EVALUATION OF BONE MINERAL DENSITY AMONG PATIENTS WITH DEPRESSION IN PENANG ISLAND, MALAYSIA

By

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Dedication

This research work is dedicated to my country, my father, my mother, my wife and my children.

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TABLE OF CONTENTS

TABLE OF CONTENT:

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

BMD	Bone Mineral Density
BMI	Body Mass Index
BUA	Broadband Ultrasound Attenuation
dB	Decibels
DEXA or DXA	Dual Energy X-ray Absorptiometry
DSM-III	Diagnostic and Statistical Manual of mental disorder 3rd edition
DSM-IV	Diagnostic and Statistical Manual of mental disorder 4th edition
HPA	Hypothalamus-Pituitary-Adrenal
GDS	Geriatric Depression Scale
GHQ	General Health Questionnaire
IGF-1	Insulin Like Growth Factor-1
IL	Interleukin
M-CSF	Macrophage-Colony Stimulating Factor
MDD	Major Depressive Disorder
NHANES III	Third National Health and Nutrition Examination Survey
OPG	Osteoprotegerin
pDEXA	Peripheral Dual Energy X-ray Absorptiometry
PTH	Parathyroid Hormone
QCT	Quantitative Computed Tomography
QUS	Quantitative Ultrasound
RA	Radiographic Absorptiometry
RANK	Receptor Activator of Nuclear Factor- kß
RANKL	Receptor Activator of Nuclear Factor- kß Ligand
RR	Relative Risk
SE-QCT	Single-Energy Quantitative Computerized Tomography
SOS	Speed of Sound
SSRI	Selective Serotonin Re-uptake Inhibitor
TCA	Tricyclic Antidepressant

TGF- ß	Transforming Growth Factor- ß
TNF- α	Tumor Necrosis Factor- α
WHO	World Health Organization

APPENDICES

CONFERENCE PRESENTATIONS

Abstract 1 Low bone mineral density of the calcaneus bone in men with depressive illnesses. (Poster in 4th AASP-MPS Pharmacy Scientific Conference, Penang, Malaysia)

Abstract 2 Association of depressive illness with low bone density in Malaysian population. (Oral in 9th ACCP, Seoul, Korea)

Abstract 3 Evaluation of the morbidity of depression in lowering bone density between sexes. (Poster in 9th ACCP, Seoul, Korea)

PENILAIAN KETUMPATAN MINERAL TULANG DALAM KALANGAN PESAKIT DEPRESI DI PULAU PINANG, MALAYSIA

ABSTRAK

Pengenalan: Depresi merupakan penyakit mental yang digambarkan melalui kesedihan, hilang minat, tidur dan selera makan yang terganggu serta tahap tenaga yang rendah. Ia juga berhubung kait dengan beberapa perubahan paras hormon endogen serta tingkah laku sosial yang teruk yang mengakibatkan perubahan dalam metabolisme tulang dan proses pembentukan semula tulang. Kajian membuktikan bahawa wujud hubungan ketara antara depresi dengan ketumpatan mineral tulang (BMD) yang rendah dan ini menggalakkan lagi usaha untuk menilai perkaitan di atas dalam konteks penduduk Malaysia melalui dalam Pulau Pinang, Malaysia. ***Metodologi:*** Kajian ini menggunakan sampel kohort 420 peserta - 140 daripadanya mempunyai rekod penyakit depresi yang diperolehi daripada klinik psikiatri Hospital Besar Pulau Pinang dan Hospital Adventist Pulau Pinang, manakala 280 lagi ialah kumpulan bukan depresi iaitu sebagai kelompok kawalan yang terdiri daripada komuniti dengan julat umur antara 25-70 tahun. BMD dinilai pada kalsanus tumit dengan mengukur T-skor dan Z-skor derivatif ultrabunyi kuantitatif menggunakan densitometri tulang Ultrabunyi Furuno CM200 bagi kesemua sampel. ***Keputusan:*** Peratusan peserta yang mempunyai BMD yang rendah seperti yang dijelaskan oleh T-skor derivatif ultrabunyi kuantitatif (< -1) adalah lebih tinggi pada pesakit depresi ($P < 0.001$) dengan risiko relatif sebanyak 1.72 (95% CI 1.40-2.11). dan signifikan dalam kumpulan hanya laki-laki dengan risiko relatif 3,0 kali ganda (95% CI 1,99-4,68) dan kumpulan-satunya perempuan dengan risiko relatif 1,37 kali ganda (95% CI 1,08-1,74) pada wanita. Setelah menyesuaikan variable pengganggu dengan menggunakan regresi logistik biner, dijumpai persatuan BMD rendah dengan kemelesetan dalam kumpulan kedua-dua jenis kelamin pada nisbah ganjil 2,76 (95% CI 1,61-4,73) dan P-nilai (<0,001) dan menunjukkan hubungan yang signifikan dengan kemurungan BMD rendah pada kumpulan laki-laki hanya dengan P-nilai (<0,001) dan aneh juadah 19,82 (95% CI 5,64-69,63). Min T-skor derivatif ultrabunyi pada pesakit depresi ternyata lebih rendah berbanding kumpulan kawalan bagi kedua-dua jantina sementara min Z-skor derivatif ultrabunyi kuantitatif adalah lebih rendah pada kumpulan depresi berbanding kumpulan sihat dalam kalangan lelaki. Ujian ANOVA tidak menunjukkan sebarang pengaruh ketara bangsa, pekerjaan, tahap pendidikan, agama dan gaya hidup yang lain terhadap BMD. subjek yang mempunyai amalan senaman yang teratur mempunyai min Z-skor lebih tinggi berbanding kumpulan yang tidak bersenam iaitu P-nilai (0.020) serta perkaitan yang ketara dengan tempoh masa bersenam per minggu dengan *P*-nilai (0.002). Ujian Spearman mendapati tiada perkaitan antara Z-skor dengan jumlah simptom yang dihidap oleh pesakit depresi *P*-nilai (0.036). Tidak ada perkaitan antara Z-skor dengan

tempoh depresi pada pesakit yang menghidapnya. Ujian ANOVA tidak menunjukkan perbezaan ketara dalam min Z-skor pada pesakit depresi yang menggunakan ubat antidepresan yang berbeza. ***Kesimpulan:*** Depresi mungkin boleh dikaitkan dengan BMD yang rendah seperti yang ditunjukkan oleh T-skor derivatif ultrabunyi kuantitatif (<-1) bagi populasi Malaysia. Kajian ini membuktikan bahawa lelaki lebih cenderung dipengaruhi oleh depresi berbanding wanita dari segi kereputan tulang. Kajian ini menilai bukti pengaruh perlindungan ke atas BMD. Ia negatif menunjukkan perhubungan ketara antara jumlah simptom dengan kereputan tulang. Penelitian ini melaporkan tidak ada keuntungan dari penggunaan ubat antidepresan atas lain terhadap BMD ini. menyarankan perhatian selanjutnya daripada pakar psikiatri berhubung dengan osteoporosis atau ketumpatan mineral tulang yang rendah semasa menangani pesakit-pesakit depresi.

EVALUATION OF BONE MINERAL DENSITY AMONG PATIENTS WITH DEPRESSION IN PENANG ISLAND, MALAYSIA

ABSTRACT

Introduction: Depression a mental illness described by sadness, loss of interest, troubled sleep and appetite and low energy levels. It is also correlating with some alterations in endogenous hormonal levels as well as poor socio-behaviors, resulting in modification in a bone metabolism and bone remodeling process. Studies have shown that there is a significant association between depression and low Bone Mineral Density (BMD) and this prompt the effort to evaluate this relationship in a Malaysian population in Penang, Malaysia. ***Methodology:*** The study employed a cohort sample of four hundred and twenty participants, 140 had depressive illnesses obtained from psychiatric clinics in Penang General Hospital and Penang Adventist Hospital, and 280 were non-depressed subjects as controls from the community, with their age ranged from 25-70 years old. BMD assessed at the heel's calcaneus by measure the quantitative ultrasound derivatives T-and Z-scores using Furuno Ultrasound bone densitometry CM200 for the whole sample. ***Result:*** The percentage of participant who had low BMD as defined by quantitative ultrasound derivatives T-scores (< -1) was significantly higher in patients with depressive illnesses ($P < 0.001$) with relative risk of 1.72 (95% CI 1.40-2.11), and significant in male only group with relative risk 3.0 folds (95% CI 1.99 to 4.68) and female only group with relative risk 1.37 fold (95% CI 1.08 to 1.74) in females. After adjusting the confounding variables by applying binary logistic regression, found association of low BMD with depression in group of both sexes at odd ratio 2.76 (95% CI 1.61-4.73) and P-value (<0.001) and showed significant association of depression with low BMD in males group only with *P*-value (<0.001) and odd ration 19.82 (95% CI 5.64-69.63). The mean ultrasound derivatives T-score in the depressed patients was significantly lower than in control group in both sexes while the mean quantitative ultrasound derivatives Z-score was significantly lower in depressed group than in healthy group among males only. ANOVA test showed no significant effect of race, employment, education level, religion and other life styles on the BMD. Subjects had regular exercise habit showed had significantly high mean Z-score comparing to those who had not with *P*-value (0.020). This study showed significant correlation of BMD in term of T- and Z-scores with the times of exercise doing per week with *P*-value (0.002). Spearman test significant negative correlation of Z-score with the number of symptoms suffered by the depressed patients *P*-value (0.036). No correlation recorded between Z-score and the duration of depression in the depressed patients. ANOVA showed no significant difference in the mean Z-score between the depressed patients using different antidepressant medications.

Conclusion: Depression may be associated with low BMD represented by quantitative ultrasound derivatives T-score (<-1) in a Malaysian population. This study concluded that males are highly affected by depression than females regarding bone loss. The study estimated the evidence of protective effect of exercise on the BMD. It showed a significant relationship of the number of symptoms with bone loss. This study reported no advantage of use antidepressant medication over the other toward the BMD. The study recommends further attention from the psychiatrist with regard to the incidence of osteoporosis or low bone mineral density when dealing with their depressed patients.

CHAPTER ONE

1.0 INTRODUCTION

1.1.0 Background

Bone fracture has been included along with other most essential health problems, especially hip or spine fracture, which costs the government and health organizations many of the human and financial resources. Bone fracture occurs due to some types of trauma to the bone as a consequence of fall, physical abuse, and vehicle accidents, or it might be due to diseases such as osteoporosis that weakens the bone and increases its fragility (Becker, 2006).

Osteoporosis occurs due to several reasons, which are either physiological changes happened normally during growing up age or pathological effect of some diseases. Some reasons related to pharmacological adverse effects of some medications.

Several diseases approve to have negative effect on the bone such as hyperparathyroidism while others still have unrecognized risk effect on the bone such as depression and that what this study tries to investigate.

1.1.1 Osteoporosis

The World Health Organization (WHO) defines osteoporosis as " a disease characterized by low bone mass and micro architectural deterioration of bone tissue, leading to ameliorate bone fragility and a consequent increase in fracture risk" (WHO, 1994).

Osteoporosis is known as a "silent disease" where the bone loss occurs with no symptoms. Lots of people may not be aware that they have osteoporosis until their skeletons become too fragile that any unexpected trauma or fall will cause a

vertebrae collapse, hip or wrist fracture. Distorted vertebrae may firstly be felt or observed in the form of loss of height, severe back pain, or spinal deformities such as kyphosis (severe stooped posture) (NRC, 2007).

It is a case in which the bone loses its proper level of mineral density and increases its porosity, which has a negative effect on the skeleton which elevates the possibility of bone fractures, leading to an elevation in morbidity, mortality and a decrease in quality of life (Lau, 2001).

According to a study by C. Cooper in 1999 with regard to worldwide prevalence of osteoporosis among 200 millions people, the prevalence is directly related to elderly population. In other words, human age has a clear intensive effect on bone tissue structure and its mineral contents where the ageing factor is enormously responsible for the incidence of osteoporosis (C.Cooper, 1999, Reginster and Burlet, 2006).

The prevalence of these osteoporotic fractures increases with time where the total number of hip fractures in both genders in 1990 was reported to be 1.26 million (Johnell and Kanis, 2006, Gullberg *et al.*, 1997). Accordingly, in 2000, the annual worldwide fracture due to osteoporosis was more than 8.9 million cases, in which more than 4.5 million cases occurred in Europe and America. An estimated number of fractures due to osteoporosis, both in men and women within 50 years old and above, is shown by regional study by WHO. The highest number of fracture is in Europe with an estimation of 3.1 million cases. South East Asia is considered the third of the regional survey with 1.55 million cases estimated while Africa is considered to have a lower level with the estimation of 0.075 million cases (WHO, 2004, Johnell and Kanis, 2006).

Osteoporosis is not a rare disease in Malaysia. The prevalence of osteoporosis in Malaysia in 2005 was reported at 24.1%, usually affecting the hip (Loh and Shong, 2007).

Osteoporotic hip or vertebral fractures have cost health institutions a lot of expenses during hospitalization, where direct costs of fractures due to osteoporosis for health care and hospital services in the year 2000 in European Union were estimated at RM 133 billion (Kanis and Johnell, 2005). In USA, 63 billion RM has been spent for the cost of osteoporotic fractures estimated in 2005, which is predicted to rise to approximately 84 billion RM within 2025 as a consequence of this increase parallel with the time of the prevalence of those osteoporotic fractures (NOF, 2008). In Malaysia, direct hospitalization cost for hip fractures in 1997, according to Malaysian Guidelines on Management of Osteoporosis, was estimated at RM22 million (Khir and Lee, 2007).

Osteoporosis is classified into two main classifications; primary osteoporosis and secondary osteoporosis. Primary osteoporosis is sub-classified into two types; Type I i.e. postmenopausal osteoporosis which relates to women after their menopause. Wrist fractures and vertebral crush fractures are usually associated with Type I osteoporosis. The second sub-classification of primary osteoporosis is Type II i.e. age-related or senile osteoporosis, which impinges on men and women of older age than 70 and is usually associated with hip breaks and vertebral wedge fractures (Riggs, 1991). Secondary osteoporosis occurs due to the effect of diseases such as hyperparathyroidism and type 2 diabetic mellitus or due to medication such as glucocorticoids, chemotherapy and insulin.

1.1.2 Bone mineral density measurement

The bone mineral density is estimated by the amount of bone mineral content in unit (gram) in the surface area in a square centimeter (cm^2) to be (g/cm^2). In evaluating bone density, a standard deviation called T-scores indicates that the amount of one's bone mineral density varies from the mean. It is scaled from positive scores, which indicate good bone density and is reduced to negative scores, which indicate low bone density. WHO puts a criteria in the diagnosis of normal bone density, osteopenia and osteoporosis i.e. the T-scores > -1 means normal bone density, while osteopenia is estimated when the T-scores is within -1 to -2.5, and if it is less than -2.5, then this indicates the osteoporosis.

In addition to the T-scores, there are Z-scores, which are the value of standard deviations in patients where their bone density differs from the normal BMD according to the age, sex, and race of these patients. Z-scores are used in premenopausal women and men under the age of 50 as well as in children.

The bone density is measured by different manners, which include Dual Energy X-ray Absorptiometry (DEXA or DXA), spinal Quantitative Computed Tomography (QCT), Peripheral Dual Energy X-ray Absorptiometry (pDEXA), Quantitative Ultrasound (QUS) and Radiographic Absorptiometry (RA). In comparing these techniques, the RA is considered to be the earliest way in measuring bone density, which has many limitations like high expense, time-consuming measurement and radiation in addition to the low accuracy. DEXA is a highly accurate absorptiometry technique of time-saving measurement, which undertakes the measurement in central axial, hip and other peripheral skeletons. DEXA is usually used in the diagnosis of osteoporosis and to approve the effect of new drug therapy. pDEXA is similar to DEXA in these advantages, but it is used only to measure bone density in peripheral

axis. The disadvantage of DEXA and pDEXA is the high cost and the radiation. For QCT, it has high expanse as well as high radiation. However, it is different from DEXA in that it estimates BMD in accurate parameter of cubic centimeters (cm^3) which is a volumetric parameter while DEXA estimates in unit area square centimeter (cm^2) and has an ability to differentiate between cortical and trabecular bones.

While osteoporosis is a systemic disease, bone density loss occurs in the whole skeleton but not at the same rate, that a study estimated one-half of those who experienced a significant decrease in spine BMD at 5 years showed no significant fall in forearm. It showed a significant contract for total hip with spine and whole body BMD than for the femoral neck concluding that changes at the commonly measured sites are discordant (Abrahamsen *et al.*, 2001).

Most QUS measure bone density on heel, forearm and fingers where this technique has its own advantages i.e. no radiation is included in this process while the machine is small, lightweight and portable in addition to the short time quantify the duration. However, the restriction of this type of measurement is that it is not highly accurate in comparison to DEXA or QCT.

Mostly, types of QUS determine the T-scores and Z-scores in calcaneus bone, which consists of 95% of trabecular bone, which is similar to the type of the bone in spin and hip, and it is located between relatively flat faces. This type of bone causes scatting of the sound wave. The idea of ultrasound absorptiometry is by measuring broadband ultrasound attenuation (BUA) in a unit decibel (dB) which is decreased in high porous bone tissue. Another technique of QUS is to measure the speed of the sound (SOS) which travels through the calcaneus tissue where this speed reduces in low bone density. The QUS is usually used in most studies as well as in the screening

of bone density and osteoporosis (Blake and Fogelman, 2002, Faulkner, 2001, Miller, 2002, Mautalen and Oliveri, 1999, Sterkel and Miller, 2000).

1.1.3 Bone physiology

In order to understand physiology and pathophysiology of osteoporosis and bone fractures as the outcome of osteoporosis and how and why they occur in most people's life, first bone structure and matrix of the bone tissue in the human body must be defined as well as get a review on the included components in the bone tissue, bone metabolic processes such as bone resorption and reformation activities and biochemical compounds that manage these activities.

Bone is a live connective tissue, which has growing ability where the skeletons are composed of cavity bones in which a solid cortical shell covers a marrow space containing variety amounts of trabecular bone. The vertebrae, pelvis, skull, and scapulae are filled with continuous trabecular network while in long bones, the trabecular bone is found only at the end of these bones. In other parts of the long bone, there is cortical bone, which concentrates on the areas under compression or subject to impact loading, where the long bones have a function as major weight bearing bone, carrying on large bending and torsion forces produced during the movement while the trabecular bone sustains lauding of the axial compression. (Bono and Einhorn, 2003, NRC, 2005).

Chemically, bone is a complex structure which consists of collagen protein matrix, upon which the crystals of calcium and phosphate are lain down in a prepared way. In addition to collagen and minerals, a large number of non-collagen proteins are present in the skeleton. These proteins play a role in signaling between cells and

matrix as well as to regulate the distribution of minerals on the collagen scaffold (Raisz *et al.*, 2005).

In addition to the supporting function of the bone and the protection of vital organs, it has a protected chamber of blood formation marrow and serves as a store for mineral ions (Ca^{+2}, $PO4^{-3}$, Mg^{+2}). Bone has a rule in protecting the body from acidosis, i.e. it can adsorb heavy metals and toxins, which lead to a decrease in their harmful effect on other body tissues (Turner, 1998).

Since the skeleton is a basic organ that supports standing and mobility of the human body, it must have two properties; first, it must have proper rigidity that improves supporting function of bone, which is obtained through the way of arrangement of minerals in bone structure, and second, it must have suitable flexibility that protects itself from being broken by any trauma and this is obtained by collagen, which is responsible for tensile strength. Therefore, to preserve these two properties and maximize bone protection, the bone is exposed to an essential process called bone remodeling process (Boskey *et al.*, 2006). Remodeling is a local removing process of the aged bone by replacing it with newly formed bone. On the other hand, the resorption activity will release calcium for physiological requirements and improve the bone structure in order to make it better for its physical role while the formation activity is to restore the bone which is lost (Martin *et al.*, 2001).

Bone remodeling is undertaken by two types of bone cells:

(a) Osteoblast cells which are responsible for forming the bone matrix in which they are usually called bone-forming cells.

(b) Osteoclast cells which are responsible for resorbing and degrading the existing bone. Even the osteoblast cells and mast cells in bone marrow are responsible for stimulating the differentiation and activating osteoclast cells.

There are another type of bone cell which do not have any role in bone remodeling process called osteocytes which are mature osteoblast cells surrounded by bone matrix.

The first "activation" stage starts with osteoclast cells which attach to the mineralized bone surface and begin the resorption by releasing hydrogen ions and lysosomal enzymes, mainly cathepsin K, which has the ability in acidic environment, to dissolve all bone matrices compounds as well as collagen protein. This resorption activity of the osteoclast cells forms irregular cavities in the cortical bone called Cylindrical Haversian Canals as well as on the trabecular bone surface called Howship lacunae. Directly, after the osteoclast completes the bone removal, the second "reversal" stage starts where in this phase, the mononuclear cells are lined on the bone surface. They dissolve collagen and deposit of proteoglycans to form a cell layer called cement line, followed by the release of a growth enzyme to start a "formation" phase. During the third "formation" stage, a final phase of the remodeling sequence, the cavities created by resorption activity, can be completely filled in by the prepared layers of osteoblast cells and release a mineralizable matrix. Once the osteoblasts have completed their work of matrix synthesis, they can become flattened lining cells on the bone surface and be hidden in the bone as an osteocyte. The osteocyte cells are vital cells for regulating fluid flow through the bone and the variations in this fluid flow may provide a signal for cellular feedback to mechanical forces such as impact loading (Raisz, 1999, Eriksen, 1986).

There are endogenous factors and biological mediators, which have massive effects on this mentioned process such as parathyroid hormones, vitamin D, estrogen, leptin and cytokines (Khovidhunkit *et al.*, 1997, Bilezikian *et al.*, 2001, Hodsman *et al.*, 2002). Any changes in the levels of these mediators lead to the modification of this

remodeling process maintenance, causing changes in regular levels of mineral ions in the bone which vary the required bone properties where this mostly decreases bone mineral density and increases the incidence of osteoporosis.

Most of the systemic calcium regulation mediators are parathyroid hormone (PTH) which is responsible for regulating serum calcium level by resorbing calcium from bone. It is a strong stimulator of bone resorption. In spite of PTH considered as an anabolic factor, PTH at high serum concentration causes acute inhibition of collagen synthesis but prolonged irregular administration of this hormone leads to the increase in bone formation.

In general, the parathyroid hormone stimulates bone resorption and formation but due to the slow bone formation process, it leads to the degradation in bone density. Ageing is one of the elevating factors of serum PTH where this may increase bone resorption which mostly occurs in cortical bone (Dempster *et al.*, 1993)

Calcitriol 1,25-dehydroxy-vitamin-D, the second calcium regulating hormone, is a metabolite of vitamin D which is synthesized from cholesterol found in the skin by the action of ultraviolet sun light. The metabolism process occurs in the liver and kidney to form active hormone of 1,25-dehydroxy-vitamin-D. This active hormone is responsible for absorbing calcium and phosphorus from intestine as well as stimulating bone resorption as a protection mechanism to provide calcium and phosphorus from the skeleton in case of deficiency of these two minerals in the intestine. The elevation in serum calcitriol level increases feedback in PTH in which it has resorption effect on the bone (Christakos *et al.*, 2006).

The third major calcium maintaining hormone is calcitonin. It is secreted from C-cells in thyroid gland as a response to the elevation in a serum calcium level where this calcitonin inhibits resorption activity of osteoclast cells (Ikegame *et al.*, 2004).

cytokine called RANKL (Receptor Activator of Nuclear factor-kß Ligand). This protein is generated from preosteoblast and activates stromal cell found in the bone marrow. These ligands are bound to the activated receptors called RANK located on osteoclast precursors and initiate differentiation of these precursors to mature multinuclear functional osteoclast cells which start the bone resorption. The interaction of RANKL and RANK is prevented by decoy receptor osteoprotegerin (OPG) which has ability to bind with RANKL and inhibits osteoclast activation where OPG is considered as anti-resorptive cytokine. Another ligand produced by preosteoblast is macrophage-colony stimulating factor (M-CSF) that binds with c-fms. A receptor is also found on the precursor of osteoclast which also induces osteoclastogenesis (Khosla, 2001). This osteoclastogenesis process is enhanced by some local cytokines and prostaglandins such as prostaglandin E2, interleukin-1, interleukin-6, tumor necrosis factor-α (TNF- α), in addition to local growth factors such as Insulin like Growth Factor-1 and transforming growth factor (TGF-ß) which have important additional function for bone remodeling including bone development (Roux and Orcel, 2000).

1.1.4 Osteoporosis pathophysiology and risk factors

In osteoporosis, there is a highly diminish of density and a mineralized matrix of the bone which increase the porosity of bone (cylindrical Haversian canals and Howship lacunae) and elevate its fragileness. This fragileness is approved through the imbalance of remodeling processes when the resorption activity of the osteoclast exceeds the reforming activity of the osteoblast within two ways, either by excessive bone resorption or defect, in reforming the damaged and resorbed bone influenced by

biological factors which rule osteoclast number and activity of these mediators systemic or local (Raisz and Rodan, 2003).

The most common osteoporosis related risk factors are listed in Table 1.1:

Table 1.1 Osteoporosis risk factors.

1. ageing
2. gender
3. race
4. Body Mass Index (BMI)
5. smoking
6. alcohol consumption
7. exercise
8. food intake
9. family history

Ageing is considered as one of the most essential causative factors in osteoporosis incidence. Bone mass modifies over the life of human being. Bone mass raises fast from puberty period until mid 20s to mid 30s when the peak of bone mass is achieved. Then, the bone loss starts at 1% rate of bone per annum (Kenny and Prestwood, 2000, Reginster and Burlet, 2006).

Osteoporosis is influenced by many factors which relate directly or inversely to the incidence of this disease. Individual ageing is first and important factor which affects the bones through different manners in which elder individuals are estimated at 20%-30% of malnutrition. This malnutrition decreases the required protein-calories intake.

Protein is one of the competent of bone tissue in addition to the calories required in the process of bone formation. On the other hand, deficiency of protein-calories intake reduces the production of IGF-1 where it is produced by osteoblast and is a major anabolic factor for bone when the serum and skeletal levels of IGF-1 decline with the ageing that may contribute to the pathogenesis of age-related osteoporosis (Rizzoli *et al.*, 2001, Rosen *et al.*, 2006). Other associations of ageing on bone density are the reduction in calcium intake and deficiency of vitamin D level which also reduce the efficient calcium intestinal absorption and lead to secondary hyperparathyroidism.

A rise in PTH is triggered by a fall in serum 25-hydroxy-vitamin-D and low dietary calcium intake in elders which can result to enhance the calcium mobilization from bone stores and diminish the bone formation and give clarification for bone loss in vitamin D insufficient and deficiency of calcium intake (Bouillon *et al.*, 1997).

Ageing enhances osteoporosis through hormonal changes which occur with ageing. It is accompanied with a reduction in the secretion of gonadotropin releasing hormone (GnRH), gonadotropin luteinizing hormone (LH), testosterone and somatotropin (growth hormone) in human which play important roles in bone formation (Veldhuis, 2007).

Second risk factor is gender which has different effects on the incidence of age related fractures. In other word, the incidence of fractures in women increases with the increase in their ages as compared to men, in addition to high prevalence of osteoporosis among women. In women, the elevation of bone fragility usually coincides with the beginning of menopause and estrogen deficiency. Bone loss relates to the estrogen deficiency, initially takes place in early rate as compared to other age-related reasons of bone loss. Therefore, bone loss is hastened in women,

leading to earlier expansion of osteoporosis in women's life span in addition to the incidence of bone fracture as compared to men. As a result, hospitalization cost after osteoporotic fractures becomes higher in female than in male. However, the morbidity is equal in both sexes while the mortality is high among men after the bone fracture (Geusens and Dinant, 2007).

Third risk factor is race where it differs in terms of its effect on the incidence of osteoporosis, depending on sub-factors - cultural, religious, dietary, geographic as well as other differences among races which are recognized as ethnicity and acculturation. Acculturation is a scale to measure how much an ethnic group assimilates the language, habits and cultural values of the country or area to which it migrates (Villa *et al.*, 2001).

Smoking has been proved to have negative effect on bone density There are evidences that smoking increases the risk of bone degradation in both men and women which increases the possibility of fractures later in their life. A meta-analysis study by Law and Hackshaw (1997) including 29 cross-sectional designed studies and 19 case-control and cohort studies report significant negative effect of smoking on postmenopausal women by accelerating bone loss in an additional 0.2% in each year, but not a significant association on premenopausal women. In general, smoking increases the possibility of hip fracture cumulatively with age where smokers at the age of 60 have possibility of 17% higher which increases with the age reaching 71% higher at 80 (Hollenbach *et al.*, 1993, Law and Hackshaw, 1997). The harmful effect of smoking - direct or indirect- is similar to the nicotine compromises bone reformation and perhaps by motivating ischemia and straight inhibitory effect on osteoblastic cells, where smoking reduces calcium absorption, elevates parathyroid

hormones serum level (Rapuri *et al.*, 2000) and is approved to increase circulating cortisol levels (Steptoe and Ussher, 2005).

Besides, alcohol intake has been varying the outcome on bone density but the vast majority of these outcomes is negative on the bone density and elevates the possibility of lower extremity fractures. Low to moderate alcohol consumption per week (1–27 drinks for male and 1–13 drinks for female) is not related to the incidence of hip fracture. In men, relative risk of hip break is gradually large for those who consume 28 drinks or further per week. Bone loss has been revealed to be increased in men with alcohol ingestion above the median and the latest conclusions record that alcohol abuse may even be correlated with a rise in the relative risk of hip fracture while it is announced that women who weekly drink 14-27 times have the relative risk of hip breakage depending on age (Malnick *et al.*, 1999). In other meta-analysis studies, it is found that there is an elevation in the risk of hip fractures directly with daily consumption of alcohol starting with low risk of 0.5 drinks per day to a higher when it reaches and passes 2 drinks per day (Berg *et al.*, 2008).This degradation effect of alcohol on bone occurs due to different manners which may be direct or by contribution of other diseases related to bone density in which alcohol approves causative factor of liver cirrhosis and chronic liver diseases which are associated with low bone mineral density (BMD) (Davies *et al.*, 2005, Uretmen *et al.*, 2005). Alcoholism contributes to hypogonadism by affecting reproductive axis and elevating cortisol level (Warren and Vu, 2003). Alcohol directly affects the bone density by diminishing osteocalcin level which is a vitamin K dependent protein synthesized by osteoblast. Serum osteocalcin concentration is raised in states of high osteoblastic activity and declined in phases of diminished bone synthesis. Furthermore, low serum level of osteocalcin for the period of acute alcohol

intoxication and in chronic alcohol consumption may point that alcohol reduces osteoblastic activity (Labib *et al.*, 1989). In addition to this harmful effect of alcohol on bone, there are several studies supporting a defensive consequence of moderate alcohol intake opposing hip fracture to moderate consumption of alcohol and this appears to be associated with lower risk of fractures and is statistically not significant. They suggest that bone destruction and fracture risk will only be significantly on rise in men with alcohol abuse and not in the condition of moderate alcohol consumption (Nguyen *et al.*, 1996).

Other risk factor on bone density which is the most important one is dairy and calcium-contained product intake alone and in combination with exercise and physical mobility. There are lots of evidences exhibiting the relationship between calcium intake and bone density and the role of exercise in decreasing bone porosity. A cross-sectional study in Japan includes male and female high school students. The BMD of the girls who exercise has improved with an increase in the times of milk ingestion to a certain peak but decreases when the milk is taken daily. Bone density of the girls who do not exercise is unaffected by the frequency of milk intake. While in the boys, bone density is intensified in both groups who doing exercise and other who do not when the milk consumption increases. These outcomes mention that the intake of milk is useful to pick up BMD in the high school boys (Yoshiia *et al.*, 2007).

A new study provides evidence on positive effects of regular childhood dairy intake on adolescent bone density. These useful effects of dairy intake on bone health are supported by diets with high meat and other non-dairy proteins which stimulate the secretion and action of IGF-1 which plays an important role in children's growing

and holds up bone formation and assists in reducing renal losing of calcium which may occur as an outcome of protein intake (Moore *et al.*, 2008).

Women should be educated to change their behaviors towards the ways of preventing osteoporosis. This means that when postmenopausal women improve the ageing with proper calcium intake and weight-bearing exercise conducts, it may be useful in hindering osteoporosis (Rachelle *et al.*, 2008).

Bone mineral density varies from person to another depending on family history. A study conclusion shows that the arrangement of early postmenopausal women with family fracture history at any age has occurred in mothers or sisters due to low trauma where this is one of the best expectance of low BMD and a fracture in that group of women (Grainge *et al.*, 1999). A meta-analysis estimates that the risk of fracture is obtained from international cohorts population-based studies which conclude that parental history of fracture, especially when we are talking about history of hip fractures, confirms an increased risk of fracture which is independent of BMD (Kanis *et al.*, 2004).

As for secondary osteoporosis, it is developed by the effect of either diseases, medication, or both of them. Recent studies show that there is unclear as to the risk consequence of depression on the bone mineral density and it might be considered as an unrecognized risk factor of secondary osteoporosis or low bone density (Cizza *et al.*, 2001) and several studies have established an involvement between antidepressant drugs usage and osteoporotic fracture (Liu *et al.*, 1999).

1.1.5 Depression

WHO defines 'depression' as "a common mental disorder, characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy and poor concentration, affecting about 121 million people worldwide" (WHO, 2008).

In order to achieve good clinical outcome treatment, it is necessary, during assessment and monitoring, to consider a wide spectrum of Major depressive disorder (MDD) in which it is composed of a number of emotional, cognitive, behavioral and physical symptoms (Truax *et al.*, 2006).

Today, depression is highly common experienced and diagnosed as mental disorder in the United States. It is estimated that 16.9% of the population shows a significant life span as well as currently exposure to depressive disorder, where up to 13.2% of men and 20.2% of women have an active MDD while higher prevalence is within the age range of 30-59 years (NCS, 2007).

While Australian national survey estimates lower than the USA survey, the total frequency rate of Diagnostic and Statistical Manual of mental disorder, 4th edition (DSM-IV) proves that the prevalence of MDD is around 3.2% among Australian, which highly occurred among women with 3.9% than in men about 2.4% (Wilhelm *et al.*, 2003).

In Malaysia, a study by Ministry of Health and Malaysian Psychiatric Association on rural survey reports that depressive disorder is highly frequent psychiatric illness identified with prevalence rate of 3.6%. The prevalence is also shown to be highly occurrence among people with physical problems and during the postpartum period (Majeed and Pereira, 2007). Depression has important risk morbidity effect and it is

correlated with the elevation of mortality 2-3 times more particularly in males (Zheng *et al.*, 1997).

1.1.6 Pathophysiological effect of depression on bone

There are many intervening processes that may conduce to the relationship between depression and bone mineral density. Two important ways in which depression is linked to straight affect BMD and risk of osteoporotic fracture are physiological changes (e.g., modification in hormonal system) and the assumption of bad health behaviors (e.g., smoking and physical immobility). It is also speculated that depression itself is not causally linked to bone strength but is associated with other conditions related to co-morbid medical conditions as well as the use of psychiatric medication.

Physiologically, and as mentioned, many endocrine hormones affect bone formation and/or bone resorption. Elevated level of hormones, either increases osteoclast (bone resorption) activity (e.g. cytokines interleukin-6 (IL-6) and (IL-1), tumor necrosis factor-alpha (TNF-α) and PTH) or inhibits osteoblast (bone formation) activity (e.g., leptin and cortisol) are envisaged to be correlated with lower BMD. Levels of many hormones that organize bone metabolism are altered in depression.

The elevation of cortisol level is the most common consequence of hypothalamus-pituitary-adrenal axis (HPA axis) activation during depression and this elevation persists for long period even after effective treatment of major depression especially among old age where this hypercortisolism has potent effects on bone metabolism (Arborelius *et al.*, 1999, Peeters *et al.*, 2004, Burke *et al.*, 2005, Beluche *et al.*, 2009). Cytokines Levels such as interleukin-6 and other inflammatory markers are also increased during depression and this elevated level of pro-inflammatory markers

is associated with low BMD (Bob *et al.*, 2009). Depression is associated with reduced levels of gonadal hormones estrogen and testosterone (Rajewska and Rybakowski, 2003, Rehman and Masson, 2005, McIntyre *et al.*, 2006), which are diminished in reproductive hormones, leading to mood disturbance (Rubinow and Schmidt, 1996, Carnahan and Perry, 2004). These sex hormones play a regulator role in bone formation and remodeling process (Keles *et al.*, 2006, Kung, 2008).

During depression, there is alteration in biochemical markers of a bone remodeling process estimated through several studies. In 2000, Herran and colleagues have compared the markers of bone turnover between first-episode subjects of MDD and controls which show that the markers of bone turnover such as osteocalcin and telopeptide are significantly higher in a patient with depression as compared to control, and it estimates a high level of cortisol among depressed patients but there are no changes regarding interlukin-6 (Herran *et al.*, 2000).

In 1996, Michelson and colleagues have estimated high cortisol urinary excretion and low serum osteocalcin among women of past and current exposure to depression (Michelson *et al.*, 1996).

Kahl and colleagues in (2005) reported elevated levels of osteocalcin, cortisol and interleukin-6 among cases of comorbid MDD and borderline personality disorder in comparison with the controls (Kahl *et al.*, 2005). Another study in (2007) by Altindag and colleagues estimated higher level of plasma cortisol and lower level of osteocalcin among outpatients depression as compared to the controls (Altindag *et al.*, 2007). Depression is associated with poor health behaviors which physiologically affect BMD. Depression is associated with smoking, alcohol abuse, less physical activity and sedentary life style which have negative effect on the bone density.

Smoking is reported to elevate depression among patients which is associated with lower BMD by inhibiting estrogen activity and calcium absorption by intestines (Hagiwara and Tsumura, 1999, Malnick *et al.*, 1999, Almeida and Pfaff, 2005, Husky *et al.*, 2008, Kuo *et al.*, 2008).

Apart from that, depression is reported to have an association with high alcohol consumption (Grant and Harford, 1995, Dixit and Crum, 2000). Alcohol dependence and heavy alcohol users are also associated with low BMD through the reduction of bone cell generation and function (Chakkalakal *et al.*, 2005, Berg *et al.*, 2008).

Depression is inversely associated with physical inactivity where low physical activity is associated with high depression scores and vice versa. Physical activity and exercise, especially resistance exercise, play an important role in the improvement of the BMD (Harris *et al.*, 2006, Korpelainen *et al.*, 2006, Adami *et al.*, 2008, Ku *et al.*, 2009).

Another way to raise the possibility of having low bone mineral density among depressed patients is antidepressant medications. Recent studies show that there is a relationship between depression and low BMD by the influence of antidepressant medication use (Schwan and Hallberg, 2009).

1.2.0 Literature review

There are several studies attempted to investigate the association of major depressive disorder with the BMD in different reigns around the world.

The first study under took the association of depression with BMD was by Schweiger and colleagues in 1994 in Germany. They used single-energy quantitative computerized tomography (SE-QCT) to measure BMD at lumber spine It was found that after age adjusting, the average of BMD values among depressed group was 15% lower than the non-depressed group (Schweiger et al., 1994b).

Most of the following studies repeated the initial finding of Schweiger et al.; however some studies estimated no significant association between depression and the BMD. The researchers conducted this investigation through different manners, the difference either in the sampled population, design of study or the utility of BMD measurement.

The majority of the studies undertook women only like a study by Coelho et al. 1999 and Petronijevic et al. 2008 (Coelho *et al.*, 1999, Petronijevic *et al.*, 2008), while are there few studies carried out males only like a study by Wong et al. 2005 (Wong *et al.*, 2005).

Some studies tried to employed cross-sectional design which demonstrated in Table 1.2 while other studies employed a cases and matched with controls that shown in Table 1.3.

Most of the studies utilized DEXA in detecting BMD; one study only utilized quantitative ultrasound densitometer which is conducted by Alice et al. (2008)(Alice *et al.*, 2008). Table 1.4 demonstrated the longitudinal studies that relied on a prospective follow up for the sample subjects to compare the rate of bone density loss between cases and controls.

Table 1.2 Cross-sectional studies assessed the relationship of depression with BMD.

First Author	Year	Location	Sample size	Participants	BMD utility	Main findings
Coelho (Coelho *et al.*, 1999).	1999	Portugal	102	Women only, age 40-80 years	Lumbar spine & femur DEXA	women with osteoporosis have notably higher level of depressive symptoms and a corresponding higher frequency of depression without any consideration of other factors strongly related with osteoporosis such as age or body mass index
Reginster (Reginster *et al.*, 1999)	1999	Belgium	121	Outpatient clinic only women, age: 48–77 yrs	Spine, total hip & femoral neck DEXA	No significant correlation between depression and BMD.
Mussolino (Mussolino *et al.*, 2004).	2004	USA	5171	Both sexes age range of 30-39	Total proximal femur DEXA	This study showed the association of major depressive episode with low bone density in men only
Wong (Wong *et al.*, 2005)	2005	Hong Kong	2000	Men only age 65-92 years	Lumbar spine, total hip & total body DEXA	Depressive disorder was allied with a 1.4- double (95% CI 1.00 to 2.08) relative risk (RR) of actuality examined with a T-score ≤ -1.0, which concluded that depression is associated with lower BMD.
Jacka (Jacka *et al.*, 2005).	2005	Australia	78	Only women, age: 45–60 yrs	Lumbar spine & total hip	it showed significant relation between low bone density and depression
Williams (Williams *et al.*, 2008).	2008	Australia	488	premenopausal women with the age range from 20–58 years	hip, forearm, spine and total body by DEXA	This study estimated the reduction in BMD among those younger women with a history of lifetime depression
Alice (Alice *et al.*, 2008)	2008	Italy	306	Both sexes age above 75 years	Calcaneus bone at heel by QUS	Significant association of _Geriatric Depression Scale with _ultrasound-derived T-score, Z-score, and Stiffness index

Table 1.3 Case and control studies assessed the relationship of depression with BMD.

First Author	Year	Location	No. of Cases	No. of control	Participants	BMD utility	Main Finding
Schweiger (Schweiger *et al.*, 1994)	1994	Germany	70	80	Inpatient clinic, community controls, both sexes age: 40–95 years	single-energy quantitative computerized tomography (SE-QCT) to measure BMD at lumber spine	after age adjusting, the average of BMD values among depressed group was 15% lower than the non-depressed group.
Michelson (Michelson *et al.*, 1996).	1996	USA	24	24	Women only mean age 41years	Lumbar spine, hip & radius DEXA	BMD in depressed women was 6.5 % at the spine while at the femoral neck, it was 13.6 % lower than normal women
Amsterdam (Amsterdam and Hooper, 1998)	1998	USA	6	5	Outpatient clinic, community controls, age: 27–53 yrs	Lumbar spine DEXA	no significant association between depression and bone density
Vrkljan (Vrkljan *et al.*, 2001)	2001	Croatia	31	17	Inpatient clinic, community controls, age: 29–45 years	Unknown	good correlation between the duration of depression and the reduction in the bone mineral density
Yazici (Yazıcı *et al.*, 2003)	2003	Turkey	25	15	Outpatient clinic, community controls only women), mean age: 31 yrs	lumbar spine and proximal femur by DEXA	Significant association of depression with low BMD
Yazici (YazIcI *et al.*, 2005)	2005	Turkey	35	30	Outpatient clinic, community controls (only women), mean age: 45 years	Lumbar spine & femoral neck DEXA	No assoc between depression and BMD
Altindag (Altindag *et al.*, 2007)	2007	Turkey	36	41	Outpatient clinic, community controls (only women), age: 26–56 yrs	Lumbar spine & femoral neck DEXA	the mean BMD of the women with depression was significantly lower at the lumbar spine in addition to all sites of the proximal femur
Petronijevic (Petronijevic *et al.*, 2008)	2008	Serbia	73	47	premenopausal women, age 40 years	lumbar spine and femoral neck by DEXA	premenopausal women with unipolar depression have significantly lower bone density than the control sample.