidence of osteoporosis in postmenopausal women is high especially in Malaysia. In this regard, there has been a shortage of data on the topic of the prevalence of osteoporosis condition among warfarin users in Penang. There are few academic and empirical published papers regarding osteoporosis knowledge and most of reviews on this subject have been conducted in western countries. In Penang, there has been a lack of data on the topic of patients knowledge regarding osteoporosis among warfarin users. Rare results have been published for the association of bone mineral density measurement and osteoporosis knowledge in patients taking warfarin for more than one year.

The clinical finding of this study will provide the fundamental basis for health care professionals to understand the logical and the appropriate utilization of health services in the management of osteoporosis among warfarin users and non-users in Malaysia. The outcomes of the present study will lead to better patient care. It will enhance patients' quality of life, and avoid possible adverse effects.

1.8 Objectives of the Study

1. To assess the incidence of osteoporotic conditions between warfarin users (patients) and non-warfarin users (control) using QUS.
2. To assess the risk factor of OP using QUS parameters (like T-scores) this is related to BMD between warfarin users and the control group.
3. To assess the potential factors that influence BMD values including warfarin use and the socio-demographic data.
4. To assess the osteoporotic knowledge levels using OKT tool and its associated factors**.**

1.9 Scope of the Study

The present study was a case-control study, which aimed at an investigation incidence of osteoporosis between users and non- users warfarin groups and risk factors affecting on OP. Also to determine the knowledge levels between two groups and its associated factors.

CHAPTER 2

LITERATURE REVIEW

2.1 Osteoporosis

Many studies considerd the osteoporosis presents as a serious and growing public health problem, as its prevalence continues to increase worldwide (Cashman, 2007; National Osteoporosis Foundation, 2013). Common sites of fracture include spine, hip, forearm and proximal hummers. Fractures of the hip incur the greatest morbidity and mortality and give rise to the highest direct costs for health services. Their incidence increases exponentially with age. Osteoporotic fractures, at other sites, are generally of less economic significance but they also give rise to significant morbidity and, in some instances, to increased mortality. They occur more commonly than hip fractures at younger ages .

A study by Johnell & Kanis (2006) showed the probability of osteoporotic fractures in women at the age of 50 years was exceeds 40% in developed countries. For hip fracture alone, the remaining lifetime probability at the age of 50 years exceeds 20% in women in these countries. In many regions of the world, the risks in men are about half of women. Over and above changes in population demography, the age- and sex-specific incidence of osteoporotic fractures appears to be increasing in developing countries. This is anticipated that the expected burden of osteoporotic fractures over the next 50 years will increase twice as much as the current situation (Johnell & Kanis, 2006).

The study by Wark (1999) illustrated the number of osteoporotic fractures would increase in both men and women (by more than 3-fold over the next 50 years) due to the aging population. It increases mostly outside of Europe and the US, particularly in Asia and Latin America (Wark, 1999).

A study by Lee & Khir (2007) which showed The incidence of hip fracture in Malaysia among individuals above 50 years of age was 90 per 100,000. There was a marked increase in the incidence among the older age group. The incidence of hip fracture is consistently higher in women. 63% of patients presenting with hip fractures were Chinese. It was 20% among Malays and 13% among Indians. Race-specific incidence data showed that the fracture rates are the highest among Chinese (160 per 100 000) followed by Indians (150 per 100 000) and Malays (30 per 100 000). Females were twice as more affected than males. Race and sex-specific incidence data showed that the incidence was the highest among Chinese females (220 per 100 000), followed by Indian females (200 per 100 000). The age-specific incidence was 500 per 100 000 for patients above 75 years, compared to 10 per 100 000 in those between 50 and 54 years (Lee J.K. & Khir, 2007).

Another study by Delaney (2006) mentioned that, Bone mass reaches to the peak level in the third decade of life and the rate of decline in BMD accelerates with advancing age and postmenopausal status in women (Delaney, 2006; Ryan, 1997).

A study which had been done in Malaysia in 2007 showed the prevalence of osteoporosis in Malaysia was reported as 24.1% in 2005, predominantly affecting the hip (Loh & Shong, 2007), while the rates of hip fracture are twofold higher in Hong Kong (Gullberg et al., 1997). In contrast, the prevalence of osteoporosis was found