THE DETERMINATION OF LOCAL MALAY FEMALE BONE MINERAL DENSITY AND ITS CORRELATION WITH GEOMETRIC PROPERTIES IN THE EVALUATION OF SKELETAL STATUS

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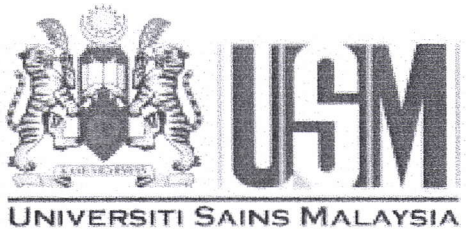

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Tujuan

Untuk menentukan danmengeluarkan data refern untuk jisim (Densiti) tulang mineral (Bone mineral density-BMD) dalam kalangan orang wanita Melayu tempatan dan untuk menetukan kaitan jisim tulang mineral dengan butir-butir geometri.

Tatacara

Seramai 137 orang wanita melayu telah bersetuju untuk menjalankan pemeriksaan jisim tulang mineral (DEXA) untuk tulang belakang, kedua tulang paha dan seluruh badan. X-ray biasa untuk tangan yang tak dominan juga telah dijalankan untuk pengiraan butir-butir geometri (geometric properties-GP) Semua luputusan dianalisa dengan teliti dan direkodkan.

Keputusan

Graf BMD (DEXA) melawan umur ditentukan daripada min dan deviasi satandard umur. BMD tempatan untuk tulang belakang dan seluruh badan adalh 12.2% dan 3.2% lebih rendah dan untuk kedua-dua paha adalah 1.2% lebih tinggi daripada data refern karkasian (US / Europe). Terdapat kaitan yang baik antara berat badan dan BMD (r= 0.344-0.642). Kaitan yang baik juga didapati antara tulang belakang, kedua-dua tulang paha dan seluruh badan BMD dengan kawasan korteks (CA) , ketabalan korteks (CT) dan metakarpal index (MCI) terutamanya metakarpal kedua. Multiliniar model kaitan untuk CA2 dan CT2 dan berat badan telah membaik pulih keupayan meneka model untuk berat badan.

Kesimpulan

BMD data ada untuk populasi luar nrgara tetapi tiada untuk masyarakat Melayu. Kewujudan data untuk sekap keturunan di Malaysia adalah pemting untuk menilaikeadaan tulang kerana tedapat perbezaan yang ketara antara masyarakat Melayu dan asing. Butir-butir geometri boleh digunakan secara murah untuk menentukan BMD dan boleh membantu dalam diagnosa kereputan tulang dan kepatahan tulang

ABSTRACT

Aims: To establish bone mineral density (BMD) reference data for local Malay female population and to determine the correlation of BMD and geometric properties

Methodology: A total of 137 Malay female volunteers who have given a written informed consent have undergone DEXA of the spine, dual femur and total body using LUNAR PRODIGY, GE Medical Systems. Plain radiographs of non-dominant hand of all the subjects were also taken for the measurement geometric properties (GP). All the readings were analysed appropriately and results were recorded

Results: A reference curve of BMD (DEXA) versus age group was obtained from the mean and standard deviation of the peak age value. The local BMD corresponding to -2.0 standard deviation from the peak adult value for vertebral and total body BMD were 12.2% and 3.2% respectively lower whereas for the dual femur it was 1.2% higher compared to the Caucasian reference data (U.S/Europe). There were fair to good correlation between weight and BMD ($r = 0.344 - 0.642$). Generally fair to good correlation was seen between vertebral, dual femur and total body BMD with cortical area (CA), cortical thickness (CT) and metacarpal index (MCI), particularly of the second metacarpal. Multi linear correlation models accounting for CA2 and CT2 in addition to weight have improved the predictive power of a model for weight alone.

Conclusion: Bone mineral density data is available currently for overseas population; but not for Malays. Establishment of database for each race in Malaysia is important for proper skeletal status evaluation, in view of significant differences in the local Malay BMD value compared to other population reference data. Geometric properties can be used as a cheapest tool to predict BMD and may improve the accuracy of diagnosis of osteoporosis and prediction of fracture risk.

KeyWords: ***Bone Mineral Density, DEXA, Geometric Properties, Cortical thickness.***

SECTION- 1

INTRODUCTION

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LITERATURE REVIEW

1. Introduction

Osteoporosis is a silent, chronic, progressive deteriorating skeletal skeletal disorder characterized by decreased bone mass and compromised bone strength. Bone strength reflects the integration of two main features: bone density and bone quality. Bone density is expressed as grams of mineral per area or volume and in any given individual is determined by peak bone mass and amount of bone loss. Bone quality refers to architecture, turnover, damage accumulation (e.g., microfractures) and mineralization. The low bone density and increased bone fragility consequently increases its susceptibility to fracture especially of the hip, spine and wrist, although any bone can be affected. Bone loss is the major risk factor that can be modified in mid-life to reduce fracture risk. Bone loss can be reduced by treatment, but it is difficult to restore the microarchitecture of the skeleton once bone has been lost.

Osteoporosis used to be considered an inevitable consequence of aging. Women are at the greatest risk. One third of Caucasian women over the age of 50 have osteoporosis, yet nearly 80% remain undiagnosed. After menopause, a woman's risk of suffering an osteoporotic spine or femur fracture is about four times that of a man. In view of these factors, prevention or early detection and intervention are crucial. There is no universally accepted algorithm for the assessment of women who are at risk or already have osteoporosis. As a result, aims of evaluation of every postmenopausal women in particular, should include identification of women at high risk for osteoporosis and fracture, establishment of correct diagnosis and identification of correctable cause of bone loss, determination of severity, extent and activity of the disease as well as selecting and monitoring therapy.

Almost all the techniques available for determination of bone density have their own limitations. Many studies were done and some still in progress to compare the efficacy of these techniques available and to improve the BMD measurement.
In the past plain radiography was generally used to assess the bone density and architecture. It is no longer used for evaluating bone mass in quantitative terms, because as much as 30% to 40% of bone mass must be lost before changes can be seen on plain radiograph. In 1959, Krokowski described a procedure for determination of bone mineral content of the spine by using two different energies. Now this is known as the dual energy X-ray absorptiometry (DEXA). This with other highly accurate and

precise quantitative techniques such as single X-ray absorptiometry (SXA), single and dual photon absorptiometry (SPA, DPA) and quantitative computed tomography (QCT), have provided a satisfacotory approach to measure the bone mineral density (BMD). DEXA and QCT are considered two widely acceptable technologies to measure BMD. However these two have some limitations. High attenuation material, extraneous calcification and sclerotic bone may increase the final result of BMD because DEXA software is unable to differentiate them from bone. QCT can exclude the unwanted high attenuation material however it gives higher radiation dose to patient. By incorporating geometric properties to BMD measurement we may eliminate or reduce these problems. Apart from providing BMD result, evaluation of geometric properties can determine bone structural strength. A combination of an expensive tool for initial BMD measurement with a lower cost tool for subsequent follow up can reduce the overall cost.

WHO in 1994 and the Japanese Society for Bone and Mineral Research in 1996 have established diagnostic criteria used for diagnosis of normal, osteopenia and osteoporosis. That criteria was revised in 1998 and also in 2000. Except for white women and part of Japanese as well Chinese women, the reference database of hip fracture risk for other races and male population is unknown. Furthermore the bone mineral content, architecture and geometry of one population are different to another due to environmental and genetic influences. Most manufacturers of bone mineral densitometer in Asia are using the Oriental Women reference database that is not specific. A standardized reference database for each skeletal site and a 'gold standard' technique to be adopted by all manufacturers are still not available. Due to this, databases for the Malays, Chinese and Indian population should be established in our continent for proper diagnosis of osteoporosis.

2. Literature Review

2.1 Prevalence of Osteoporosis

The incidence of osteoporosis in East Asian countries is ever increasing. In Japan 24% of women aged 50 years or older are affected with osteoporosis (Hu J.F. et al, 1993). In 1997, the incidence of hip fracture in Malaysia among individuals above 50 years of age was 90 per 100,000. The Malaysian Chinese had the highest incidence

of hip fracture followed by Malaysian Indians and Malays (Clinical Guidelines on Management of Osteoporosis, 2001). Crude hip fracture rates (per 100 000) in Chinese, Malay and Indian female populations living in Malaysia are 220, 43, 204 respectively and in Singapore Crude hip fracture rates (per 100 000) are 437, 233 and 242 respectively. Lau et al (2001), found that the incidence rates of hip fracture among Hong Kong and Singaporean Chinese women reached 80% of Caucasians. The incidence of osteoporosis among the white and oriental races is higher compared to others. Osteoporosis affects more than 75 million people in the United States, Europe and Japan (Morii H. & Genant H.K., 1998). In the United States alone, Osteoporosis is a major public health threat for an estimated 44 million Americans, or 55 percent of the people 50 years of age and older. In the U.S., 10 million individuals are estimated to already have the disease and almost 34 million more are estimated to have low bone mass, placing them at increased risk for osteoporosis. Of the 10 million Americans estimated to have osteoporosis, eight million are women and two million are men. Over 28 million people are at high risk of developing osteoporosis. One in two women and one in four men over age 50 will have an osteoporosis-related fracture in her/his remaining lifetime.

Osteoporosis is responsible for more than 1.5 million fractures including over 300,000 hip fractures and approximately 700,000 vertebral fractures 250,000 wrist fractures and 300,000 fractures at other sites that occur in a year. Annual National health care expenditures related to osteoporosis are over $18 billion per year in 2002, and the cost is rising. While osteoporosis is often thought of as an older person's disease, it can strike at any age. The incidence increases with age and four times higher in women than men. 80% of those affected by osteoporosis are women. 25% of non-Hispanic white and Asian women aged 50 and older are estimated to have osteoporosis, and 52 percent are estimated to have low bone mass. 5% of non-Hispanic black women over age 50 are estimated to have osteoporosis; an estimated additional 35 percent have low bone mass that puts them at risk of developing osteoporosis. 10% of Hispanic women aged 50 and older are estimated to have osteoporosis, and 49 percent are estimated to have low bone mass. Twenty percent of those affected by osteoporosis are men. 7% of non-Hispanic white and Asian men aged 50 and older are estimated to have osteoporosis, and 35 percent are estimated to have low bone mass. 4% of non-Hispanic

black men aged 50 and older are estimated to have osteoporosis, and 19 percent are estimated to have low bone mass. 3% of Hispanic men aged 50 and older are estimated to have osteoporosis, and 23 percent are estimated to have low bone mass.

2.2 Pathogenesis of Osteoporosis

2.2.1 The physiological basis of osteoporosis

The skeletal system serves as mechanical support to the body and protects important vital organs. It maintains the serum homeostasis of calcium and phosphate ions. The physiological regulation of calcium homeostasis involves three main organs: the gut, the kidney and the skeleton. The physiological control of calcium metabolism and of skeletal remodeling is under the regulation of systemic hormones, especially the calcium regulating hormones, parathyroid hormone (PTH),1,25- dihydroxy vitamin D (calcitriol) and calcitonin, acting with other hormones such as thyroid and pituitary hormones and adrenal and gonadal steroids and local mediators. The set-point for plasma calcium concentrations is determined mainly by the renal tubular reabsorption of calcium and the effects of PTH on this process. Intestinal absorption of calcium is enhanced by calcitriol but the efficiency of absorption may be lowered with age. Production of calcitriol may be impaired, particularly if renal function is reduced. PTH values rise with age, possibly in response to impaired intestinal absorption of calcium, and this may contribute to bone loss.

Bone is a highly active specialized connective tissue. A healthy skeleton continually undergoes bone resorption and remodelling. This process is controlled by parathyroid hormone, vitamin D metabolism and oestrogen. Failure in bone remodelling occurs when the balance between bone resorption and replacement is altered, leading to osteoclastic activity more than osteoblastic activity (Miller P.D. & Bonnick S.L.,1999). With increasing age, formation of new bone tissue declines causing a permanent bone deficit at each remodelling cycle. Osteoporosis is the most common clinical disorder of bone metabolism. Its pathophysiological basis includes a genetic predisposition to low peak bone mass, and subtle alterations in bone remodeling, due to changes in systemic and local hormones, coupled with environmental influences . The etiology and development of osteoporosis among elderly population include hormonal, environmental and (Lau E.M.C., 1997).

2.2.2 The role of estrogen deficiency

The effects of estrogen in bone are of particular interest in relation to the loss of bone after the menopause in women and the therapeutic use of estrogen to prevent this. Estrogen receptors (and isoforms)are widely distributed in the body and there are many ways that estrogens can exert their effects on their various target tissues. Some effects of estrogens are mediated by non-genomic means. The bone loss associated with estrogen deficiency is accompanied by increased bone resorption. Part of this may be due to loss of direct effects on osteoclasts and their precursors, but indirect actions on the immune system may also be involved. The production of cytokines such as IL-1,TNF-and IL-6,all of which can potentially enhance bone resorption, can be suppressed by physiological doses of estrogen.

It is also possible that estrogens have significant anabolic effects on bone by stimulating osteoblasts or their precursors. The pathogenesis of osteoporosis in men is less well studied than in women but is clinically important, with secondary causes, e.g. hypogonadism, being common. It is now thought that estrogens derived by metabolism from androgens play an important role in protecting against bone loss in men 20,21 . Interestingly the challenges of pregnancy and lactation seem to have lasting adverse effects on bone.Examples of osteoporosis associated with pregnancy are exceedingly rare. In women the loss of estrogen at the menopause is the major change leading to loss of bone but many other factors contribute, and there is a strong interplay between genetic and environmental influences.

2.2.3 The cellular basis of osteoporosis

Osteoblasts within trabecular bone differentiate from stromal cell precursors in bone marrow and manufacture a complex extracellular matrix, which subsequently mineralizes. The older concept that the bone matrix is entirely normal in osteoporosis is undergoing revision as knowledge increases. For example, there may be subtle and also in cross-linking within collagen. Many growth factors affect bone formation. These include insulin-like growth factors (IGFs), broblast growth factors (FGFs), and especially members of the transforming growth factor (TGF)-family, particularly the bone morphogenetic proteins (BMPs). Many of these factors are produced by bone cells themselves and can be deposited in bone matrix. Changes in the production and

action of these many regulatory factors are clearly potentially important in the pathogenesis of osteoporosis but detailed knowledge is very limited at present. Osteoclasts are the major cells involved in bone resorption. Osteoclasts differentiate from hematopoietic stem cell precursors under the direction of factors that include cytokines such as the RANK/RANK-ligand system, colony stimulating factors (CSFs, especially m-CSF), interleukins (e.g.IL-1,IL-11)and other factors. Prostaglandins and nitric oxide (NO) are other endogenous mediators that have complex effects on osteoclast function. Bone loss is a feature of several inflammatory diseases. This loss may be systemic, leading to fractures, as in rheumatoid arthritis, while local erosive lesions occur in bone in osteomyelitis, rheumatoid arthritis and periodontal disease. The pathogenic mechanisms probably involve proinflammatory cytokines such as IL-1,TNF and IL-6,and aberrant expression of RANK-ligand. Apoptosis (programmed cell death)is emerging as a major means of regulating the life span of bone cells of all lineages, osteoclasts, osteoblasts and osteocytes. This may contribute to changes in bone turnover under physiological and pathological conditions. Drugs with adverse effects on bone such as glucocorticoids induce osteoblast and osteocyte apoptosis, while therapeutic agents that inhibit bone resorption, including estrogens and bisphosphonates, shorten the lifespan of osteoclasts. Increased apoptosis of osteocytes is a feature seen in fractures of the femoral neck in patients with osteonecrosis.

2.2.4 Rates of bone turnover and bone loss

There is increasing use of biochemical measurements to assess and monitor rates of bone resorption and formation. High rates of bone turnover predict fractures independently of other factors such as BMD. There is evidence that rates of bone loss vary, and that patients defined as 'fast 'losers based on biochemical measurements do lose more bone mass than 'slow 'losers. Responses to treatment may be greater in those with high turnover

2.2.5 Hormonal

There is progressive bone loss of about 1% per annum in women, beginning at menopause. In men, from midlife the rate of bone loss is half of that of women (Hirotoshi et al, 1998). The factors that put women to higher risk are at menopause

there is an increase activation of remodelling sites and bone resorption is increased, resulting in deeper resorption cavities, which may perforate trabecular plates. Furthermore there is reduction of oestrogen level and relative increase in androgen. The exact mechanism of action of oestrogen on the skeleton is not yet known. However based on few studies, bone may contain specific oestrogen receptors or a receptor mediated inhibition of osteoclast formation and bone resorption. Oestrogen also opposes the action of parathyroid hormone and slows resorption of bone (Miller P.D. & Bonnick S.L., 1999).

2.2.6 Environmental

Nutritional factors and osteoporosis

Dietary calcium is obviously a potentially important factor in osteoporosis. Calcium restriction in experimental animals results in osteopenia. In humans, calcium deficiency in childhood leads to rickets. Although low calcium intake might be expected to be associated with osteoporosis, the nature of the relationship between calcium intake and osteoporosis remains controversial. Results from calcium balance studies suggest that pre-menopausal women require calcium intakes in excess of about 800mg per day to avoid net bone loss, whereas postmenopausal women may require as much as 1500mg per day, perhaps less if receiving sex hormone replacement therapy. Calcium supplementation in many trials in patients with osteoporosis results in gains in bone mass but to a lesser extent than can be achieved when anti-resorptive drugs are given as well.

Dietary calcium intake during growth may play a role in the development and maintenance of peak BMD. It is likely that various other environmental and lifestyle factors, particularly exercise, may modulate this effect. Calcium supplementation in growing children produces small increases in BMD, which tend not to be maintained, and may represent increased mineralization of existing osteons rather than true and sustained increases in bone mass. Poor nutrition in pregnancy may affect bone in postnatal life, since low birth weight is associated with low bone mass in later life.

Calcium is not the only component of diet that may affect bone; magnesium also may be important. Vitamin D is vital for optimal absorption of calcium from the diet. In many countries vitamin D is added to food stuffs; otherwise adequate skin exposure to ultraviolet light is necessary to maintain vitamin D levels from endogenous synthesis. There is little evidence that micronutrients such as zinc, copper boron have major effects on bone health. Some diet, particularly those rich in soy protein, can provide significant sources of estrogens. Excessive salt and caffeine intake may have adverse effects on bone, perhaps by increasing urinary calcium excretion directly and thus contributing to a negative calcium balance. However, these effects are probably relatively minor. Alcohol is another dietary component that may be quite important, with adverse effects in excess.

2.2.7 Physical activity, mechanical loading and osteoporosis

Mechanical forces exert strong influences on bone shape and modeling. At a cellular level, the osteocytes, which lie embedded within individual lacunae in mineralized bone, are believed to be the cellular system responds to mechanical deformation and loading. Osteocytes connect with each other via the canalicular system and thus form a cellular network much like a neural network. Early biochemical responses mechanical loading may include induction of prostaglandin synthesis, increased nitric oxide production and later increases in IGFs, changes amino acid transporters and eventually increases in new bone formation. There may be a 'mechanostat ',so far hypothetical only, that senses and responds to loading. Estrogens may affect the set-point at which bone responds. Immobilization, for example following major injury and illness, associated with rapid bone loss. If sustained, as in patients with paraplegia or hemiplegia, fractures can occur. The excessive bone resorption associated with immobility can result in 'immobilization hypercalcemia ',particularly in the presence renal impairment.

Bone loss associated with microgravity may be a limiting factor long-term space flight. The positive effects of mechanical loading on bone mass can be seen weight lifters and other athletes. Sometimes the increased bone density localized to the loaded side, for example in tennis players ' arms. Physical inactivity correlates with low BMD and fractures in epidemiological studies. However the potential beneficial effects of

exercise programs may only produce limited changes in bone mass and have not been shown to reduce fractures.

2.2.8 Drugs and osteoporosis

Several drugs have adverse effects on the skeleton and thereby reduce bone mass and increase the risk of fracture. Glucocorticoids are among the most important of these and are an important cause of bone and fractures. Anticonvulsant drugs such as phenytoin and various barbiturates have long been thought to modify vitamin D metabolism but their contribution to osteoporosis is probably not major. Heparin is another agent reduces bone mass. Since deficiency of estrogen and testosterone both contribute to bone loss, drugs that reduce sex hormone levels cause bone loss. Androgen deprivation therapy with agonists of gonadotropin releasing hormone now frequently used in the treatment of recurrent and Metastatic prostate cancer because it induces medical castration, which renders these men hypogonadal. This is becoming an important iatrogenic cause osteoporosis. The use of tamoxifen appears to cause bone loss by antagonizing estrogen in pre-menopausal women with breast cancer, whereas it has weak protective effect against bone loss in postmenopausal women. Depot medroxyprogesterone used as a contraceptive in pre-menopausal women can result in bone loss. Epidemiological studies show that tobacco smoking is a risk factor for osteoporotic fracture. The mechanisms are uncertain but may include direct adverse effects on bone, induction of early menopause, changes in acid –base status and increased falling secondary to cerebrovascular disease.

In contrast, several drugs may increase bone mass and reduce fractures. Thus, thiazide diuretics decrease urinary calcium excretion and have been associated with increased BMD and reduced hip fracture rates. There has also been much recent interest in the statins. These drugs are used to reduce cholesterol and have been shown experimentally to induce BMP-2 and increase bone mass in rats. A variety of epidemiological studies suggest that statin users have lower rates of hip fracture than non-users but it has proved dif .cult to demonstrate large effects on bone mass and turnover in prospective clinical trials. Of course, those drugs actually used in the therapy of osteoporosis increase bone mass. They include sex hormone replacement therapy with estrogens, calcitonin, selective estrogen receptor modulators and the bisphosphonates, all of which reduce bone resorption and decrease the rate of incident

vertebral fractures. Only estrogen and the nitrogen-containing bisphosphonates have been shown to reduce the risk of non-vertebral fractures in postmenopausal women. Anabolic agents, such as intermittent PTH given as a daily subcutaneous injection, increase bone formation and reduce fracture risk.

Several studies conducted in Asia showed that the environment and lifestyle are major factors effecting bone mineral content. Comparison among Japanese, Japanese-Americans and Americans Caucasians geographically, showed that the prevalence of vertebral fracture was greatest among Japanese. The contributing factors were Japanese women attained menarche later, earlier menopause and have smaller body built than Japanese-American (Fujiwara S. & Ross P.D., 1997). A study involving children and adolescent in Hong Kong and Jiangmen showed that there were slower acquisition of bone mineral content in children and adolescent from Jiangmen. However, no difference in BMD by the age of 35 years in women. They shared the same ethnicity but had different life styles. Children and adolescent in Hong Kong lead a more sedentary lifestyle though they have higher calcium intake. Children in Jiangmen compensated their lower calcium diet through their high physical activity such as walking or cycling to school and climbing stairs (Leung S.S.F et al, 1997).

Hu et al (1993), selected 5 regions which were geographically scattered across China and divided them into three areas. There were pastoral (area where the population consume most dairy food), semipastoral and non-pastoral. These areas were selected because there was vast diversity of dietary pattern, distinct lifestyles and very little residential mobility. They found that the bone mineral content of those living in pastoral area were higher than the other two areas. Similarly Matkovic et al (2001), reported differences in fracture rate and bone mass between two rural districts of Croatia. The diets of the two populations were made up of foods produced locally. People of one district, who consume most dairy diet, had 50% higher calcium intake than the other which did not have access to dairy food. The people of the low calcium (i.e., non-dairy) district had lower bone mass and higher hip fracture rates. However the fracture rate for the distal forearm was the same for both groups, a point emphasizing the heterogeneity and complexity of osteoporotic fragility just like Asian who has shorter and less angled hip axis. These aspects have shown that apart from other factors, geometric properties hence are important in determining bone structural strength.

2.2.9 The genetic basis of osteoporosis

The many genetic factors that regulate skeletal development and function are rapidly being identified, and recent examples include the *CBFA1* gene for osteoblast differentiation and the RANK/RANK-ligand system for osteoclasts. Osteoporosis is common and there are strong genetic contributors to skeletal size and composition. Comparisons of identical and non-identical twins have led to estimates that more than 50%of peak bone mass is determined by genetic factors. Overall physique affects susceptibility to osteoporosis and may underlie racial differences in prevalence. Hip fractures typically occur in the thin and frail rather than the fat and robust, and low body weight is a risk factor. Hip axis length is a quantifiable geometric measure related to fracture risk. Rarely, osteoporosis or unusually high bone mass can occur as the result of mutations in a single gene. Thus inactivating mutations in the lipoprotein receptor-related protein 5 gene are the cause of the osteoporosis –pseudoglioma syndrome, whereas the high bone mass syndrome is caused by activating mutations of the same gene 22. In the various forms of osteogenesis imperfecta (brittle bone disease) defects in the synthesis or structure of type I collagen occur due to a range of different mutations in type I collagen genes. In the commoner forms of osteoporosis, genetic factors play an important role in regulating skeletal size and geometry, BMD, ultrasound properties of bone, and bone turnover, as well as contributing to the pathogenesis of osteoporotic fracture 23. These phenotypes are determined by the combined effects of several genes and environmental influences. Genome-wide linkage studies in man have identified loci on chromosomes 1p36,1q21, 2p21, 5q33 –35, 6p11 –12 and 11q12 –13 that show definite or probable linkage to BMD but so far the causative genes remain to be identified. A research on genome, a series of sibling-pairs with osteoporosis have suggested linkage of chromosomes 1p36, 2p23-p24 and 4q32-34 to spine or hip BMD (Devoto et al, 2001). Niu et al (1999) in their search for loci that regulated forearm BMD of healthy sib-pairs from a Chinese population suggested linkage of chromosome 2p23-24 to BMD. Chromosome 1q21-23 have also been suggested to be linked to lumbar spine BMD of healthy Caucasian and African-American females (Koller et al, 2000). Multiple environmental influences and population admixtures are also taken into account, making the task more challenging.

Other genes were found to be associated with the pathogenesis of osteoporosis. They were the vitamin D receptor gene/VDR [12q12-q14] , calcitonin receptor gene

[7q21.3], Parathyroid hormone receptor 1 gene [3p22-p21.1], calcium-sensing receptor gene [3q21-q24] and Type 1 Collagen gene [17q21.3-q22.1] (Peacock et al, 2002). Looking for susceptibility genes for osteoporosis is one of the several important approaches toward the long- term goal of understanding the molecular biology of the normal variation in bone strength and how it may be modified to prevent osteoporosis. Linkage studies in mice have similarly ident- fied several loci that regulate BMD. Most research has so far been done on candidate genes. Among the best studied are the vitamin D receptor and the collagen type I 1 gene. Polymorphisms of vitamin D receptor have been associated with bone mass in several studies, and there is evidence to suggest that this association may be modified by dietary calcium and vitamin D intake. A functional polymorphism affecting an Sp1 binding site has been identified in the collagen type I 1 gene that predicts osteoporotic fractures independently of bone mass by influencing collagen gene regulation and bone quality 24. An important problem with most candidate gene studies is small sample size, and this has led to inconsistent results in different populations. This is also complicated by the multiple clinical endpoints (BMD, fracture, rates of bone loss, etc.) to which genetic factors may contribute in different ways. There is evidence that genetic variants in various hormones and cytokines and their receptors that are involved in bone remodeling may also contribute to the development of osteoporosis.

2.3 Risk factors for osteoporosis:

Low bone density is one of the risk factors for developing osteoporosis that can be altered, along with hormone levels, diet, exercise and other lifestyle choices. Risk factors that can't be changed include gender, age, family history, body size (to some extent) and ethnicity.). A fracture occurs when a failure-inducing force (e.g., trauma) is applied to osteoporotic bone. Thus, osteoporosis is a significant risk factor for fracture, and a distinction between risk factors that affect bone metabolism and risk factors for fracture must be made.

Risk Factors	Details
Gender	Women have less bone tissue and lose bone more rapidly than men because of the menopausal. Changes.
Aging	Bones become less dense and weaker as you advance in age.
Heredity	Genetic factors account for about three-fourths of the variance in peak bone mass. • Family history of fractures--especially maternal history of hip fracture • Bone structure -- a small, slender body build (less than 125 pounds); tallness (more than 5'7") • Race -- Although all races may develop the disease, fair skin /a Caucasian or Asian background are at higher risk
Prolonged sex hormone deficiencies	Estrogen deficiency (women) • Post menopause • Early menopause(before age 45): surgical /chemotherapy-induced ovarian failure • Testosterone deficiency (men)*

Nutrition	• Low calcium and Vitamin D deficiency
	• Eating disorders like anorexia nervosa or bulimia
	• Increased urinary excretion of calcium caused by a high salt, high phosphorous diet
	• A high protein diet
	  • Gastrectomy
	  • Malabsorption

Body weight	• People who weigh less and have less muscle are more at risk for developing osteoporosis. • Nearly 30 percent of patients who have weight-loss surgery develop nutritional deficiencies. • weight loss due to extreme weight control
Other lifestyle factors	
Lack of exercise Vision:	Clinical studies have shown that one of the best ways to prevent osteoporosis is through a medically sound, planned exercise program. Impaired eyesight despite adequate correction, recurrent falls insufficient exposure to sunlight, muscle paralysis, zero gravity(astronauts)

Smoking	Cigarette smoking appears to negatively impact premenopausal bone density, particularly in the spine. Studies suggest that women who smoke tend to have an earlier menopause than those who don't.
Excessive caffeine	Consistently more than three cups a day of coffee, tea, colas. Moderate caffeine consumption is not linked to bone loss in premenopausal women with adequate calcium intakes.
Excessive alcohol	Consistently more than two drinks a day. Chronic alcohol abuse has been associated with hormonal deficiencies, irregular menstrual cycles, and low bone mineral density in premenopausal women. Moderate use, however, is not believed to be harmful to bone mineral status.
Illnesses/prolonged use of certain medications	
Naturalglucocorticoids	Cushing's disease -- leads to accelerated bone loss.
Synthetic glucocorticoids (steroids — cortisone, prednisone)	Results in loss of absorption of calcium or Vitamin D. Usually taken to control: Arthritis; bursitis; chronic obstructive pulmonary disease; allergic conditions; chronic active hepatitis; lupus erythematosus; psoriasis; dermatitis; leukemia; lymphoma; ulcerative colitis; Crohn's disease; multiple sclerosis; organ transplantation; glaucoma
Other medications that affect bones	• Anti-convulsants • Thyroid hormone • Antacids that contain aluminum • Methotrexate -- used to treat a variety of cancers, immune disorders, and resistant arthritic conditions • Cyclosporine A -- used in organ transplantation and for the treatment of some diseases of the immune system • Gonadotropin Releasing Hormone (GnRH) Analogues – used in the long-term treatment of endometriosis • Heparin -- used to prevent blood clotting • Cholestyramine -- used to control blood cholesterol levels • The oral, progestational contraceptive medroxyprogesterone isoniazid, lithium

Other diseases that affect bones	• Amenorrhea (missed periods)
	• Malabsorption
	  • Untreated celiac disease
	  • Cystic fibrosis
	• Renal disease -- due to a decrease in serum levels of vitamin D
	• Cancer of the bone marrow -- can trigger osteoclasts to destroy surrounding bone tissue
	  • Endocrine, marrow, gastrointestinal and connective tissue disorder
	• Dementia, Despression,
	• Insulin dependent (type I) diabetes mellitus
	  • Hyperparathyroidism

Table 1: A concise list of various known risk factors

2.4 Diagnostic criteria for primary osteoporosis

National Institutes of Health Consensus Development Conference (March 27-29, 2000) released a statement on Osteoporosis Prevention, Diagnosis, and Therapy. There are a variety of tests available, which help screen for osteoporosis or osteopenia, but one reliable method is to measure the bone density test, which helps:

- Detect osteoporosis before a fracture occurs
- Predict the chances of fracturing in the future
- Determine the rate of bone loss and/or monitor the effects of treatment if the test is repeated at intervals of a year or more.

A BMD test is quick, accurate, painless, and safe. It is commonly used to measure the density of various bones throughout the body, including the spine, wrist, hip, heel, or hand. A BMD test can detect low bone density before a fracture occurs and confirm osteoporosis. The bone density measurement currently considered the gold standard is dual-energy x-ray absorptiometry (DXA), which allows measurement of any skeletal site as well as the complete skeleton. The technique is highly accurate and precise. Attenuation of x-rays through the skeleton allows the estimation of bone mineral for each region of interest within the spine, hip, forearm, or total body. A measure of the area of mineral is used to provide a result that is, at least in part, corrected for the size of the skeleton. Results are

reported as bone mineral density (content in grams divided by area in cm^2). Because absolute bone density values vary by skeletal site and by manufacturer, it is standard practice to compare the quantitative bone density results with the average of a reference population of the same race, age, and sex. This comparison produces a ***z* score** (graph 2.1), which is calculated by the following equation: patient results - average for reference population divided by the standard deviation of the population. In addition, the individual's results are compared with a young population (peak bone mass) of the same race and sex, producing the ***t* score.**

Graph 2.1. Illustration of a 59-year-old patient with a z score of -1 and a *t* -score of -2.5.

The *Z* score can be clinically useful to sensitise the clinician to the possibility of secondary causes of bone loss. When low *z* scores (below -2.0) are seen, consideration must be given to investigation of the patient for factors other than age or menopause that may be adversely influencing the skeleton. It is the *t* score that is used for osteoporosis diagnosis. The World Health Organization defined osteoporosis as a *t* score of -2.5 or below, whereas normal bone mass is defined as a *t* score above -1. An intermediate category (osteopenia or low bone mass) is considered a *t* score between -1 and -2.5.

Other methods of bone mass measurement that can be used to measure the spine and hip include computed tomography (CT) by using special software. Peripheral CT units can be used to measure bone in the forearm or tibia. The results obtained from CT are different from all others currently available, because this technique yields a pure sample of trabecular bone and measures true volumetric density. Specialized dual-

energy x-ray machines are also available to measure peripheral bone, usually the forearm or the heel. Ultrasound measurements of bone mass depend on the attenuation of a band of ultrasound as it passes through bone or the speed with which the ultrasound traverses the bone. Each produces somewhat different results, although both are related to the amount of bone that is present. The concept that ultrasound measurements can provide additional information about bone quality has not been confirmed.

US Food and Drug Administration (FDA) approval for bone density techniques is based on their capacity to predict the risk of fracture. Hip fracture risk is best predicted by DXA measurements of the hip, which are also good predictors of risk for all osteoporosis-related fractures. Therefore, a DXA measurement of the hip is the preferred site of measurement in most individuals. In younger recently postmenopausal individuals, spine measurement may be a more sensitive indicator of bone loss. In most centres, the DXA test routinely measures both the spine and hip regions. All women should have a bone density measurement by the age of 65, because age alone is such an important risk factor for osteoporosis. Bone mass measurement should be performed in younger women at the time of menopause if they have risk factors for osteoporosis. All men by age 70-75 years and in younger men, if clinical suspicion is high, due to underlying diseases, prior vertebral fractures, or multiple adulthood nonspinal fractures, bone density testing should be performed. It is important to distinguish primary from secondary because the treatments are often different.

Common causes of secondary osteoporosis include:

- *Endocrine disorders* (hypogonadism, Cushings disease, hyperthyroidism, hyperparathyroidism, diabetes mellitus)
- *Marrow disorders* (multiple myeloma, disseminated cancer, chronic alcohol use, lymphoma)
- *Collagen disorders* (osteogenesis imperfecta, Marfans syndrome)
- *Gastrointestinal disorders*(Malabsorption, malnutrition)
- *Medications* (Aluminum antacids, anti-convulsants, chemotherapy, glucocorticoid therapy, thyroid hormone replacement)

Additional Radiologic Procedures

The presence of height loss exceeding 1.5 in, or significant kyphosis or back pain (particularly with onset after menopause), indicates that lateral spine radiography should be performed to exclude the possibility of vertebral compression fractures. Vertebral morphometry is a recently developed technique that uses novel DXA software, which provides a lateral view of the spine from upper thoracic to lower lumbar levels. If morphometry provides possible evidence of a compression fracture, a standard radiograph can be performed to confirm the fracture. This test may therefore serve as a screening tool to identify patients with prevalent vertebral deformities who may be at very high risk of future fractures, and who might have otherwise not been candidates for treatment. In some circumstances CT, magnetic resonance imaging (MRI), or radionuclide scans may be helpful, particularly to help define partial, mild, or stress fractures, or sometimes to help distinguish osteoporotic fractures, particularly in the spine, from distinct bone or metabolic bone pathology.

Laboratory Evaluation

When a diagnosis of osteoporosis is made, a general laboratory evaluation, including CBC, serum calcium, and tests of renal and hepatic function, is warranted. In those with vertebral fractures and in those with particularly low *z* scores (-2 or below), an additional evaluation to exclude hyperthyroidism (thyroid-stimulating hormone [TSH]), hyperparathyroidism (PTH), 25-hydroxyvitamin D, celiac disease (transglutaminase antibody), multiple myeloma (protein electrophoresis and/or immunofixation), and renal hypercalcinuria (24 hour urine calcium) should be performed. If clinically suspected, a 24-hour urine cortisol or a dexamethasone suppression test should be performed to exclude Cushing's disease, and a serum tryptase can be considered to look for evidence of mastocytosis.

Biochemical markers of bone turnover.

Several biochemical tests are now available that provide an index of the overall rate of bone remodelling (at a single point in time). Biochemical markers are usually characterized as those related primarily to bone formation (most common is bone-

specific alkaline phosphatase) or bone resorption (serum or urine *N*-telopeptide). Their clinical utility has been limited by high biological and analytic variability within and between individuals. Markers of bone resorption may help predict the risk of fracture, particularly in older individuals, adding to the predictive value of bone densitometry results. [91, 164-166] In women 65 years of age or older, when bone density results are equivocal regarding need for treatment, a high level of bone resorption may be used similarly to a clinical risk factor and suggest the need for treatment at a higher bone mass level. Another use of biochemical markers is in monitoring response to treatment

The WHO criteria for the diagnosis of normal, osteopenia and osteoporosis were completed in 1994. The peak age bone mass (PABM) and cutoff of more than – 2.5 standard deviation (S.D) below PABM for the diagnosis of osteoporosis was derived from young adult and postmenopausal white women respectively. Except for the elderly white women the relation between the WHO diagnostic categories and hip fracture risk for other races or gender is unknown. Furthermore the reference database for skeletal sites other than the hip is non-uniform. Consequently an individual may be classified quite differently if different sample populations are used to create the reference database with which the patient is compared (Miller P.D. & Bonnick S.L., 1999).

In 1995, the Japanese Society for Bone and Mineral Metabolism (now the Japanese Society for Bone and Mineral Research) established a committee that proposed the diagnostic criteria for primary osteoporosis. Revision of the criteria was done in 1998 and 2000. At present, primary osteoporosis is diagnosed when no disease causing low bone mineral density other than osteoporosis and no secondary osteoporosis is observed. Figure 2.3 shows the algorithm for diagnosis of primary osteoporosis (Orimo et al, 2001).

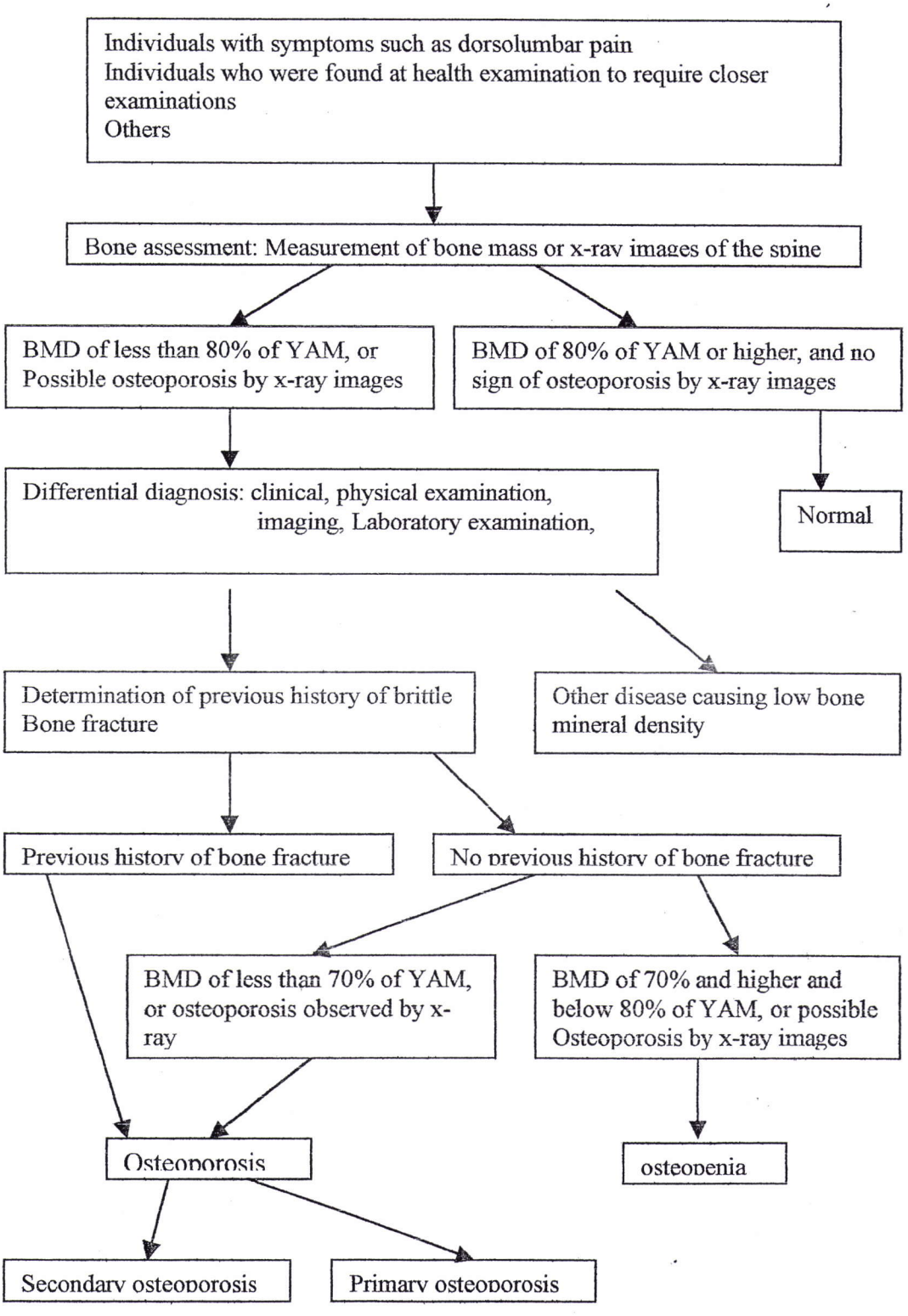


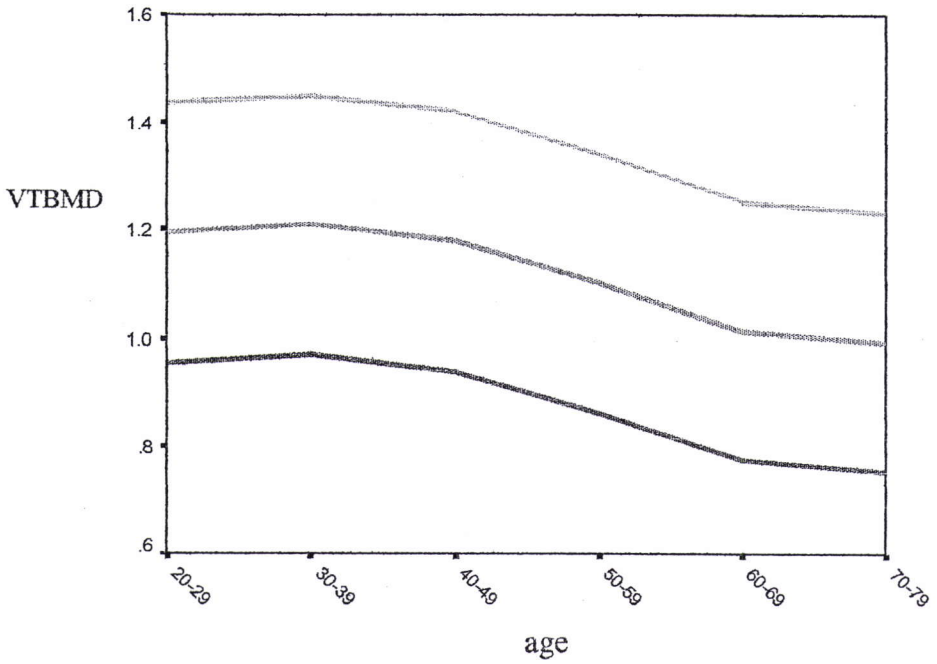
Figure 2.3. Diagnosis of primary osteoporosis

In China, almost all research centers are still using Oriental Women reference databases provided by the manufacturer to diagnose osteoporosis. There is difference between the Oriental Women (from the Hologic QDR 4500A bone densitometer) and CWD reference curves. The BMD rises with age in CWD whereas the Hologic reference curve inclined to decline continuously (Er-Yuan et al, 2003). In view of these differences, it is not appropriate to use reference curves of one population on another population.

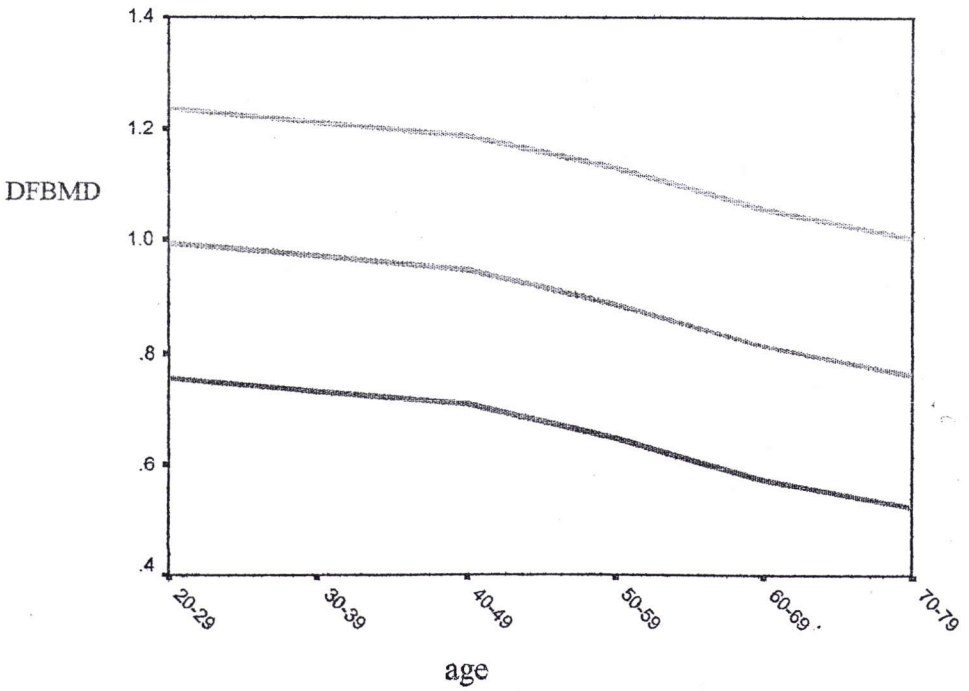
Graphs 2.2 to 2.4 show the U.S/Europe reference curves for vertebra, dual femur and total body obtained from Lunar DPX (Primer on the metabolic bone diseases and disorders of mineral metabolism, 1999). The curve plateau from 20-29 to 30-39 age group, then gradually declined with age in all the three skeletal sites measured. (This reference curves will be compared to the local Malay female data in our research analysis) In table-2, BMD of U.S/Europe population measured with Lunar DPX versus age is given. . (Data obtained from Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 1999)

BMD / AGE	Vertebra	Dual Femur	Total Body
20 – 29	1.196 ± 0.24	1.006 ± 0.24	1.120 ± 0.16
30 – 39	1.210 ± 0.24	0.997 ± 0.24	1.141 ± 0.16
40 – 49	1.180 ± 0.24	0.982 ± 0.24	1.123 ± 0.16
50 – 59	1.102 ± 0.24	0.935 ± 0.24	1.086 ± 0.16
60 – 69	1.015 ±0.24	0.871 ± 0.24	1.030 ± 0.16
70 – 79	0.993 ±0.24	0.811 ± 0.24	0.998 ± 0.16

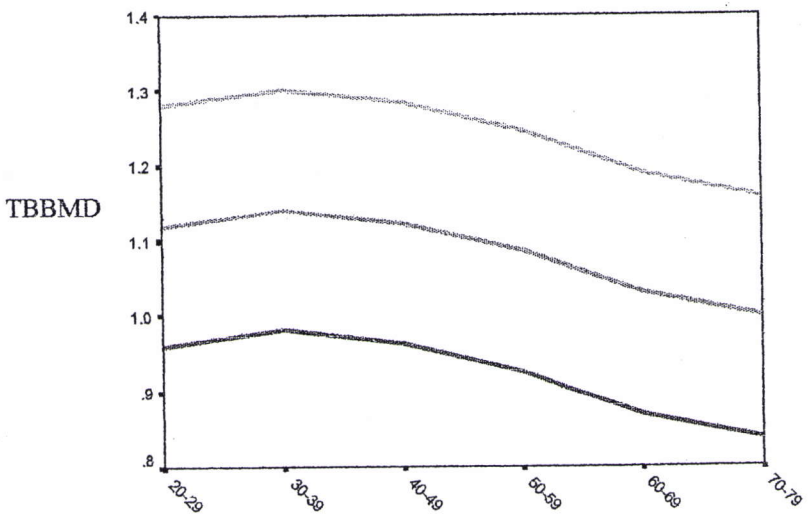
Table 2.: Caucasian (US/Europe) mean and ± 2SD for vertebra, dual femur and Total body of each age group



Graph 2.2: VTBMD of US/Europe population correlated with Age



Graph 2.3: DFBMD of US/Europe population correlated with Age



Graph 2.4: TBBMD of US/Europe population correlated with Age

The WHO chose to define osteoporosis based on comparisons of the patient's BMD/BMC with the average BMD/BMC of the young adult by using the T score rather than the Z score (age-matched peers). This is because declining bone mass increases the risk of fracture and the prevalence of fracture increase with age. Therefore using aged-matched Z scores would result in under diagnosis of osteoporosis. If healthy girls and elderly women reference data are based on T score, their BMD value will be lower. Age-matched data are appropriate for comparison in the growing child or adolescent. It must be emphasized that bone density and fracture risk are continuously related and the classification by T score, although useful in epidemiological studies, should not be given undue weight in clinical decisions. Other relevant risk factors should be considered when validating the BMD result. On account of rapid bone loss and elevated levels of biomarkers of bone resorption, a close follow up is indicated. Patient with intermediate BMD (T score between –1 and +1 for a peripheral measurement), it should be validated by spinal measurement in women up to age 65 and by hip measurement in older women. If confirmed, no intervention is indicated, but measurement should be repeated in 2 years in postmenopausal women and other high-risk subjects, perhaps 3 to 5 years in elderly men. If T score falls below –1, intervention should be considered to prevent bone loss and further measurements made at roughly

annual intervals to ensure the bone is stable. T scores below –2.5 need formal investigation and appropriate treatment. (Morii H. & Genant H.K., 1998).

2.4 Other details of imaging modalities

2.4.1 Radiographic Absorptiometry

Radiographic absorptiometry (R.A) is a method in which radiograph of the hand is scanned or digitized and based on photographic density calculated by a computer, patients' BMD are obtained. One of the first quantitative techniques used to assess bone mass and density/attenuation is the R.A. Its' in vivo precision errors are about 1% and accuracy errors about 5% (Miller P.D. & Bonnick S.L., 1999). R.A BMD between the phalanges and metacarpals of the hand as well as lumbar spine were moderately correlated. The phalanges are particularly very sensitive to early bone resorption. Some studies have found that R.A can predict fracture risk (Gulam et al, 2000; Rosholm et al, 2001). The older generation of R.A needs a wedge for the hand radiograph. Currently R.A is computed-assisted, which are digital image processing (DIP) and digital x-ray radiogrammetry (DXR). In contrast to both DEXA and RA, DXR does not use the intensities of the image in a quantitative manner, but relies on geometric measurements (Rosholm et al, 2001). These methods have reduced operator errors and shortened data-acquisition time. Other benefits of DXR are, it is also used to quantify structural parameters, porosity and striation. Apart from that, the cortical bone index can be assessed with Metacarpal Index (MCI). MCI is a ratio of the combined cortical thickness to bone width. Originally the second metacarpal was chosen because there is less variation in its form, shape and length than in the other metacarpals (Pronosco user manual). Current MCI measurement include the second to fourth metacarpal and their values are combined as average of these three bones. The in vivo precision error of DXR in post-menopausal and premenopausal-women are 0.61% and 0.68% respectively (Pronosco user manual).

2.4.2 Single Photon and Dual Photon Absorptiometry

Single photon absorptiometry (SPA) and dual photon absorptiometry (DPA) are methods using radioisotope source to obtain bone density measurement. Single photon involves absorption of low energy photons by a 125I source. Dual photon absorptiometry uses a 153Gd, as the source however produces two different energies. The accuracy and precision of SPA is 2% to 5% and 1% to 2% respectively whereas for

DPA is 1% to 10% and 2% to 4 % respectively. The examination takes approximately 15 minutes with SPA and 20 minutes for each site with DPA (Morii H. & Genant H.K., 1998).

2.4.3 Dual Energy X-Ray Absorptiometry.

Dual energy x-ray absorptiometry (DEXA) is a widely accepted and currently most accurate method in bone densitometry (Miller P.D. & Bonnick S.L., 1999; Morii H. & Genant H.K., 1998). Compared to single x-ray absorptiometry, DEXA used two x-ray energies to allow differentiation of bone and soft tissue during the scan. Measurement of BMD is made at the lumbar spine, proximal femur, the forearm, whole body and calcaneum. Different equipment will give different results. Therefore to minimize the differences, the spine and total femur are the standard regions of interest for BMD. Some studies claimed that total body BMD is as good as the femur and spine BMD. Herd et.al found that there were significant correlations between total body BMD and BMD in the lumbar spine ($r = 0.76$) and femoral neck ($r = 0.72$). Precision errors of DEXA are about 1% to 2% and accuracy errors are about 4% to 8%. DEXA can detect changes in bone density six to twelve months after a previous measurement. Time taken to perform the procedure is approximately twenty to thirty minutes. Radiation exposure is very low approximately 2.5 milirems (0.025mSievert) that is 1/10 the dose of a chest radiograph.

Guidelines for measurement of BMD are based on T-scores, defined as the standard deviation from the mean of healthy young adults. A T-score represents the mean peak of bone mass (Miller P.D. & Bonnick S.L., 1999). The heel has a slower bone loss rate than other sites in the body, such as the hip, spine, or forearm. This means that if the T-score used from other skeletal areas were used to measure T score calcaneum, then it would underestimate BMD loss (Miller P.D. & Bonnick S.L., 1999). The World Health Organization (WHO) T-score for hip, spine, and forearm is defined as normal at greater than -1, low bone density (osteopenia) at a reading between -1 and -2.5, and osteoporosis at a T-score less than - 2.5.

2.4.4 Quantitative Computed Tomography and Peripheral Quantitative Computed Tomography

Compared to DXA, QCT allows density measurement of the trabecular bone within the vertebral bodies, excluding the cortical bone. This provides a true volumetric density(g/cm3). Measurement of density in two dimensions is strongly influenced by bone depth or body size but with true volumetric density this influence is eliminated. Volumetric density of spinal trabecular bone is strongly associated with vertebral fracture therefore it is a sensitive site for serial measurement. pQCT is another alternative which comprise of a smaller CT scanner. It has a reasonable precision and the radiation dose is lower. This technique measures the volumetric bone density of trabecular bone. The coefficient of variation for the measurement at the distal metaphyseal trabecular bone and the diaphyseal total bone by pQCT were 0.4% and 1.7%, respectively (Ito et al, 2003). Biomechanical parameters or geometric properties that reflect bone strength can be calculated by analysis of the scanned bone.

2.4.5 Quantitative Ultrasonography

This technology does not expose patients to ionizing radiation and less expensive than DEXA. The common site to measure is the calcaneum. It is also portable and has a potential for wide application including as a screening tool for osteoporosis. Velocity and attenuation of sound waves are the parameters. The velocity parameter known as speed of sound (SOS) and the slope of relationship (rate of energy attenuated with increasing frequency) is known as broadband ultrasound attenuation (BUA) (Sievanen et al, 2001). Its' variables reflect the structural anisotropy of bone which parallels the anisotropy of elasticity and bone strength rather than density of bone as in BMD. There is moderate correlation between QUS and calcaneal, spine or proximal femur BMD (Tromp et al, 1999). However calcaneal BUA showed higher correlations with BMD values of the lumbar spine, femoral neck, trochanter and total body than calcaneal and tibial SOS ($_r$ = 0.48-0.64, $_r$ = 0.30-0.47, $_r$ = 0.35-0.47, respectively. Therefore QUS results cannot be used to predict BMD at the main fracture sites. Two types of QUS available, non-imaging guided and imaging guided. QUS measurement of the stiffness of the calcaneus was obtained with the non-imaging-guided unit. QUS measurement of the broadband ultrasound attenuation and speed of sound of the calcaneus were obtained with imaging-guided unit. The correlation coefficients between DEXA of the hip and DEXA of the spine with non-imaging or

imaging QUS were low. The T score obtained with QUS is also lower. In imaging guided QUS the speed of sound is lower than for broadband ultrasound attenuation (Krestan et al, 2001; Lomoschitz et al, 2003).

2.4.6 Magnetic Resonance Imaging (MRI)

A non-invasive and non-ionizing technique but expensive and time consuming. It provides three-dimensional images in arbitrary orientations and can depict trabecular structures. These additional values enable in vivo monitoring of trabecular structural changes as well as understanding the pathophysiology of various disease processes and the action of various therapeutic regimes. It is useful for identifying high-risk patients after an initial bone densitometry and subsequently assigning them to more aggressive therapy. Kang et al., compared MRI measurements of calcaneum with DEXA and ultrasound and found that calcaneal T2' (MRI) was significantly correlated with calcaneal BMD ($r = -0.79$, $p < 0.0001$), BUA ($r = -0.59$, $p = 0.0004$) and SOS ($r = -0.58$, $p = 0.0006$). However the precision of the MRI technique was poor relative to the DXA and ultrasound techniques.

SECTION 2

OBJECTIVES

&

METHODOLOGY

3. Objectives and hypothesis

3.1 Objectives of the study

General objectives

1. To obtain BMD of normal local Malay women.
2. To correlate with geometric properties and DXR.

Specific objectives

1. To obtain bone mineral density reference data for local Malay women.
2. To determine the correlation of geometric properties and BMD.
3. To determine the correlation of DXR and DEXA.

3.2 Hypothesis

Null hypothesis

There is no correlation between BMD measurement and geometric properties in the evaluation of skeletal status.

4. Methodology

4.1 Methods and materials

Study design – This was a comparative, cross sectional prospective research study performed at Hospital Universiti Sains Malaysia and is approved by the Research committee on 18 June 2002 under USM short term grant. and by ethical committee of Universiti Sains Malaysia on 11 April 2002. The study starts from July 2002 and extended until June 2005.

Inclusion criteria:

Normal Malay female volunteers from Kelantan, age more the 20 years old.

Exclusion criteria-

(i) Current or recent use of bone-active drugs

Bisphosphonates, more than 1 week over.

Calcitonin, within 3 months.

Therapeutic doses (>1000 I.U. daily) of vitamin D, within 6 months.

Estrogens or SERM within 6 months.

Therapeutic doses (> 2 mg/day) fluoride within 3 years.

Drugs under research protocols within 2 years.

As yet unstudied or unapproved drugs - investigator's discretion.

(ii) Presence of metabolic bone disease

Hyper- or hypo-parathyroidism within 5 years.

Osteitis deformans (Paget's disease of bone).

Renal osteodystrophy.

Osteomalacia.

(iii) Gastrointestinal malabsorption, gastrectomy, celiac disease.

(iv) Liver disorders.

(v) Chronic renal disease.

(vi) Unstabilized hyper- or hypothyroidism.

(vii) Hyper- or hypoadrenocorticism.

(viii) Concomitant use of oral corticosteroids, if less than or equivalent of 7.5

mg daily of prednisone, within the past 6 months; if greater dosage, then within the past year.

(ix.) Use of anti-seizure drugs, barbiturates, anticoagulants and thiazide diuretics within past 6 months

(x) Stroke with total or partial paralysis with residual disability lasting more than 3 months.

(xi) Pregnant women.

(xii) History of fracture.

Flow chart:

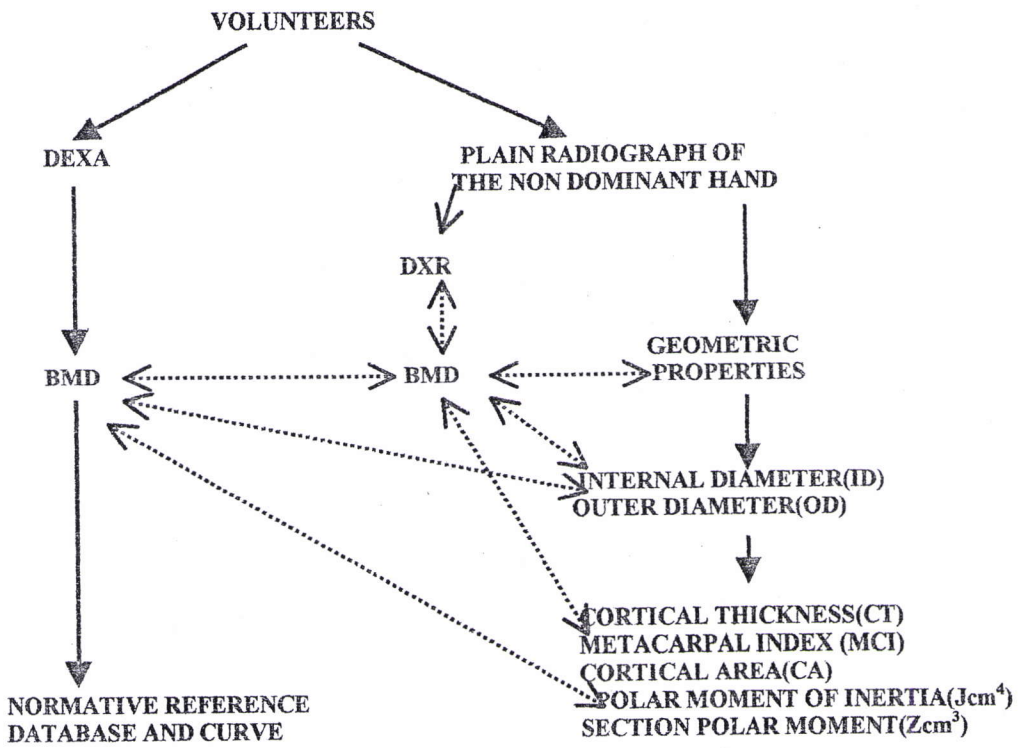


Figure 4.1: Flow chart on volunteers in our research

4.2 Bone mineral density measurement

The methods of this study is summarised in Figure 4.1. Bone mineral density (BMD) measurement of volunteers were performed using LUNAR PRODIGY, GE Medical Systems. AP view of Spine, dual femur and total body were the skeletal site measured. Volunteers who had agreed to join the study were required to change into gowns provided. Attenuating objects such as jewellery or ornaments were removed. After the volunteer's identification, height and weight had been entered into the directory screen, the measurement site was selected. Software would automatically calculate scan length and scan mode based upon the volunteer's height and weight.

4.2.1 Measurement

For AP spine measurement (Figure 4.1), the volunteer must lie supine with legs on support block with arms outside of scan area. The position is selected using a position laser light. Position of transverse plane is between the anterior superior iliac spine and the anterior iliac crest. Position of longitudinal plane is midline. start icon to be selected to begin measurement. The spine should appear in the center of the image window and begin in the middle of L5 vertebral body. Iliac crests should be visualized. If positioned incorrectly, the measurement is to be aborted to adjust starting position or reposition from console as needed and new measurement to be taken.

For dual femur technique, patient lie supine on scan table with feet strapped in foot brace and arms outside scan window. Both femurs should be properly rotated. Localize the position by positioning the laser light in the center of thigh being measured, and three inches below the greater trochanter. When the measurement of the particular femur is complete, the software retains the measurement information from the left femur and automatically measures the contralateral femur with the same variables. Femoral neck (Figure 4.2) should appear in the center of the image window. If positioned incorrectly, the measurement to be aborted and new measurement to be taken.

Total body measurement (Figure 4.3) done with the position of patient parallel to long axis of table. Midline of patient should be over the midline of the table top. Volunteer's whole body should be inside the scan area indicated by the the gray lines on the scan table pad. Hands may be tucked under the soft tissue of the hips. Head

should be approximately 3cm below head line on table pad. Legs and feet strapped. scan to br aborted if positioned incorrectly.

4.2.2 Analysis

Correction of an analysis of the site measured can be done if the region is obviously incorrect. Adjust image intensity and magnification if unable to identify landmarks. Labelling of vertebrae bodies using pelvis/L5 and ribs/T12 as landmarks if intervertebral markers need to be adjusted. If sample points are incorrectly classified, 5 X 5 rule point typing where bone is sampled as bone, neutral is sampled around bone, tissue should be sampled on both sides of bone, air includes any air visible and artefacts should include any artefacts present. Each femoral neck can be adjusted independently.

ROI of the femoral neck should be in the approximate center of the femoral neck and perpendicular to the axis of the femoral neck. ROI should not include any trochanter or ischium if possible. Neck ROI should extend into soft tissue on both sides of the femoral neck. If necessary, ROI should be repositioned at top (proximal end) of femoral neck.

ROI locations for total body should be as follows:

Head – Immediately below the chin.

Left and Right **Arm** – Through the shoulder joints and close to the body as possible. Ensure the ROI separates the hands and arms from the body.

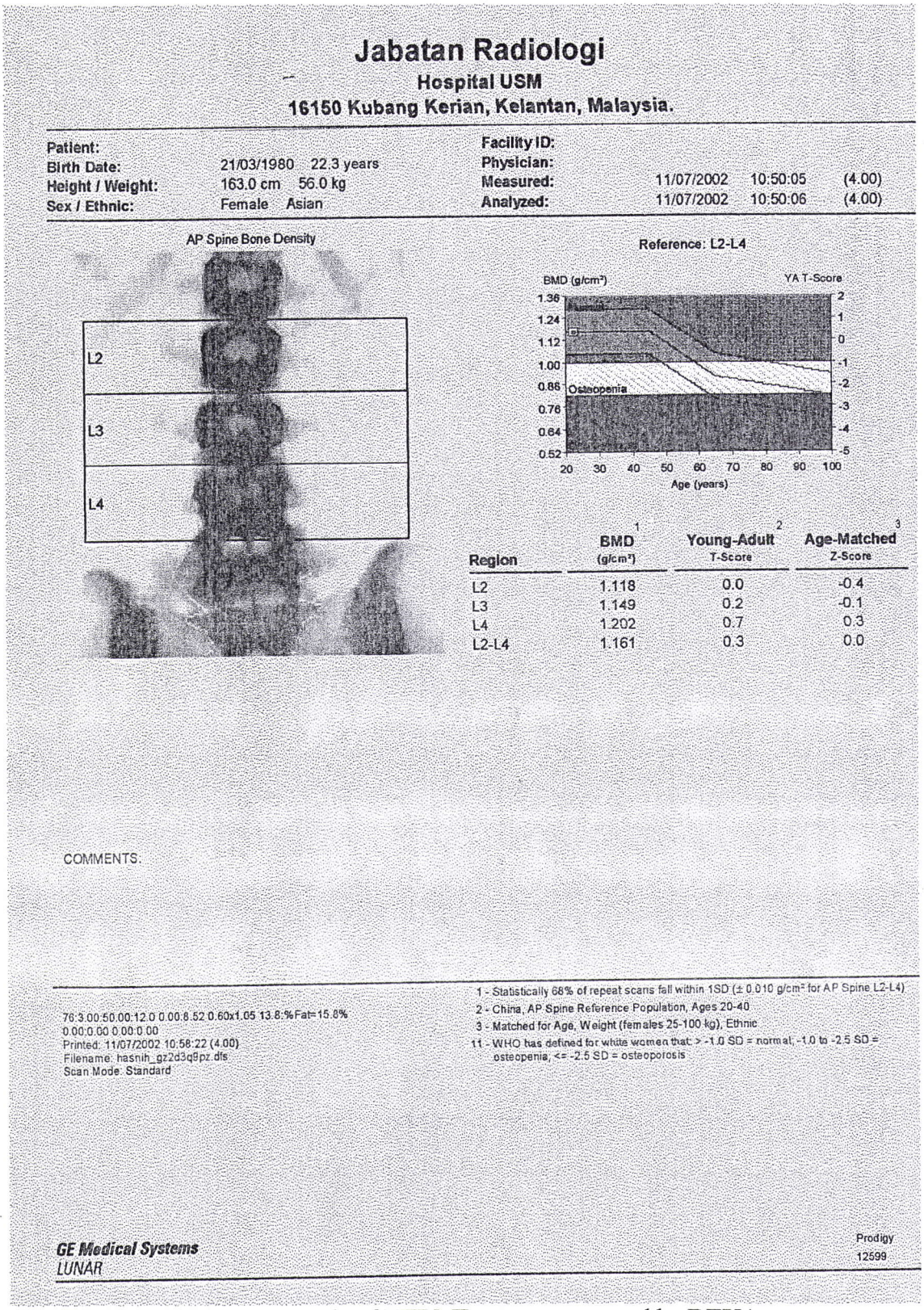
Left and Right **Spine** – As close to the spine as possible without including the rib cage.

Left and Right **Pelvis** – Through the femoral necks and not touching the pelvis.

Pelvis Top – Immediately above the top of the pelvis.

Left and Right **Leg** – Separates the hands and forearms from the legs.

Center of leg – Centered between the legs.



Jabatan Radiologi
Hospital USM
16150 Kubang Kerian, Kelantan, Malaysia.

Patient:		**Facility ID:**	
Birth Date:	21/03/1980 22.3 years	**Physician:**	
Height / Weight:	163.0 cm 56.0 kg	**Measured:**	11/07/2002 10:50:05 (4.00)
Sex / Ethnic:	Female Asian	**Analyzed:**	11/07/2002 10:50:06 (4.00)

AP Spine Bone Density

Reference: L2-L4

Region	BMD [1] (g/cm²)	Young-Adult [2] T-Score	Age-Matched [3] Z-Score
L2	1.118	0.0	-0.4
L3	1.149	0.2	-0.1
L4	1.202	0.7	0.3
L2-L4	1.161	0.3	0.0

COMMENTS:

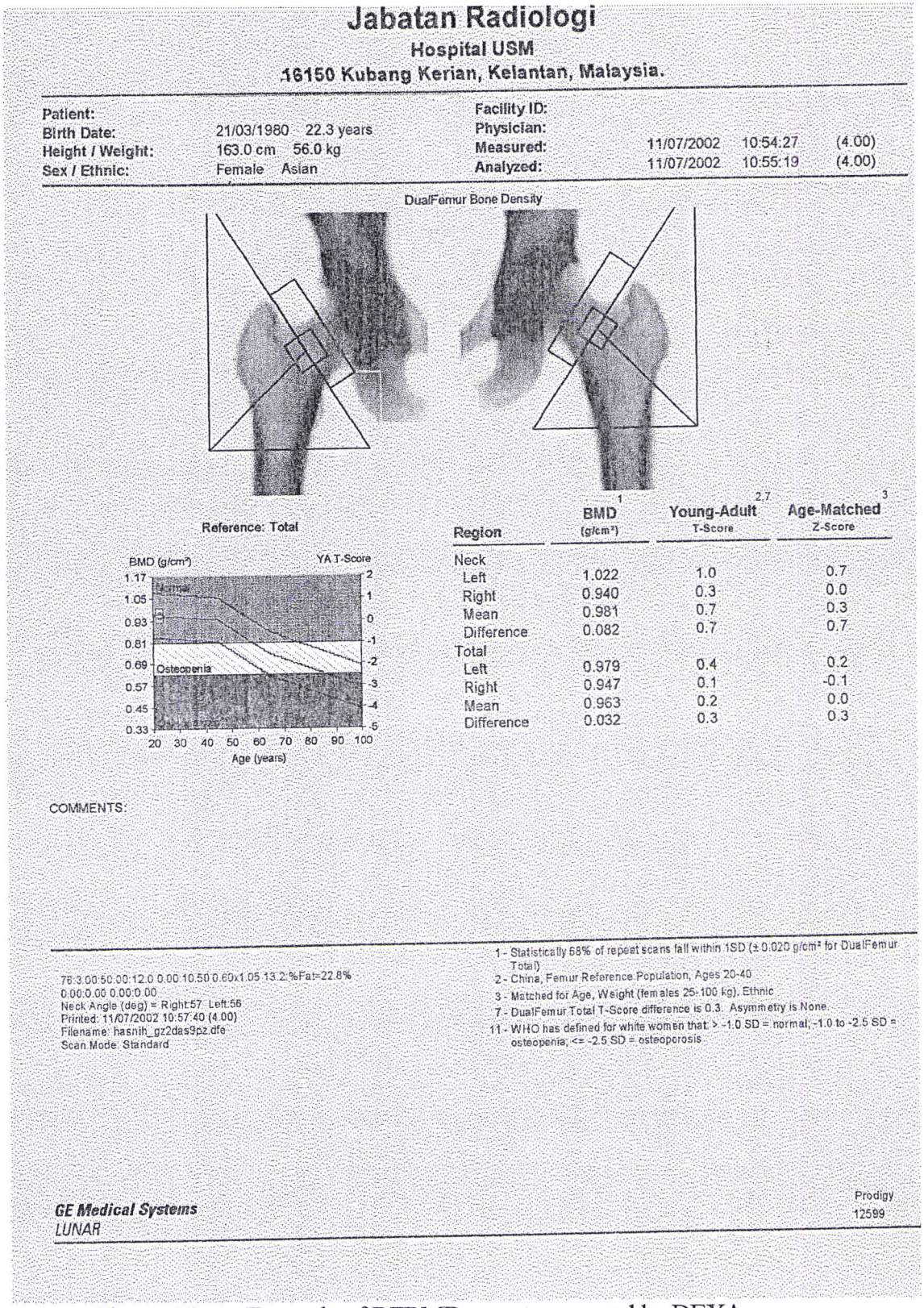
76:3.00:50.00:12.0 0.00:8.52 0.60x1.05 13.8:%Fat=15.8%
0.00:0.00 0.00:0.00
Printed: 11/07/2002 10:58:22 (4.00)
Filename: hasnih_gz2d3q9pz.dfs
Scan Mode: Standard

1 - Statistically 68% of repeat scans fall within 1SD (± 0.010 g/cm² for AP Spine L2-L4)
2 - China, AP Spine Reference Population, Ages 20-40
3 - Matched for Age, Weight (females 25-100 kg), Ethnic
11 - WHO has defined for white women that: > -1.0 SD = normal, -1.0 to -2.5 SD = osteopenia, <= -2.5 SD = osteoporosis

GE Medical Systems
LUNAR

Prodigy
12599

Figure 4.1 Example of VTBMD report measured by DEXA



Jabatan Radiologi

Hospital USM

16150 Kubang Kerian, Kelantan, Malaysia.

Patient:		**Facility ID:**			
Birth Date:	21/03/1980 22.3 years	**Physician:**			
Height / Weight:	163.0 cm 56.0 kg	**Measured:**	11/07/2002	10:54:27	(4.00)
Sex / Ethnic:	Female Asian	**Analyzed:**	11/07/2002	10:55:19	(4.00)

DualFemur Bone Density

Region	BMD [1] (g/cm²)	Young-Adult [2,7] T-Score	Age-Matched [3] Z-Score
Neck			
Left	1.022	1.0	0.7
Right	0.940	0.3	0.0
Mean	0.981	0.7	0.3
Difference	0.082	0.7	0.7
Total			
Left	0.979	0.4	0.2
Right	0.947	0.1	-0.1
Mean	0.963	0.2	0.0
Difference	0.032	0.3	0.3

COMMENTS:

76.3.00:50.00:12.0 0.00:10.50 0.60x1.05 13.2:%Fat=22.8%
0.00:0.00 0.00:0.00
Neck Angle (deg) = Right:57 Left:56
Printed: 11/07/2002 10:57:40 (4.00)
Filename: hasnih_gz2das9pz.dfe
Scan Mode: Standard

1 - Statistically 68% of repeat scans fall within 1SD (± 0.020 g/cm² for DualFemur Total)
2 - China, Femur Reference Population, Ages 20-40
3 - Matched for Age, Weight (females 25-100 kg), Ethnic
7 - DualFemur Total T-Score difference is 0.3. Asymmetry is None.
11 - WHO has defined for white women that: > -1.0 SD = normal; -1.0 to -2.5 SD = osteopenia; <= -2.5 SD = osteoporosis

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Figure 4.2 Example of DFBMD report measured by DEXA

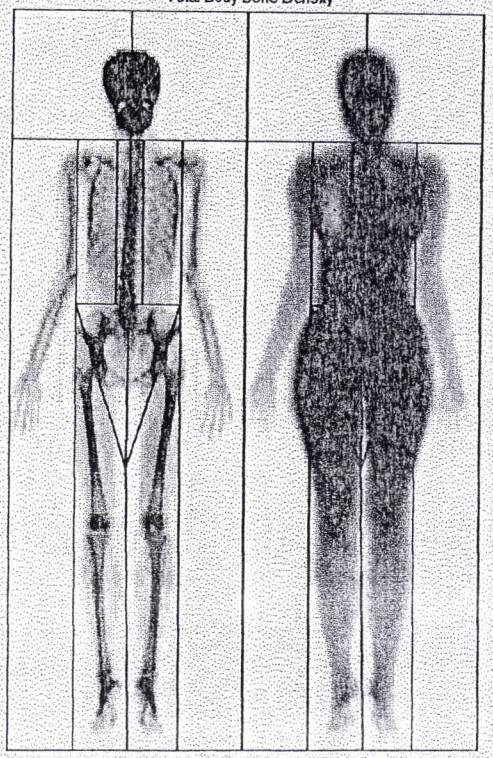
Jabatan Radiologi

Hospital USM

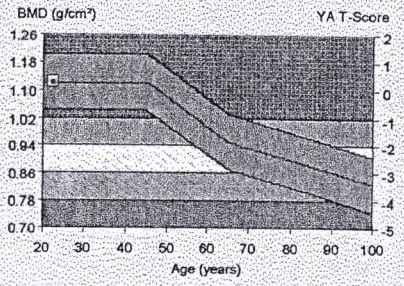
16150 Kubang Kerian, Kelantan, Malaysia.

Patient:		**Facility ID:**	
Birth Date:	21/03/1980 22.3 years	**Physician:**	
Height / Weight:	163.0 cm 56.0 kg	**Measured:**	11/07/2002 10:46:06 (4.00)
Sex / Ethnic:	Female Asian	**Analyzed:**	11/07/2002 10:46:08 (4.00)

Total Body Bone Density



Reference: Total



Region	[1] BMD (g/cm²)	[2] Young-Adult T-Score	[3] Age-Matched Z-Score
Head	2.252	-	-
Arms	0.752	-	-
Legs	1.197	-	-
Trunk	0.896	-	-
Ribs	0.658	-	-
Pelvis	1.162	-	-
Spine	1.003	-	-
Total	1.122	0.3	0.0

COMMENTS:

76:0.15:153.85:31.2 0.00:-1.00 4.80x13.00 9.5:%Fat=36.2%
0.00:0.00 0.00:0.00
Printed: 11/07/2002 10:59:10 (4.00)
Filename: hasnih_gz2csg9pz.dfb
Scan Mode: Standard

1 - Statistically 68% of repeat scans fall within 1SD (± 0.010 g/cm² for Total Body Total)
2 - China, Total Body Reference Population, Ages 20-40
3 - Matched for Age, Weight (females 25-100 kg), Ethnic

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Figure 4.3 Example of TBBMD report measured by DEXA

System quality assurance will be done daily using aluminium phantom, to monitor the long-term precision of the Prodigy. Patient dose varies with image sites and system or devices. For prodigy the entrance dose is shown in Table 4.1.

Scan Site	Scan Mode (mA)	Entrance Dose
AP Spine	Thick 3.00 Standard 3.00 Thin 0.75	8.2 mrads 3.7mrads 0.9mrads
Femur	Thick 3.00 Standard 3.00 Thin 0.75	8.2 mrads 3.7mrads 0.9mrads
Total Body	Thick 0.15 Standard 0.15 Thin 0.15	0.08 mrads 0.04mrads 0.04mrads
Forearm (Rt, Lt)	0.15	0.18mrads
Lateral Spine	3.00	8.2mrads
LVA	3.00	8.2mrads

Table 4.1 Entrance dose scan sites for prodigy

4.3 Digital x-ray radiogrammetry (DXR)

Bone mineral density (BMD) measurement was done using digital x-ray radiogrammetry, Pronosco X-posure System software. After a volunteer identification data has been entered, the non-dominant hand radiograph of the subject was placed on the scanner and <scan> selected to automatically start the procedure. When scanning was completed, the hand radiograph image with the ROI boxes outlining second, third and fourth metacarpals were automatically shown on the screen (Figure 4.4). When the ROI boxes were placed correctly and that the three metacarpals were distinct as well as correctly located <ok> selected to verify. If the image did not meet the three criteria, the procedure was stopped and returned to scan menu to reposition the hand radiograph and perform second scan. If the result was still invalid, the hand radiograph might be unacceptable and it should be replaced. The normative reference database obtained from a population of 'normal' Chinese women, provided by the Pronoscor software.

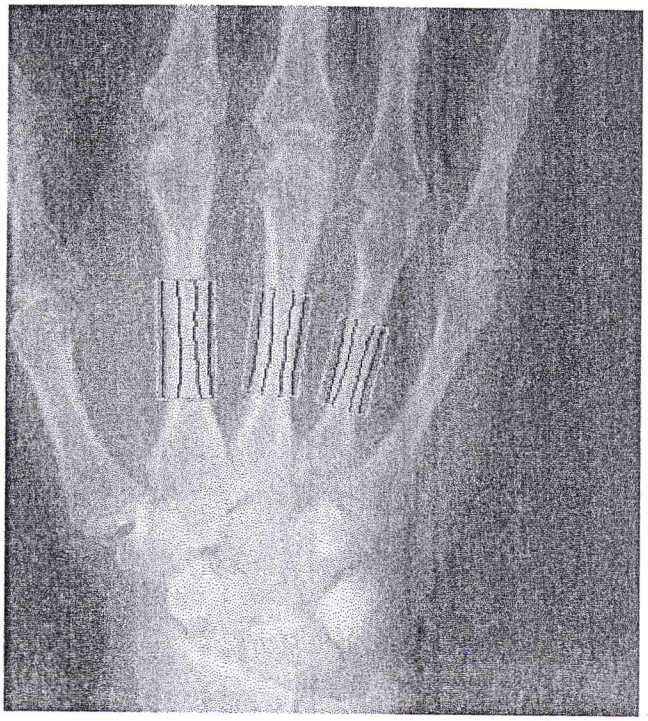


Figure 4.4 Region of interest in DXR

4.3 Hand Radiograph

PA hand radiograph was performed on the non-dominant hand using Optimus RAD, Philips Medical Systems. The volunteer's pelvis was shielded by a gonad shield and seated comfortably to reduce the chances of unwanted movements. The exposure field was cleared from irrelevant metal or plastic objects. The hand was ensured to lie within the Kodak X-Omatic cassette (Lanex regular screen) which was placed on the top of the table. Double emulsion film for extremities, size 18cm X 24cm was used. Tube voltage is 50kV with mAs of 1.5 to 3.0. Focal spot is 0.6mm. Film-focus distance was 100cm. Filtration, grid or wedge were not used.

The hand radiograph would be used for measurement of geometric properties and radiographic absorptiometry. The measurement of cortical thickness was being done manually with a vernier calliper, where reading can be done up to 0.02mm. Figure 4.5 illustrates measurement of internal and external diameter of the second, third and fourth metacarpal bones.

4.4 Establishment of T score

$$\text{Mean } (x^*) = \frac{\Sigma x}{n}$$

$$\text{Standard deviation } (SD^2) = \frac{\Sigma [xl - x^*]^2}{n - 1}$$

$$SD = \sqrt{\frac{\Sigma [xl - x^*]^2}{n - 1}}$$

The graph of vertebral, dual femur and total body BMD plotted against age with the standard deviation (SD) obtained from the peak age SD.

4.5.1 Definition of inner and outer diameter of metacarpal measurement

From the hand radiograph: second, third and fourth metacarpal inner and outer diameter is measured at middle of the shaft of the longitudinal axis. The measurement were taken on the mid-shaft. The outer measurement (R) was taken from the lateral most outer-cortical point of the metacarpal to the medial most outer-cortical point of that metacarpal. The inner measurement (r) was taken from the lateral most inner-cortical point of the metacarpal to the medial most inner-cortical point of that metacarpal. The cortical thickness of that metacarpal was obtained by subtracting (r) from (R).

4.5.2 Parameters and Formulas

OD – mediolateral outer diameter (mm) R = OD/2 mm

ID – mediolateral inner diameter (mm) r = ID/2 mm

CT – cortical thickness (mm) = R- r

CA – cortical area mm^2

J – polar moment of inertia (mm^4)

Z – section polar moment (mm^3)

MCI – Metacarpal index

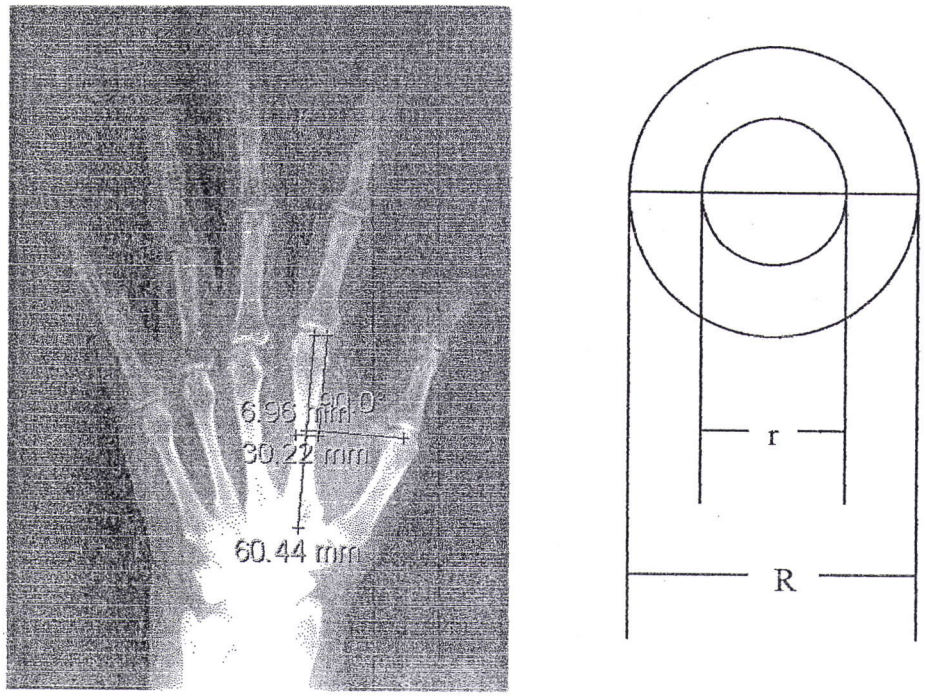


Figure 4.5: Illustration on internal and outer diameter measurement of the metacarpal bone. The right figure is the schematic representation of a cross section of a tubular bone.

4.5.3 Geometric properties formula

Formulas derived from the above parameters:

1) $CT = (OD-ID)/2OD$

2) $CA = \pi R^2 - \pi r^2$

$= \pi (R^2 - r^2)$

3) $J = 2\pi (OD^4 - ID^4)/ 64$

$= \pi(OD^4 - ID^4)/ 32$

4) $Z = 2J/OD$

5) $MCI = (OD-ID)/ OD$

The first twenty BMD data obtained using DEXA and DXR as well as the non dominant hand radiographs measurements were analysed and validated. Thereafter all the data were analysed by the author.

4.6 Statistical analysis

The data collected in this study were entered and analysed using SPSS version 10.0 for Windows statistical software. The means and standard deviations (SD) for vertebral, dual femur and total body were calculated and expressed as mean $\pm$ SD. A graph of BMD (DEXA) versus age group was obtained from the mean of each age group with the ± 1 and ± 2 standard deviation obtained from the peak age bone mineral density group. The local reference data and graphs were compared with reference database of Caucasian (US/Europe) and Chinese female.

The relationships between BMD and geometric properties (GP) of total 137 volunteers were analysed with Pearson correlation analysis. The strength and direction of the relationship between vertebral BMD (VTBMD), dual femur BMD (DFBMD) and total body BMD (TBBMD) respectively with each geometric properties which were CT, CA, J and Z of second, third and fourth metacarpal. Interpretation of correlation coefficient were, no or poor correlation when $r < 0.25$, fair if $0.26 - 0.50$, good when $r = 0.51 - 0.75$ and excellent when $r = 0.76 - 1.0$.

The relationships between BMD and Geometric properties according to age group were also analysed with Pearson correlation analysis if n (number of volunteers) were more than 20 and Spearman correlation if $n < 20$.

Significantly correlated results were selected using MANOVA and entered into a stepwise regression to determine the major factors, which were the age, weight, height body mass index (BMI) as well as geometric properties in prediction of vertebral, dual femur and total body BMD.

The correlation of the three skeletal sites BMD and DXR were made using linear regression correlation.

For all the analysis of significance, α value of 0.05 is used.

4.7 Limitation and problems during the research

Installation of DEXA, Prodigy was in August 2001 and by the time radiographers completed their training and get used to the equipment, there were time lag of about two months. Data collection was delayed. Occasionally there were inadequate trained radiographers therefore the procedure was performed only once or twice a week. The postgraduate master student who was in-charge and assisting us was also posted to General Hospital Kuala Lumpur for compulsory intervention course for three months, from early March until end of May 2002. During this period. This was because the written inform consent and screening of volunteers (to make sure they fulfil the inclusion criteria) were mainly done by the her. Therefore data collection was disrupted for approximately five months during the research study. The principal researcher was on long leave for about a year. Then the co-researcher was given the authority to carry on the research.

Most of the older age group volunteers were excluded due to numerous reasons Such as hypertension and diabetes. Some of them were on hormonal replacement therapy for more than six months.

There were also few instances where the data collected were not complete due to several technical factors. For example the head exceed the gray line on the table-top during total body BMD acquisition. Due to this the rest of the scan i.e the vertebral and dual femur BMD although properly done will be excluded as well.

All these limitations contribute to the small sample size. The target sample size was 240 (40 in each age group) but a total of 137 volunteers were included. In view of the small sample size, some of the results may not be statistically significant particularly when the data were analysed according to age group. However, this can be a starting point or foundation for future larger scale study.

5. Results

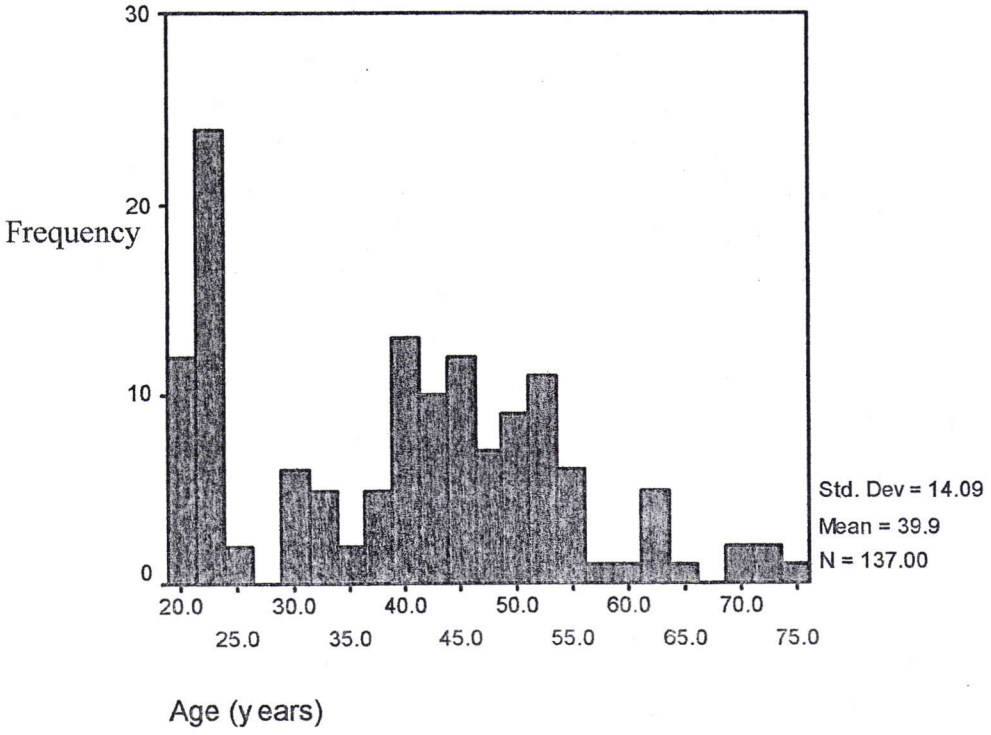
The number of volunteers involved in this study and who have met the inclusion criteria were 137. They ranged from 20.2 to 75.3 years old. No volunteer was more than 80 years of age. Therefore the age group iwa limited to six age groups. The number of volunteers for 20-29 age group were 40, 30-39 (n= 24), 40-49 (n=39), 50-59 (n=22), 60-69 (n=8) and 70-79 (n=4).

SECTION- 3

RESULTS

5.1 Demographic data

5.1.1 Age distribution



Graph 5.1: Histogram showing the age distribution of volunteers

5.1.2 Mean and standard deviation of parameters

Age	39.9 ± 14.1
Weight	58.4 ± 12.2
Height	152.7 ± 6.3

Table 5.1: Mean and SD for age, weight and height for the 137 volunteers

Weight	20-29	30-39	40-49	50-59	60-69	70-79
Mean	51.9	57.9	61.1	64.4	64.4	53.8
Minimum	39.6	41.5	39.0	48.0	55.0	48.0
Maximum	72.0	79.0	98.0	120.0	76.0	60.1
Std Dev	7.6	10.8	12.8	16.1	6.4	6.1

Table 5.2: Mean, Standard Deviation(SD), maximum and minimum weight in kg for each age group

Age	20-29	30-39	40-49	50-59	60-69	70-79
Mean	155.5	152.2	153.3	150.7	147.2	142.9
Minimum	142.0	141.0	144.0	131.5	142.0	131.5
Maximum	169.0	163.0	174.0	160.0	150.5	152.0
Std Dev	5.3	5.3	6.0	6.5	3.0	9.8

Table 5.3: Mean, Standard Deviation(SD), maximum and minimum height in Centimeters(cms) for each age group.

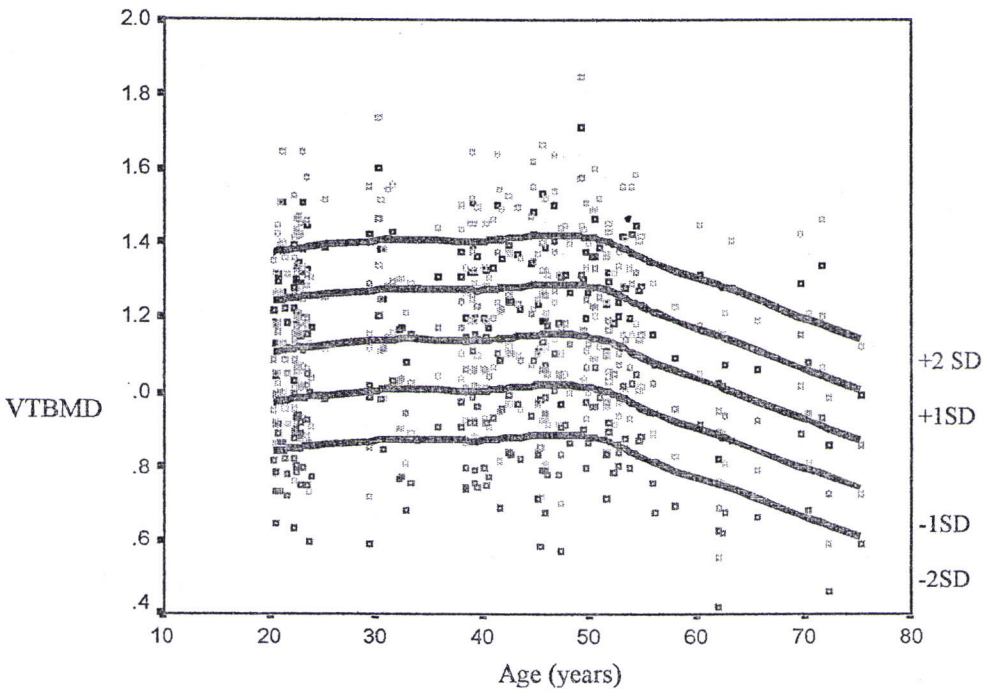
Age	20-29	30-39	40-49	50-59	60-69	70-79
Mean	21.48	25.11	26.01	28.46	29.72	26.60
Minimum	17.26	18.08	16.44	21.71	25.45	20.78
Maximum	29.97	35.63	39.76	54.05	33.55	30.46
Std Dev	3.09	5.40	5.39	7.39	2.65	4.17

Table 5.4: Mean, Standard Deviation(SD), maximum and minimum body mass index (BMI) for each age group.

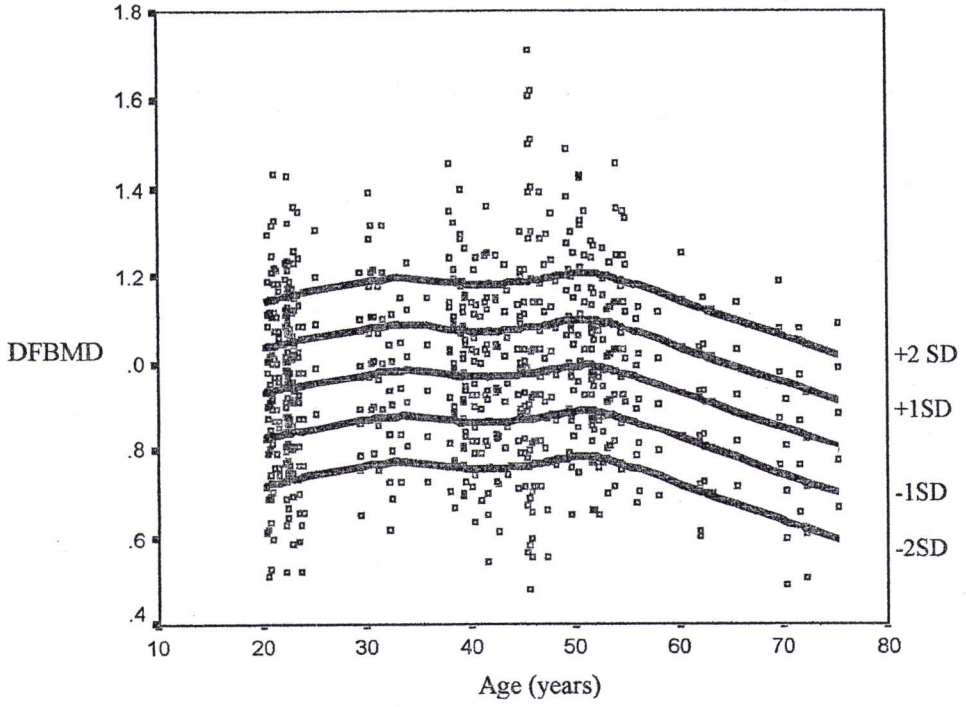
BMD / AGE	Vertebra	Dual Femur	Total Body
20 – 29	1.115 ± 0.128	0.946 ± 0.126	1.078 ± 0.065
30 – 39	1.149 ± 0.133	1.005 ± 0.106	1.108 ± 0.067
40 – 49	1.154 ± 0.152	0.987 ± 0.166	1.118 ± 0.102
50 – 59	1.142 ± 0.115	1.017 ± 0.121	1.126 ± 0.088
60 – 69	0.977 ±0.170	0.918 ± 0.073	1.084 ± 0.089
70 – 79	0.933 ±0.201	0.793 ± 0.096	0.978 ± 0.106

Table 5.5: Local BMD mean and ± 1SD for vertebra, dual femur and total body of each age group

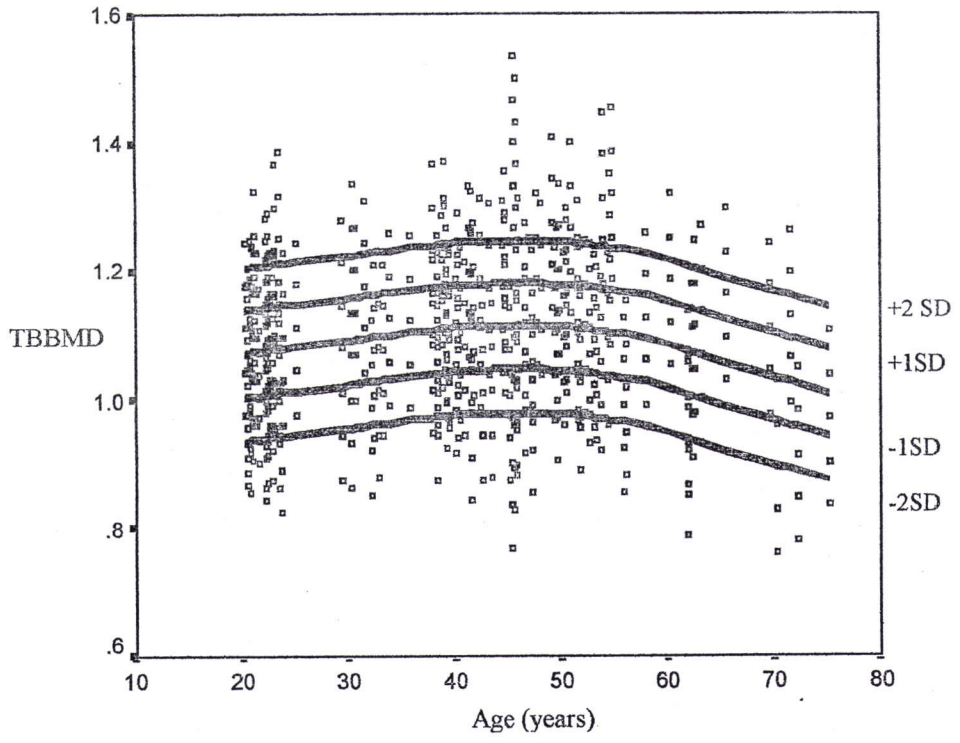
The mean and SD of BMD are shown in Table 5.2. From these data, a scatter plot for BMD of each skeletal sites versus age was generated to demonstrate local population T score with the SD obtained from peak age bone mineral density. The peak age bone density for VTBMD is 40-49, for DFBMD and TBBMD are 50-59.



Graph 5.2: Scatter diagram showing the BMD of vertebra with ± 1 and ± 2 SD versus age



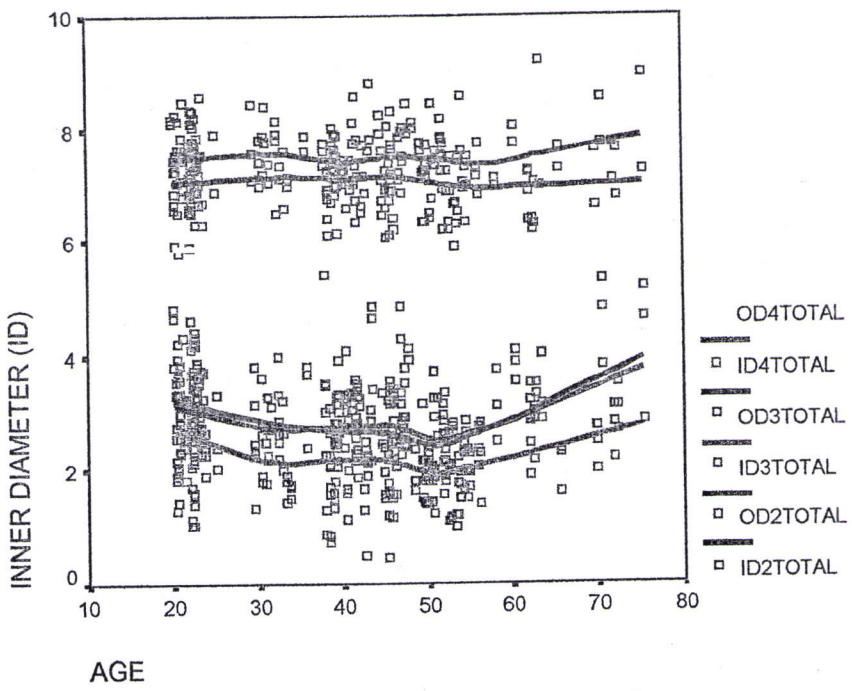
Graph 5.3: Scatter diagram showing the BMD of dual femur with ±1 and ±2 SD versus age



Graph 5.4: Scatter diagram showing the BMD of total body with ±1 and ±2 SD versus age

Age group		Second metacarpal		Third Metacarpal		Fourth Metacarpal	
		ID2	OD2	ID3	OD3	ID4	OD4
20-29	Mean	3.12	7.49	3.01	7.04	2.53	5.84
	SD	0.85	0.63	0.79	0.57	0.72	0.58
30-39	Mean	2.67	7.46	2.63	7.08	2.09	5.77
	SD	0.68	0.51	0.70	0.61	0.71	0.55
40-49	Mean	2.71	7.47	2.81	7.16	2.14	5.73
	SD	0.74	0.63	0.88	0.55	0.78	0.58
50-59	Mean	2.31	7.39	2.41	6.92	1.89	5.69
	SD	0.63	0.60	0.66	0.54	0.62	0.44
60-69	Mean	3.11	7.43	3.13	6.93	2.48	5.70
	SD	0.59	0.84	0.15	0.69	0.75	0.47
70-79	Mean	4.20	8.23	3.91	7.21	2.89	6.00
	SD	1.23	0.63	0.93	0.40	0.68	0.26

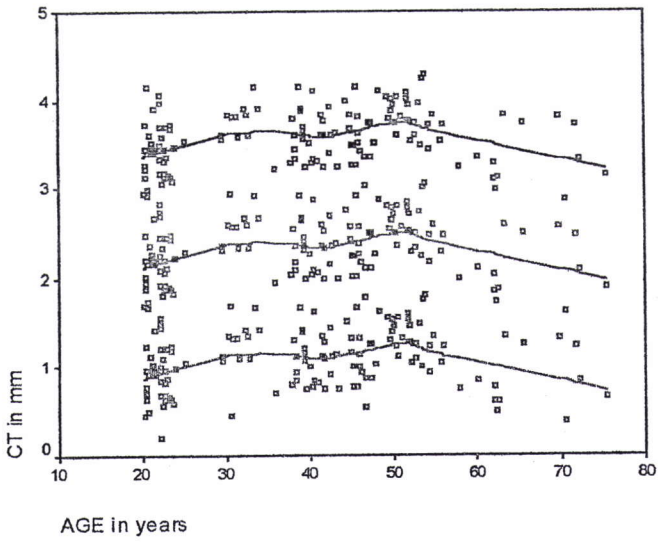
Table 5.6: Mean and SD of ID and OD



Graph 5.5: Inner diameter versus age

Table 5.7: Mean and SD of second, third and fourth metacarpal cortical thickness (CT)

Age group		CT2	CT3	CT4
20-29	Mean	4.37	4.02	3.32
	SD	0.62	0.67	0.61
30-39	Mean	4.79	4.45	3.68
	SD	0.63	0.44	0.65
40-49	Mean	4.76	4.35	3.59
	SD	0.59	0.72	0.65
50-59	Mean	5.07	4.51	3.80
	SD	0.53	0.52	0.59
60-69	Mean	4.32	3.80	3.22
	SD	0.70	0.77	0.84
70-79	Mean	4.04	3.31	3.11
	SD	0.71	0.63	0.45



Graph 5.6: The graph showing age versus cortical thickness with mean and ±2SD.

Age group			CA			J			Z		
			2MC	3MC	4MC	2MC	3MC	4MC	2MC	3MC	4MC
20-29	N= 40	Mean	36.00	31.53	21.48	308.13	238.50	115.20	80.77	66.59	38.42
		SD	5.40	5.01	4.38	98.27	43.32	70.82	19.31	14.94	11.06
30-39	N = 24	Mean	37.98	33.85	22.57	305.38	247.26	117.25	80.83	68.58	39.65
		SD	5.27	4.68	4.56	78.35	76.84	52.22	15.79	16.65	14.70
40-49	N = 39	Mean	37.98	32.95	21.91	311.01	256.53	108.66	81.42	69.80	36.86
		SD	5.70	5.95	4.15	98.52	73.86	42.44	19.24	16.98	10.76
50-59	N = 22	Mean	38.64	32.80	22.52	297.17	228.01	104.90	79.15	64.83	36.19
		SD	5.93	5.01	3.79	95.23	68.59	35.54	18.93	14.62	8.87
60-69	N = 8	Mean	36.04	30.15	20.49	310.45	227.35	101.22	80.58	64.00	34.95
		SD	8.81	7.36	4.72	162.14	94.37	31.14	30.13	20.11	8.45
70-79	N = 4	Mean	38.72	28.44	21.48	420.24	240.31	119.59	101.10	66.35	46.93
		SD	3.39	3.06	1.23	108.61	43.16	14.92	18.38	8.28	16.92

Table 5.8: Mean and SD of geometric properties (CA, J, Z) of the second, third and fourth metacarpal (MC).

5.2

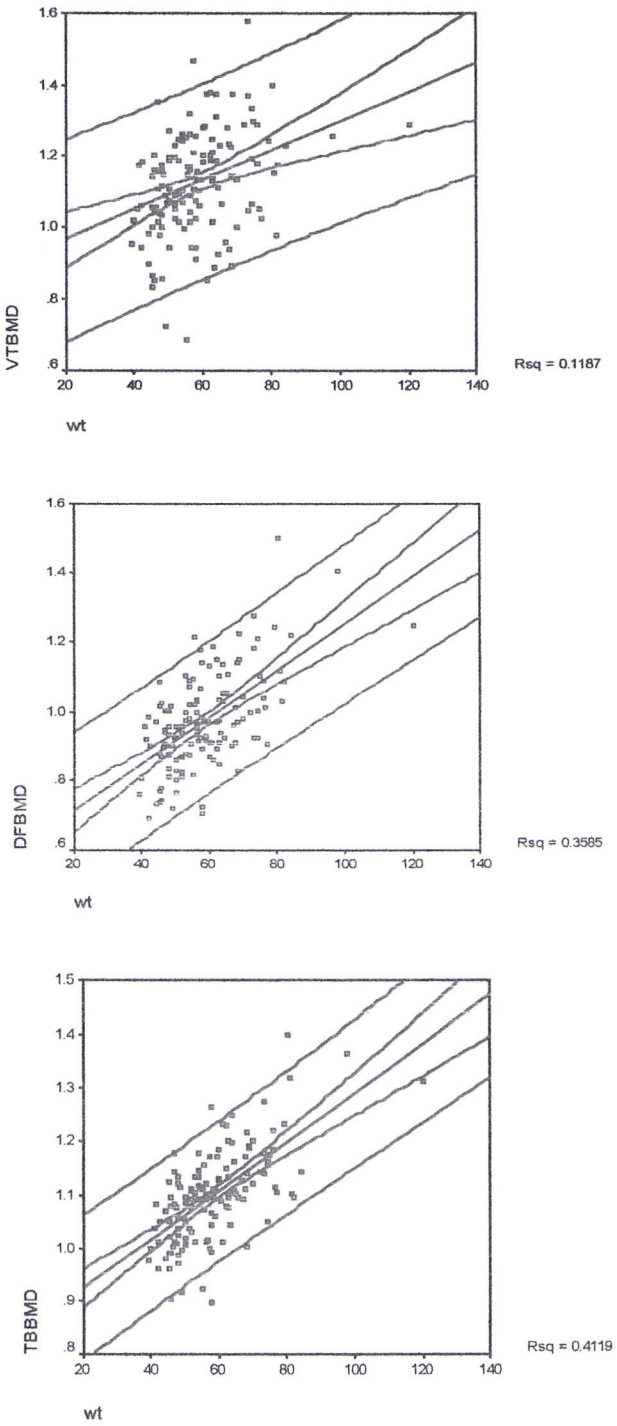
5.2 Statistical analysis

5.2.1 Correlation of anthropometric data and BMD

Table 5.9: Correlation between anthropometric (AP) data - age, weight, height, body mass index (BMI) and BMD of vertebral (VTBMD), dual femur (DFBMD) and total body (TBBMD).

AP / BMD		Age	Weight	Height	BMI
VTBMD	r	-0.143	0.344	0.230	0.235
	p	0.096	0.000	0.007	0.006
DFBMD	r	-0.001	0.599	0.123	0.508
	p	0.995	0.000	0.153	0.000
TBBMD	r	0.057	0.642	0.158	0.535
	p	0.507	0.000	0.065	0.000

Good correlation between weight and DFBMD as well as TBBMD whereas the correlation between weight and VTBMD were fair. The total body BMD (TBBMD) has the greatest correlation with weight. There were no correlation between age and height with VTBMD, DFBMD and TBBMD.

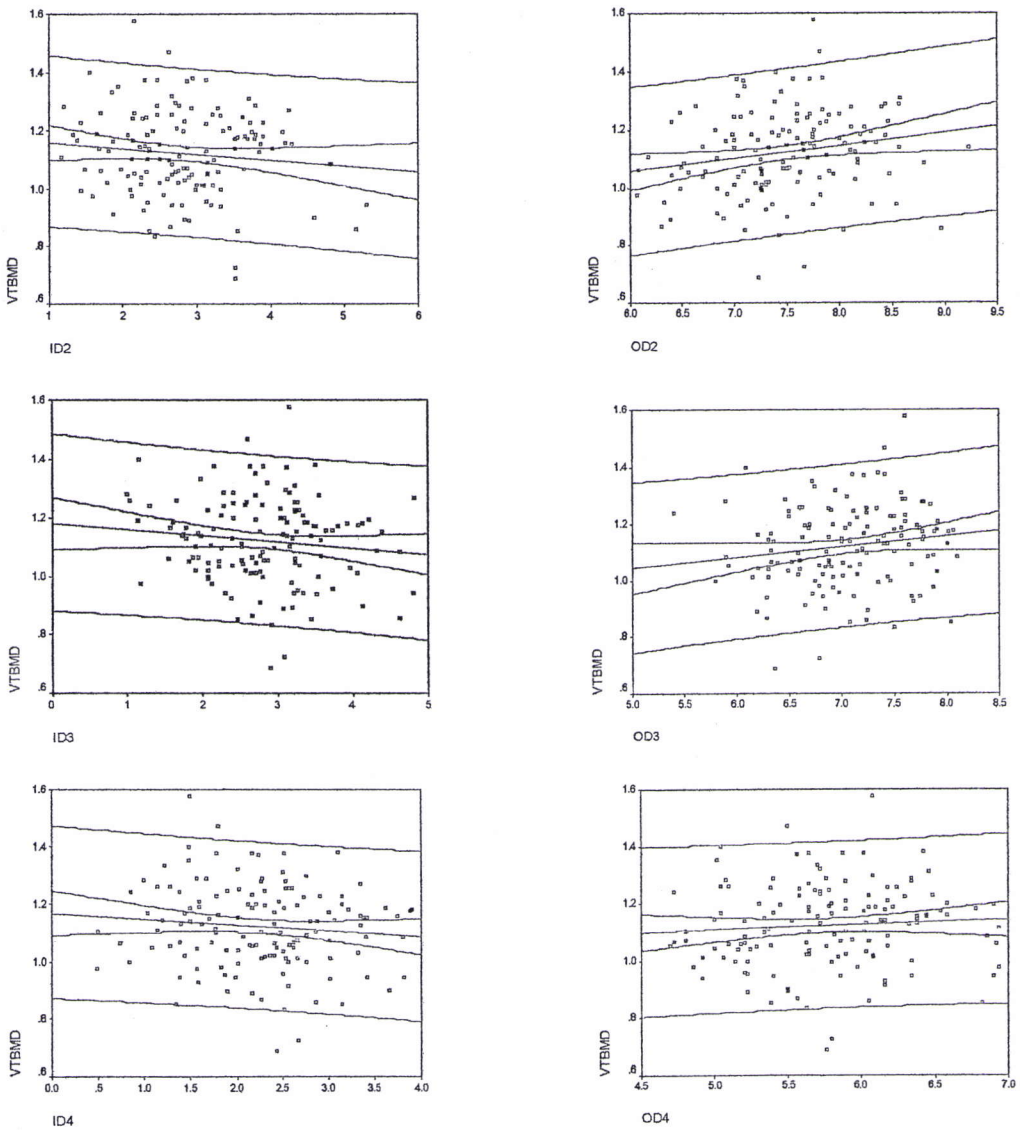


Graph 5.7: Scatter plot showing the correlation of weight with VTBMD, DFBMD and TBBMD.

5.2.2 Correlation of BMD and Geometric properties

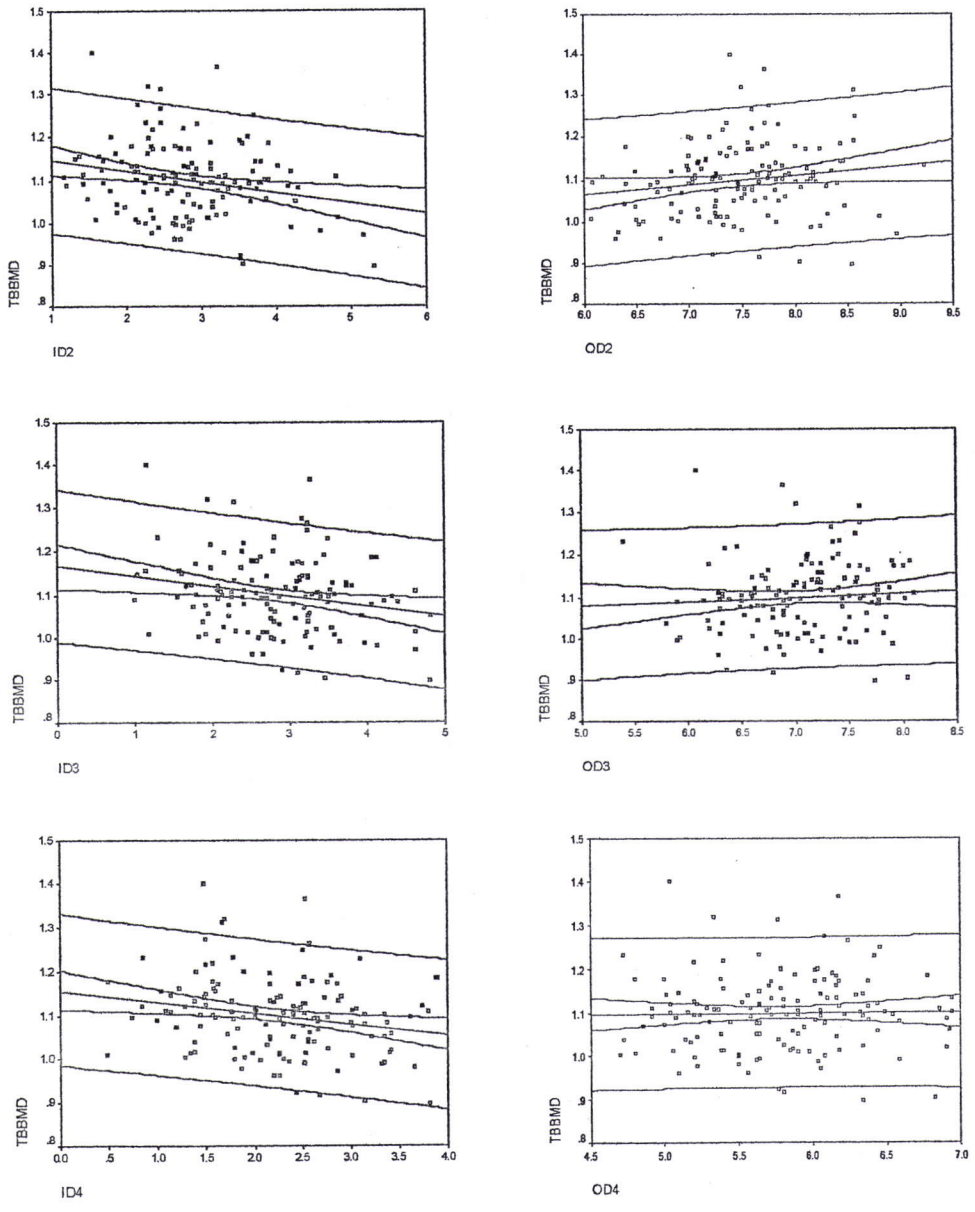
Diameter / BMD		Second Metacarpal		Third Metacarpal		Fourth Metacarpal	
		ID2	OD2	ID3	OD3	ID4	OD4
VTBMD	r	-0.112	0.192	-0.117	0.145	-0.105	0.066
	p	0.191	0.025	0.175	0.090	0.223	0.442
DFBMD	r	-0.209	0.113	-0.229	0.030	-0.262	0.015
	p	0.014	0.187	0.007	0.732	0.002	0.860
TBBMD	r	-0.237	0.157	-0.217	0.066	-0.223	0.015
	p	0.005	0.067	0.011	0.447	0.009	0.863
DXRBMD	r	-0.404	0.175	-0.453	0.253	-0.402	0.189
	p	0.000	0.041	0.000	0.003	0.000	0.027

Table 5.10: Correlation of VTBMD, DFBMD,TBBMD and DXRBMD with internal diameter(ID) and outer diameter(OD) of second, third and fourth metacarpal.



Graphs 5.8: Scatter plots showing the correlation between internal diameter(ID) and outer diameter(OD) of second (ID2,OD2), third (ID3,OD3) and fourth (ID4,OD4) metacarpal with VTBMD

The graphs showed poor or no correlation between ID2, ID3, ID4, OD2, OD3, OD4 with VTBMD.



Graphs 5.10: Scatter plots showing the correlation between internal diameter(ID) and outer diameter(OD) of second (ID2,OD2), third (ID3,OD3) and fourth (ID4,OD4) metacarpal with TBBMD

The graphs showed poor or no correlation between ID2, ID3, ID4, OD2, OD3, OD4 with TBBMD.

CT / BMD		Second Metacarpal	Third Metacarpal	Fourth Metacarpal
		CT2	CT3	CT4
VTBMD	r	0.324	0.261	0.175
	p	0.000	0.002	0.041
DFBMD	r	0.372	0.299	0.318
	p	0.000	0.000	0.000
TBBMD	r	0.448	0.314	0.269
	p	0.000	0.000	0.001
RABMD	r	0.675	0.753	0.618
	p	0.000	0.000	0.000

Table 5.11: Correlation of BMD with cortical thickness of second (CT2), third (CT3) and fourth (CT4) metacarpal.

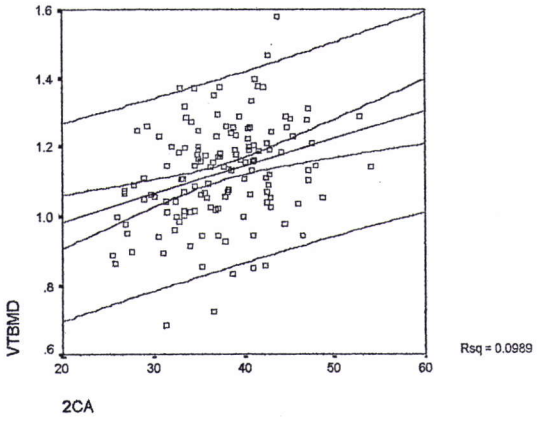
CT / BMD		Second Metacarpal	Third Metacarpal	Fourth Metacarpal
		MCI2	MCI3	MCI4
VTBMD	r	0.196	0.198	0.149
	p	0.021	0.020	0.082
DFBMD	r	0.280	0.283	0.310
	p	0.001	0.001	0.000
TBBMD	r	0.320	0.274	0.264
	p	0.000	0.001	0.002
DXRBMD	r	0.526	0.598	0.516
	p	0.000	0.000	0.000

Table 5.12: Correlation of BMD with metacarpal index of second (MCI2), third (MCI3) and fourth (MCI4) metacarpal

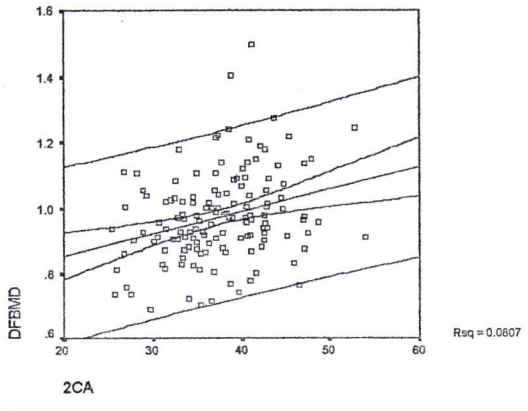
Overall, positive correlation was seen between cortical thickness(CT) and metacarpal index (MCI) of the second, third and fourth metacarpals with BMD of the three skeletal site measured by DEXA as well as the BMD measured by DXR. Good association between DXRBMD and CT2, CT3, CT4 as well as MCI2, MCI3, MCI4. Otherwise DFBMD and TBBMD were fairly correlated with the CT2, CT3, CT4, MCI2, MCI3 and MCI4. VTBMD has fair correlation with CT2 and CT3 but not with CT4. The VTBMD and MCI2, MCI3, MCI4 were also poorly associated. All fair to good correlation $p<0.05$.

BMD \ GP		2CA	2J	2Z	3CA	3J	3Z	4CA	4J	4Z
VT	r	0.314	0.192	0.215	0.229	0.173	0.183	0.127	0.079	0.070
	p	0.000	0.024	0.011	0.007	0.043	0.032	0.138	0.356	0.415
DF	r	0.284	0.124	0.146	0.180	0.066	0.086	0.181	0.054	0.036
	p	0.001	0.149	0.088	0.035	0.444	0.320	0.035	0.529	0.679
TB	r	0.360	0.168	0.198	0.199	0.101	0.119	0.158	0.058	0.030
	p	0.000	0.049	0.021	0.020	0.240	0.168	0.065	0.503	0.729
DXR	r	0.500	0.213	0.238	0.551	0.330	0.343	0.473	0.237	0.188
	p	0.000	0.012	0.005	0.000	0.000	0.000	0.000	0.005	0.028

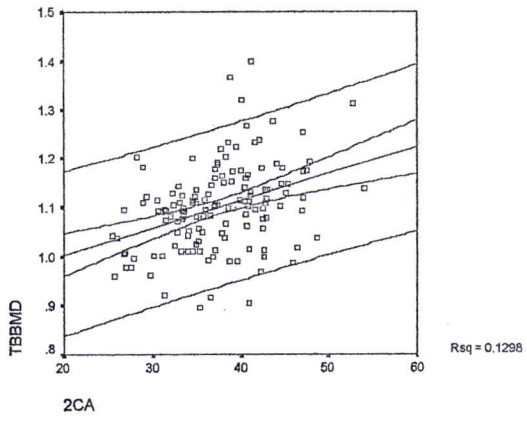
Table 5.13: Correlation of vertebral, dual femur and total body BMD with GP of second, third and fourth metacarpal (n = 137).



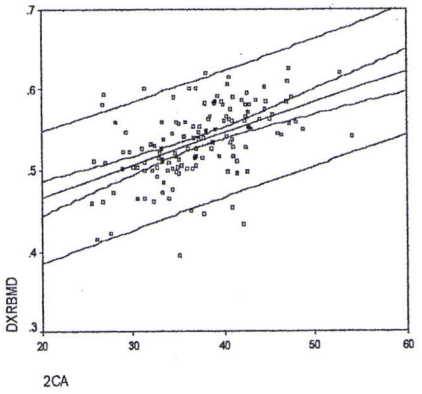
Graph 5.11: Scatter plot showing VTBMD correlates with 2CA



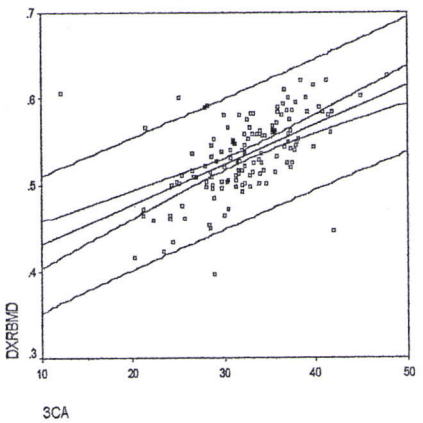
Graph 5.12: Scatter plot showing DFBMD correlates with 2CA



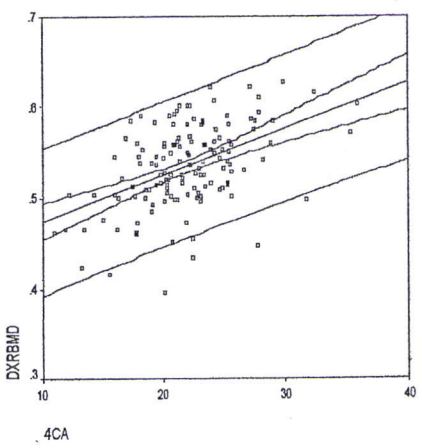
Graph 5.13: Scatter plot showing TBBMD correlates with 2CA



Graph 5.14: Scatter plot showing DXRBMD correlates with 2CA



Graph 5.15: Scatter plot showing DXRBMD correlates with 3CA



Graph 5.16: Scatter plot showing DXRBMD correlates with 4CA

5.2.3 Multi linear regression analysis

Dependent Variable	Source	Sig
VTBMD	Age	0.006
	Wt	0.009
	CA2	0.090
DFBMD	Wt	0.001
	Age	0.008
TBBMD	Wt	0.000
	CA2	0.010
	J2	0.021
	Age	0.112
	Z2	0.078

Table 5.14: Significant variables, Age-Wt-Ht-BMI and geometric properties (CA2, J2, Z2, CA3, CA4) were selected for each model in prediction of VTBMD, DFBMD, TBBMD

	r	R^2	p	Regression Parameters	
				Intercept	Slope
Weight	0.344	0.119	0.000	0.882	4.127E-03
Weight Age	0.440	0.193	0.000 0.001	0.935	5.284E-03 -3.01E-03
Weight Age CA2	0.497	0.230	0.000 0.000 0.002	0.755	4.458E-03 -3.09E-03 6.175E-03

Table 5.15: Analysis of significant predictor variables (weight, age and CA2) and the outcome variable which was vertebra BMD

	r	R^2	p	Regression Parameters	
				Intercept	Slope
Weight	0.599	0.359	0.000	0.580	6.732E-03
Weight Age	0.635	0.404	0.000 0.002	0.619	7.575E-03 -2.19E-03

Table 5.16: Analysis of significant predictor variables which were weight and age and the outcome variable which was dual femur BMD

	r	R^2	p	Regression Parameters	
				Intercept	Slope
Weight	0.642	0.412	0.000	0.833	4.568E-03
Weight CA2	0.666	0.444	0.000 0.006	0.750	4.175E-02 2.829E-04
Weight CA2 J2	0.701	0.491	0.000 0.000 0.001	0.662	3.958E-03 8.708E-03 -3.82E-02
Weight CA2 J2 Age	0.724	0.524	0.000 0.000 0.000 0.003	0.676	4.394E-03 9.020E-03 -3.96E-04 -1.19E-03
Weight CA2 J2 Age Z2	0.734	0.539	0.000 0.008 0.011 0.010 0.037	0.539	4.311E-03 6.192E-03 -2.06E-03 -1.03E-03 9.309E-03

Table 5.17: Analysis of significant predictor variables which were weight, CA2, J2, age, Z2 and the outcome variable which was total body BMD

Dependent Variable	Source	Sig
VTBMD	Wt	0.000
	Age	0.000
	CT2	0.011
DFBMD	Wt	0.000
	CT2	0.014
	Age	0.000
TBBMD	Wt	0.000
	CT2	0.000
	Age	0.002

Table 5.18: Significant variables, Age-Wt-Ht-BMI and geometric properties (CT2, CT3, CT4) were selected for each model in prediction of VTBMD, DFBMD, TBBMD, DXRBMD

	r	R^2	p	Regression Parameters	
				Intercept	Slope
Wt	0.344	0.119	0.000	0.882	4.127E-03
Wt Age	0.440	0.193	0.000 0.001	0.935	5.284E-02 -3.01E-04
Wt Age CT2	0.511	0.261	0.000 0.000 0.000	0.708	4.479E-03 -3.23E-03 0.121

Table 5.19: Analysis of predictor variables weight, age, CT2 (cortical thickness of second metacarpal) and the outcome variable vertebra BMD (VTBMD)

	r	R^2	p	Regression Parameters	
				Intercept	Slope
Wt	0.599	0.359	0.000	0.580	6.732E-03
Wt CT2	0.637	0.405	0.000 0.001	0.402	6.042E-03 9.403E-02
Wt CT2 Age	0.677	0.458	0.000 0.000 0.000	0.429	6.899E-03 0.102 -2.38E-03

Table 5.20: Analysis of predictor variables weight, age, CT2 (cortical thickness of second metacarpal) and the outcome variable dual femur BMD

	r	R^2	p	Regression Parameters	
				Intercept	Slope
Wt	0.642	0.412	0.000	0.833	4.568E-03
Wt CT2	0.701	0.492	0.000 0.000	0.685	3.995E-03 7.800E-03
Wt CT2 Age	0.726	0.528	0.000 0.000 0.002	0.699	4.441E-03 8.200E-02 -1.24E-03

Table 5.21: Analysis of predictor variables weight, age, CT2 (cortical thickness of second metacarpal) and the outcome variable total body BMD (TBBMD)

Multiple linear regression model accounting for age, CA2 in addition to weight improved the predictive power of a model for weight alone in VTBMD outcome. Another model to predict VTBMD has age and CT2 in addition to weight also improved the predictive power. Similar findings noted in prediction of DFBMD and TBBMD. The two separate models for DFBMD outcome were weight-age and weight-CT2-age (Table 5.16 and Table 5.20). The models for TBBMD were CA2-J2-age-Z2 and CT2-age into weight (Table 5.17 and Table 5.21).

5.2.4 Correlation of BMD with Geometric Properties according to age group

20-29		VTBMD	DFBMD	TBBMD	DXRBMD
2MC	ID	.202	-.124	.006	-.320*
	OD	.501**	.235	.461**	.342*
3MC	ID	-.001	-.168	-.065	-.434**
	OD	.331*	.284	.432**	.418**
4MC	ID	.071	-.217	-.033	-.469**
	OD	.362*	.149	.345*	.205

Table 5.22: Correlation of VTBMD, DFBMD, TBBMD and DXRBMD with ID and OD of second (2MC), third(3MC) and fourth (4MC) metacarpal in 20-29 age group [$p < 0.001$ if **; $p < 0.05$ if *]

30-39		VTBMD	DFBMD	TBBMD	DXRBMD
2MC	ID	.136	-.161	-.145	-.386
	OD	.294	-.174	-.184	.139
3MC	ID	.061	-.355	-.315	-.388
	OD	.260	-.301	-.288	.166
4MC	ID	.010	-.477*	-.320	-.443*
	OD	.057	-.344	-.181	.163

Table 5.23: Correlation of VTBMD, DFBMD, TBBMD and DXRBMD with ID and OD of second (2MC), third(3MC) and fourth (4MC) metacarpal in 30-39 age group [$p < 0.05$ if *]

Table 5.24: Correlation of VTBMD, DFBMD, TBBMD and DXRBMD with ID and OD of second (2MC), third(3MC) and fourth(4MC) metacarpal in 40-49 age group [$p < 0.001$ if **; $p < 0.05$ if *]

40-49		VTBMD	DFBMD	TBBMD	DXRBMD
2MC	ID	-.120	-.097	-.219	-.414**
	OD	.110	.171	.174	.183
3MC	ID	-.079	-.151	-.199	-.517**
	OD	-.059	-.158	-.187	.183
4MC	ID	-.169	-.191	-.244	-.392*
	OD	-.102	.057	-.033	.304

50-59		VTBMD	DFBMD	TBBMD	DXRBMD
2MC	ID	-.237	.130	.096	.102
	OD	-.026	.410*	.364	.736**
3MC	ID	-.116	.126	.142	.062
	OD	-.118	.349	.318	.652**
4MC	ID	-.070	.090	.064	.107
	OD	-.100	.215	-.016	.597**

Table 5.25: Correlation of VTBMD, DFBMD, TBBMD and DXRBMD with ID and OD of second (2MC), third(3MC) and fourth(4MC) metacarpal in 50-59 age group [$p < 0.001$ if **; $p < 0.05$ if *]

60-69		VTBMD	DFBMD	TBBMD	DXRBMD
2MC	ID	.190	-.167	.143	.833*
	OD	.738*	.262	.643	.214
3MC	ID	.738	.071	.214	.548
	OD	.500	.214	.595	.095
4MC	ID	.405	.167	.310	.643
	OD	.366	.122	.561	.220

Table 5.26: Correlation of VTBMD, DFBMD, TBBMD and DXRBMD with ID and OD of second (2MC), third(3MC) and fourth(4MC) metacarpal in 60-69 age group [$p < 0.05$ if *]

70-79		VTBMD	DFBMD	TBBMD	DXRBMD
2MC	ID	-.200	-.400	-.800	-1.000**
	OD	.200	.400	.000	-.600
3MC	ID	.105	-.316	-.632	-.949
	OD	.400	-.200	-.400	-.800
4MC	ID	-.200	-.400	-.800	-1.000**
	OD	.105	-.316	-.632	-.949

Table 5.27: Correlation of VTBMD, DFBMD, TBBMD and DXRBMD with ID and OD of second (2MC), third(3MC) and fourth(4MC) metacarpal in 70-79 age group [$p< 0.001$ if **; $p< 0.05$ if *]

Age group	GP	Second metacarpal			Third Metacarpal			Fourth Metacarpal		
		CA	J	Z	CA	J	Z	CA	J	Z
	r	.536	.515	.526	.397	.343	.356	.391	.375	.382
20-29	p	.000	.001	.000	.011	.030	.024	.013	.017	.015
	r	.248	.288	.287	.347	.327	.334	.067	.115	.140
30-39	p	.242	.172	.174	.097	.119	.111	.757	.593	.514
	r	.186	.073	.116	.051	.059	.025	.053	.136	.118
40-49	p	.258	.657	.481	.757	.720	.880	.751	.408	.475
	r	.071	.021	.006	.033	.094	.097	.093	.147	.129
50-59	p	.754	.926	.978	.883	.678	.668	.680	.513	.569
	r	.571	.738	.738	.333	.500	.500	.143	.262	.262
60-69	p	.139	.037	.037	.420	.207	.207	.736	.531	.531
	r	.000	.200	.200	.800	.800	.800	.400	.400	.400
70-79	p	1.00	.800	.800	.200	.200	.200	.600	.600	.600

Table 5.28: Correlation of geometric properties and vertebral BMD measured by DEXA

Age group	GP	Second metacarpal			Third Metacarpal			Fourth Metacarpal		
		CA	J	Z	CA	J	Z	CA	J	Z
	r	.405	.250	.273	.466	.303	.326	.314	.167	.189
20-29	p	.009	.119	.089	.002	.057	.040	.048	.303	.242
	r	.102	.162	.162	.194	.225	.210	.136	.123	.076
30-39	p	.635	.449	.451	.364	.290	.325	.526	.566	.724
	r	.251	.159	.187	.094	.139	.094	.177	.044	.061
40-49	p	.123	.332	.253	.568	.400	.570	.282	.789	.710
	r	.263	.064	.087	.385	.147	.158	.092	.247	.245
50-59	p	..283	.778	.701	.076	.514	.484	.685	.267	.272
	r	.119	.262	.262	.190	.214	.214	.119	.048	.048
60-69	p	.779	.531	.531	.651	.610	.610	.779	.911	.911
	r	1.00	.400	.400	-.400	-.400	-.400	.800	-.200	-.200
70-79	p	.000	.600	.600	.600	.600	.600	.200	.800	.800

Table 5.29: Correlation of geometric properties and dual femoral BMD measured by DEXA

Age group	GP	Second metacarpal			Third Metacarpal			Fourth Metacarpal		
		CA	J	Z	CA	J	Z	CA	J	Z
	r	.593	.481	.497	.563	.453	.470	.454	.350	.363
20-29	p	.000	.002	.001	.000	.003	.002	.003	.027	.021
	r	.146	.206	.200	.203	.247	.242	.026	.051	.097
30-39	p	.496	.334	.350	.342	.244	.254	.905	.814	.652
	r	.337	.157	.206	.104	.155	.103	.097	.039	.021
40-49	p	.036	.338	.208	.530	.345	.533	.558	.815	.899
	r	.415	.401	.397	.296	.313	.316	.047	.019	.020
50-59	p	.055	.064	.067	.181	.156	.151	.834	.933	.928
	r	.452	.643	.643	.524	.595	.595	.214	.524	.524
60-69	p	.260	.086	.086	.183	.120	.120	.610	.183	.183
	r	.800	.000	.000	.200	-.200	-.200	1.00	-.400	-.400
70-79	p	.200	1.00	1.00	.800	.800	.800	.000	.600	.600

Table 5.30: Correlation of geometric properties and total body BMD measured by DEXA

Age group	GP	Second metacarpal			Third Metacarpal			Fourth Metacarpal		
		CA	J	Z	CA	J	Z	CA	J	Z
	r	.673	.394	.417	.812	.459	.501	.529	.225	.262
20-29	p	.000	.012	.007	.000	.003	.001	.000	.163	.102
	r	.165	.184	.199	.128	.121	.144	.145	.044	.052
30-39	p	.442	.389	.352	.550	.573	.501	.499	.837	.808
	r	.125	.233	.223	.063	.174	.170	.033	.166	.165
40-49	p	.449	.154	.172	.702	.290	.301	.842	.313	.315
	r	.845	.754	.760	.793	.699	.700	.581	.587	.594
50-59	p	.000	.000	.000	.000	.000	.000	.005	.004	.004
	r	-.024	.214	.214	-.071	.095	.095	-.286	.071	.071
60-69	p	.955	.610	.610	.867	.823	.823	.493	.867	.867
	r	.400	-.600	-.600	.400	-.400	-.400	.800	-.800	-.800
70-79	p	.600	.400	.400	.600	.600	.600	.200	.200	.200

Table 5.31: Correlation of geometric properties and BMD measured by DXR

SECTION- 4

DISCUSSION

The correlation between geometric properties with VTBMD, DFBMD and TBBMD according to age group showed the greatest association was seen in the younger age group (20-29). All geometric properties of second, third and fourth metacarpals of second decade group $p < 0.05$ when correlated with VTBMD, DFBMD and TBBMD except for J and Z of second and fourth metacarpal when correlated with DFBMD. The older age group 60-69 and 70-79 also showed good to excellent correlation but statistically not significant due to small sample size.

5.2.5 Correlation of BMD measured by DXR with BMD of Vertebra, Dual Femur and Total Body measured by DEXA

BMD		DXRBMD
VT	r	0.369
	p	0.000
DF	r	0.455
	p	0.000
TB	r	0.443
	p	0.000

Table 5.32: Correlation of DXRBMD with VTBMD, DFBMD and TBBMD

6. Discussion

6.1 Demographic data

The total number of volunteers involved in this study is smaller than expected due to several reasons as mentioned in the section on limitation of the study. This study mainly concentrate on Malay female because 90% of Kelantan population are Malay. Due to the fact that the remaining 10% are Chinese and Indian, we may not achieve the target sample size in approximately 24 months, therefore database for other race will be done in future study.

There were six age groups. The numbers of volunteers in 20-29 are n =40, 30-39 (n=24), 40-49(n =39), 50-59 (n =22), 60-69 (n = 8) and 70-79 (n = 4). The last two groups have the smallest sample because most of them were on prolonged medication that may affect the bone.

6.2 Determination of local Malay female BMD reference data

The peak age BMD for VTBMD is 40-49, for DFBMD and TBBMD are 50-59 (Table 5.2). The mean peak age VTBMD and TBBMD of local Malay females were 4.6% and 1.3% lower than the Caucasian whereas the DFBMD was 1.1% higher than the Caucasian (Table 2.3). However, the Malay females' VTBMD and DFBMD were 10.7% and 13.6% respectively higher than the peak bone mass values of Hong Kong Chinese women (Ho S.C., 1997). The values of peak bone mass of the spine and femoral neck for Hong Kong Chinese women were 1.03 $\pm$ 0.12 and 0.86 $\pm$ 0.11 g/cm^2 respectively. The Malay female BMD corresponding to -2.0 standard deviation from the peak adult value for vertebral and total body were 12.4% and 3.2% respectively lower compared to the Caucasian reference data whereas the dual femur was 1.2% higher than the Caucasian reference data. The BMD value below two standard deviation (-2 SD) for Hong Kong Chinese females was 7.1% and 17.4% lower than that of Malay female. These findings indicate that if the Malay female reference data for dual femur were based on -2 SD of Caucasian or Hong Kong Chinese female, they will be under diagnose for osteoporosis and appear to have lower fracture risk of the hip. If the -2 SD of Caucasian is used to diagnose osteoporosis in Malay female, this will overestimate the incidence of osteoporosis in Malay female. Similarly if local Chinese female BMD are based on Hong Kong Chinese female reference data, the diagnosis may not be accurate even though they come from the same descendent. As reported by previous study in which the BMD of Japanese overall are lower than Japanese living in the United States though they are of similar genetic stock (Fujiwara S. & Ross P.D, 1997). These could be attributed to adaptation of new life style, which eventually affects the individual body built. The rate of bone loss is also different among populations of same ethnicity. Er-Yuan et al (2003), found that there is remarkable difference in the reference figures between the newly established Chinese Women BMD Reference Databases (CWD) and the Oriental Women reference curves from the Hologic QDR 4500A bone densitometer. The CWD curve rises with age whereas the

Hologic reference curve inclined to decline continuously. In addition the rate of decent after the peak value of CWD figure of AP spine, lateral spine and radius as well as ulna site is remarkably greater than that of Hologic Reference figure. These findings suggest that factors such as differences in genetic, environmental and life styles should be taken into account. Due to this complex relationship between BMD and the factors involved, it is important to establish a local database for correct diagnosis of osteoporosis.

Numerous report have also suggested of higher BMD in Caucasian than Asian population (Fujiwara S. & Ross P.D., 1997; Lau et al, 1997). Similar findings noted in a longitudinal study of bone mineral acquisition in healthy Asian, Hispanic, Black and Caucasian youth. Asian females had lower mean femoral neck BMD, whole body BMD and whole body BMC/height ratio than Whites and Hispanics (Bachrach et al, 1999). Many factors could contribute to these higher BMD in Caucasian than Asian. The Caucasian females may have higher health and fitness conscious and maintain this awareness throughout their life. Taechakraichana et al, 2003 found that most Bangkokian women regarded menopause as a natural change of life although some think treatment is needed. In addition more than 50% of the total respondents did not have enough clear information on menopause and hormonal replacement therapy (HRT). However increased knowledge and awareness may overcomes ethnic differences (Gupta et al, 2001). Nevertheless many Asian women living in the United Kingdom have fears and concerns similar to those of the Caucasian population but they still prefer to enquire more information from female doctors who can communicate in their own language (Sethi K, Pitkin J. 2000). This means that unawareness of HRT among Asian ladies may not be the sole factor that causes less Asian female seeking treatment for osteoporosis or postmenopausal symptoms but the preferences of these women on how to get the treatment and their cultural background should be taken into account.

In our study, the vertebral BMD of fifth decade group as well as the total body BMD of sixth and seventh decades were higher than Caucasian. This could be related to higher weight in these age groups (mean weight for fifth decade=64.4kg, sixth decade=64.4kg and seventh decade=53.8kg). More weight gain is associated with less

bone loss. In postmenopausal women, the advantages of higher body weight on bone mass are due to aromatise activity in adipose tissue which eventually results in more oestrogen formed from circulatory androgens (Hui et al, 2002).

In the analysis of correlation of BMD and anthropometric data, we found that there is fair to good correlation between BMD and weight (r= 0.344 – 0.642). Previous studies also reported that there is linear correlation between BMD and weight. Bauer et al (1993), in their study on appendicular bone mass in older women found that weight loss after age 50 was associated with lower bone mass. Each 10 kg of weight loss was associated with 3.9% reduction in bone mass. Hence strong association of lower weight with low bone mass may eventually lead to an increased risk for hip fracture. Therefore clinicians should be alert to the increased risk for fracture in slender women (Orwoll et al, 1996). Our results also show that the highest correlation was between weight and BMD of the three skeletal sites, with the vertebral BMD (r = 0.344), dual femur (r =0.599) and total body (r = 0.642).

Apart from weight, other factors such as dietary, exercise habits, reproductive and lactation history could also attributed to higher VTBMD and TBBMD in older age group of local Malay women. Numerous studies showed that optimal exercise and dietary intake particularly calcium were beneficial to bone mass (Going et al, 2003; Papaioannou A., 2003; Fujita et al, 1999). However, the relationship between parity/lactation and bone mineral density is still controversial. During pregnancy, bone mass may decrease owing to high calcium demand or due to secondary osteoporosis such as patient on chronic heparin, anticonvulsant or corticosteroid therapy (Kovacs et al, 1999). On the contrary, bone mass may increase due to higher oestrogen level in the third trimester of pregnancy and the increased bone loading as a result of weight gain during pregnancy. Gur et al (2003) suggested that the number of pregnancy has significant correlation with BMD of the spine, trochanter and Ward's triangle but there is no correlation with femur neck BMD. There is evidence that some bone loss does occur soon after delivery but no long-term adverse clinical implication noted in healthy Colombian women who had at least one ongoing pregnancy. In addition, Cure-Cure et al (2002) found that BMD is increased with each delivery and that prolonged lactation has no effect on the risk of fractures. They also suggested that multiple pregnancies might be one of the protective factors against development of osteoporosis and fractures during the postmenopausal period. Similarly, Kaur et al (2003) concluded that

small changes in the trochanteric region of the hip are too small to cause pregnancy-associated osteoporosis.

On contrary to vertebral and total body BMD, the dual femur BMD of Malay women in all age group are higher than the Caucasian except for second and seventh decade group. Lau et al (2001), in their study on the incidence of hip fracture in Asian countries, found that Chinese men and women in Singapore and Malaysia have higher hip fracture rates. The fracture rates for Indian subjects were comparable to the Chinese while Malays had lower rates. Malay women have less risk of hip fracture than other race possibly due to higher BMD as shown in our study when compared to the Caucasian reference data. Other explanation could be related to the rate of bone loss as reported by Xiaoge et al (2000). They found that BMD and the rate of bone loss in Chinese women were lower than reference curves (Caucasian women) at all age groups and all sites, except for the femoral neck and Ward's triangle. From their observation, Chinese women take longer time to reach peak BMD and have a lower BMD decrease rate at the neck and Ward's triangle after peak BMD is attained. This may be the factor, which protects them against hip fractures. In spite of that, local Malay female reference curves showed that there is a transient rise from 20-29 to 30-39 age group then plateau until 50-59. Thereafter the rate of decent for local reference curve is steeper compare to Caucasian indicating the rate of bone loss is higher in local Malay female.

Somewhat similar findings found by Wu et al (2003), where the average T-scores for BMD loss at various sites in Chinese women were higher than those for both Japanese and Caucasian women except at the femoral neck. To explain this controversial finding, a possible cause could be related to the angle and the length of the femoral neck, although in our study, the hip dimension was not evaluated. In a study on geographic comparisons of Japanese, Japanese-Americans and Americans Caucasians showed that the incidence of hip fracture among Japanese is similar to Japanese-American in Hawaii and only about one-half that in American and European Caucasians. This was because, Japanese have shorter hip dimension than the Caucasians. It was found that longer femoral neck is associated with increase fracture risk. Other lifestyle like usage of bed and western style toilet may lead to weaker femoral neck (Fujiwara S. & Ross P.D., 1997).

No correlation was found between age and height with BMD of Malay women. Bauer et al (1993) reported that taller women had higher bone mass and each

10-cm increase in height was associated with a 5.7% increase in bone mass. This possibly attributed to the bone area size whereby the larger the skeletal size, the greater the bone area. However in this study, height was not significantly correlated with BMD, possibly because not much difference in height among the volunteers noted. The mean height was 152.7 with a standard deviation of 6.3.

6.3 Correlation between Geometric properties and BMD

Throughout life, the skeletal growth is region, surface, gender and race specific. The bone size grows more rapidly than bone mineral content, so that bone size is nearer completion of growth than the mineral content. Apart from that the appendicular growth is more rapid than the axial skeleton. Before puberty there is reduced endocortical expansion relative to periosteal apposition. However during and after puberty there is greater endocortical expansion and increased in periosteal diameter (Seeman E., 1998; Bass et al, 1999) resulting in an increase in cortical thickness or width. When women age, cortical bone is lost at the endosteal surfaces at a more rapid rate than it is gained in the periosteal surfaces, thus leading to a reduction of approximately 30% to 50% in bone thickness.

Our results show no or poor correlation between BMD with ID and OD. The internal diameter (ID) of second, third and fourth metacarpal have poor inverse correlation with VTBMD, DFBMD, TBBMD. There was greater negative correlation between DXRBMD and ID of second ($r = -0.404$), third ($r = -0.453$) and fourth ($r = -0.402$) metacarpal, suggesting a closer relationship between ID and DXRBMD than VTBMD, DFBMD and TBBMD. As mentioned above, theoretically the ID increased with age after puberty, but our result showed that the bone is still in the process of mineralization until the age of 50-59, evidenced by overall BMD plateau from third to fifth decade. This is possibly due to the difference in the rate of bone resorption at different skeletal sites. Therefore ID and OD may not be good parameters to combine with BMD for the evaluation of skeletal status at different site. However ID can be used to predict the bone strength of the same skeletal site where the BMD was taken in view of greater correlation seen between ID and DXRBMD.

The periosteum tends to grow or expand with age. Although it occurs at a slower rate than bone loss in the endosteal surface this process results in a slight

increase in overall total bone width. When bone width increase and cortical thickness decrease, the Metacarpal Index (MCI) will decrease with age. Cortical index represent the degree of osteoporosis. In our local Malay female population data there was no linear correlation of CT and MCI with age. Nevertheless CT and MCI declined with age (Table 5.7). Somewhat similar findings have been reported by Russo et al, (2003). They compared the changes in trabecular and cortical bone in men and women using pQCT and found no significant age-related difference in cortical bone area in men and women before the age of 60 years old but became progressively lower in women after the age of 60 years. They hypothesized that this could be attributed to postmenopausal reduction in sex hormones. Other possible explanation to the difference in this parameter in men and women would be sex-related differences in lifestyle, such as physical activity and nutrition. Apart from reduction of sex hormone in postmenopausal women, a decline in cortical thickness may also be related to imbalance level of sex hormone. Hui et al (2002) found that higher levels of Follicular stimulating hormone (FSH) and Luteinizing hormone (LH) and lower levels of E1 sulfate and E2 were associated with faster bone loss in premenopausal women. E1 sulphate is formed from both E1 and E2. They suggested that some premenopausal women despite not having any symptom might have suboptimal level of sex hormones.

Generally fair correlation between BMD with CT and MCI was observed in our study except for VTBMD. The highest correlation was between DXRBMD with CT and MCI ($r = 0.618$ -0.753 and $r = 0.516 - 0.598$ respectively). This implies that CT and MCI have linear correlation with BMD. Following are a few studies that also found significant correlation between cortical thickness and bone width with BMD. In their study on effects of projective BA of the spine on area bone mineral density (aBMD) and diagnosis of osteoporosis in healthy pre-menopausal women, Wu et al (2003), found positive relationship between bone area (BA) and aBMD. The fact that aBMD actually was adjusted for the effect of the projected BA but not for the effect of bone thickness, therefore when bone width increases this will lead to an increase in aBMD. However bone width also increases with BA. From the mathematical equation, BMD that actually represent area bone mineral density (aBMD) obtained from bone mineral content (BMC) divided by bone area (BA). Hence aBMD and BA have inverse relationship. Larger aBMD is associated with smaller BA when adjusting for BMC. If there is rapid increase in BMC than BA, aBMD will increase as well (Deng et al,

2002). Remember that bone width or outer diameter of the bone has linear correlation with BA. In view of this CT and MCI may be useful in the determination of BMD and assessment of risk of fracture risk.

Generally fair correlation was seen between total body and vertebral BMD with cortical area (CA) of second metacarpal with r = 0.360 and 0.314 respectively. This probably due to a non-significant reduction in BMD with age particularly in the first five decades in TBBMD and VBBMD compared to DFBMD. A study conducted in Denmark by Warming et al (2002) also showed no significant changes in distal forearm BMD in women less than 50 years old. However there was statistically significant fall in BMD at the hip and lumbar spine. The explanation to this, possibly related to the rate of trabecular and cortical bone loss whereby the former is greater than latter. If the rate of trabecular bone loss is slow, this appears to level off with the changes in the cortex. Therefore no gross changes to the human eye will be seen in the cortex of the bone but the micro architecture within the bone may change. In addition, intracortical resorption within cortical haversian canals can be detected radiographically and are best observed in the cortex of the second metacarpal bone. As predicted, the geometry properties (ID, CT, CA, J and Z) of the second metacarpal were correlated well with BMD than the third and fourth metacarpal.

DXRBMD has the best correlation with GP because the geometric properties obtained from the same skeletal site. As expected densitometry properties are better correlated with geometric properties from the same skeletal site. Overall, CA has stronger correlation with DXRBMD than section polar moment (Z) followed by polar moment of inertia (J). From multi linear regression analyses, the BMD of the three skeletal sites are primarily related to weight. When geometric properties particularly from the second metacarpal were added into the model they improved the prediction power.

Geometric properties (ID, OD, CA, J and Z) associated with BMD were also done according to age group. Parameters that derived from the second decade group showed fair to good correlation. Possible cause could be owing to cortical growth level off with bone mineral content at this age. This may indicate that geometric properties values obtained from this group can be used as the peak age values and its' standard deviation will form the 'T score' as in BMD. There were also good to excellent correlation between the older age group but the sample size were too small in these two

age group (60-69 and 70-79) to draw a conclusion. Further studies with larger sample size are needed to support this postulation.

6.4 Correlation between DXR and DEXA

Fair correlation was found between DXR and DEXA of the spine (r = 0.369), dual femur (r = 0.455) and total body (r = 0.443) of local Malay female. Bouxsein et al (2002) in their study of DXR to predict hip, wrist and vertebral fracture risk in elderly women, the association of DXRBMD with radius, proximal radius, femoral neck, lumbar spine and calcaneus BMD were r = 0.68, r = 0.75, r = 0.5, r = 0.44 and r = 0.59 respectively. The femoral neck BMD has greater correlation than lumbar spine, which was similar to our findings. Earlier Black et al (2001) in their study to establish reference ranges for DXR method and to compare the measurement to DEXA with BMD obtained from the wrist and hip. The correlation between DXRBMD and BMD measured by DEXA was 0.90 at the wrist and 0.61 at the hip. These results showed that DXRBMD has better correlation with DEXA when measurement made at the same site than at a distant site.

Our data showed a lower correlation between DXRBMD and BMD measured by DEXA. One of the factors could be due to the small sample size. Besides that DXRBMD can be affected by different type of film used but unaffected by radiographic exposure (Ward et al, 2003). Nevertheless, this study only used one type of film for all the hand radiographs; therefore the results were not affected. Ward et al (2003) also found that moderate correlations between DXRBMD and lumbar spine BMD (r = 0.56), femoral neck (r = 0.77) and total hip (r = 0.77). The association of DXRBMD with femoral BMD was better than lumbar spine BMD, probably owing to artifacts produced by vertebrae osteophytes. Similar possible explanation can be applied to our study, which also showed better association of DFBMD with DXRBMD than VTBMD and TBBMD with DXRBMD.

Other studies done using an older version of this technology which is the Radiographic Absorptiometry (RA), also found that this technique is useful for assessing women with age or menopause related bone loss and for detection of women with osteoporosis. There was good correlation between DEXA of the spine and RA with r = 0.56 (Takada et al, 1997). Cosman et al (1996) found the correlations between RA and the standard techniques were also good to excellent (r = 0.58-0.9). Significant

association of were observed at both spine and femur DEXA scores with RA scores (R = 0.70 and 0.68), respectively (Swezey R.L., Draper D., 1996). Comparing these findings with the above DXR technology, which is an improved radiogrammetry technique, DXR may prove useful as an alternative of DEXA (Rosholm et al, 2001). Their report showed a close correlation between DXRBMD and the distal forearm BMD (r = 0.86), spine (r = 0.62), total hip (r = 0.69) and femoral neck (r =0.73).

SECTION- 5

CONCLUSION

&

RECOMMENDATIONS

7. Conclusions and Recommendation

7.1 Conclusion

Osteoporosis is a complex, multi-factorial serious health problem worldwide, resulting in progressive health deterioration and morbidity that may progress silently for

decades – there may be no symptoms until fractures occur. Overall the –2SD of VTBMD and TBBMD for local Malay female are lower than the Caucasian and the –2SD for DFBMD is higher. However the –2SD for VTBMD and DFBMD are higher than the Hong Kong Chinese female. In view of these differences, local Malay women reference curve have been established for proper and accurate diagnosis of osteoporosis.

CT, MCI and CA particularly from the second metacarpal are the geometric properties that fairly correlated with VTBMD, DFBMD and TBBMD. Furthermore when geometric properties (CA, CT and MCI) were added into models that consist of anthropometric data (weight and age), they increase the predictive power. This implies that incorporation of these geometric parameters with BMD is possible for the evaluation of skeletal status. The following are formulas to predict BMD, derived from multi linear regression analysis.

VTBMD = 0.708 + 0.121 (CT2)

VTBMD = 0.755 + 0.006175 (CA2)

DFBMD = 0.429 + 0.102 (CT2)

TBBMD = 0.699 + 0.0820 (CT2)

TBBMD = 0.539 + 0.00619 (CA2)

Fair correlation was found between DXRBMD and BMD measured by DEXA (VTBMD, DFBMD and TBBMD). Based on these results DXR may not be able to diagnose osteoporosis accurately. However it is possible to apply this method for follow up cases in remote areas provided that patients have an initial DEXA result combine with DXRBMD. The initial DXRBMD will be compared to the follow up DXRBMD. This method is also convenient to patients where they do not need to travel to centers that have DEXA. Overall cost can be reduced because during follow up only a non-dominant hand radiograph will be taken. In addition DXRBMD has good to

excellent correlation with geometric properties, which indicates that geometric properties should be used to predict BMD of the same skeletal site.

7.2 Recommendation

Based on these results, the author would like to suggest that apart from local Malay population reference curve, other races data should be established for better evaluation of BMD. In addition, a multicenter study is more appropriate as the data reflects the whole Malaysian population. Prediction of fracture risk of a skeletal site is more accurate when it is done on the same site. Similarly geometric properties of a particular region may predict fracture risk of the same region better than other sites. Therefore when DXR is used to evaluate or predict fracture risk at different site, some deviation from the actual skeletal BMD is expected. In view of these problems, it is recommended that, a baseline non-dominant hand radiograph for DXR should be taken in the initial BMD measured by DEXA. So the BMD obtained by using DXR can be evaluated retrospectively and can be compared to DXRBMD taken on subsequent follow up.

The author would also like to suggest further study on applicability of DXR in detecting individuals who are at risk of fracture and hence referring them for proper axial BMD measurement using DEXA. A larger sample size and more detail information regarding subjects dietary habits, physical activity, profession, medical, obstetric and gynecological history, duration of lactation, menopausal history as well as family history of osteoporosis should be included. The relationships among these factors should be look into when assessing the skeletal status.

SECTION- 6

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