Sudan University of Science and Technology

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Assessment of osteoporosis in patients with prostate cancer using bone scintigraphy and computed radiography

تقويم هشاشة العظام لمرضى سرطان البروستات باستخدام المسح الذري والأشعة السينية الرقمية

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الآيـة

قال الله تعالى:

بسم الله الرحمن الرحيم

(وَعَلَّمَكَ مَا لَمْ تَكُنْ تَعْلَمُ ۚ وَكَانَ فَضْلُ اللَّهِ عَلَيْكَ عَظِيمًا)

صدق الله العظيم

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DEDICATION

*This thesis is dedicated **TO MY PARENTS** for endless love, support and encouragement*

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There are many people who have helped me during the PhD. There is not enough space, nor time, to acknowledge everyone to the extent they deserve. I hope people understand the brevity of this part. First and foremost, I want to thank my supervisor **Prof. Mohamed E. M. Gar-Elnabi** Without his immense work effort and patience, I surely would not be writing this paragraph.

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Abstract

The development of radiology and medical imaging was much helper in all fields of medicine with new technologies such as DEXA technology, which measures the fragility, hardness and bone mass by measuring the mineral density of bone.

DEXA is an important technique for specialists and the general public because the osteoporosis has become an important problem for women over the age of 40 and the elderly of both sexes. Osteoporosis has been the subject of many researches, many devices and different techniques have been developed to measure the most important indicators of bone density and bone mineral content.

This study, in an attempt to measure osteoporosis with other available techniques, was used to establish caution in early stages of vulnerability. We assessment of osteoporosis in patients with prostate cancer using bone scintigraphy (Gamma camera) and computed radiography (CR).

Before bone scintigraphy (G.C), patients undergo digital X-ray imaging (CR) of the lumbar spine and hip bone, which is the most vulnerable according to previous studies, and also gives accurate readings of any change in density.

The images were collected on flash memory (USB) and then re-processed and analysing the image with Interactive Data Language IDL software version 6.1 to measure the grey level variation of images in the lumbar spine and hip bone area.
The study was conducted at Radiation Isotopes Canter of Khartoum and Antalya Medical Center in Khartoum State from July 2014 to July 2017.

The data was available for 200 patients, 70 abnormal patients with prostate cancer was taken CR and G.C images for hip and spine, and 130 normal patients CR for spine and hip taken as a control group.

The results show that: The mean of normal hip CR and normal spine CR were 619.67± 86.39, 598.77 ±73.34, *The mean of* abnormal hip CR and abnormal spine CR were 2526.43 ± 310.63, 1988.03±592.445, and the mean of abnormal spine Gamma Camera and abnormal hip Gamma camera were 630.67±87.57, 582.57± 87.57

And by using T.Test Show that there is no significant difference between **normal CR and abnormal CR** for hip and spine regions. The Linear regression results show rate of change between normal CR and abnormal CR for hip and spine decreasing by rate 0.0596 and 0.0172 for normal versus one unite of abnormal CR. The study show that there is significant difference between **normal CR and abnormal G.C** for hip and spine regions. And the Linear regression results show rate of change between normal CR and up normal G.C hip was increasing by rate 0.8301 for normal CR versus one unit of abnormal G.C hip, and by rate of 0.6607 for normal CR spine versus one unit of abnormal G.C spine. Also show that there is no significant difference between **abnormal CR and abnormal G.C** for hip and spine regions. And the Linear regression results show rate of change between abnormal CR and abnormal G.C hip was decreasing by rate 0.0369 for abnormal CR versus one unit of abnormal G.C hip, and increasing by rate of 0.0147 for abnormal CR spine versus one unit of abnormal G.C spine.

And the most effected age was 69-74 years, and the effected period of treatment 1-1.8 years, the PSA most effected value 6-7.4 ng/ml and the most frequency of body mass index 25.8-28.8 kg)cm2 .

الخلاصة:

تطور علم الأشعة والتصوير الطبي تطورا كبيرا خلال السنوات الأخيرة بظهور تقنيات جديدة ومنها تقنية الديكسا التي تقيس هشاشة وصلابة وكتلة العظام من خلال قياس الكثافة المعدنية للعظم .

ويعتبر جهاز قياس امتصاص طاقة الاشعة المزدوج المعروف بديكسا تقنية هامة للمختصين والعامة لان موضوع هشاشة العظام أصبح من المواضيع الهامة للسيدات فوق سن 40 وكبار السن من الجنسين ولان مرض هشاشة العظام كان مثارا لكثير من الأبحاث فقد ظهرت أجهزة عديدة وتقنيات مختلفة كلها تهدف لقياس أهم المؤشرات لكثافة العظم الأسفنجي والمحتوى المعدني الكلسي .

ونظرا لعدم توفر أجهزة الديكسا الا في المراكز الخاصة وتكلفة الفحص العالية في دولة السودان اجريت هذه الدراسة كمحاولة لقياس هشاشة العظم بتقنيات اخرى متوفرة وذلك لوضع الحيطة والحذر في مراحل مبكرة للهشاشة ,قمنا بدراسة لحالات مرضى سرطان البروستات وذلك بتقييم هشاشة العظم في مرضى سرطان البروستات بواسطة المسح الذري والأشعة السينية الرقمية .

قبل المسح الذري بالجاما كاميرا يخضع المرضى للتصوير الرقمي بالأشعة السينية للفقرات القطنية ولعظم الورك التي تعتبر اكثر الأجزاء تعرضا للهشاشة وايضا تعطي قراءات دقيقة لأي تغير يحدث في الكثافة.

تم جمع الصور على ذاكرة فلاش ومن ثم اعيد معالجتها وتحليلها بواسطة برنامج لغة البيانات التكراري لقياس التغير في مستوى التباين في صورة عظم الفقرات القطنية وعظم الورك

أجريت هذه الدرسة في مركز الخرطوم للعلاج بالأشعة والطب النووي ومركز انطاليا الطبي في ولاية الخرطوم في الفترة من يوليو 2014 – يوليو 2017

كانت العينة كالتالي : 70حالة مصابة بسرطان البروستات خضعت للتصوير الرقمي والمسح الذري و 130 حالة سليمة خضعت للتصوير الرقمي فقط كمجموعة تحكم .ومن النتائج تبين ان متوسط قراءة صور الأشعة السينية الرقمية للحالات السليمة لعظمة الورك كانت 86.39 ±619.67 وللفقرات القطنية كانت 598.77 ±73.34 .ومتوسط قراءة صور الأشعة الرقمية للحالات المريضة لعظمة الورك كانت ± 2526.43 310.63 وللفقرات القطنية كانت 592.445±1988.03 .وقراءة صور المسح الذري للمرضى لعظمة الورك كانت 87.57 ±582.57 وللفقرات القطنية كانت 87.57±630.67 .

وبأستخدام T.Test اظهرت الدراسة أن هناك لا فرق واضح بين قراءة صور الأشعة الرقمية الطبيعية والغيرطبيعية لكل من عظمة الورك والفقرات القطنية وكان معدل الانحدار يقل بمعدل 0.0596 و 0.0172 لصورة الطبيعية مقابل وحدة واحدة من الصورة الغير طبيعية .

وايضا ظهر أن هناك فرق احصائي بين قراءة صورالاشعة الرقمية الطبيعية وقراءة صور الجاما كاميرا لمرضى سرطان البروستات لكل من عظمة الورك والفقرات القطنية ومعامل الانحدار الخطي يشير الى أن معدل التغير بينهم يزيد بمعدل 0.830 و 0.660 لكل وحدة واحدة لصور الجاما كاميرا مقابل الأشعة الرقمية.

واظهرت الدراسة انه لا يوجد فرق بين قراءة صورة الاشعة الرقمية والجاما كاميرا لعظمة الورك والفقرات القطنية لمرضى سرطان البروستات ومعامل الانحدار الخطي لعظمة الورك يقل بمقدار 0.0369 لصورة الاشعة الرقمية مقابل وحدة واحدة من صورة جاما كاميرا ..ومعامل الانحدار لعظمة الفقرات القطنية يزيد بمعدل 0.0174 لصورة الاشعة مقابل صورة جاما

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List of abbreviations

PSA	Prostate-Specific Antigen
TC^{99M}	Technetium -99m
ADT	Androgen Deprivation Therapy
GnRH	Gonadotropin- Releasing Hormone
BMD	Body Mass Density
WHO	World Health Organization
DXA	Dual X-ray Absorptiometry
SD	Standard Deviation
DEXA	Dual Energy X-ray Absorptiometry
QCT	Quantitative Computed Tomography
HRCT	High Resolsion Computed Tomography
QUS	Quantitative Ultrasonography
PQCT	Peripheral Quantitative Computed Tomography
DPA	Dual Photon Absorptiometry
ROIs	Region of Interest
SPECT	Single Photon Computed Tomography
CR	Computed Radiology
BMI	Body Mass Index
PCa	Prostate Cancer
NCR	National Cancer Registry
SEER	Surveillance Epidemiology and End Results
DRE	Digital Rectal Examination
TRUS	Trans-Rectal ultrasound guided
MRI	Magnetic resonance imaging
DES	Diethylstilbestrol
LHRH	Luteinizing – hormone releasing hormone
NIH	National Institute of Health

SEM	Scanning Electron Micrograph
BMU	Basic Multicenter Unite
PTH	Parathyroid Hormone
BMP	Bone Morphogenetic Protein
ESR-1	Estrogen Receptor
LRP5	Lipoprotein Receptor Related Protein
RANKL	Receptor Activator of Nuclear factor-KB Ligand
OPG	OsteoProteogen
IGF	Insulin like Growth Factor
TFG-B	Transforming Growth -Beta
SPA	Single Photon Absorptiometry
SXA	Single x-ray Absorptiometry
AP	Anteroposterior
FRAX	Fracture Risk Assessment X--ray
RICK	Radiation and Isotopes Center of Khartoum
MDP	Methylene Dephosphate
IDL	Interactive Data Language
G.C	Gamma Camera

Chapter one

Introduction

Chapter one

Introduction

1.1 introduction

Prostate cancer (PCa) is the second most common cancer in men and the sixth leading to death among men worldwide with an estimated 899 000 new cases and 258 000 new deaths in 2008 (Ferlay et al,2010). The worldwide Prostate Cancer burden is expected to grow to 1.7 million new cases and 499 000 new deaths by 2030 simply due to the growth and aging of the global population (Ferlay et al, 2010).

Prostate cancer is very common among men in America. It is the second most leading cause of cancer deaths in men. In 2010, 217,730 men were diagnosed with prostate cancer and 1545 men died from the disease (Prasad et al, 2012)

In the UK it is the third largest cause of death from cancer in males, exceeded only by deaths from cancer of the lung and large bowel, 20 000 new cases were recorded in 1997 (European Union 134 000 new cases), from USA statistics, both incidence and mortality are considerably higher in black than white men (Greenlee et al, 2001) In Africa ,almost 60,000 new cases estimated in 2012, cancer of the prostate is the most frequently diagnosed cancer in men, although in North Africa, it lies in fourth position (after lung, liver, and bladder). It is the third most common neoplasm overall (after breast and cervix), both in Africa as a whole and in Sub-Saharan Africa (Parkin et al, 2012).

Prostate cancer is the most common cancer in Sudanese men (Serum, P. 2011). The age standardized rate is 10.3 and mortality is 8.7 per 100,000 population. It ranked second among all cancers in both sexes after breast in 2012 (Ferlay et al, 2012).

Prostate cancer mortality trends range widely from country to country in the industrialized world (IARC, 2012), Mortality has decreased in most Western countries but the magnitude of the reduction varies between countries, the reduced mortality seen recently in the USA is considered to be partly due to a widely adopted aggressive Prostate Cancer screening policy (Etzioni et al, 2013). However, there is still no level 1 evidence that prostate-specific antigen (PSA) screening reduces mortality due to Prostate Cancer (Ilic et al, 2013).

The risk factors for prostate cancer are increasing age, African-American ethnicity, and family history of the disease, there is some evidence that a diet high in animal fat may be risk factor,

However obesity has a high prevalence in patients with prostate cancer (Giovannucci et al, 2003). Also Smoking and alcohol increased the risk of prostate cancer (Grönberg et al,1997).Farmers; certain occupations and industries with exposures to cadmium, herbicides, and fertilizers; and men with low occupational physical activity levels have elevated prostate cancer risk (Wagner et al,2000).

The choice of most appropriate therapy among patients with prostate cancer is based on the proper staging of the disease at the time of diagnosis. Clinical staging procedures include digital serum PSA measurements, rectal examination, bone scan scintigraphy, and, if necessary in the case of enlarged adenoma and high probability of metastases other than to bone in some patients, computer tomography or magnetic resonance imaging studies. Bone is considered the second most common site, after lymph nodes, for metastases from prostate cancer. Around 5% to 15% of patients first diagnosed with prostate cancer already have bone metastases as well. In patients who actually die of prostate cancer, metastases to the skeleton are found in more than 80% of patients. Thus proper staging and screening for the presence of bone metastases have a major impact on both the prognosis and choice of treatment for each individual patient (Parnes et al, 2013; Heidenreich et al, 2011; Heidenreich et al, 2008).

Bone scan scintigraphy with the use of Tc-99m-labeled methylene diphosphate is superior to all other imaging modalities and, thanks to its high accuracy in the detection of metastatic bone disease, is considered the most sensitive staging method for prostate cancer (Schröder and Wildhagen, 2001; Heidenreich et al, 2011; Heidenreich et al, 2008)

One of the routinely used methods in prostate cancer staging is prostate gland biopsy. The Gleason grading system is used for proper evaluation. Basically, a Gleason score is given to prostate cancer based upon its microscopic appearance in material obtained via biopsy, Cancers with higher Gleason scores tend to be more aggressive and have a worse prognosis than those with lesser scores, According to current international convention, the Gleason score of cancers detected in a prostate biopsy consists of the Gleason grade of the dominant (most extensive) carcinoma component plus the highest grade detected in other material, regardless of its extent. Then the two grades are added together to make a total Gleason score. The Gleason grade ranges from 1 to 5 and the Gleason score from 2 to 10, with 10 indicating the worst prognosis (Heidenreich, 2008).

The majority of men with prostate cancer are diagnosed with localized disease (80%), however, a significant number of men are diagnosed with advanced (biochemical recurrence or metastatic) disease (16%) (Altekruse et al., 2010; Cooperberg, Lubeck, Meng, Mehta, & Carroll, 2004; Trask, 2004).

Androgen deprivation therapy (ADT) is the mainstay of the treatment choices available for advanced prostate cancer patients. However, men treated with ADT experience a larger number of physiological and psychological sequelae, than men who are not treated with ADT for prostate cancer, these side effects include loss of libido and erectile dysfunction (Potosky et al., 2002a; van Andel & Kurth, 2003), hot flashes (Holzbeierlein, 2006), gynecomastia, breast tenderness (See et al., 2002), osteoporosis (Higano, Shields, Wood, Brown, & Tangen, 2004; Wei et al., 1999).

1.1.2 Androgen deprivation therapy and related to osteoporosis

The most common treatment for advanced prostate cancer is hormone therapy, also known as androgen deprivation therapy (ADT), to reduce testosterone and slow the cancer's growth, testosterone has many functions in the body. When it is reduced, the body may react in a way that affects your quality of life, hormone therapy for prostate cancer is a major cause of male hypogonadism. Gonadotropin-releasing hormone (GnRH) agonists are the mainstay of treatment for metastatic prostate cancer and a routine part of management for many men with locally advanced or recurrent nonmetastatic prostate cancer (Sharifi et al, 2005). GnRH agonists increase bone turnover in men with prostate cancer (Maillefert et al, 1999; Smith et al, 2001). Biochemical markers of osteoclast and osteoblast activity increase progressively after treatment with a GnRH agonist and seem to reach a plateau after 6 months (Smith et al, 2001). In prostate cancer, GnRH agonists increase parathyroid hormone mediated osteoclast activation (Leder et al, 2001), suggesting that changes in skeletal sensitivity to parathyroid hormone play an important role in the pathogenesis of hypogonadal bone loss. Estrogens play an important role in skeletal homeostasis in healthy men. Osteoblasts and osteoclasts express estrogen receptors (Need et al, 1996; Eriksen et al, 1988; Oursler et al, 1994). Estrogens contribute to the regulation of both osteoclast and osteoblast activity in men (Falahati-Nini et al, 2000; Leder et al, 2003).Serum estradiol levels are positively associated with spinal bone mineral density and negatively associated with vertebral fracture risk in healthy older men (Slemenda et al, 1997; Khosla et al, 1998; Greendale et al, 1997). GnRH agonists significantly decrease bone mineral density in men

with prostate cancer, most studies have reported a 2% to 3% decrease per year in bone mineral density of the hip and spine during initial therapy. Notably, significant bone loss has been observed despite concurrent administration of supplemental calcium and vitamin D and careful exclusion of secondary causes of osteoporosis (Smith et al, 2001; Smith et al, 2003)

Results of multiple studies have shown that bone mineral density (BMD) of the femoral neck, lumbar spine, and total hip decreases by up to 4.6% annually in prostate cancer patients without bone metastases who receive ADT, a rate that is four to eight times higher than the normal bone loss rate (0.5–1% per year) observed in otherwise healthy aging men (Higano, 2004; Michaelson et al, 2007).

As bone loss increases the probability of fracture, prostate cancer patients who receive ADT are at an increased risk for fracture and related morbidity and mortality (Smith et al, 2005; Shahinian et al, 2005).Indeed, men with prostate cancer and no bone metastases receiving ADT are up to 37% more likely to experience a fracture than patients not receiving ADT; fracture-related hospitalizations are also more common in patients receiving ADT compared with patients not receiving ADT (4.9 versus 2.2%; $p<0.001$) (Shahinian et al,2005).

1.1.3 Osteoporosis

Osteoporosis is the major metabolic bone disease seen worldwide and resulting fragility fractures are recognized as a major public health issue (Cooper et al, 1992). According to the WHO working group estimations in 1994, nearly 30% of European women over 50 years have osteoporosis (WHO, 1994). In general, osteoporosis is commoner among Caucasians and Asians while women of Afro-Caribbean descent have a less likelihood to develop the disease , and it is defined as “a disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk” (WHO, 1994).it is now recognized as a ‘silent epidemic disorder’ (Njeh et al, 1997) It is estimated that, 30 to 50% of women and 15 to 30% of men experience an osteoporosis-related fracture during their lifetime (Randell et al, 1995). And affects an estimated 75 million people in Europe, the United States and Japan (CDC, 1997). In the United States it affects more than 25 million people, predisposes to more than 1.3 million fractures annually (CDC, 1993) and costs the nation in excess of US$13.8 billion (NOF, 1997).Osteoporosis-related fractures are associated with increased mortality, morbidity and reduced quality of life (Keene et al, 1993).

Osteoporosis in men is substantially underdiagnosed, undertreated, and underreported and inadequately researched (**Kiebzak et al, 2002; Looker et al, 1997**). Although osteoporosis is often viewed as a disease of women, studies show that osteoporotic fractures also result in substantial morbidity, mortality, and financial expenses in men (**Pacini et al, 1999; Halling et al, 2005; Stehman-Breen et al, 1999**). The prevalence of osteoporosis is estimated to be 7% in white men, 5% in black men, and 3% in Hispanic men. Data on prevalence in Asian-American men and other ethnic groups are lacking (**Looker et al, 1997**). With the aging of the population, rates of osteoporosis in men are expected to increase nearly 50% in the next 15 years, and hip fractures rates are projected to double or triple by 2040 (**Looker et al, 1997**).

Current diagnosis of osteoporosis is largely based on measurement of BMD, using dual energy X-ray absorptiometry (DXA) of the hip or lumbar spine (WHO, 1994).

There are a variety of techniques are available to measure bone mass, to detect osteoporotic fractures, and/or to assess bone strength and fracture risk. These include: Conventional skeletal radiology, Dual energy X-ray absorptiometry (DXA), Quantitative computed tomography (QCT) and high resolution CT (HRCT), Quantitative ultrasound (QUS), Tools to assess the peripheral skeleton (e.g. pQCT, pDXA), and Other specialized techniques to assess bone density and/or structure, In general, BMD assessment is appropriate for men with a history of no traumatic fracture, hypogonadism (natural or drug induced), hyperthyroidism, excessive alcohol intake, glucocorticoid therapy, or other causes of secondary osteoporosis (including gastrointestinal disease and such systemic illnesses as rheumatoid arthritis and multiple myeloma) (National Osteoporosis Foundation.2004).

Dual energy X-ray absorptiometry (DEXA) is the standard method of choice for BMD measurement in most cases. DEXA can be performed at a variety of central and peripheral anatomic locations, such as the spine, hip, or radius (Miller et al.1996).

Quantitative computed tomography (CT) scanning is more sensitive but less specific than DEXA for detecting osteoporosis in men. The major advantage of CT is that it measures the central portion of the vertebrae directly, thus avoiding areas affected by osteoarthritis, In general the choice of skeletal site for BMD assessment depends on the goals of the test for example; when assessing the future risk of hip fracture, it's best to obtain a hip BMD measurement (Stepan et al.1989). In such patients, the lateral projection view is better for detecting osteoporosis, in a small, case-controlled, prospective study of gonadotropin releasing

hormone analog therapy in older men with prostate cancer, the total hip and distal radius demonstrated the most bone loss during 12 months of therapy, suggesting that DEXA of these skeletal sites is most informative in such patients, By contrast, studies in younger men with hypogonadism show significant losses at the spine (Oefelein et al.2002). Indicating that DEXA of the spine may be more useful in this situation given the increased incidence of bone loss in men with prostate cancer treated with ADT (orchiectomy or LHRH agonist therapy), Maillefert et al(1999), recommend baseline evaluation with a DEXA scan usually of the hip .If the baseline value is normal, a follow-up test should be performed every one to two years after the patient has received at least one year of ADT. This recommendation is based on the data showing an increased incidence of osteoporosis after more than a year of ADT (Maillefert et al.1999).

DXA is an x-ray imaging technique primarily used to derive the mass of one material in the presence of another through knowledge of their unique X ray attenuation at different energies, Two images are made from the attenuation of low and high average x-ray energy, DXA is a special imaging modality that is not typically available with general use x-ray systems because of the need for special beam filtering and near perfect spatial registration of the two attenuations. Dedicated commercial DXA systems first became available in the late 1980s (KELLY et al.1989). DXA is an extension of an earlier imaging technique called dual energy photon absorptiometry (DPA). The DXA technique differs from DPA only in that DPA uses the attenuation of monochromatic emissions from a radioisotope (i.e.Gd^{153}), while DXA uses polychromatic x-ray spectra for each image, centered at different energies, DXA's primary commercial application has been to measure BMD to assess fracture risk and to diagnose osteoporosis; the X ray energies used are optimized for bone density assessment. For osteoporosis diagnosis, the lumbar spine, proximal hip and, sometimes, the distal forearm are scanned, the ROIs used and the diagnostic criteria are well defined. The whole body can also be scanned to measure whole body bone mass and soft tissue body composition (LASKEY et al.1996). In image areas that contain only soft tissue, lipid and lean tissue can be assessed (PIETROBELLI et al.1996).from which per cent lipid mass can be calculated, while areas that contain bone use an estimated per cent lipid from the surrounding tissue (BLAKE et al.1997). In contrast, the measurement of bone density using a computed tomography (CT) system, called quantitative computed tomography (QCT), can measure the true volume and volumetric bone

density. Bone size varies as a function of age. Thus, DXA bone density values increase from birth to adulthood, primarily because the bones become larger. Bone size is also influenced by ethnic differences and sex. One has to be careful to compare DXA bone density values to a similar population or results can be easily misinterpreted. Asians typically have lower DXA bone density values compared to sex and age matched Caucasians, Partly due to bone size differences (ROSS et al.1996).When evaluating bone density using DXA to diagnose osteoporosis, there are several common measurement sites, including the lumbar spine, the proximal hip and the forearm. The standard protocol is to scan two sites, typically the spine and hip. If one of these sites is not available, then the forearm is used. The current standards for using DXA for diagnosing osteoporosis can be found in the position statements of the International Society for Clinical Densitometry (ISCD) (BAIM et al.2007).

1.1.4 Bone scintigraphy and osteoporosis

Osteoporosis is characterized by a decrease in bone mass with thinning of the cortex and trabecular and a reduction in the number of trabeculae. Bone densitometry is the most diagnostic procedure for the detection of reduced bone mass. The bone scan has not been found to have an important role to play in the diagnosis of osteoporosis. This is a disorder where gradual change in bone mass may occur over many years, the bone scan appearances are usually normal and shows very low radio phosphate uptake in the skeleton, poor vertebral definition and low bone to soft tissue ratio (Fogelman and Carr.1980). However, the scan images may on occasion appear poor in quality because of relatively low bone uptake of tracer with a “washed-out” pattern activity in the axial and appendicular bones. It has been suggested that this occurs in severe or “end- -stage” osteoporosis caused by markedly reduced or even absent osteoblastic activity. Loss of vertebral height and closeness of the rib cage to pelvis in patients with multiple vertebral fractures may be observed in bone scan (Ryan PJ and Fogelman I.1997). These features are not diagnostic, but their presence may alert on the presence of osteoporosis. In practice the bone scan provides a less reliable means of diagnosing osteoporosis than radiography (Sy WM.19981).

Osteoporotic bones are abnormally brittle and are at high risk of fractures from mild trauma, these are easily recognizable on the bone scan and are seen as focal areas of increased tracer uptake. If vertebral collapse is present, the classical appearance of a fracture in bone scan is a focal horizontal linear uptake on blood pool and static images at the site of the fracture. This in-

tense uptake usually decreases over a period of 6 to 18 months, and thus the scan is of value in assessing the age of vertebral collapse (Sy WM.1981). Even when scan appearances are quite typical of benign vertebral collapse, tumour cannot definitely be excluded and radiographs should be obtained. In the diagnosis of a patient with acute back pain with evidence of vertebral collapse on X-ray, the bone scan can help in the evaluation of the cause of pain. A normal scan would exclude a recent vertebral fracture, and other causes for back pain should then be considered. Bone scan can also suggest other causes of vertebral collapse or back pain such as metastases, infection, or Paget's disease. In a study by Rico et al., bone to soft tissue uptake indices in recent osteoporotic vertebral collapse using bone scan were examined (Rico et al.199), the study suggests that bone scan may be useful in monitoring response to therapy, but seems to have limited clinical yield. SPECT studies may help to increase image contrast in bone scan. It has the capacity to separate uptake above and below the areas of interest, which means that, in the spine, uptakes can be separately identified in the different sites of one vertebra. Bone scan plays a very important role in the early detection of clinical suspected fractures with a negative or uncertain X-ray image. It may also allow the detection of clinically unsuspected fractures of the neck of femur, humerus , scapula, radius and ribs. In a study of Kobb et al., the bone scan was the only technique able to find unrecognized fractures of pelvis that produced back pain similar to vertebral collapse pain (Kobb et al.1992). Bone scan is capable of finding not only fractures but also fracture complication such as osteomyelitis and non-union. It is usually able to detect and to exclude alternative diagnosis or coexistent diseases at the same time, bone scintigraphy might thus become an important diagnostic tool necessary to help improve the quality of life of prostate cancer patients (Rico et al.199).

1.2 Problems of study:

Up to present the researcher noticed that, not all the patients with prostate cancer are investigated for osteoporosis involvement, but as follow up of the patients with prostate cancer must be presenting to nuclear medicine to do bone scintigraphy for detection of bone metastasis, however the difficulty with availability, high cost using DEXA; this study try to correlate bone scan and X-ray image by using software to estimate osteoporosis using both x-ray intensity and hence bone counts in bone scintigraphy.

1.3 **Objectives**:

1.3.1 The general objective to assessment of osteoporosis in patients with prostate cancer using bone scintigraphy and computed radiography (CR)

1.3.2 Specific objectives

- To find out the most affected sites of the osteoporosis
- To correlate between bone scintigraphy and signal CR.
- To correlate between the PSA with age, BMI and the time after the treatment.
- To estimate bone scintigraphy counts from CR signal
- To find out the effect of age, BMI, PSA and period of treatment on bone density.

Overview of the study:

This study is concerned assessment of osteoporosis in patients with prostate cancer using bone scintigraphy and computed radiography, it falls into five chapters. Chapter one which include introduction, problem of study, objectives and overview of the study. While Chapter two will include anatomy, physiology, pathology and previous studies. Chapter three deals with the methodology, where it provides an outline of material and methods used to acquire the data in this study as well as the method of analysis approach. While the results were presented in chapter four, and finally Chapter five include discussion of results, conclusion and recommendation followed by references and appendices.

Chapter two

Literature Review

Chapter two

Theoretical background

2.1 Prostate gland anatomy:

The prostate gland is located in the subperitoneal compartment between the pelvic diaphragm and the peritoneal cavity. It is located posterior to the symphysis pubis, anterior to the rectum, and inferior to the urinary bladder, thus allowing digital palpation for examination. Classically described as "walnut-shaped," it is conical in shape and surrounds the proximal urethra as it exits from the bladder. The prostate gland is composed of a base, an apex, anterior, posterior, and inferiorlateral surfaces. The base is attached to the neck of the bladder and the prostatic urethra enters the middle of it near the anterior surface, which is narrow and convex. The apex rests on the superior surface of the urogenital diaphragm and contacts the medial surface of the levator ani muscles. The posterior surface is triangular and flat, and rests on the anterior wall of the rectum. The inferior-lateral surface joins the anterior surface and rests on the levator ani fascia above the urogenital diaphragm. The human prostate is composed of glandular and stromal elements, tightly fused within a pseudocapsule. The inner layer of the prostate capsule is composed of smooth muscle with an outer layer covering of collagen. There are two anatomic defects in the prostatic capsule: at the apex (anterior and anterolaterally) and at the site of entry of the ejaculatory ducts. In these areas, it can be challenging to determine the pathologic stage of adenocarcinoma of the prostate (McNeal et al, 1986).

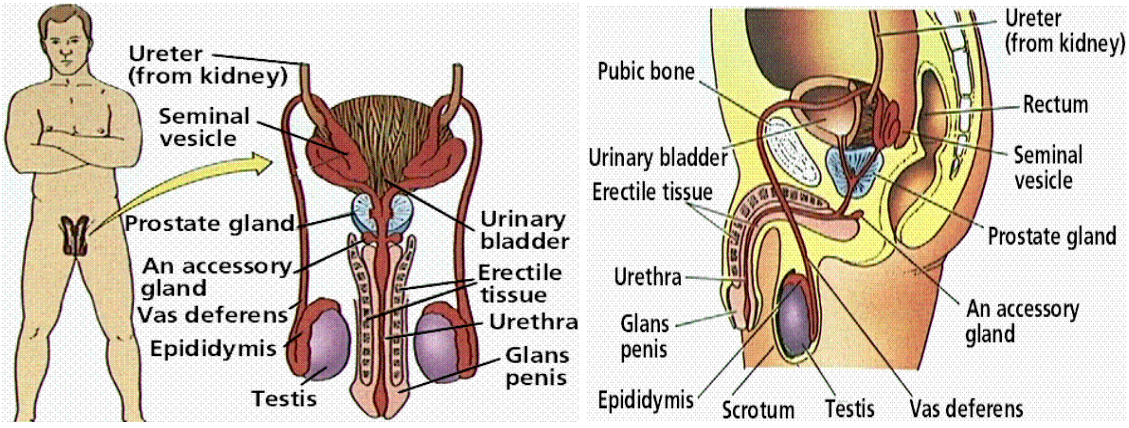


Figure 2.1 show **male reproductive system (**Purves et al,2003**)**

2.2 Prostate Gland physiology

The prostate gland secretes a thin, milky fluid that contains calcium, citrate ion, phosphate ion, a clotting enzyme, and a profibrinolysin. During emission, the capsule of the prostate gland contracts simultaneously with the contractions of the vas deferens so that the thin, milky fluid of the prostate gland adds further to the bulk of the semen. A slightly alkaline characteristic of the prostatic fluid may be quite important for successful fertilization of the ovum, because the fluid of the vas deferens is relatively acidic owing to the presence of citric acid and metabolic end products of the sperm and, consequently, helps to inhibit sperm fertility. Also, the vaginal secretions of the female are acidic (pH of 3.5 to 4.0). Sperm do not become optimally motile until the pH of the surrounding fluids rises to about 6.0 to 6.5. Consequently, it is probable that the slightly alkaline prostatic fluid helps to neutralize the acidity of the other seminal fluids during ejaculation, and thus enhances the motility and fertility of the sperm. Semen, which is ejaculated during the male sexual act, is composed of the fluid and sperm from the vas deferens (about 10 per cent of the total), fluid from the seminal vesicles (almost 60 per cent), fluid from the prostate gland (about 30 per cent), and small amounts from the mucous glands, especially the bulbourethral glands. Thus, the bulk of the semen is seminal vesicle fluid, which is the last to be ejaculated and serves to wash the sperm through the ejaculatory duct and urethra. The average pH of the combined semen is about 7.5, the alkaline prostatic fluid having more than neutralized the mild acidity of the other portions of the semen. The prostatic fluid gives the semen a milky appearance, and fluid from the seminal vesicles and mucous glands gives the semen a mucoid consistency. Also, a clotting enzyme from the prostatic fluid causes the fibrinogen of the seminal vesicle fluid to form a weak fibrin coagulum that holds the semen in the deeper regions of the vagina where the uterine cervix lies. The coagulum then dissolves during the next 15 to 30 minutes because of lysis by fibrinolysin formed from the prostatic profibrinolysin. In the early minutes after ejaculation, the sperm remain relatively immobile, possibly because of the viscosity of the coagulum.As the coagulum dissolves, the sperm simultaneously become highly motile. (Guyton and Hall, 2006)

2.3 Prostate pathology

2.3.1 Prostatitis

Prostatitis is divided into four categories: (1) acute bacterial prostatitis (2% to 5% of cases), caused by the same organisms associated with other acute urinary tract infections;

(2) *chronic bacterial prostatitis* (2% to 5% of cases), also caused by common uropathogens;

(3) *chronic nonbacterial prostatitis, or chronic pelvic pain syndrome* (90% to 95% o ases), in which no uropathogen is identified despite the presence of local symptoms; and (4) *asymptomatic inflammatory prostatitis* (incidence unknown), associated with incidental identification of leukocytes in prostatic secretions without uropathogens.

The prostate is usually not biopsied in men with symptoms of acute or chronic prostatitis, since the findings are usually non-specific and are not helpful in managing patients. The exception is in patients with granulomatous prostatitis, in which a specific etiology may be established.

In the United States, the most common cause is instillation of bacille Calmette-Guérin (BCG) within the bladder for treatment of superficial bladder cancer. BCG is an attenuated tuberculosis strain that produces a histologic picture in the prostate indistinguishable from tuberculosis. Disseminated prostatic tuberculosis is rare in the Western world. Fungal granulomatous prostatitis is typically seen only in immune compromised hosts. Nonspecific granulomatous prostatitis is relatively common and represents a reaction to secretions from ruptured prostatic ducts and acini. Postsurgical prostatic granulomas also may be seen.

Clinically, acute bacterial prostatitis is associated with fever, chills, and dysuria; it may be complicated by sepsis. On rectal examination, the prostate is exquisitely tender and boggy. Chronic bacterial prostatitis usually is associated with recurrent urinary tract infections bracketed by asymptomatic periods. Presenting manifestations may include with low back pain, dysuria, and perineal and suprapubic discomfort. Both acute and chronic bacterial prostatitis are treated with antibiotics. The diagnosis of chronic nonbacterial prostatitis (chronic pelvic pain syndrome) is difficult. It requires completion of the NIH Chronic Prostatitis Symptom Index survey by the patient, digital rectal examination, urinalysis, and sequential collection of urine and prostatic fluid specimens, before, during, and after prostatic massage. This technique of collecting samples prevents contamination from the bladder and urethra and is used to document prostatic inflammation (by presence of leukocytes) in the absence of infection. There are no proven therapies for chronic pelvic pain syndrome

2.3.2 *Benign Prostatic Hyperplasia (Nodular Hyperplasia)*

Benign prostatic hyperplasia (BPH) is an extremely common abnormality. It is present in a significant number of men by the age of 40, and its frequency rises progressively with age, reaching 90% by the eighth decade of life. BPH is characterized by proliferation of both stromal and epithelial elements, with resultant enlargement of the gland and, in some cases, urinary obstruction. Although the cause of BPH remains incompletely understood, it is clear that excessive androgen-dependent growth of stromal and glandular elements has a central role. BPH does not occur in males castrated before the onset of puberty or in men with genetic diseases that block androgen activity. Dihydrotestosterone (DHT), the ultimate mediator of prostatic growth, is synthesized in the prostate from circulating testosterone by the action of the enzyme 5α reductase, type 2. DHT binds to nuclear androgen receptors, which regulate the expression of genes that support the growth and survival of prostatic epithelium and stromal cells. Although testosterone can also bind to androgen receptors and stimulate growth, DHT is 10 times more potent. Clinical symptoms of lower urinary tract obstruction caused by prostatic enlargement may also be exacerbated by contraction of prostatic smooth muscle mediated by α1-adrenergic receptors. Clinical manifestations of prostatic hyperplasia occur in only about 10% of men with pathologic evidence of BPH. Because BPH preferentially involves the inner portions of the prostate, the most common manifestations are related to lower urinary tract obstruction, often in the form of difficulty in starting the stream of urine (hesitancy) and intermittent interruption of the urinary stream while voiding. These symptoms frequently are accompanied by urinary urgency, frequency, and nocturia, all indicative of bladder irritation. Similar symptoms also may arise from urethral stricture or as a consequence of impaired bladder detrusor muscle contractility in both men and women. The presence of residual urine in the bladder due to chronic obstruction increases the risk of urinary tract infections. In some affected men, BPH leads to complete urinary obstruction, with resultant painful distention of the bladder and, in the absence of appropriate treatment, hydronephrosis, Initial treatment is pharmacologic, using targeted therapeutic agents that inhibit DHT formation (Finestride) or that relax smooth muscle by blocking alpha adrenergic blockers (Flomax). Various surgical techniques are reserved for severely symptomatic cases recalcitrant to medical therapy.

2.3.3 Prostate cancer

2.3.3.1 Epidemiology:

Almost 899 000 Prostate Cancer cases and 258 000 Prostate Cancer deaths are estimated to have occurred in 2008 worldwide, with 72% of the cases and 53% of the deaths in developed countries (all regions of Europe plus North America, Australia/New Zealand, and Japan), representing <20% of the world population. Prostate Cancer incidence rates varied 24-fold worldwide in 2008 with the highest estimated rates in Australia/New Zealand, western Europe, North America, and the Caribbean and the lowest in south central Asia, northern Africa, and eastern Asia .In contrast, estimated PCa mortality rates varied 10-fold with the highest rates in the Caribbean, but also in a number of countries in southern and western Africa, and in South America; the lowest rates were observed in most parts of Asia, northern Africa, as well as North America . Although PCa is the most commonly diagnosed cancer among men in 2008 in many regions of the world (including all of Australia/New Zealand, North America, and South America, as well as most of western and northern Europe and parts of sub-Saharan Africa) it is estimated as the most common cause of cancer deaths in only a handful of countries, located primarily in the Caribbean, South America, and sub-Saharan Africa (Cente et al, 2012).During 2014 in the US an estimated 233,000 new cases of prostate cancer. And consider the most frequently diagnosed cancer in men aside from skin cancer. For reasons that remain unclear, incidence rates are about 60% higher in African Americans than in non-Hispanic whites. Incidence rates for prostate cancer changed substantially between the mid-1980s and mid-1990s and have since fluctuated widely from year to year, in large part reflecting changes in the use of the prostate-specific antigen (PSA) blood test for screening. From 2006 to 2010, incidence rates decreased by 2.0% per year. **Deaths:** With an estimated 29,480 deaths in 2014, prostate cancer is the second-leading cause of cancer death in men. Prostate cancer death rates have been decreasing since the early 1990s in men of all races/ethnicities, though they remain more than twice as high in African Americans as in any other group. Overall, prostate cancer death rates decreased by 3.1% per year from 2006 to 2010(ACS, 2014) It appears that one in six American men will develop a clinically recognized invasive prostate cancer during his lifetime. Ninety-one percent of cases were expected to be diagnosed of local or regional stage disease for which the 5-year relative survival rate approaches 100%. The age-adjusted annual incidence rate increased 6.4% per year between 1983 and 1989(Lu-Yao& Greenberg, 1994).

In Southern African men, prostate cancer has an incidence of 40.5 per 100 000 of the population per year, and a mortality rate of 22.5 per 100 000 per year (Parkin et al. 2005). In South Africa, prostate screening is recommended across all men from age of 45 years on wards in the absence of identifiable risk factor (SAPCF, 2013).

In Sudan, Prostate cancer is the most common cancer in Sudanese men. The first National Population-based Cancer Registry (NCR) was established in Sudan In 2009. During 2009–2010, 6771 new cancer cases were registered in Khartoum state. Of those, 3646 (53.8%) cases were in women and 3125 (46.2%) were in men. The most commonly diagnosed cancer among women was breast followed by leukemia, cervix, and ovary, and among men it was prostate cancer followed by leukemia, lymphoma, oral, colorectal, and liver (Saeed et al, 2014).

2.3.3.2 PATHOGENESIS

Clinical and experimental observations suggest that androgens, heredity, environmental factors, and acquired somatic mutations have roles in the pathogenesis of prostate cancer.

2.3.3.2.1 **Androgens** are of central importance. Cancer of the prostate does not develop in males castrated before puberty, indicating that androgens somehow provide the "soil," the cellular context, within which prostate cancer develops. This dependence on androgens extends to established cancers, which often regress for a time in response to surgical or chemical castration. Notably, tumors resistant to anti-androgen therapy often acquire mutations that permit androgen receptors to activate the expression of their target genes even in the absence of the hormones. Thus, tumors that recur in the face of anti-androgen therapies still depend on gene products regulated by androgen receptors for their growth and survival. However, while prostate cancer, like normal prostate, is dependent on androgens for its survival, there is no evidence that androgens initiate carcinogenesis.

2.3.3.2.2 **Heredity** also contributes, as there is an increased risk among first-degree relatives of patients with prostate cancer. Incidence of prostatic cancer is uncommon in Asians and highest among blacks and is also high in Scandinavian countries. Genome-wide association studies have identified a number of genetic variants that are associated with increased risk, including a variant near the *MYC* oncogene on chromosome 8q24 that appears to account for some of the increased incidence of prostate cancer in males of African descent. Similarly, in white American men, the development of prostate cancer has been linked to a susceptibility locus on chromosome 1q24-q25.

2.3.3.2.3 **Environment** also plays a role, as evidenced by the fact that in Japanese immigrants to the United States the incidence of the disease rises (although not to the level seen in native-born Americans). Also, as the diet in Asia becomes more Westernized, the incidence of clinical prostate cancer in this region of the world appears to be increasing. However, the relationship between specific dietary components and prostate cancer risk is unclear.

2.3.3.2.4 **Acquired somatic mutations,** as in other cancers, are the actual drivers of cellular transformation. One important class of somatic mutations is gene rearrangements that create fusion genes consisting of the androgen-regulated promoter of the *TMPRSS2* gene and the coding sequence of ETS family transcription factors (the most common being ERG). ***TMPRSS2-ETS* fusion genes** occur in approximately 40% to 50% of prostate cancers; it is possible that unregulated increased expression of ETS transcription factors interfere with prostatic epithelial cell differentiation. Other mutations commonly lead to activation of the oncogenic PI3K/AKT signaling pathway; of these, the most common are mutations that inactivate the tumor suppressor gene *PTEN*, which acts as a brake on PI3K activity (Kumar, 2003).

2.3.3.3 Pathophysiology

In prostate cancer, the cells of these prostate glands mutate into cancer cells. The prostate glands require male hormones, known as androgens, to work properly. Androgens include testosterone, which is made in the testes, dehydroepiandrosterone, made in the adrenal glands; and dihydrotestosterone, which is converted from testosterone within the prostate itself. Androgens are also responsible for secondary sex characteristics such as facial hair and increased muscle mass.Prostate cancer is classified as an adenocarcinoma, or glandular cancer, that begins when normal semen-screening prostate gland cells mutate into cancer cells. The region of prostate gland where the adenocarcinoma is most common is the peripheral zone. Initially, small clumps of cancer cells remain confined to otherwise normal prostate glands, a condition known as carcinoma in situ or prostate intraepithelial neoplasia(PIN).Although there is no proof that PIN is a precursor, it is closely associated with cancer. Overtime, these cancer cells begin to multiply and spread to the surrounding prostate tissue (the stroma) forming a tumor. Eventually, the tumor may grow large enough to invade nearby organs such as the seminal vesicles, or the rectum, or the tumor cells may develop the ability to travel in the blood stream and lymphatic system. The invasion of other organs is called metastasis. Prostate cancer most commonly metastasizes to the bones, lymph nodes, and may invade rectum, bladder and lower ureters after local progression.

The route of metastasis to bone is thought to be venous as the prostatic venous plexus draining the prostate connects with the vertebral veins (Kumar, 2003).

2.3.3.4 Risk factors

2.3.3.4.1 ***Age***

Over 80% of prostate tumors in the US are diagnosed among men over age 65 (Parkin et al,1999) and the incidence of prostate cancer increases exponentially with advancing age an increase that is faster than that for any other malignancy . Estimates from the Surveillance, Epidemiology, and End Results (SEER) program from 1996–2000 indicate that for US men under 65 years of age and 65 years and over, age-adjusted prostate cancer incidence rates were 56.8 and 974.7 per 100,000 person-years, respectively (Ries et al,2003).

2.3.3.4.2 ***Racial/Ethnic Variation***

Another consistently observed but poorly understood risk factor is ethnicity. African-Americans have the highest incidence rate in the world, roughly 60 times that of the ethnic group with the world's lowest rates, in Shanghai, China (Hsing et al,2000).

2.3.3.4.3 Hormones and Growth Factors

Androgens play a key role in the development and maintenance of the prostate gland; however, the precise role of androgens in the etiology of prostate cancer is unclear. Prostate cancer is notably absent in castrated men, and laboratory studies show that administration of testosterone induces prostate cancer in rats and that androgens promote cell proliferation and inhibit prostate cell death (Huggins &Hodges,1941; Niu et al,2001; Noble,1977).

Vitamin D is a steroid hormone obtained primarily from dermal synthesis in response to sunlight exposure. Vitamin D and its analogs have potent anti-proliferative, pro-differentiative, and pro-apoptotic effects on prostate cancer cells. In addition, vitamin D inhibits prostate tumor growth *in vivo*. In general, laboratory data are consistent and support the hypothesis that vitamin D may protect against prostate cancer. However, results from epidemiologic studies investigating serum vitamin D levels have been inconsistent (Zhao&Feldman, 2001)

2.3.3.4.4 Diet

Ecologic studies have shown a strong correlation between the incidence of prostate cancer and dietary fat intake. A western diet has been linked to a higher risk of prostate cancer, and it has been suggested that the western diet, high in fat, increases production and availability of both

androgen and estrogen, while Asian (low-fat, high-fiber) and vegetarian diets lead to lower circulating levels of these hormones(Hill et al,1979).

2.3.3.4.5 Occupation

Occupation is highly correlated with socioeconomic status and lifestyle factors. There is a large body of literature on prostate cancer and occupation, and one consistent result from these studies is that farmers and other agricultural workers have a 7–12% increased risk (Sharma-Wagne et al, 2000; van der Gulden et al, 1995).

2.3.3.4.6 Vasectomy

Several, but not all, studies investigating the association between vasectomy and prostate cancer risk suggest a modest positive association. men undergoing vasectomies are more likely to have prostate cancer detected than men who do not. Vasectomy is linked to elevations in anti-spermatozoa antibodies, decreased seminal hormone concentrations and decreased prostatic secretion (Bernal-Delgado et al, 1998).

2.3.3.4.7 Sexually Transmitted Diseases

Chronic inflammation induced by bacterial or viral agents has been implicated as a potential underlying mechanism for the link between STDs and prostate cancer. One recent large, population-based study showed two- to three-fold increased prostate cancer risks associated with STDs, particularly syphilis and recurrent gonorrhea infections (Hayes et al,2000).

2.3.3.4.8 ***Genetic Factors***

Prostate cancer etiology has a hereditary component. Numerous studies have consistently reported familial aggregation of prostate cancer, showing a two- to three-fold increased risk of prostate cancer among men who have a first-degree male relative (father, brother, son) with a history of prostate cancer (Stanford &Ostrander,2001).

2.3.3.4.9 Other Factors

Several other risk factors, such as smoking, use of alcohol, diabetes and liver cirrhosis, have been investigated, but their roles in prostate cancer are weak or unclear based on data in the current literature (Giovannucci E, 2006).

2.3.3.5 Prostate Cancer Diagnosis

2.3.3.5.1 PSA

PSA is an enzyme in the form of a 237 amino acid glycoprotein produced primarily by cells lining the acini and ducts of the prostate gland. Its main biological function is the dissolution of the gel-forming proteins in the freshly ejaculated semen. PSA is also present in normal male serum in small quantities, and is often elevated in prostate cancer. It is, however, not specific to prostate cancer and can be elevated by other conditions such as benign prostate hyperplasia, urinary tract infection, inflammation and trauma (such as catheterisation). Hence, PSA levels tend to increase as men age, regardless of whether or not they have underlying prostate cancer. Approximately 25% of patients with a level of 4–10 ng/ml will be identified as having prostate cancer on biopsy.

More recently, clinicians have adopted a more refined approach to PSA testing in an attempt to improve its sensitivity and specificity utilizing age-adjusted levels (Table 2.2), PSA isoforms, PSA density and PSA velocity.

Table 2.1: Age-specific reference ranges for serum PSA

Age range	PSA reference range
40–49 yr	0–2.5 ng/mL
50–59 yr	0–3.5 ng/mL
60–69 yr	0–4.5 ng/mL
70–79 yr	0–6.5 ng/mL

Source; (Richardson and Oesterling,1997)

2.3.3.5.2 Digital rectal examination (DRE)

A DRE can detect palpable prostate cancer even in the early disease stage as it generally occurs on the periphery of the gland. In localized disease where the cancer is confined to the prostate, the clinician may palpate a firm nodule within the prostate. Once the gland feels very abnormal with an irregular outline or distorted anatomy, it often suggests that the disease is locally advanced.

2.3.3.5.3 A prostate biopsy

To Confirmation of the diagnosis, if the clinician has any clinical or biochemical suspicion of prostate cancer, the diagnosis can be confirmed by taking a biopsy. This is most commonly

performed by following the trans-rectal ultrasound-guided approach (TRUS) using a tru-cut needle. The procedure is usually performed in the clinic under local anaesthetic with or without sedation (Dasgupta & Kirby,2011).

2.3.3.5.4 Imaging of Prostate Cancer

2.3.3.5.4 .1 plain imaging

The prostate is the commonest primary site for sclerotic bone metastases in men and the identification of such lesions, which may be an incidental finding in those with skeletal pain. Widespread sclerotic lesions in an elderly male patient should be regarded as likely metastatic prostate cancer until proven otherwise. The presence of destructive lesions within long bones is associated with a risk of pathological fracture. With the advent of more modern imaging modalities, plain imaging has only a limited role in the management of prostate cancer. (Dasgupta & Kirby,2011)

2.3.3.5.4.2 Trans-rectal ultrasound (TRUS)

The anatomical position of the prostate immediately anterior to the rectum lends itself well to trans-rectal ultrasound with a high-frequency (5–7.5 MHz) probe. Since its introduction in 1971, TRUS has become the commonest imaging modality of the prostate, typically requested after an abnormal DRE or elevated PSA measurement. Prostate cancer is typically hypoechoic (dark) and located in the peripheral zone (see Figure 2.1) (Dasgupta & Kirby,2011).

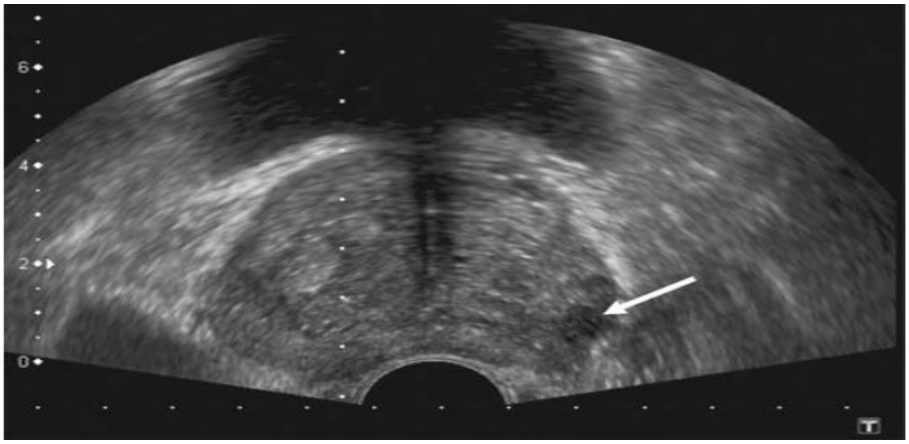


Figure 2.2 show Transverse section TRUS image of a prostate. Note the small rounded hypoechoic (dark) focus within the left periphery of the gland (white arrow). Targeted biopsy proved carcinoma of the prostate.

2.3.3.5.4.3 Computed tomography (CT)

The role of CT in assessing local prostate cancer extent is limited by its poor contrast resolution, with the gland being indistinguishable. From the adjacent bladder base and seminal vesicles. Its role is reserved for staging of advanced disease and typically for assessment of organ and lymph node metastases.As a guide, in asymptomatic patients with a PSA <20 ng/ml, CT is generally not required due to the low (<1%) probability of a positive study. (Dasgupta & Kirby,2011)

2.3.3.5.4.4 Magnetic resonance imaging (MRI)

Unlike CT, MRI is vastly superior for soft tissue resolution and is the best imaging modality for local disease assessment and staging. Endorectal MRI has better spatial resolution but is an uncomfortable examination and standard pelvic (external) coils are the preferred method in most centres. On T1-weighted studies, the gland is of uniformly low/mid -signal intensity and neither the normal prostate zonal anatomy nor tumours are seen. T2-weighted images are the sequence of choice for both appreciation of zonal anatomy and cancer detection. Prostate cancer appears as round or ill-defined foci of low signal intensity (dark), highlighted against the normally high signal (bright) peripheral zone (PZ), where the majority of cancers arise (see Figure 2.2) (Dasgupta & Kirby,2011).

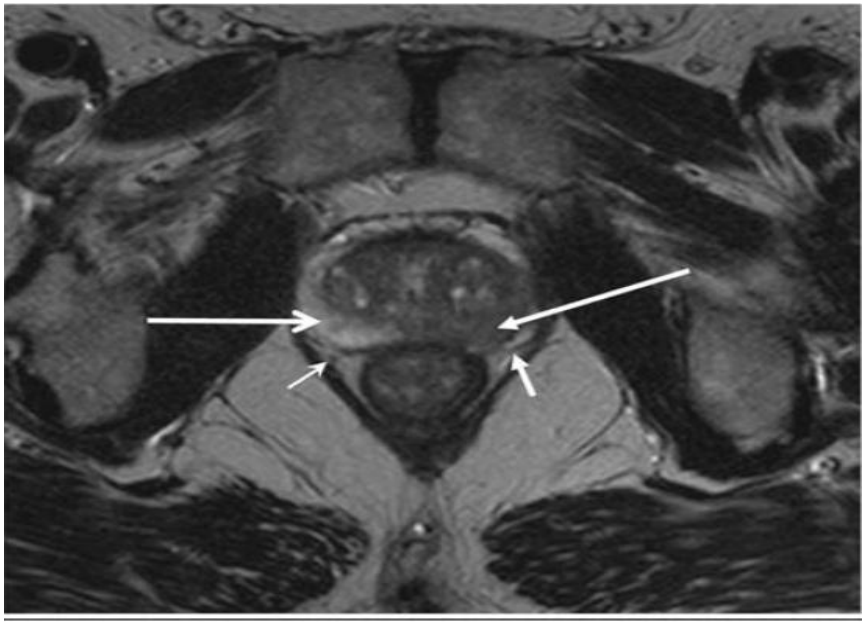


Figure 2.3 show Axial T2-weighted MRI image of prostate cancer. Note the focal area of abnormal low signal (dark) change within the left peripheral zone posterolaterally (long closed arrow). Compare with the normal high signal (white) peripheral zone of the right aspect of the gland (long open arrow).

2.3.3.5.4.5 Radionuclide bone scintigraphy (bone scan)

Bone deposits are the commonest manifestation of prostate cancer metastases and the risk rises with increasing PSA level and Gleason grade. They have a predilection for the axial skeleton, such as the pelvis, vertebrae and ribs. A radioisotope bone scan is the modality of choice for their detection. A study involves an intravenous injection of 99mTc (the radioisotope which emits gamma rays) linked to a phosphonate (which allows skeletal uptake). Prostate cancer metastases are osteoblastic and associated with increased tracer uptake, appearing 'hot' relative to the background skeleton (Figure 2.3). The technique has a very high sensitivity. In a patient with a significantly elevated PSA, multiple areas of increased uptake within the axial skeleton are virtually diagnostic for metastatic disease. Interpretation difficulty occurs with other causes of increased bone turnover, such as spinal degenerative disease or rib fractures. Correlation with plain films or MRI imaging will help resolve these difficult cases. (Dasgupta & Kirby,2011)

The potential for bone metastases rises with increasing PSA levels. Abuzallouf et al. (2004) performed a meta-analysis and reported that a PSA <10 ng/ml carries a 2.3% chance of a bone scan being positive. Levels of 10–20 and 20–50 have a risk of 5.3% and 16.2% respectively. If disease is confined to the prostate, the chance of bone metastases is around 6%, increasing to nearly 50% with locally advanced disease. A Gleason score of less than or equal to 7 is associated with a 5.6% chance of bone metastases, which increases to almost 30% with a score of 8 or above. As such, a bone scan should be considered if the PSA is above 20, locally advanced disease or a Gleason score is >8.

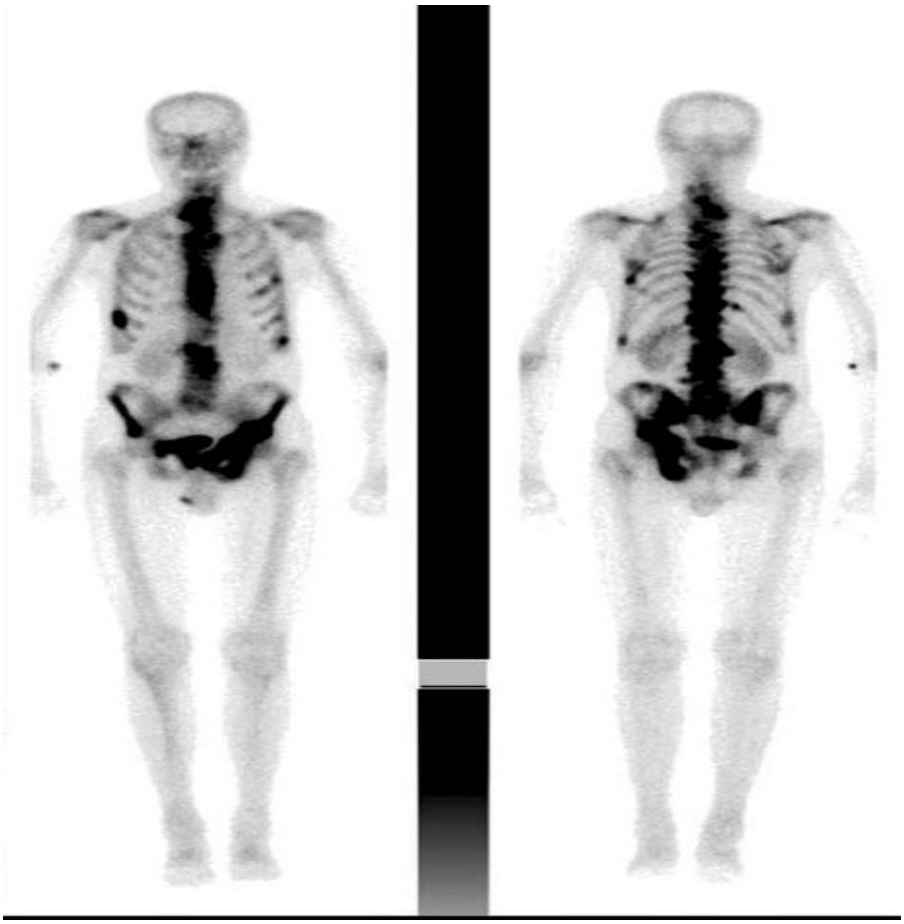


Figure 2.4 Multiple prostatic bone metastases on isotope bone scan. Note the multiple foci of abnormal uptake scattered throughout the ribs, vertebrae and pelvis. The PSA at the time of the study was greater than 1200.

2.3.3.6 Treatment

Treatment options vary depending on age, stage, and grade of cancer, as well as other medical conditions. The grade assigned to the tumor, typically called the Gleason score, indicates the likely aggressiveness of the cancer. Although scores as low as 2 are theoretically possible, in practice most cancers are assigned scores ranging from 6 (low grade, less aggressive) to 10 (high grade, very aggressive).

Early stage disease may be treated with surgery (open, laparoscopic, or robotic-assisted), external beam radiation, or radioactive seed implants (brachytherapy). Data show similar survival rates for patients with early stage disease treated with any of these methods, and there is no current evidence supporting a “best” treatment for prostate cancer. Hormonal therapy may be used along with surgery or radiation therapy in some cases. Treatment often impacts a man’s

quality of life due to side effects or complications, such as urinary and erectile difficulties, that may be short or long term. Accumulating evidence indicates that careful observation ("active surveillance"), rather than immediate treatment, can be an appropriate option for men with less aggressive tumors and for older men.

More advanced disease is treated with hormonal therapy, chemotherapy, radiation therapy, and/or other treatments. Hormone treatment may control advanced prostate cancer for long periods by shrinking the size or limiting the growth of the cancer, thus helping to relieve pain and other symptoms. An option for some men with advanced prostate cancer that is no longer responding to hormones is a cancer vaccine known as sipuleucel-T (Provenge). For this treatment, special immune cells are removed from a man's body, exposed to prostate proteins in a lab, and then re-infused back into the body, where they attack prostate cancer cells. Newer, more effective forms of hormone therapy, such as abiraterone (Zytiga) and enzalutamide (Xtandi), have been shown to be beneficial for the treatment of metastatic disease that is resistant to initial hormone therapy and/or chemotherapy. Radium-223 (Xofigo) was recently approved to treat hormone-resistant prostate cancer that has spread to the bones (ACS, 2014).

2.3.3.6.1 Androgen deprivation therapy and related to osteoporosis

Androgen deprivation as a form of treatment for prostate cancer was first discovered by Huggins and Hodges in 1941, when Charles Huggins found that diethylstilbestrol (DES) as a castrating agent in men with metastatic PC gave a complete blockade of testosterone production and favorably affected prostate cancer markers [Huggins &Hodges ,1941], resulting in the Nobel Prize for medicine in 1966. Initially, androgen deprivation was achieved via orchiectomy, then later by using estrogen. There was poor patient acceptance of orchiectomy, however, and problems with thromboembolic and cardiovascular events with the early use of estrogen. Fortunately, in the mid-1980s the approval of luteinizing hormone releasing hormone (LHRH) agonists by the FDA provided many prostate cancer patients with an alternative method to achieve androgen deprivation. This class of drugs has become very popular due to its ease of use via depot delivery systems. Indeed, a recent report by Cooper berg et al. [2003] documented the dramatic rise in the use of androgen deprivation therapy (ADT) from 1989 to 2001. Most dramatic was the increased use of external beam radiotherapy, from 9.8% to 74.6% of patients. Also contributing to the increased use of LHRH agonists are data suggesting a survival advantage for the early use of LHRH agonist therapy for men with metastatic prostate cancer

[messing et al,1999]. In addition, other data have shown an improvement in outcomes after radiation for higher stage tumors in patients who received concomitant hormone therapy [Bolla et al, 1997]. In light of the increasing use of these newer, longer acting forms of medical castration, it is important for the treating physician to be familiar with the potential complications and side effects of these agents (Table 2.3). Physicians can then counsel their patients about these side effects as well as institute measures to prevent many of the complications associated with the use of these agents.

Table2.2: Side effects of Androgen therapy

Hot flashes	50–80%
Osteoporosis	1.4–2.6%/year
Anemia	Common
Erectile dysfunction	50–100%
Muscle wasting	Common
Fatigue	Common
Depression	Common
Decline in vitality and physical activity	Common
Increase in fat apposition	Common
Decline in cognitive function	Common

For years, osteoporosis after menopause has been recognized as a serious health problem in women. At present, however, 33% of all hip fractures occur in men, and interestingly men are more likely to die from complications due to hip fracture than women [Morote et al,2003]. Stoch and colleagues reported that 50% of men with hip fractures had biochemical evidence of hypogonadism, accounting for a fivefold increase in hip fracture risk when compared with eugonadal men. This has led to an increased concern amongst physicians regarding osteoporosis seen in men on ADT who are being treated for prostate cancer.

Despite the fact that ADT has been used to treat prostate cancer since the 1940s, it was not until 1989 that Stepan et al first reported the association between androgen deprivation and osteoporosis. In this retrospective study, it was demonstrated that there was progressive loss of bone mineral content in the lumbar spine of men who had undergone orchiectomy for sexual delinquency as compared with eugonadal men. In a more recent study, Melton et al looked at 429 men treated with bilateral orchiectomy for prostate cancer from 1956 to 2000. Even with

pathologic and incidental fractures excluded from analysis, overall fracture risk was still increased by twofold.

The previously mentioned studies document the effect of orchiectomy on osteoporosis, but evidence also exists that LHRH agonists result in significant changes in both bone mineral density (BMD) and bone mineral content (Stoch et al,2001). Stoch et al evaluated 60 men with prostate cancer. Of this group, 19 received LHRH agonist therapy and 41 did not. A control group of 197 healthy men with no prostate cancer was included. The BMD as measured by dual X-ray absorptiometry (DXA) scan of multiple areas was statistically significantly lower in the patients receiving LHRH agonists compared with the m untreated men with prostate cancer. Furthermore, biochemical markers of bone turnover were significantly altered compared with untreated patients. This study confirms that LHRH agonists can lead to osteoporosis, and that the changes in bone are not due to prostate cancer alone.

The greatest concern regarding osteoporosis and LHRH agonists is the increased risk for bone fractures. Osteoporotic bone fractures have become a major health concern due to the increasing elderly population. The morbidity and mortality associated with these types of fractures, particularly hip and spine fractures, are significant with respect to quality of life and healthcare costs. A mortality rate of 30% has been associated with hip fractures in men over 75 years of age (Townsend et al,1997).

2.4 The Osteoporosis

The term osteoporosis was first introduced in France and Germany during the last century. It means “porous bone” and initially implied a histological diagnosis, but the term was later refined to mean bone that had normal mineralization but was reduced in quantity (Nancy & Sambrook, 2006). Osteoporosis is a disease characterized by weak bone. It is a major public health problem, affecting hundreds of millions of people worldwide, predominantly postmenopausal women. The main clinical consequence of the disease is bone fractures. It is estimated that one in three women and one in five men over the age of fifty worldwide will sustain an osteoporotic fracture. Hip and spine fractures are the two most serious fracture types, associated with substantial pain and suffering, disability, and even death (Arch Osteoporos, 2013).People with osteoporosis have fragile bones because their bone mass is low and the structure of the bone is poor. The combination of low bone mass and changes in bone structure leads to bone fragility, and many people with osteoporosis will suffer fractures (Nancy, 1999).

2.4.1 The WHO and NIH definitions

Osteoporosis is currently defined by the World Health Organization (WHO) as a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue (Figure 2.4), with a consequent increase in bone fragility and susceptibility to fracture, which usually involves the wrist, spine, hip, ribs, pelvis or humerus. (WHO,1994)

The National Institutes of Health (NIH) define osteoporosis as a disease characterised by compromised bone strength predisposing to an increased risk of fracture. (NIH,2004)

In 1994, the WHO proposed four diagnostic categories largely based on a subject's bone mineral density (BMD), expressed in relation to the young adult reference mean (the T-score), viz (i) normal, (ii) low bone mass or osteopenia, (iii) osteoporosis and (iv) severe osteoporosis (Table 2.5) (WHO,1994).

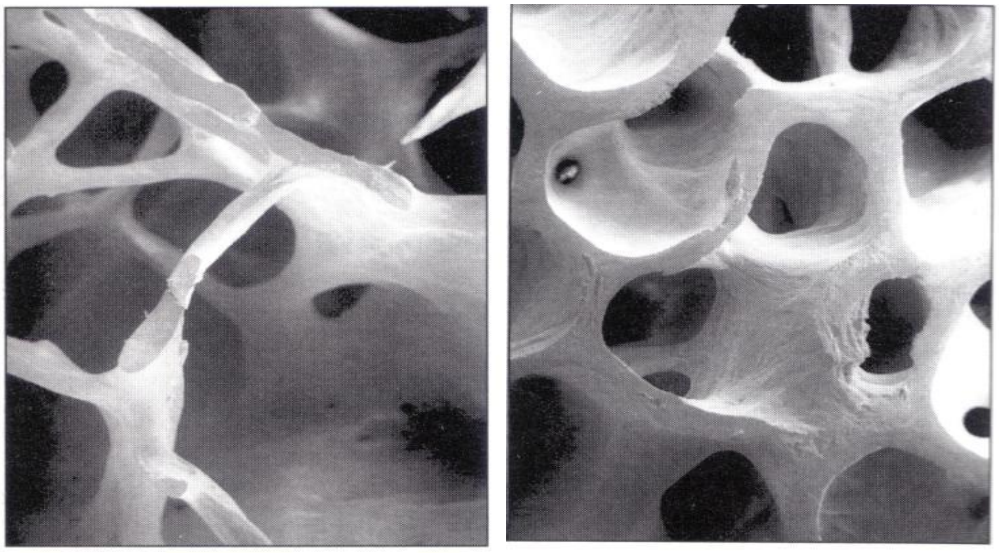


FIGURE 2.5 SEM of osteoporotic and of normal trabecular bone* (Compston et al., 1995). *SEM = scanning electron micrograph

Table 2.3: World Health Organization classification of osteoporosis

Definition	Criteria
Normal	BMD value (measured with DXA at either the spine, total hip or femur neck) within 1 SD of the young adult reference mean (T-scorec at or above -1.0)
Low bone mass	T-score between -1.0 and - 2.5
Osteoporosis	T-score is 2.5 SD or more
Severe osteoporosis	T-score is more than 2.5 SD

These criteria as reference to measure BMD, *SD= standard deviation *BMD=body mass density.

2.4.2 Epidemiology

Osteoporosis affects more than 75 million people worldwide, and apart from the fractures that occur, it can cause people to become bedridden with secondary complications (Zizic, 2004). In the USA, at least 1.3 million fractures per year are attributable to this condition of which 700000 are vertebral fractures and 300000 are hip fractures figure 2.5 (Melton, 1990). It is estimated that in the USA, 8 million women aged 50 or older have osteoporosis and 22 million have low bone mass, by 2010, these numbers are predicted to increase to 9 million and 26 million, respectively (NOF, 2002). Osteoporosis is the most important cause of fracture in the elderly in the Western world and the three most common sites of osteoporotic fracture are the distal radius, the vertebral body and the upper femur (Melton, 1986).

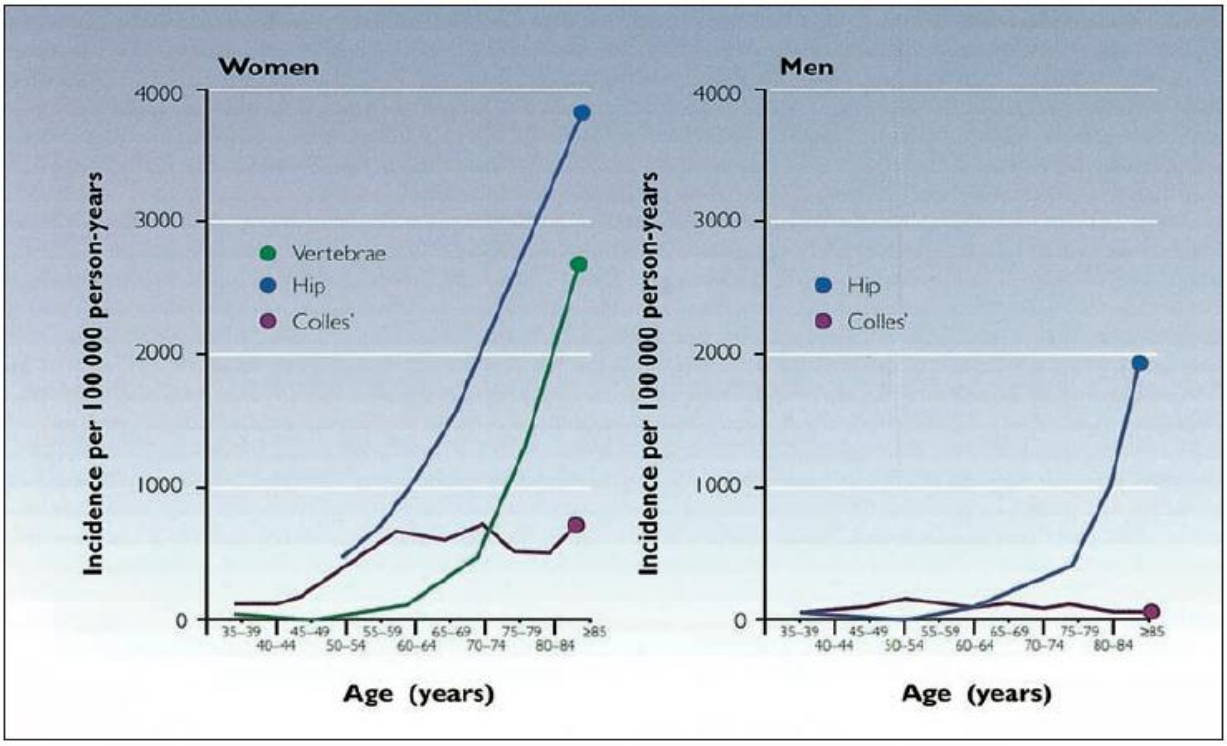


Figure 2.6 Incidence rates for the three most common osteoporotic fractures, plotted as a function of age at time of fracture. Rates are much lower in men and occur at a later age than in women.

In the EU in 2010, twenty two million women and 5.5 million men were estimated to have osteoporosis; and 3.5 million new fragility fractures were sustained, comprising 620,000 hip fractures, 520,000 vertebral fractures, 560,000 forearm fractures and 1,800,000 other fractures (i.e. fractures of the pelvis, rib, humerus, tibia, fibula, clavicle, scapula, sternum and other femoral fractures). The economic burden of incident and prior fragility fractures was estimated at € 37 billion. Incident fractures represented 66 % of this cost, long-term fracture care 29 % and pharmacological prevention 5 %. Previous and incident fractures also accounted for 1,180,000 quality adjusted life years lost during 2010. The costs are expected to increase by 25 % in 2025. The majority of individuals who have sustained an osteoporosis-related fracture or who are at high risk of fracture are untreated and the number of patients on treatment is declining. (Arch Osteoporos, 2013)

2.4.2.1 Epidemiology of Osteoporosis in Men

The incidence of all fractures is higher in men than women from adolescence through middle life (Melton et al., 1988) (Fig.2.6), and the personal and economic impact of these early life

fractures is enormous. The average number of hospitalizations for fractures in men between the ages of 18 and 44 years in the US, and the annual number of lost work days for men due to fractures, are large (Orthopaedic Surgeons, 1992). Despite the importance of early life fractures in men, little has been done to understand their causation. Many result from serious trauma, but to some extent relative bone fragility may contribute to fracture risk during this period. For instance, long-term follow-up of men who had sustained traumatic tibial or forearm fractures in early to midlife revealed that they were at much greater risk for later hip fracture (Karlsson, 1993). At about age 40 to 50 years there is a reversal of this trend, with fractures in general and in particular with those of the pelvis, humerus, forearm, and femur becoming much more common in women. However, the incidence of fractures due to minimal-to-moderate trauma (particularly hip and spine) also increases rapidly with aging in men (Fig.2.7), and presumably reflects an increasing prevalence of skeletal fragility as well as an increasing risk of falls (*Sambrook and Cooper, 2010).*

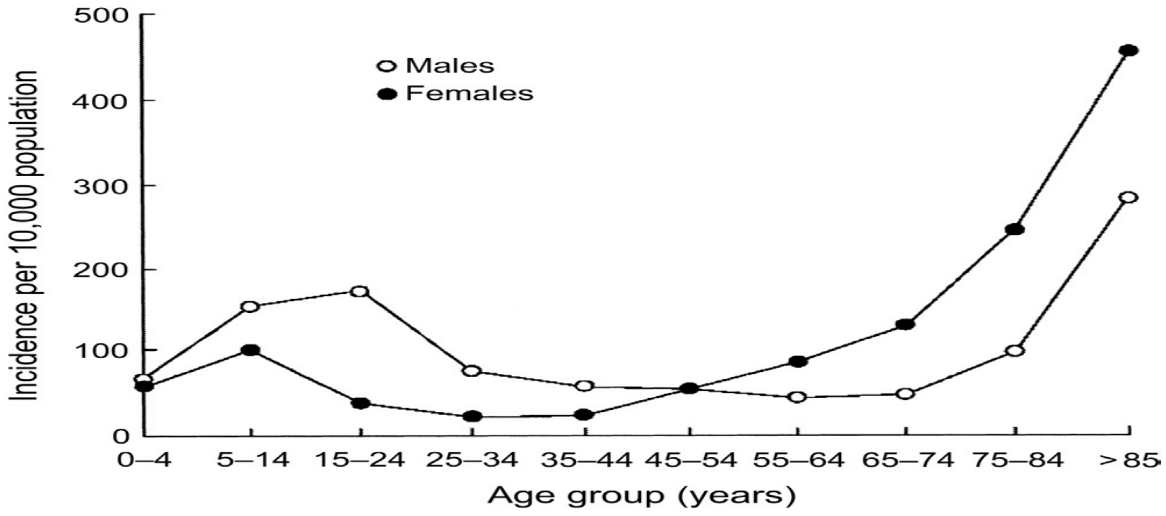


FIGURE 2.7 Average annual fracture incidence rate in males and females per 10,000 population, by age group. *Source: Donaldson et al. (1990)*

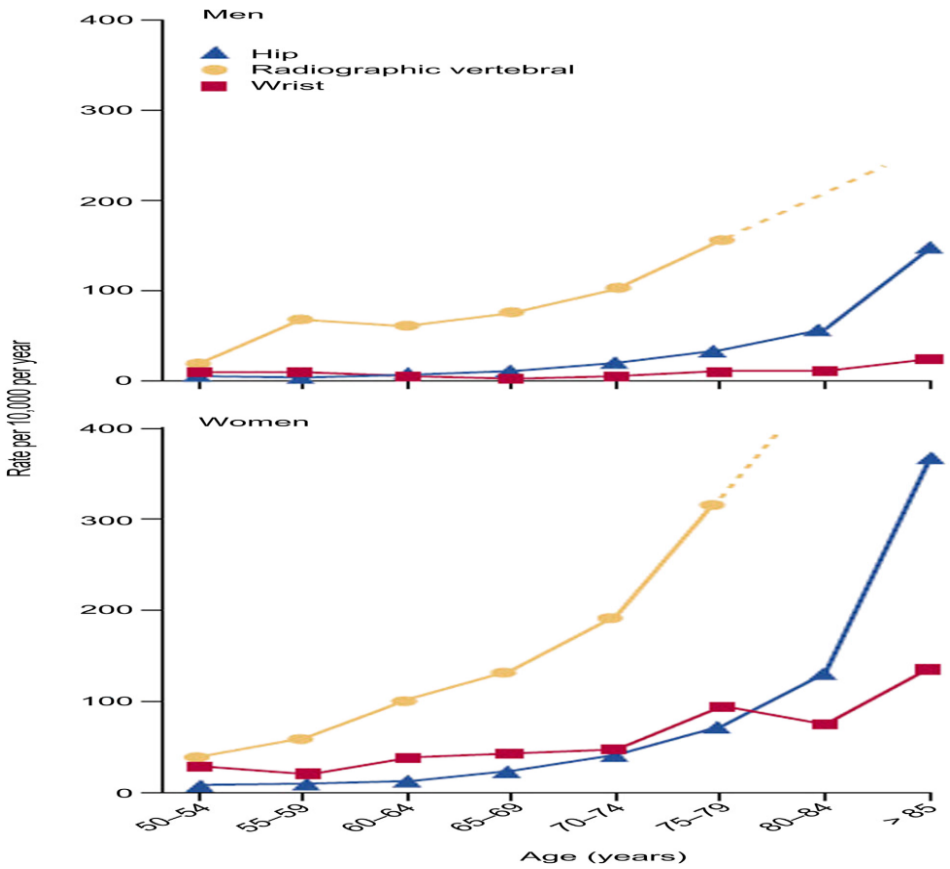


FIGURE 2.8 Age-specific and sex-specific incidence of radiographic vertebral, hip, and distal forearm fractures in Europe. *Source: Sambrook and Cooper (2010)*

2.5 Bone Biology

Bone is a specialized form of mineralized connective tissue that is built by various types of metabolically active cells during embryonic and postnatal development, in the adult, the same cells contribute to the maintenance of structural and functional integrity, and accomplish the healing process following injury, bone not only shows a marked rigidity and mechanical stability while still maintaining some degree of elasticity, but also constitutes the most important storage site for calcium and inorganic phosphate (Baron, 1993). Osteoporosis is a systemic disease where rigidity and mechanical stability of bone declines, until bone loses the ability to withstand functional loading or weak traumata. A transient but disproportional bone loss of 20%–30% trabecular and 5%–10% cortical bone is most apparent in women during the first postmenopausal decade. The following slow phase accounts for 20%–30% of trabecular and cortical bone loss in both sexes. Epidemiologic data show that the lifetime risk to acquire hip fractures is 17% for white women and 6% for white men (Cummings and Melton 2002; Melton 1995).

At the structural level, two different forms of bone can be distinguished: cortical or compact bone, which, for example, forms the diaphysis of long bones, thus providing protection for the medullary cavity. Trabecular, cancellous, or spongy bone, which in long bones is found at their ends, at the epiphyses, makes up the greater part of vertebral bodies. The total skeleton comprises around 20% trabecular bone. Trabecular bone has a porosity of 50%–90%, cortical bone of approximately 10% (Sikavitsas et al., 2001).

2.5.1 The Bone Cells

2.5.1.1 Osteocytes are cells that are embedded in the mineralized matrix of both woven and lamellar bone. They emerge at the end stage of osteoblast differentiation and become trapped within the mineralized matrix. Osteocytes probably act as mechanosensors that signal the need for bone modelling to adapt the bone to functional loading according to Wolff's law (Frost 2004) and remodelling to repair microstructural changes within the bone matrix. Osteocytes can detect changes in the levels of hormones, such as oestrogen and glucocorticoids that influence their survival rate. Since osteocytes forma network spanning the skeletal system, they may well, through their residual metabolic activity, play a role in bone turnover (Knothe Tate et al. 2004; Manolagas 2000; Marks 2002; Nijweide 2002).

2.5.1.2 Osteoblasts are mesenchymal cells located on the surface of the mineralized matrix and are responsible for formation of new bone; that is, they synthesize and regulate the deposition and mineralization of the extracellular matrix. Osteoblasts form a dense monolayer of approximately 100–400 cells clustering at each bone-forming site (Anderson et al. 2005).

2.5.1.3 Osteoclasts are large polykaryons containing between 3 and 30 nuclei, and are considered to be the exclusive bone-resorbing cell. Osteoclasts are located at bone surfaces within Howship's lacunae, also called resorption lacunae. Under normal conditions, osteoclasts are rarely found in bone, i.e. only 2–3/μm3, but they appear in increased numbers at sites of high bone turnover, such as in the metaphysis of growing bone or in trabecular bone in postmenopausal osteoporosis (Marks 2002; Roodman 1996; Salo et al. 1997; Teitelbaum 2000).

2.5.2 Bone Remodeling

Bone remodelling is the result of the coordinated action of bone-resorbing osteoclasts and bone-forming osteoblasts. Osteoblasts and osteoclasts interact within a spatial structure known as the basic multicellular unit (BMU) in cortical bone and in analogy, bone structural units in trabecular bone. BMUs are functional in the developing and growing skeleton during the process of

modelling and during remodelling of mature bone. The birth, life, and death of osteoblasts an osteoclasts within the BMU is fundamental to understand the pathophysiology of skeletal diseases such as osteoporosis (Manolagas,2000). Osteoblasts, osteoclasts, and their respective progenitors are exposed to a variety of systemic hormones and local factors that regulate the tight balance of bone remodeling. Systemic hormones are brought into the BMU by means of blood capillaries and cells release local factors in an autocrine/ paracrine mode of action. Local and systemic factors can influence the activation frequency, which defines the number of BMUs at a given time point, in addition to the remodelling balance of the cells within each BMU. Therapeutic agents that can cause bone loss such as glucocorticoids and osteoporosis regimes act through modulating the balance of bone remodelling. Bisphosphonate treatment, for example, lowers high bone remodeling in postmenopausal osteoporosis by decreasing the activation frequency of BMUs and the average life span and activity of osteoclasts. Under the bisphosphonate alendronate, activation frequency was reduced by 87%, and osteoblasts have more time to rebuild the excavated resorption site, leading to a positive remodelling balance (Chavassieux et al. 1997). Lower bone remodelling is refl ected by the decrease in resorption parameters by about 40%–60% (Delmas et al. 2000). Under bisphosphonate therapy, osteoblasts produce a higher mineralized structure and lower the porosity of cortical bone that together increase the strength of osteoporotic bone (Roschger et al. 2001). A decreased number of BMUs can add to the mechanical properties of osteoporotic bone.

2.6 Determinants of skeletal strength and fracture risk

A large number of risk factors for osteoporotic fractures have been identified. The main ones include bone mineral density (BMD), age, sex, and history of fracture.Other risk factors show relatively poor specificity and sensitivity in predicting either bone mineral density or fracture risk (Cummings et al,.1995).

Bone strength is largely determined by a combination of its mass and its qualitative Properties. **Bone mass** (bone mineral density, BMD), which is a function of (i) peak bone mass attained during early adulthood, (ii) age-related bone loss, and (iii) total duration of bone loss Poor et al.,1995).

2.6.1 Peak bone mass *is* mainly determined by heredity, body size and gender, although nutrition (particularly total energy and calcium intake), physical activity, normal pubertal development and good general health may exert a significant influence. More than 30 candidate

genes (including those encoding the vitamin D receptor, parathyroid hormone (PTH) receptor, estrogen receptor, bone collagen, cytokines and bone matrix proteins like bone morphogenetic protein, BMP), have been linked to bone mass. Genetic factors also significantly influence bone size, bone quality and bone turnover (Baldock & Eisman, 2004; Ralston, 2005).

Recently, polymorphisms in the genes encoding the estrogen receptor (ESR-1), the lipoprotein receptor-related protein (LRP5), the receptor activator of nuclear factor-κβ ligand (RANKL) and osteoprotegerin (OPG) were shown to be significantly associated with bone mineral density (BMD) and fracture risk in Caucasian women

(Hirschhorn, 2004; Styrkarsdottir, 2008; Richards, 2008).

2.6.2 Age-related bone loss

2.6.2 .1 *Age-related increases in bone resorption*

Appear to result mainly from:

1. Menopausal estrogen deficiency that results in increased osteoclastic bone resorption secondary to the elaboration of osteoclastogenic proinflammatory cytokines, such as interleukin-1 (IL-1) and tumour necrosis factor-alpha (TNF-α), which are negatively regulated by estrogen (Kimble et al,1995; Lorenzo et al,1998).
2. Estrogen-independent, age-related mechanisms, including secondary hyperparathyroidism caused by vitamin D deficiency, poor calcium intake and/or impaired intestinal absorption of calcium (Lips P, 2004).
3. Additional factors are clearly operative (all women age and become estrogen deficient, yet not all develop osteoporosis), which may involve alterations in the RANK/RANKL/ OPG system that regulates osteoclastogenesis or various cytokines, leukotrienes, prostaglandins and other systemic or locally produced bone-resorbing factors (Raisz LG,2005).

2.6.2.2 Age-related impaired bone formation

The remodeling imbalance characterized by impaired bone formation that accompanies ageing may be due, in part, to osteoblast senescence and an age-related decrease in their capacity to replicate and differentiate. It also seems likely that defects in the production of local and systemic growth factors (e.g. BMP; insulin-like growth factor, IGF; transforming growth factor-beta, TGF-β), alterations in signalling pathways and transcription factors which regulate osteoblast differentiation and function (e.g. Wnt, LPR5, sclerostin), a decrease in physical

activity, and reduced mechanical loading may contribute to the impaired bone formation (NOFSA, 2010).

2.6.2.3 Age-related (involutional) vs. pathological bone loss

If lifestyle factors (poor nutrition, lack of physical exercise, smoking, alcohol abuse), systemic disease, and/or the use of bone-toxic drugs are superimposed on this age-related (involutional) bone loss, significant osteoporosis may ensue (NOFSA, 2010).

2.6.3 qualitative structural and functional properties

2.6.3.1 Macroarchitecture factors

Numerous studies have demonstrated that smaller bones are more prone to fracture than larger bones. Skeletal geometry, including the length and angle of the hip axis, also has a significant bearing on bone strength. These factors may, in part, explain gender and population differences in fracture rates.

2.6.3.2 Microarchitecture factors

Ageing is accompanied by increased *cortical* thinning and porosity. A decrease in *trabecular* size and number also occurs subsequent to impaired bone formation. Increased bone resorption causes a loss of trabecular connectivity, which results in an exponential decrease in bone strength with little, if any, change in bone mass.

2.6.3.3 Bone turnover

Bone turnover increases markedly around the menopause, following immobilization, when the calcium balance is negative, and in certain diseases (e.g. hyperthyroidism, primary hyperparathyroidism). If bone turnover is increased, a proportionally larger amount of bone will be occupied by remodeling units and less by mineralized bone. Increased bone turnover will also increase the amount of unmineralised bone. Accelerated resorption may also perforate trabecular rods and plates. Increased bone turnover, therefore, not only decreases bone mass, but also causes qualitative structural defects in bone (NOFSA, 2010).

2.6.5 Falls and fracture

Fragile bones are subjected to trauma, particularly those not protected by an adipose cushion, fractures may occur. An increased risk of trauma may result because of an increased propensity to fall and/or the loss of normal protective responses to a fall. Moreover, the frequency, severity and type of fall (e.g. sideways, forwards, backwards) appear to be important determinants of fracture risk (NOFSA, 2010)

2.7 Diagnosis of osteoporosis

The World Health Organization (WHO) defines osteoporosis as a BMD 2.5 standard deviations or more below the mean value for young adults (a T score < −2.5), and severe osteoporosis as a BMD below this cut-off and one or more fragility fractures and defines osteopenia as a BMD T score between −1.0 and −2.5 (WHO,1994).

2.7.1 RADIOGRAPHY

Radiography reveals recognizable bone loss only when 25–30% of bone density has been lost, at which time osteoporosis is generally considered to have developed. In the past, radiogrammetry has been used to assess bone mineral density of the peripheral skeleton, usually at the metacarpals. The metacarpal cortical thickness was used for many years to diagnose and predict the risk of osteoporosis. However, the sensitivity of radiography is poor (Stulberg, 1989; Hurxthal, 1969) and the results of metacarpal measurement do not reflect bone mineral density at more important sites such as the hip and spine (Stevenson et al,1987 ; Doyle FH,1972). Although there is a correlation between bone mineral density in the peripheral and central skeleton (Stevenson et al, 1987), the association is not strong enough to predict central bone mineral density from peripheral measurements in a given subject (Stevenson et al, 1987; Grubb, 1984).At present, the main role of radiography is in the diagnosis of fractures secondary to osteoporosis (Figures 2.8, 2.9).

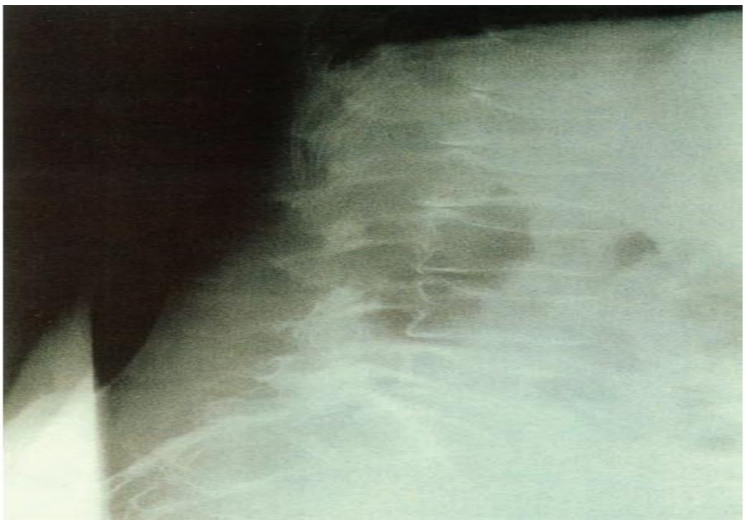


Figure 2.9 Lateral radiograph of the lumbar spine of a patient with osteoporosis shows wedging and compression of several vertebrae. Courtesy of Ms Linda Banks (Stevenson& Marsh,2007)

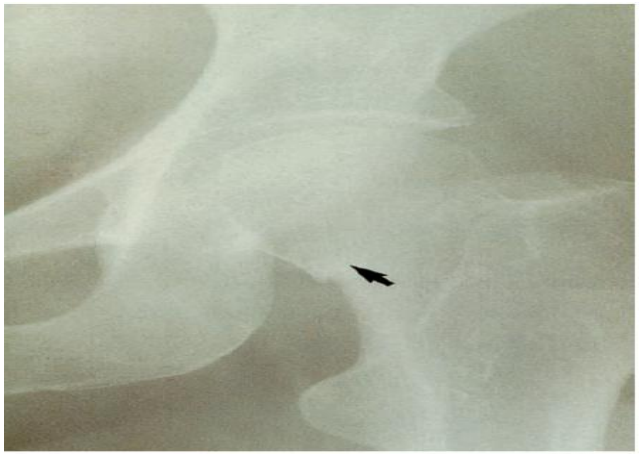


Figure 2.10 Radiograph of the proximal femur showing an intracapsular hip fracture. Courtesy of Mr Paul Allen (Stevenson& Marsh,2007)

2.7.2 QUALITATIVE MORPHOMETRY

Qualitative morphometric techniques for the assessment of bone density have been in limited use for over 50 years. Grading systems for the spine relied on the appearance of the trabecular patterns within the vertebral body and the appearance and thickness of the cortical shell (Aitken M, 1994). Vertebrae were graded from IV down to I as the vertical trabecular pattern became more pronounced with the loss of the horizontal trabeculae and the cortical shell became progressively thinned. The spine shown in Fig 2.10 demonstrates a pronounced vertical trabecular pattern. The cortical shell appears as though it was outlined in white around the more radiotranslucent vertebral body(Bonnick,1998).

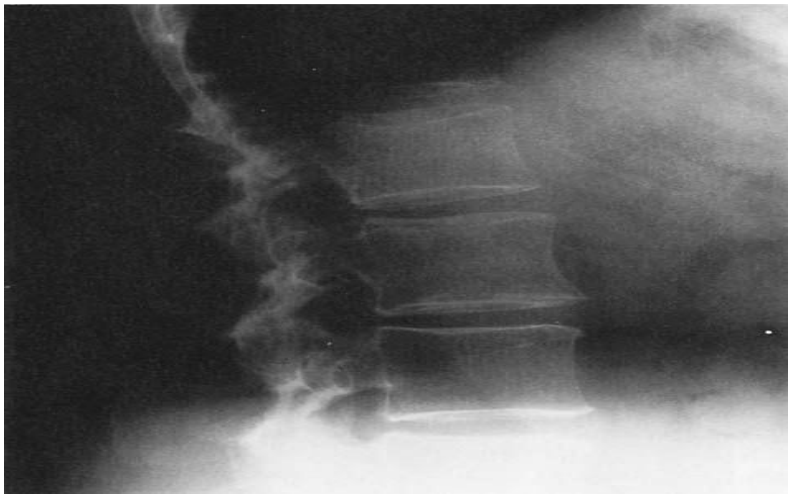


Fig. 2.11. Quantitative spine morphometry. The vertebrae on this lateral lumbar spine X-ray demonstrate marked accentuation of the vertical trabecular pattern and thinning of the cortical shell. This is a Grade 2 spine.(Bonnick,1998)

2.7.3 The Singh Index

The Singh Index is a qualitative morphometric technique that was similarly based on trabecular patterns, but based on those seen in the proximal femur (Singh et al, 1970). Singh and others had noted that there was a predictable order in the disappearance of the five groups of trabeculae from the proximal femur in osteoporosis. Based on the order of disappearance, radiographs of the proximal femur could be graded 1–6 with lower values indicating a greater loss of the trabecular patterns normally seen in the proximal femur. (Bonnick, 1998)

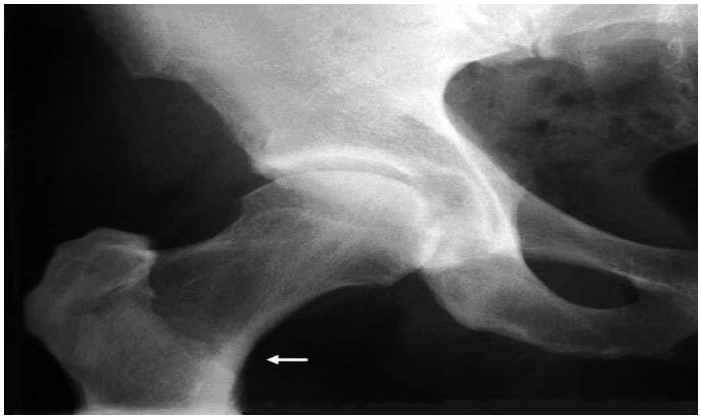


Fig. 2.12 The Singh Index and *calcar femorale* thickness. A Grade 2 Singh Index would be assessed based on having only remnants of the principle compressive group visible. This is indicative of osteoporosis (Bonnick, 1998).

2.7.3 Radiogrammetry

Radiogrammetry is the measurement of the dimensions of the bones using skeletal radiographs. Metacarpal radiogrammetry has been in use for almost 50 years. As originally practiced, the dimensions of the metacarpals were measured using a plain radiograph of the hand and fine calipers or a transparent ruler. The total width and medullary width of the metacarpals of the index, long, and ring fingers were measured at the midpoint of the metacarpal. The cortical width was calculated by subtracting the medullary width from the total width (Bonnick, 1998).

2.7.4 The Radiologic Osteoporosis Score

The radiologic osteoporosis score combined aspects of both quantitative and qualitative morphometry (Barnett & Nordin, 1961). Developed by Barnett and Nordin, this scoring system utilized radiogrammetry of the femoral shaft and metacarpal as well as an index of biconcavity of the lumbar vertebrae. In calculating what Barnett and Nordin called a peripheral score, the cortical thickness of the femoral shaft divided by the diameter of the shaft and expressed as a percentage was added to a similar measurement of the metacarpal. A score of 88 or less was

considered to indicate peripheral osteoporosis. The biconcavity index was calculated by dividing the middle height of the third lumbar vertebra by its anterior height and expressing this value as a percentage. A biconcavity index of 80 or less indicated spinal osteoporosis. Combining both peripheral score and biconcavity index resulted in the total radiologic osteoporosis score, which indicated osteoporosis if the value was 168 or less(Bonnick, 1998).

2.7.5 RADIOGRAPHIC PHOTODENSITOMETRY

photodensitometry, broad-beam X-ray exposures of radiographs were obtained and the density of the skeletal image was quantified using a scanning photodensitometer. The effects of variations in technique such as exposure settings, beam energy, and film development were partially compensated by the simultaneous exposure of a step wedge of known densities on the film. This technique could only be applied to areas of the skeleton in which the soft tissue coverage was less than 5 cm such as the hand, forearm, and heel. This restriction was necessary because of technical limitations from scattered radiation in thicker parts of the body and "beam hardening" or the preferential attenuation of the softer energies of the polychromatic X-ray beam as it passed through the body. (Bonnick, 1998)

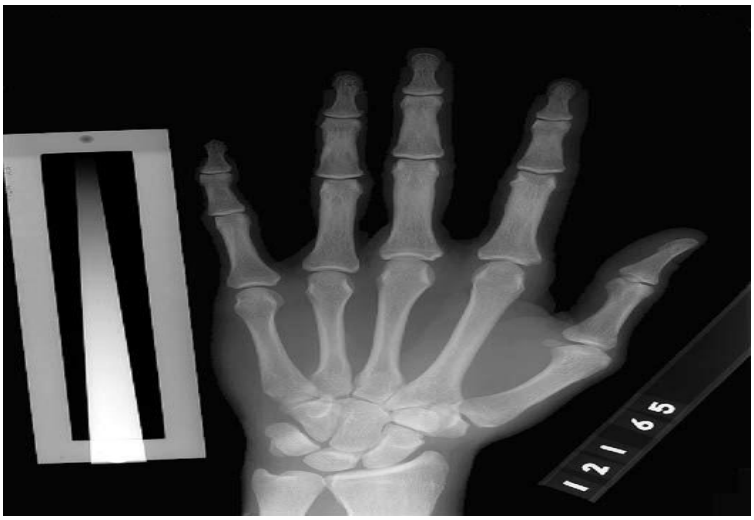


Fig. 2.13 A radiographic photodensitometry hand film taken in 1965 of one of the Gemini astronauts. The Texas Woman's University aluminum wedge is seen next to the little finger (Bonnick,1998).

2.7.6 PHOTON ABSORPTIOMETRY TECHNIQUES

2.7.6.1 Single-Photon Absorptiometry

SINGLE-PHOTON AND SINGLE X-RAY ABSORPTIOMETRY

Single-photon absorptiometry (SPA) involves passing a collimated beam of monoenergetic photons from a radioiodine (125I) source through a limb and measuring the transmitted radiation, using a sodium iodide scintillation detector. There is differential absorption of photons by bone and soft tissues, which allows the total bone mineral content in the path of the beam to be calculated and expressed in grams per centimeter. The method cannot differentiate between cortical and trabecular bone, and interference from surrounding tissue limits its use to the measurement of peripheral sites, such as the distal or mid-radius. At the mid-radius, the cortical-to-trabecular bone ratio is approximately 95:5, whereas at the distal radius it is about 75:25 (Chrischilles et al, 1994).SPA became superseded by single X-ray absorptiometry (SXA) (Borg et al, 1995).

2.7.6.2 DUAL-ENERGY X-RAY ABSORPTIOMETRY (DEXA)

Dual-energy X-ray absorptiometry (DEXA; Figure2.13) measures bone mineral density by determining the absorption of two beams of photons at two different energies. DEXA is able to measure bone mineral density (as mass/area) in the proximal femur and lumbar spine as well as the total body, but it cannot differentiate between cortical and trabecular bone. The cortical-to trabecular ratio is 1:2 in the spine (Banks & Stevenson, 1990) and 3:1 in the femoral neck (Lindsay R, 1988). Thus, measurements of the total BMD at these sites are more a reflection of trabecular bone density than are measurements taken in the peripheral skeleton. DEXA enables bone mineral density to be measured at the hip or spine with greater precision than with the methods described above (precision error: 0.5–2%). The technique is able to measure bone mineral density in the spine (Figures 2.14, 2.15), proximal femur (Figures 2.16 and 2.17) and the total body (Figure 2.18). The scanning time is around 5 min at each site. The radiation dose is low, approximately 1mrem for each site. Most techniques involve measurements taken from anteroposterior view. Early reports suggested that lateral views may be better than anteroposterior views in the diagnosis of osteoporosis (Guglielmi et al, 1994), and that volumetric bone mineral density measured by DEXA from both anteroposterior and lateral views may better predict fracture than DEXA from anteroposterior view alone (Jergas et al,1995).The precision of lateral measurement appears satisfactory (Briggs et al,2005) , but these techniques

have not been adopted and cannot be recommended for clinical use(Hamdy et al,2002). However, lateral views can now be used to give morphometric evaluations of vertebrae to determine vertebral deformities and fractures.

Figure 2.14 Dual-energy X-ray absorptiometry (DEXA) system (Hologic Discovery). Courtesy of Hologic Inc,Bedford, MA. (Stevenson& Marsh,2007)

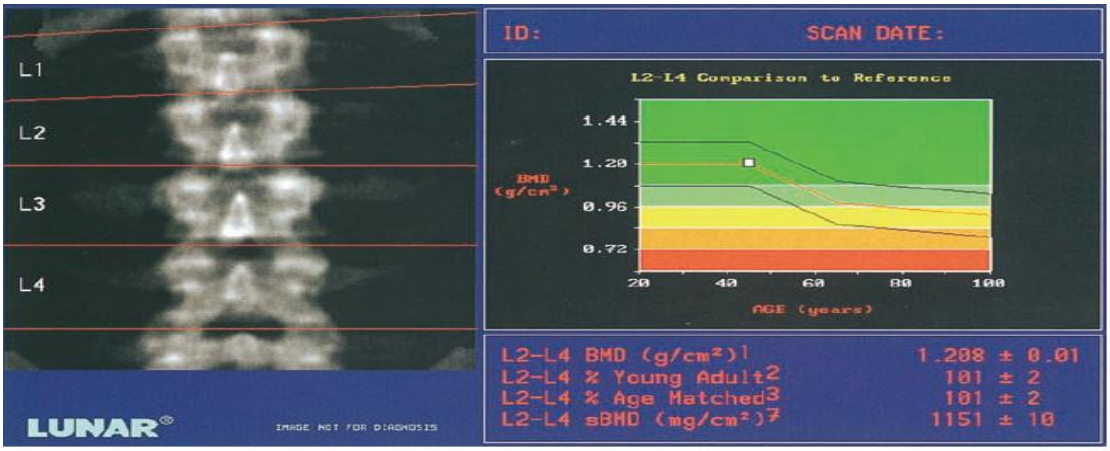


Figure 2.15 DEXA (Lunar DPX-IQ) measurements of lumbar spine bone density in a normal woman (anteroposterior (AP) view). Courtesy of GE Lunar, Madison, WI. (Stevenson& Marsh,2007)

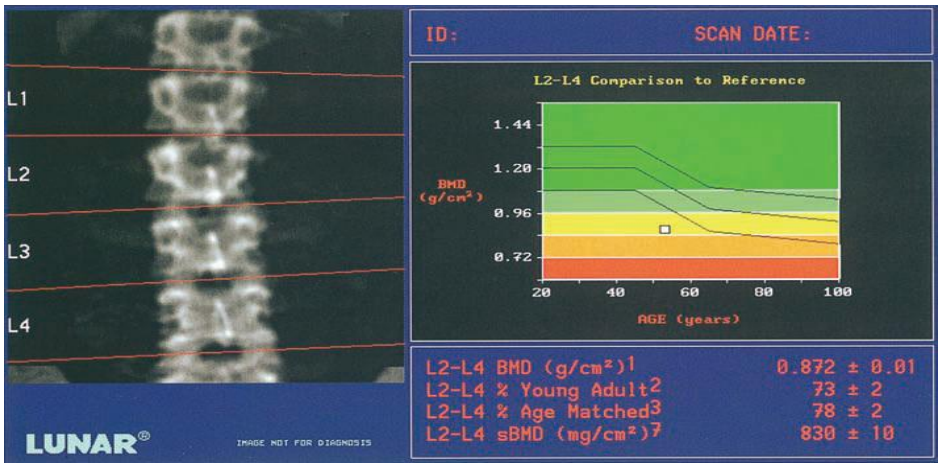


Figure 2.16 DEXA (Lunar DPX-IQ) measurements of lumbar spine bone density in an osteoporotic woman (AP view). Courtesy of GE Lunar, Madison, WI. (Stevenson& Marsh,2007)

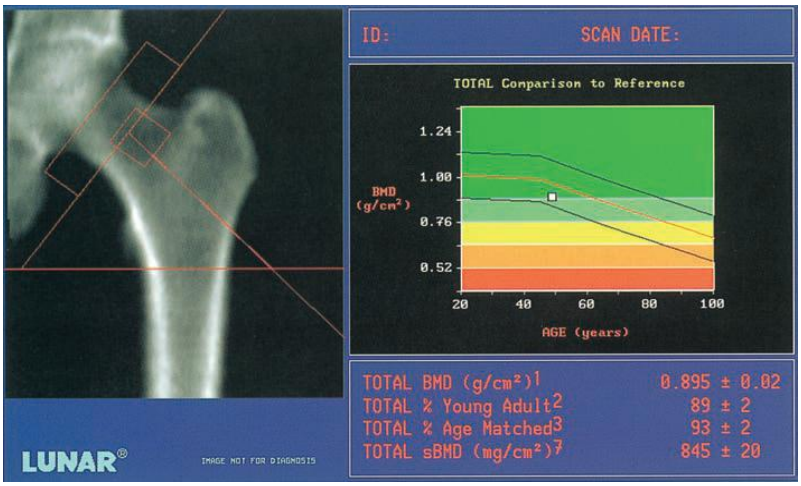


Figure 2.17 DEXA (Lunar DPX-IQ) measurements of femoral neck bone density in a normal woman (AP view). Courtesy of GE Lunar, Madison, WI.(Stevenson& Marsh,2007)

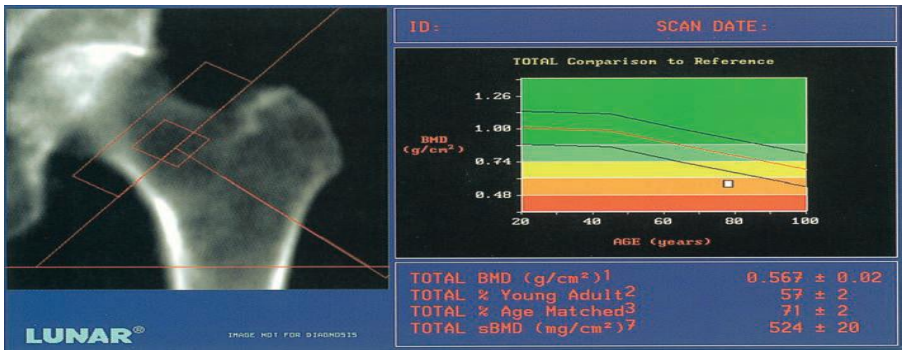


Figure 2.18 DEXA (Lunar DPX-IQ) measurements of femoral neck bone density in an osteoporotic woman (AP view). Courtesy of GE Lunar, Madison, WI (Stevenson& Marsh,2007)

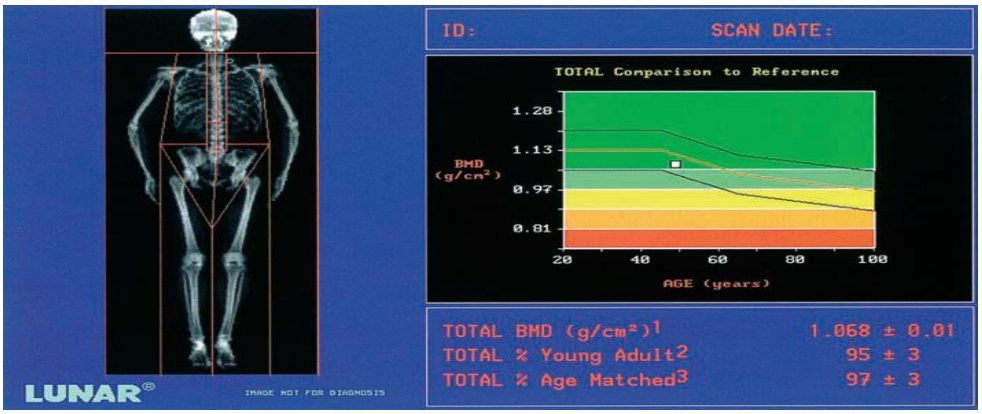


Figure 2.19 DEXA (Lunar DPX-IQ) measurements of total body bone mineral density in a normal woman (AP view). Courtesy of GE Lunar, Madison, WI (Stevenson& Marsh,2007)

2.7.7 Quantitative Computed Tomography

Quantitative computed tomography (QCT) with a suitable software package enables the absorption by different calcified tissues to be determined so that areas of particular interest, such as the vertebral body (which has a cortical-to trabecular ratio of approximately 5:95), may be studied (Banks &Stevenson, 1990). The technique measures true density (Grampp et al, 1996), with the results expressed in g/cm3. Software automation allows accurate determination of the region of interest, and the tissue density is compared with a solid calibration phantom (Figure 2.19). At present, CT scanning is chiefly used to assess trabecular bone density in the spine (Figure 2.20), although it has been reported to be useful in measuring radial density18–20. The precision and accuracy of spinal measurements are approximately 2–4% and 5–10%, respectively, but there is considerable variation depending on the method used (Mundinger et al, 1993).

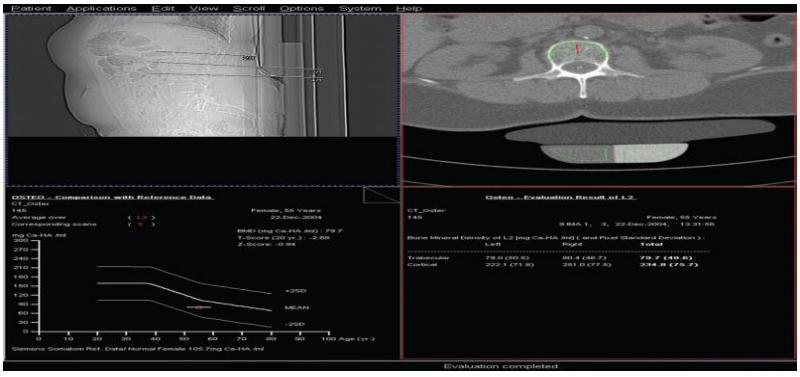


Figure 2.20(a) Lateral quantitative computed tomography (QCT) showing midpoint identification L1–L3 vertebrae.(b) Transverse QCT at the midpoint showing normal bone density for cortical and trabecular bone. Courtesy of Drs Kroll and Winter, Siemens AG, Berlin. (Stevenson& Marsh,2007)

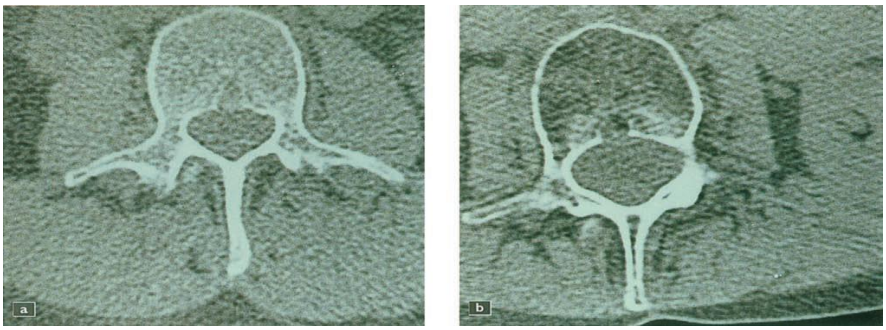


Figure 2.21 Transverse QCT (Siemens Somatom Plus 2) of lumbar vertebrae in a normal subject (a) and a patient with osteoporosis (b). The clear distinction between outer cortical and inner trabecular bone enables measurement of each component. Courtesy of Ms Linda Banks. (Stevenson& Marsh,2007)

Trabecular diameter and intertrabecular spaces can be measured using high resolution CT, and abnormal trabecular architecture can be identified (Mundinger et al, 1993). The recent development of three-dimensional (3-D) CT (Figure 2.21) allows assessment of 3-D trabecular structural characteristics and may improve the ability to understand the pathophysiology of osteoporosis, to test the efficacy of pharmaceutical intervention, and to estimate bone biomechanical properties (Jiang et al,2005).

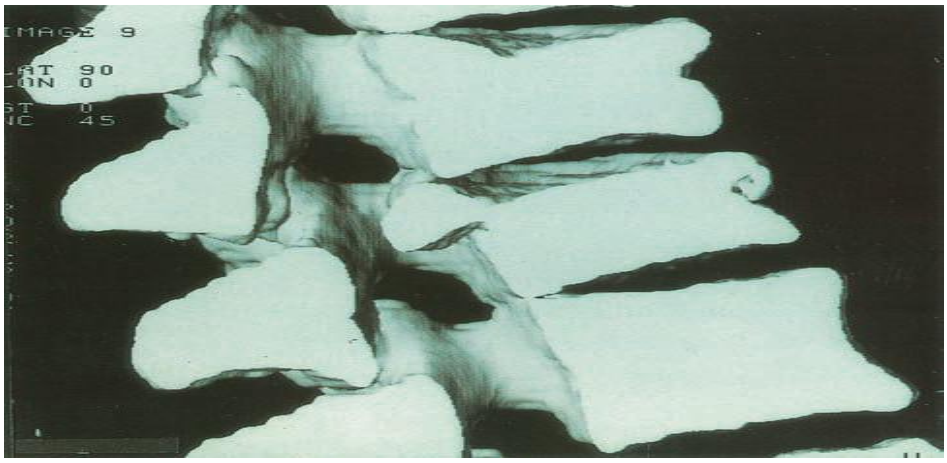
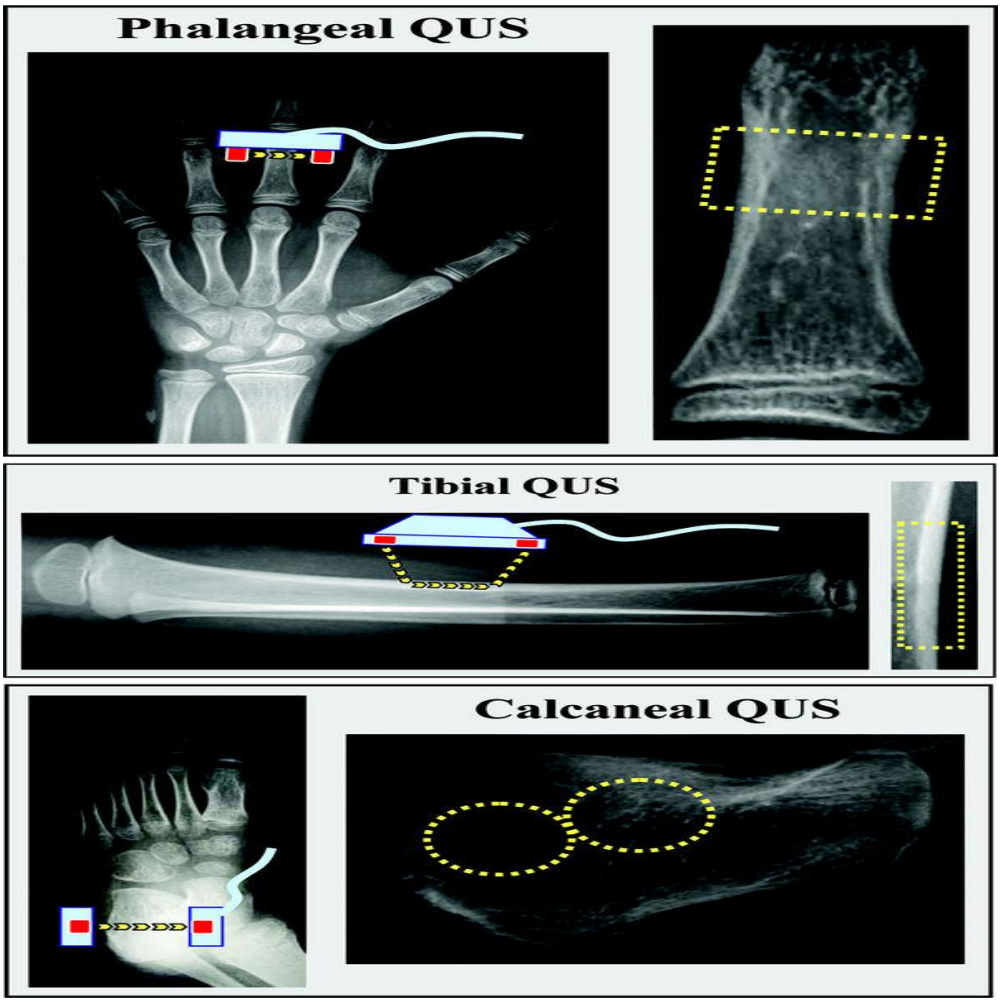


Figure 2.22 Three-dimensional CT of osteoporotic vertebral crush fractures (lateral view). Courtesy of Siemens AG, Erlangen, Germany. (Stevenson& Marsh,2007)

2.7.8 Quantitative ultrasound

A number of ultrasound variables have been employed to assess bone density (structure) and include; velocity (e.g. speed of sound, SOS), attenuation (e.g. broadband ultrasound attenuation, BUA), and reflection (e.g. ultrasound critical angle reflectometry, UCR). QUS can be performed

at the heel, tibia, patella and other peripheral skeletal sites (NOFSA, 2010).These variables, either alone or in combination, have been shown to predict fracture risk in both cross-sectional and longitudinal studies (Young et al,2005).



Quantitative Ultrasound Methods to Assess Bone Mineral Status in Children (Baroncelli ,2008)

2.8 Previous studies

Diamond et al, (2003) in their study on Osteoporosis in Men with Prostate Carcinoma Receiving Androgen-Deprivation Therapy, found that ADT resulted in significant bone loss in men with prostate carcinoma. Bone mineral density (BMD) of the hip, as measured by dual-energy X-ray absorptiometry (DXA), is considered the preferred site of assessment in older men. Spinal BMD is equally important, although careful interpretation of spinal DXA values is required, because of

coexisting facet joint disease and extravertebral calcification. Osteoporosis is diagnosed when BMD is _ 2.5 standard deviations below a reference mean. Men with prostate carcinoma who were treated with ADT had average BMD measurements below those of eugonadal men. Rates of bone loss ranged from 2% to 8% in the lumbar spine and from 1.8% to 6.5% in the femoral neck during the initial 12 months of continuous ADT. Retrospective data indicated an increased risk of fracture in men with prostate carcinoma who were treated with ADT.

Dickman et al, (2004) assessed hip fracture in men with prostate cancer treated with orchiectomy. They found that Men treated with orchiectomy were at increased risk for hip fracture. The estimated relative risk comparing men who underwent orchiectomy to population controls was 2.11 (95% CI 1.94 to 2.29) for femoral neck fractures and 2.16 (95% CI 1.97 to 2.36) for intertrochanteric fractures. An increased risk of hip fracture was observed as early as 6 months after orchiectomy and the relative risk remained fairly constant up to 15 years following orchiectomy.

Mittan *et al*. (2002) in their paper about Bone Loss following Hypogonadism in Men with Prostate Cancer Treated with GnRH Analogs. They prospectively examined the effects of GnRH analogs on the rate and sites of bone loss and bone turnover in men with prostate cancer after testosterone withdrawal and compared the findings to age- and sex-matched controls .they found The total hip and ultra-distal radius BMD at 12 months decreased significantly (P _ 0.001) in the men with prostate cancer receiving GnRH analog therapy compared with the controls. The mean bone loss was 3.3% and femoral neck (2.3%), mid radius (2.7%), and one third radius (1.6%) was not statistically significant. There was also a significant decrease in the BMD of the total radius from baseline to 12 months. No significant bone loss was observed in the control subjects. This suggests that bone loss is evident at 12 months after androgen deprivation and occurs in all sites. BMD measurements of the total hip and ultra-distal radius sites are the most sensitive in demonstrating the loss.

McLeod et al.(2006) reviewed their published literature on the prevention and anagement of osteoporosis secondary to ADT in men with prostate cancer by researching the MEDLINE database (from January 1966 to April 2005) and the abstracts and texts from recent meetings. They found Excess bone loss and osteoporosis is a common problem in men on ADT for prostate cancer. These patients are at increased risk of fracture related morbidity and mortality and therefore minimization of the impact of ADT on bone loss should be a priority at the initiation of

therapy. Standard osteoporosis screening and management recommendations for prostate cancer patients on ADT are still evolving, particularly for those with early stages of disease. Evidence suggests that screening with DEXA scans should take place at the initiation of ADT, and then approximately every year after its commencement. Lifestyle modification measures aimed at limiting bone loss such as smoking cessation, alcohol reduction, regular weight bearing exercise, together with calcium and vitamin D supplementation are essential in all patients commencing ADT therapy. Treatment with oral bisphosphonates should be considered for any patient with an insufficiency fracture or DEXA proven osteoporosis. Intravenous bisphosphonates should be considered in patients with bony prostatic metastases, especially those with hormone resistant disease.

(Wang et al, 2008**)** in their study about Bone mineral density in Japanese prostate cancer patients under androgen-deprivation therapy. They performed a cross-sectional study to elucidate the influence of ADT on bone metabolism in Japanese patients. In total, 101 native Japanese patients with Prostate Cancer were enrolled. They consisted of 58 ADT-treated and 43 hormone-naive patients. The BMD in the lumbar spine, total hip, and femoral neck was measured by dual energy X-ray absorptiometry and expressed in S.D. units relative to young adult men (T-score) or age-matched men (Z-score). Serum levels of bone metabolism markers were also measured. The BMDs at the three sites revealed that 2.3% (1/43) and 8.6% (5/58) of the hormone-naive and ADT-treated Prostate Cancer patients had osteoporosis respectively, but this difference failed to achieve statistical significance (PZ0.294). The two groups also did not differ significantly in their Z-scores of the three sites, and univariate and multivariate analyses indicated that ADT was not a significant risk factor for decreased BMD. In addition, a significant correlation between the duration of ADT and BMD was not observed for all three sites measured. However, the ADT-treated patients had significantly higher serum levels of N-terminal telopeptide of type I collagen (NTx) than the hormone-naive patients (PZ0.017). To our knowledge, this is the first study to demonstrate the low prevalence of osteoporosis in both ADT-treated and hormone-naive Japanese Prostate Cancer patients.

Katherine et al.(2011) assessed bone mineral density (BMD) and fracture risk in men with prostate cancer receiving androgen deprivation therapy (ADT) . They looked at possible predictors of decreased BMD and increased fracture risk in men with prostate cancer; most of whom were on ADT. In a retrospective study, they analyzed serum, BMD, and clinical risk

factors used in the Fracture Risk Assessment (FRAX) tool and others in 78 men with prostate cancer with reported height loss. The subjects were divided in two groups: 22 men with and 56 without vertebral fractures. 17 of the 22 men with vertebral fractures on spine X-rays did not know they had a vertebral fracture. Of those 17 men, 9 had not previously qualified for treatment based on pre radiograph FRAX score calculated with BMD, and 6 based on FRAX calculated without BMD. Performing spine films increased the predictive ability of FRAX for vertebral fracture. Vertebral fracture was better predicted by FRAX for other osteoporotic fractures than FRAX for hip fractures. The inclusion of BMD in FRAX calculations did not affect the predictive ability of FRAX. The PSA level showed a positive correlation with lumbar spine BMD and accounted for about 9% of spine BMD.

SerpaNeto et al(2010) found that patients with prostate cancer under androgen deprivation therapy had lower levels of BMD and higher rates of osteoporosis and fractures than patients with Prostate Cancer not under ADT and healthy controls. Prostate cancer per se does not seem to be a risk factor for osteoporosis. However, the incidence of fractures was higher than that found in healthy controls, indicating that these patients may have had an additional, albeit unknown, mechanisms that could explain these findings. Although several studies in the literature have shown similar results, their study analyzed a larger number of studies and patients, providing consistent evidence on Prostate Cancer, androgen deprivation therapy, osteoporosis and fracture risk.

J. Kälvesten et al. (2016) reviewed their published on Digital X-ray radiogrammetry in the study of osteoporotic fractures: Comparison to dual energy X-ray absorptiometry and FRAX ,The study compared the performance of DXR with FRAX® and DXA in discriminating major osteoporotic fracture (MOF) (hip, clinical spine, forearm or shoulder), hip fracture and femoral neck osteoporosis. This prospective cohort study was conducted on 5278 women 65 years and older in the Study of Osteoporotic Fractures (SOF) cohort. Baseline hand X-ray images were analyzed and fractures were ascertained during 10 years of follow up. Age-adjusted area under receiver operating characteristic curve (AUC) for MOF and hip fracture and for femoral neck osteoporosis (DXA FN BMD T-score ≤ -2.5) was used to compare the methods. Sensitivity to femoral neck osteoporosis at equal selection rates was tabulated for FRAX and DXR. DXR BMD, FRAX (no BMD) and lumbar spine DXA BMD were all similar in fracture discriminative performance with an AUC around 0.65 for MOF and 0.70 for hip fractures for all three methods.

As expected femoral neck DXA provided fracture discrimination superior both to other BMD measurements and to FRAX. AUC for selection of patients with femoral neck osteoporosis was higher with DXR-BMD, 0.76 (0.74–0.77), than with FRAX, 0.69 (0.67–0.71), (p b 0.0001).

Andrew et al. (2016) evaluating bone Mineral Density, The objective of the study was to evaluate the ability of fellowship trained hand surgeons to assess for osteoporosis in the office using a qualitative assessment of digital x-rays of the hand and wrist, the method was prospectively evaluated for female patients older than 65 years who presented to their hand clinic with digital hand and wrist X-rays as part of their evaluation over six months. Patients who had a fracture and were without DEXA scans within the past two years were excluded. Five fellowship-trained hand surgeons, blinded to DEXA T-scores, evaluated the x-rays over two assessments separated by four weeks and classified them as osteoporotic, osteopenic, or normal BMD. Accuracy relative to DEXA T-score, interobserver and intraobserver rates were calculated, Thirty four patients met the inclusion criteria and a total of 340 x-rays reviews were performed. The assessments were correct in 169 cases (49%) as compared to the DEXA T-scores. A mean weighted kappa coefficient of agreement between observers was 0.29 (range 0.02-0.41) reflecting a fair agreement. The first and second assessment for all five physicians was 0.46 (range 0.19-0.78) reflecting a moderate agreement. Grouping osteoporosis and osteopenia together compared to normal, the accuracy, interobserver and intraobserver rates increased to 63%, 0.42 and 0.54 respectively.

W. Glinkowski et al.(2013) in their poster at **Congress:** ECR 2013 The comparison of two methods for measuring the optical density of radiographs to predict long bone fracture callus maturity, The aim of the study was to compare the use of two methods of measuring the optical density of radiographs. The study comprised 108 radiographs at different stages of fracture healing. Two independent software having the ability to measure the optical density supporting standard DICOM 3.0 were used for the analysis (Image J software, recommended by the U.S. National Institutes of Health and the DICOM Viewer). The study have shown good agreement between the measurement and evaluation method DICOM Vision and Image J software use. The results for cortical bone by Dicom Vision was 190,41 and the cortical bone by Image J was 191,66 , The optical density for fracture gap by Dicom Vision was 78,88 and by Image J was 79,16. This confirms the suitability of the two methods to evaluate discrete changes in optical density of radiographs in the fracture gap.

S. Wagner et al. (2005) in their study "Diagnosis of osteoporosis: visual assessment on conventional versus digital radiographs" the purpose of the study was to analyze the visual detection of osteopenia/osteoporosis with both digital and conventional radiographs. In 286 patients they retrospectively evaluated radiographs of the lumbar spine in two planes. One hundred twenty-eight patients had conventional and 158 patients had digital radiographs. Patients with pre-existing vertebral fractures were excluded. Four experienced musculoskeletal radiologists blinded to the values of DXA and to the patients' ages assessed independently from each other whether the bone density of the lumbar spines was normal or decreased. The results of dual X-ray absorptiometry served as the standard of reference. The threshold value for the diagnosis of osteopenia was a T-score less than) 1 SD according to the WHO classification of osteoporosis. Sensitivity/specificity was 86%/ 36% for conventional and 72%/47% for digital radiographs. The overall diagnostic accuracy was 68% for conventional and 64% for digital radiographs. Eighty percent of the patients with osteopenia and 96% of the patients with osteoporosis were correctly assessed as true positive on conventional radiographs and 65% (osteopenia) and 82% (osteoporosis) on digital radiographs. Interobserver agreement was markedly lower for digital (35%) than for conventional radiographs (73%). However the differences were not statistically significant. There is no major difference in diagnostic accuracy in the assessment of osteopenia/osteoporosis using digital and conventional radiographs, respectively. However, the high interobserver variance on digital radiographs indicates that visual assessment of osteoporosis/osteopenia is problematic, which may be due to image processing and postprocessing algorithms that manipulate the visual aspect of bone density

Chapter three

methodology

Chapter Three

Material and Methods

3.1 Material:

3.1.1 Machines

Medical imaging system (dual head gamma camera) model Mediso, All general purpose collimator.

X-ray Philips machine model Duo diagnost 2.3.6/2.3.1 free-arm-fluoroscopy with digital radiography system.

CR system consist of: Fujifilm computer, FCR PRIMA T2 scanner, film 14*17 inch

3.1.2 Area of study

The research study was conducted at **RICK** and Antalya medical center, all the patients were come referred by oncologist to done bone scan as follow up. The Radiation Isotopes Center of Khartoum is a major center for treatment of cancer and nuclear medicine in Sudan.

3.1.3 **Type of study**

This is a cross-sectional descriptive study.

3.1.4 Duration of study

The study was carried out over a duration of 3 years from July 2014 to July 2017

3.1.5 Sample of study

200 patients 130 normal case using as a control group and 70 patients abnormal

3.1.5.1 Inclusion criteria.

The patients with prostate cancer that treated with Androgen deprivation therapy (ADT) for one year or longer was collected.

3.1.5.1 Exclusion criteria.

Excluded Patients who had prior fractures in spin or hip bone, and patients which not receiving hormone therapy or receiving for less than one year.

3.1.6 Variables

Table 3.1 show variables

Age	Period of Treatment	High	Weight	BMI	PSA	N CR	Abnormal CR	G.C

3.1.7 Data analysis

Data analyzed using Microsoft Excel and statistical package social science SPSS version 20 software's.

3.2 **Methods**

3.2.1 Procedures

The process of identifying participants was much more complicated as the researcher had to examine the medical records of all patients manually, that were available at the registrar office to identify patients who had been diagnosed with prostate cancer, and Participants were interviewed.

The patients who met eligibility based on the inclusion criteria, and if they were accepting to participate in the study, required from them to sign the consent to participation form.

From medical file; medical history, medications, last PSA test, period of treatment, Then researcher take the patient to the radiology department in x-ray room there the diagnostic technologist will be start of x-ray examination for Lumber spine is the most widely used anatomical site for the evaluation of osteoporosis the measures take in the bodies of vertebrae L1-L4 and hip bone where the most serious of osteoporosis, the measures take in hip bone, femoral neck, trochanter ,inter trochanter .

After that, return to nuclear medicine department there the nurse take the height and weight then inject the patient with small amount of radioisotopes 740 MBq of technetium -99m-MDP

(TC^{m99} MDP) and stay in waiting room 2-3 hours , in gamma camera room there performed whole-body bone scan for 30 minutes.

The images of x-ray collected as software by flash USB and bone scan images were collected as hard copy and then rescan it by computer and printer under resolution 600 dpi (dots per inch),and enter in Dicom format programme.

After that analysing the images with Interactive Data Language IDL software version 6.1 to measure the grey level variation of images with spine and hip area,

3.2.2 Ethical consideration

Before I start a search took approval from director of the hospital, as well as all of the patients who took their data and examines, i asked them the accepting and to sign a consent form.

Chapter four

The results

Chapter four

Results

Table 4.1 shows statistical parameters for all patients

	Mean	Median	STD	Min	Max
Age	69.43	70.5	10.51	45	89
PT	2.41	2	1.28	1	7
PSA	5.36	5.3	2.33	0.02	10.4
BMI	25.96	26.35	3.46	15.4	33.49
N hip CR	619.67	618.50	86.39	440	760
N spine CR	598.77	599	73.34	417	711
Hip CR	2526.43	2505.5	310.63	1978	3197
Spine CR	1988.03	1926	592.445	1245	3184
Hip G.C	630.67	620.5	87.572	357	711
Spine G.C	582.57	584.5	87.57	357	711

Table (4.2) shows age distribution of all patients (years)

Age group	Frequency	percent
45 – 50	4	5.7
51 - 56	6	8.6
57 – 62	6	8.6
63 – 68	13	18.6
69 - 74	19	27.1
75 - 80	11	15.7
81 - 86	11	15.7
Total	70	100

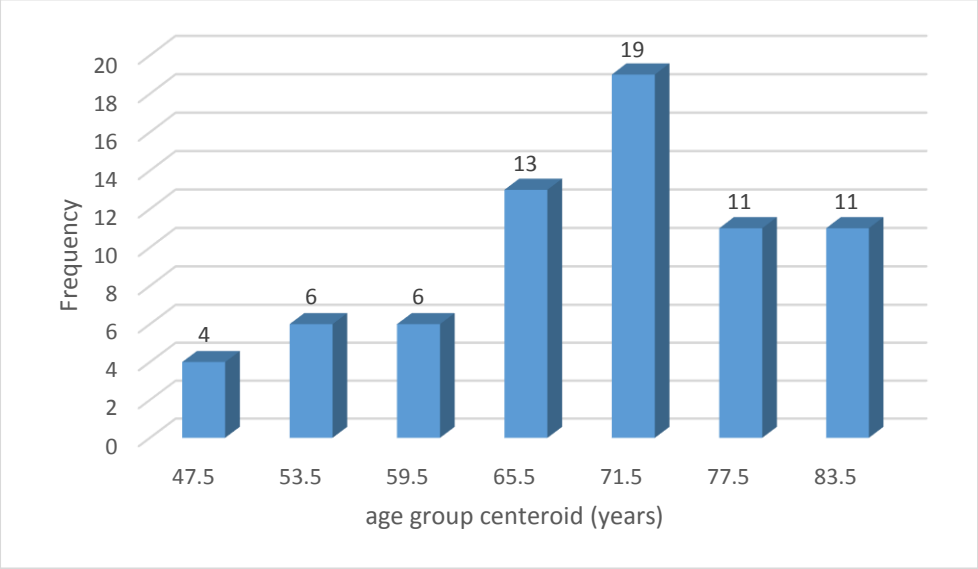


Figure (4.1) shows age group distribution of prostate cancer patients (years)

Table (4.3) show the period of treatment (years)

Period of treatment (ys)	frequency	percent
1 - 1.8	26	37.1
1.9 – 2.7	25	35.7
2.8 – 3.6	9	12.9
3.7 – 4.5	5	7.1
4.6 – 5.4	2	2.9
5.5 – 6.3	2	2.9
6.4 – 7.2	1	1.4
Total	70	100

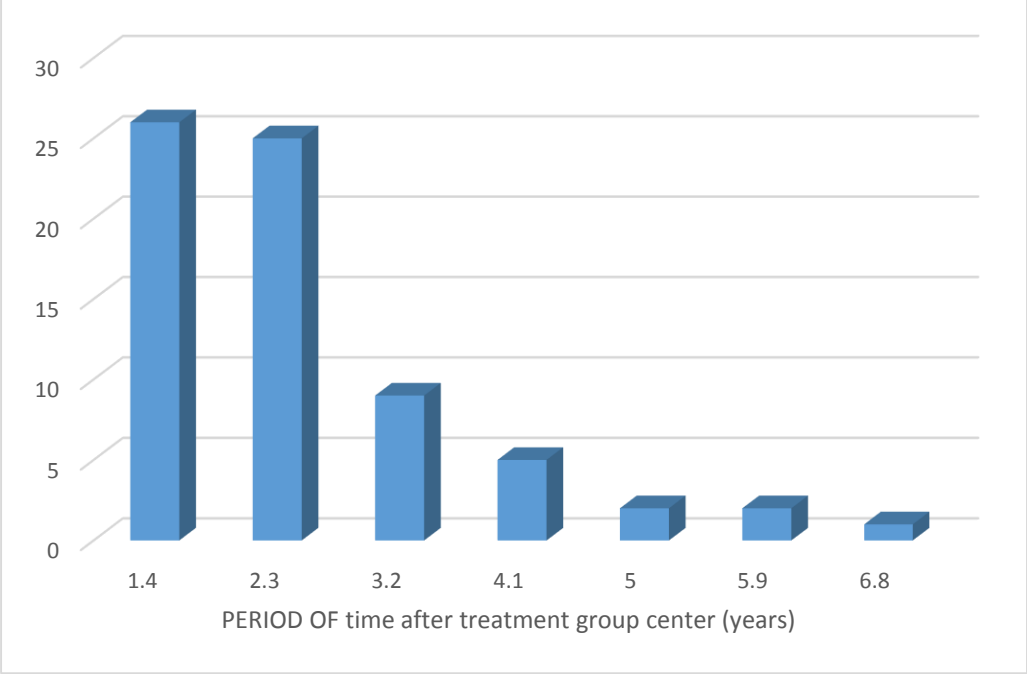


Figure (4.2) show the distribution period of treatment group (years)

Table (4.4) show of Prostate Specific Antigen distribution of all patients

PSA	frequency	percent
0.2 – 1.4	3	4.3
1.5 – 2.9	11	15.7
3 – 4.4	11	15.7
4.5 – 5.9	15	21.4
6 – 7.4	17	24.3
7.5 – 8.9	8	11.4
9 – 10.4	5	7.1
Total	70	100

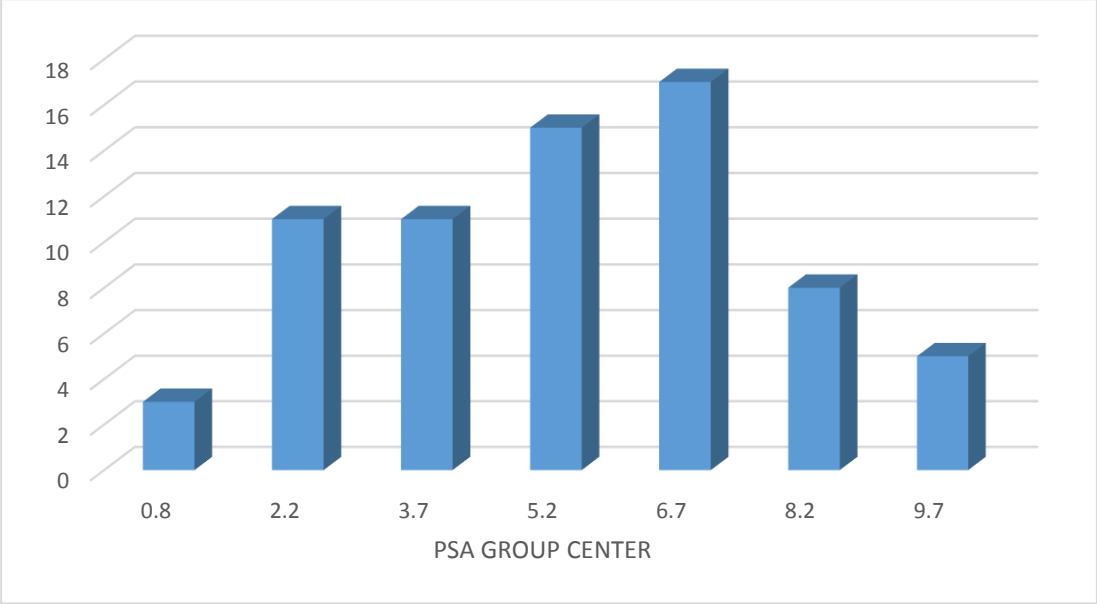


Figure (4.3) show PSA group distribution

Table (4.5) show Body Mass Index distribution (kg/m2)

BMI	Frequency	percent
15.4 – 17.9	2	2.9
18 – 20.5	1	1.4
20.6 – 23.1	9	12.9
23.2 – 25.7	21	30
25.8 – 28.7	24	34.3
28.8 – 30.9	6	8.6
31 – 33.49	7	10
Total	70	100

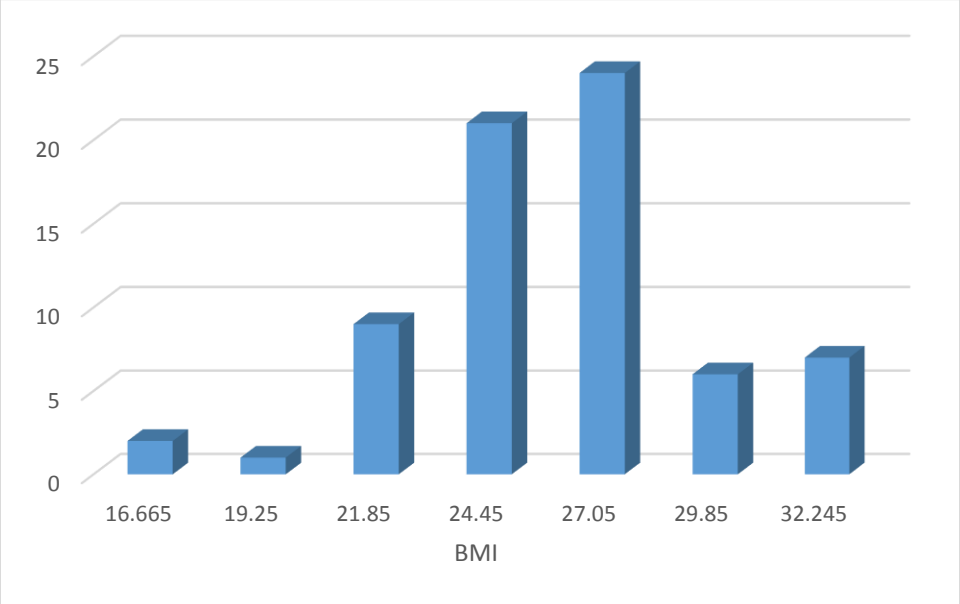


Figure (4.4) show BMI group distribution (kg/m2)

Table 4.6 show paired sample between Hip and Spine

		Mean	*Std. Deviation*	*Std. Error Mean*
Pair 1	***hip CR***	2526.43	310.629	56.713
	G.C Hip	630.67	92.642	16.914
Pair 2	***spine CR***	1988.03	592.445	108.165
	G.C spine	582.57	87.572	15.988
Pair 3	***CR N Hip***	619.67	86.397	15.774
	CR N Spine	598.77	73.345	13.391

Table 4.7 show correlation between abnormal (CR and Gamma Camera)

		Correlation	P.value
Pair 1	***hip CR & G Hip***	-.124	.514
Pair 2	***spine CR & G spine***	.100	.601

Table 4.8 show paired sample statistic for Normal and Up normal CR patients

		Mean	*Std. Deviation*	*Std. Error Mean*
Pair 1	***CR N Hip***	619.67	86.397	15.774
	hip CR	2526.43	310.629	56.713
Pair 2	***CR N spine***	598.77	73.345	13.391
	spine CR	1988.03	592.445	108.165

Table 4.9 show correlation between Normal and Up normal CR patients

		Correlation	P.value
Pair 1	CR N Hip & hip CR	-.214	.255
Pair 2	CR N spine & spine CR	-.139	.464

Table 4.10 show sample statistic of patients from CR and G.C examinations

		Mean	Std. Deviation	Std. Error Mean
Pair 1	G.C Hip	630.67	92.642	16.914
	CR N Hip	619.67	86.397	15.774
Pair 2	G.C spine	582.57	87.572	15.988
	CR N spine	598.77	73.345	13.391

Table 4.11 show correlations between patients from normal CR and G.C examinations

		Correlation	P.value
Pair 1	G.C Hip & CR N Hip	.890	.000
Pair 2	G.C spine & CR N spine	.789	.000

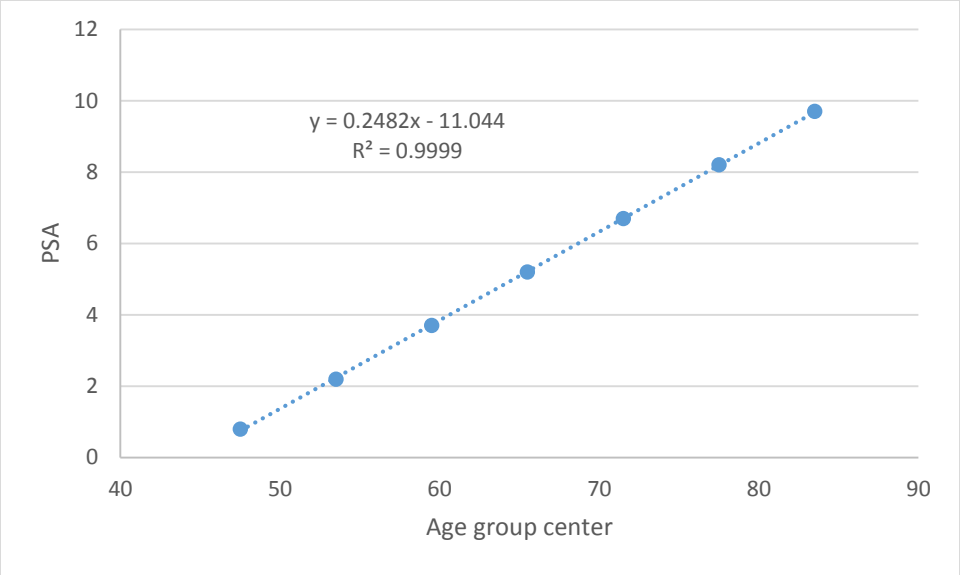


Fig 4.5 show the relation between age group center (years) and PSA group center

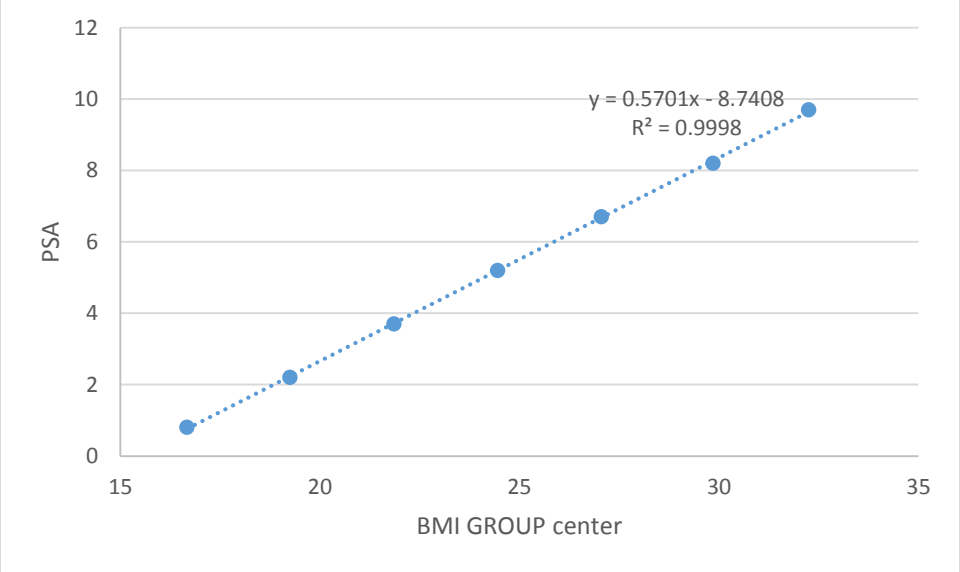


Fig 4.6 show the relationship between BMI (kg/m2) group center and PSA group center

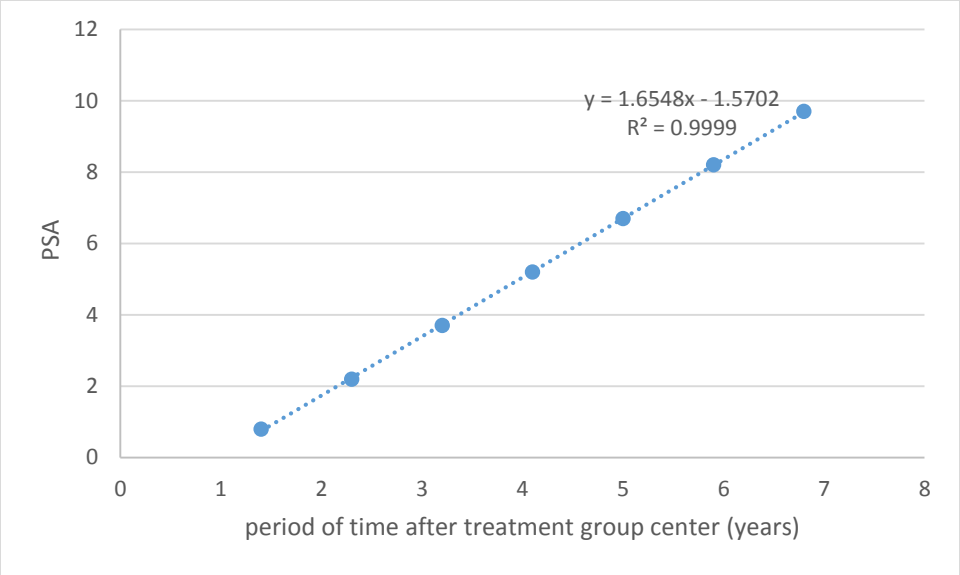


Fig 4.7 show the relationship between period of time group center (years) and PSA group center

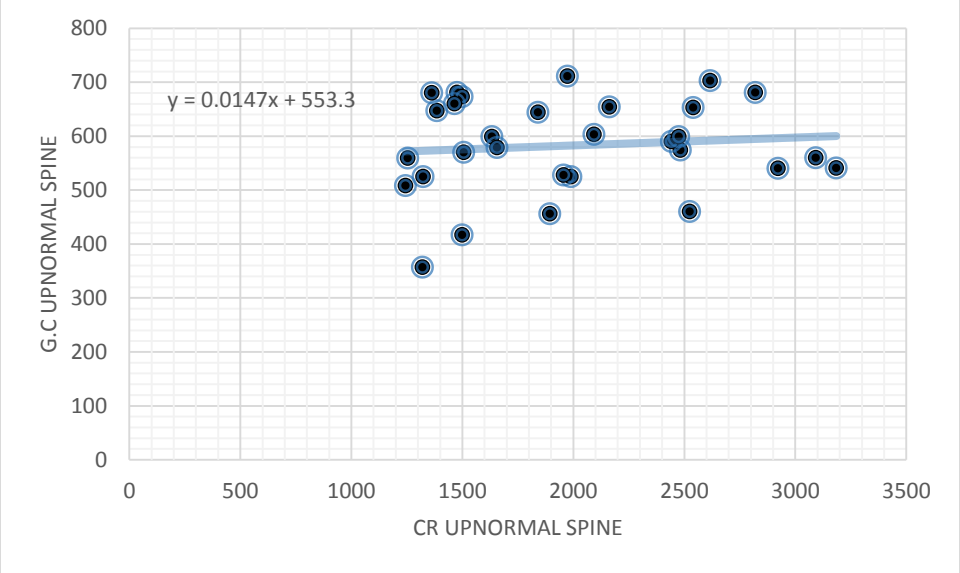


Fig 4.8 show correlation between CR up normal and G.C Up normal for spine

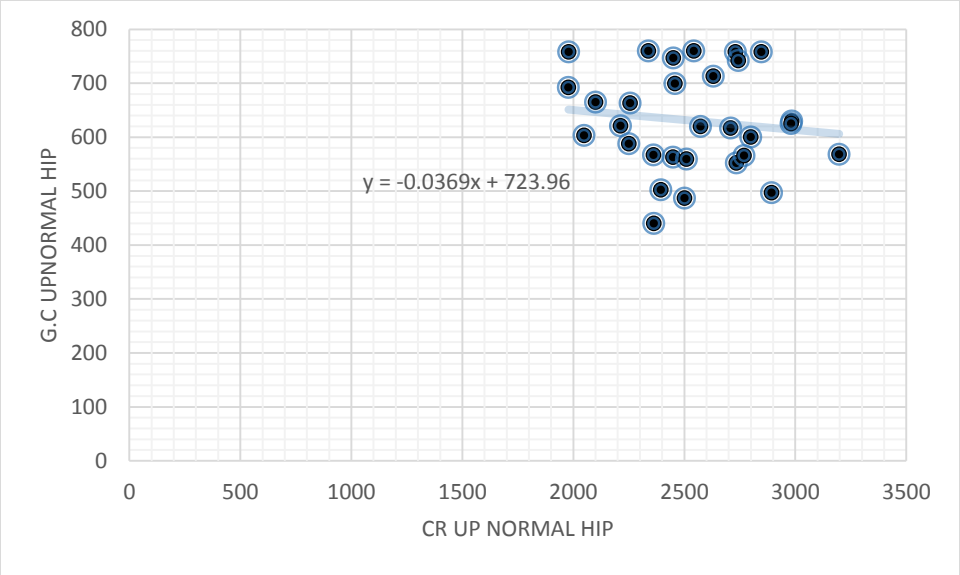


Fig 4.9 show correlation between CR up normal and G.C Up normal for hip

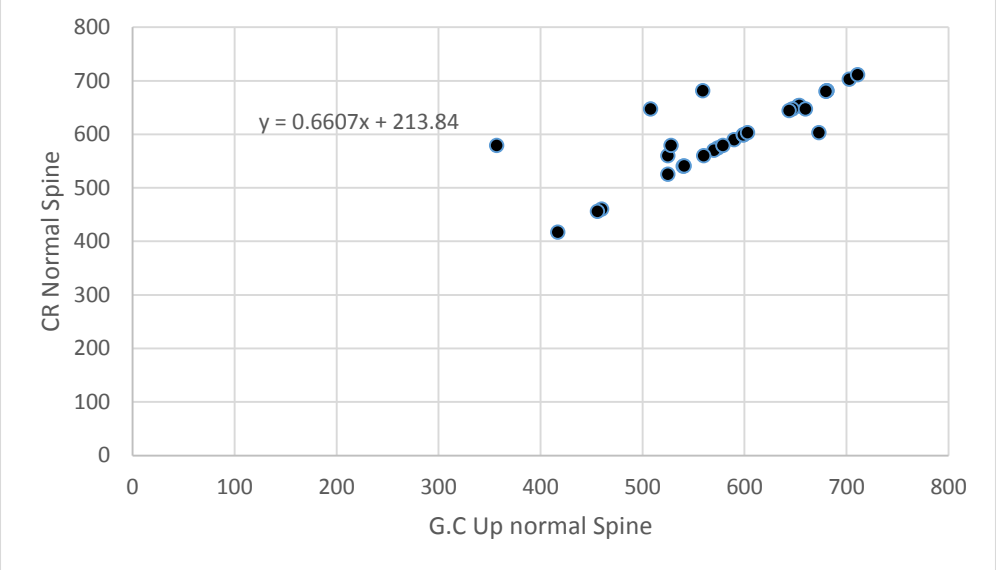


Fig 4.10 show correlation between CR normal and G.C Up normal for spine

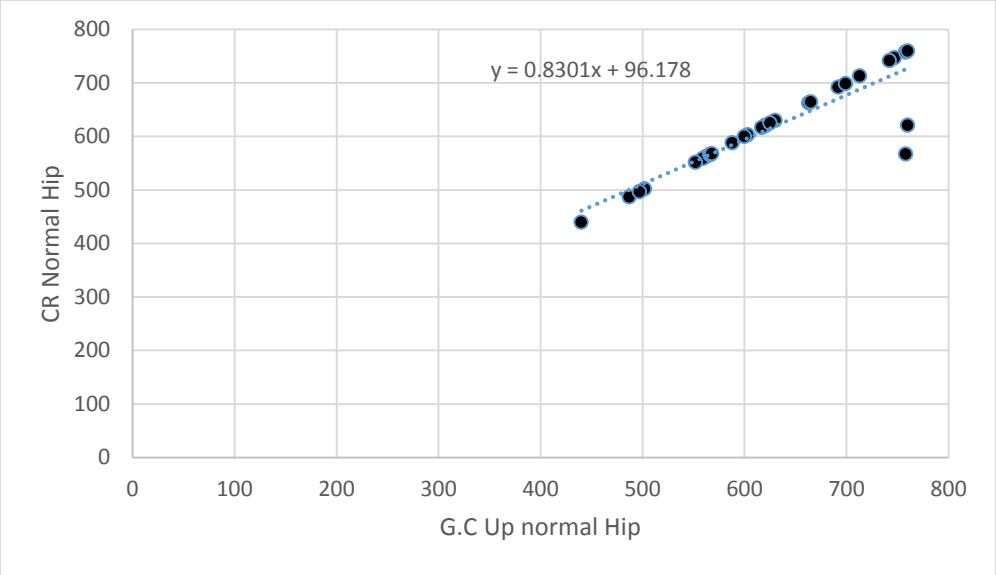


Fig 4.11 show correlation between CR normal and G.C Up normal for hip

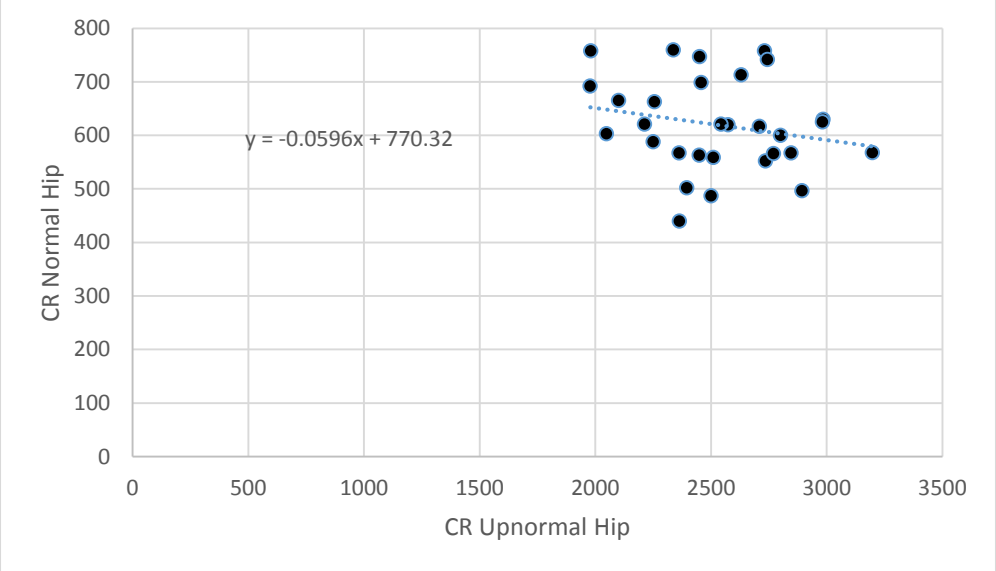


Fig 4.12 show correlation between CR normal and CR Up normal for hip

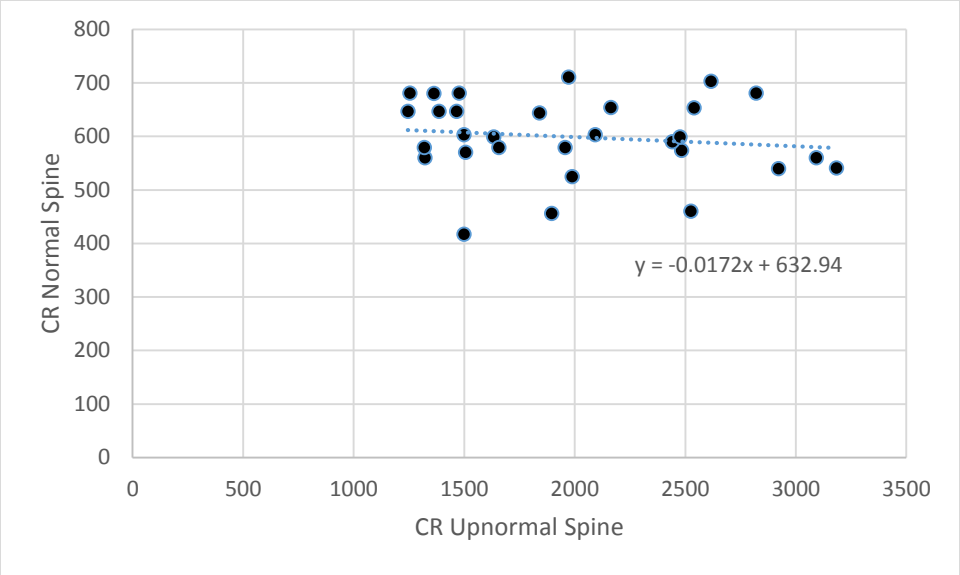


Fig 4.13 show correlation between CR normal and CR Up normal for spine

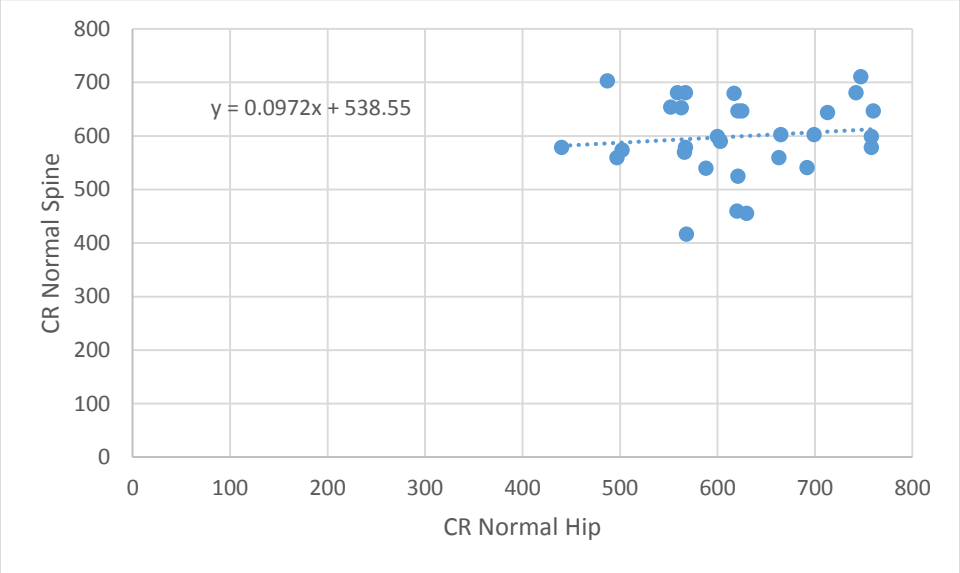


Fig 4.14 show correlation between CR normal spine and CR normal for hip

Chapter five

Discussion, conclusion
And
Recommendation

Chapter five

Discussion, conclusion And Recommendation

5.1 The Discussion

This study carried out to assessment of osteoporosis in patients with prostate cancer using bone scintigraphy (Gamma camera) and computed radiography (CR).the study was conducted at radiation Isotopes Center of Khartoum (**RICK)** and Antalya center duration of 3 years from July 2014 to July 2017, the sample of study consisted of seventy patients and 130 normal case used as a control group and we using statistical parameters to show the data. **In table 4.1** show statistical parameters for all patients for age , period of treatment , Prostate Specific Antigen , Body Mass Index , normal hip CR , normal spine CR, abnormal hip CR , abnormal spine CR , abnormal spine Gamma Camera , abnormal hip Gamma camera. Were the mean ± SD for age 69.43 ± 10.51, for period of treatment was 2.41 ± 1.28, Prostate Specific Antigen was 5.36 ± 2.33, Body Mass Index was 25.96 ± 3.46, normal hip CR was 619.67± 86.39, normal spine CR was 598.77 ±73.34, abnormal hip CR was 2526.43 ± 310.63, abnormal spine CR was 1988.03±592.445, abnormal spine Gamma Camera was 630.67±87.57, abnormal hip Gamma camera was 582.57± 87.57.**Table 4.2** show age group distribution for all patients, were the patients in period 69-74 years was more frequently with 27% then the group from 63-68 years with 18.6 % , and the lower age period frequently was 45-50 years with 5.7 % (as shown in figure 4.2) **In table 4.3** show the period of time after treatment (years) and the more frequently period was 1-1.8 year with 37.1% then from 1.9-2.7 years with 35.7% , while the lower period frequently was 6.4-7.2 years with 1.4%(as shown in figure 4.3) **In table 4.4** show of PSA distribution and the more frequently Prostate-specific antigen (PSA) level was 6-7.4 ng/mL with 24.3% then from 4.5-5.9 ng/mL with 21.4% , while the lower period frequently was 0.2 -1.4 ng/mL with 4.3% (as shown in figure 4.4) .**In the table 4.5** show BMI distribution (kg/m2) and the more frequently period was 25.8 -28.7 kg/m2 with 34% then from 23.2 -25.7 kg/m2 with 30%, while the lower value frequently was 18-20.5 kg/m2 with 1.4 % (as shown in figure 4.5). **Table 4.6** show paired sample statistics for patients with hip and spine (CR, gamma camera) in pair. Between hip CR and hip G.C the mean ± SD for hip CR was 2526.43 ± 310.629 and for hip G.C was 630.67 ±92.642. Between spine CR and G.C spine the mean ± SD for spine CR was 1988.03±592.44 and for G.C spine was 582.57±87.572.between *CR Normal Hip and CR Normal*

Spine the mean ± SD was (619.67 ±86.397) and (598.77±73.345) respectively .**Table 4.7** show correlation between hip (CR and Gamma Camera) and spine (CR and Gamma camera). Were the P.value for hip CR and hip G.C 0.514 which mean there is no significant difference? And the P.value for *spine CR & G spine were 0.6*01 which mean there is no significant difference also. **Table 4.8** show paired sample statistic for Normal and abnormal CR patients between normal Hip CR and abnormal hip CR the mean ± SD were (619.67±86.397) and (2526.43±310.629) respectively, and between normal CR spine and abnormal spine CR the mean ± SD were (598.77±73.345) and (1988.03±592.445). **Table 4.9** show **correlation between Normal and abnormal CR patients were** the P.value for CR Normal Hip & CR abnormal hip .255 which mean there is no significant difference, And the P.value for CR Normal spine & CR abnormal spine .464 which mean there is no significant difference **Table 4.10** how sample statistic of patients from CR and G.C examinations For G.C abnormal Hip and CR Normal Hip the mean ± SD were (630.67±92.642) and (619.67±86.397) respectively , and for G.C abnormal spine and CR Normal spine the mean ± SD were (582.57±87.572) and (598.77±73.345) respectively. **Table 4.11** show correlations between patients from CR and G.C examinations, the P.value for G.C abnormal Hip & CR Normal Hip was 0.000 which mean there is significant difference, And the P.value for G.C abnormal spine & CR Normal spine 0.000 which mean there is significant difference.

Figure 4.5 show correlate between abnormal CR spine and abnormal G.C spine were the linear regression results show that the rate of change between abnormal CR spine and abnormal G.C spine images increasing by rate 0.0147 for abnormal G.C spine versus one unit of abnormal CR spine. **Figure 4.6** show correlation between abnormal CR and abnormal G.C for hip were the linear regression results show that the rate of change between abnormal CR hip and abnormal G.C hip images increasing by rate 0.0369 for abnormal G.C hip versus one unit of abnormal CR hip. **Figure 4.7** show correlate between normal CR spine and abnormal G.C spine the linear regression results show that the rate of change increasing by rate 0.6607 for normal CR spine versus one unit of abnormal G.C spine. **Figure 4.8** show correlate between normal CR hip and abnormal G.C hip linear regression results show that the rate of change increasing by rate 0.8301 for normal CR hip versus one unit of abnormal G.C hip. **Figure 4.9** show correlate between normal CR hip and abnormal CR hip, the linear regression results show that the rate of change increasing by rate 0.0569 for normal CR hip versus one unit of abnormal CR hip.

Figure 4.10 show correlate between normal CR spine and abnormal CR spine, the linear regression results show that the rate of change increasing by rate 0.0172 for normal CR spine versus one unit of abnormal CR spine. **Figure 4.11** show correlate between normal CR for spine and hip, the linear regression results show that the rate of change increasing by rate 0.0972 for normal CR spine versus one unit of normal CR hip.

5.2 Conclusion

This study carried out to assessment of osteoporosis in patients with prostate cancer using bone scintigraphy (Gamma camera) and computed radiography (CR).the study was conducted at radiation Isotopes Center of Khartoum (**RICK)** and Antalya center duration of 3 years from July 2014 to July 2017, the sample of study consisted of seventy patients and 130 normal cases.

The study Show that there is no significant difference between **normal CR and abnormal CR** for hip and spine regions. The Linear regression results show rate of change between normal CR and abnormal CR for hip and spine decreasing by rate 0.0596 and 0.0172 for normal versus one unite of abnormal CR.And estimated of *values between the normal and up normal* hip and spine calculated using the following linear equations:

CR normal hip = - 0.0596 (up normal CR hip) +770.32
CR normal spine = - 0.0172 (up normal CR spine) + 632.94

The study show that there is significant difference between **normal CR and abnormal G.C** for hip and spine regions. And the Linear regression results show rate of change between normal CR and up normal G.C hip was increasing by rate 0.8301 for normal CR versus one unit of abnormal G.C hip, and by rate of 0.6607 for normal CR spine versus one unit of abnormal G.C spine. And estimated of *values between the normal CR and up normal* G.C hip and spine images calculated using the following linear equations:

CR normal hip = 0.8301(up normal G.C hip) +96.178

CR Normal spine = 0.6607(up normal G.C spine) + 213.84

Also show that there is no significant difference between **abnormal CR and abnormal G.C** for hip and spine regions. And the Linear regression results show rate of change between abnormal CR and abnormal G.C hip was decreasing by rate 0.0369 for abnormal CR versus one unit of abnormal G.C hip, and increasing by rate of 0.0147 for abnormal CR spine versus one unit of abnormal G.C spine.

And estimated of *values* calculated using the following linear equations:

Abnormal hip G.C = 0.0147 (Abnormal hip CR) +553.3
Abnormal spine G.C = -0.0369 (Abnormal spine CR) + 723.9

And the most effected age was 69-74 years, and the effected period of treatment 1-1.8 years, the PSA most effected value 6-7.4 ng/ml and the most frequency of body mass index 25.8-28.8 kg)cm2 .

5.3 Recommendation

- *Using other modalities.*
- *Study with bigger groups to reach a more significantly results.*
- *Development of software aimed at processing images and understanding the density of bone to detection of osteoporosis easier.*
- *Prostate cancer patients and others patients that have hormone therapy must be scan periodically to ensure bone integrity from Osteoporosis and the risk of fractures.*
- *Osteoporosis is a risk and threat to many older people and patients who are subject to hormonal drugs and to prevent it should be interested in sports and eating foods rich in calcium and vitamin D*
- *In men The appropriate age to start risk assessment by age 60 therefore, assessment before this age is reasonable*

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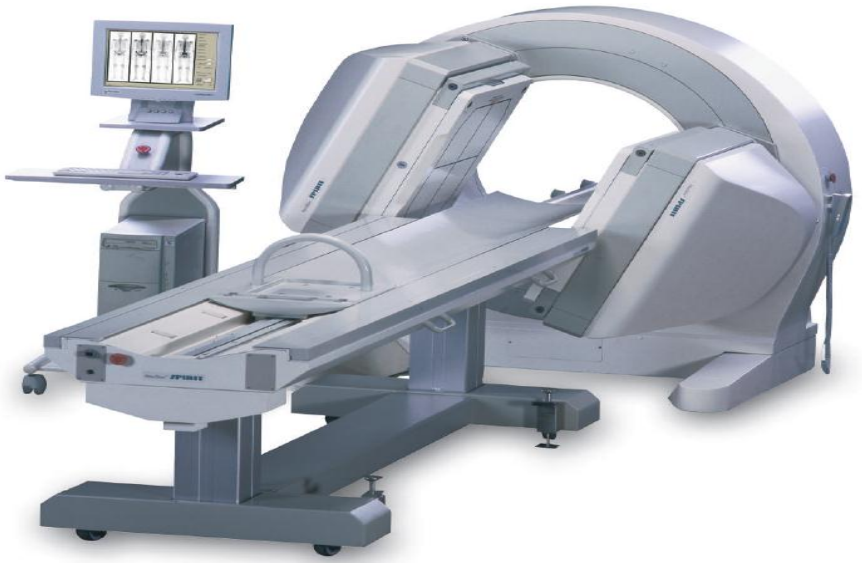
APPENDICES

Appendix A-1

Show Dual-head gamma camera (Mediso **medical imaging system)**



Appendix A-2

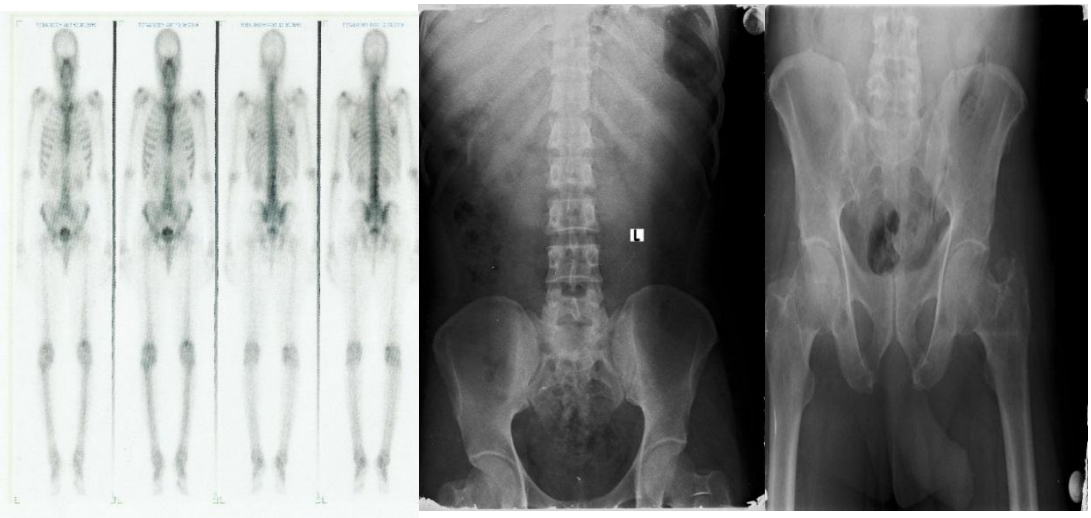
x-ray Philips machine model Duo diagnost

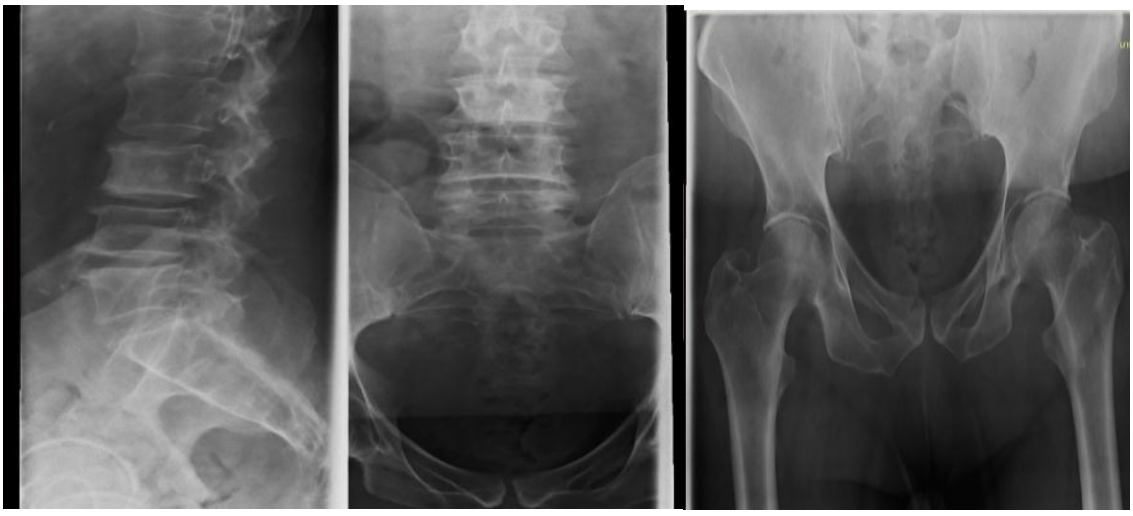
Appendix A-3

Computed radiography system

Appendix B-1

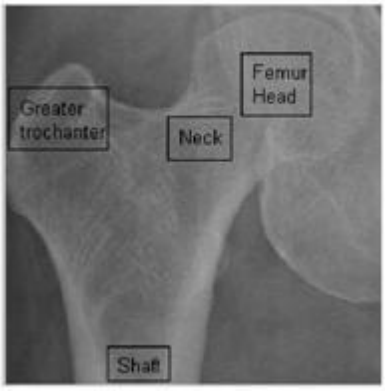
Show Bone scan using gamma camera and spine, hip x-ray examinations





Appendix B-2

Right femur digital x-ray image with marked ROIs



Appendix C-1

Consent form

SUDAN UNIVERSITY OF SCIENCE AND TECHNOLOGY

Department Of Nuclear Medicine

College Of Graduate Studies

Consent form

Title of Study: Assessment of osteoporosis in patients with prostate cancer using bone scan and computed radiography.

Ayman Salem Zain Alwi, MSc

PhD Student in Nuclear Medicine, SUST

Supervisor:

Mohammed Elfadel Mohammed, PhD

Associate Prof. Dr. College of Medical Radiologic Science, SUST

Introduction:

You are being invited to participate in this research study because you belong to one of men with prostate cancer who are receiving hormone during period of treatment

It is entirely up to you whether you want to take part in this study or not. The health care that you usually get will not be changed in anyway by the choice you make about taking part in this study. You can change your mind and withdraw from this study at any time.

Background:

Prostate cancer is the most commonly diagnosed cancer in men, affected one in seven men during his lifetime. Although treatments such as surgery and radiation offer a very good prognosis for the majority of men, in approximately 35% of men the prostate cancer may return. Androgen deprivation therapy is an essential treatment for many patients with prostate cancer, but its effects on bone mineral density can be severe. Studies show that men who receive hormone deprivation therapy for prostate cancer have increased risk of developing osteoporosis and bones Fractures.

Dual energy X-ray absorptiometry (DEXA) is the method of choice for BMD measurement and assessment of osteoporosis. Not all patients with prostate cancer are investigated for osteoporosis involvement, but as follow up of the patients with prostate cancer must be presenting to nuclear medicine to doing bone scintigraphy for detecting of bone metastasis .however the difficulty with availability, high cost and limits use of DEXA. We in this research try to improve the image of bone scan and x-ray image by using some computer software so as to detecting of osteoporosis and better understand the extent and progression of disease in prostate patients.

Purpose:

The purpose of this project will be to assess the osteoporosis in patients with prostate cancer using Gamma camera and computed radiography.

What does the study involve?

Overview of the Study

This study is taking place at the **Radiation Isotopes Center of Khartoum** and will involve the participation of 200 male volunteers which assigned to participate, all of them have prostate cancer.

To determine whether you meet the study criteria, your medical file will be reviewed for information on: prostate cancer diagnosis; treatment chosen; hormone therapy use and length of therapy; medical history; and prescription medications, and you will be asked a series of questions over the telephone.

Study Procedures

If you agree to take part in this study, the procedures you can expect will include the following:

Interview

You will be asking to complete an interview at a place most convenient for you, the entire interview will take approximately 10 minutes.

The interview will include a few questions about the period of treatment, the medication, and the history about the skeletal health, if there any prior fracture.

Examinations

You will be asked to promise to take x-ray images for hip and spine (3 images).

One take in Lateral position and two images take in supine position and to period of 10-15 minutes.

Risk and Potential Benefits:

There are no anticipated risks or harms associated with participating in this study.

No one knows whether or not you will benefit directly from this study. There may or may not be direct benefits to you from taking in this study. We hope that the information learned from this study can be used in the future to benefit men with prostate cancer being treated with hormone therapy.

Consent:

It is entirely up to you whether you want to take in this study or not. The health care that you usually get will not be changed in anyway by the choice you make about taking part in this study. You can change your mind and withdraw from this study at any time. By signing this consent form, you are agreeing to participate in this study and acknowledge that you have

received a copy of this consent form for your own records. By signing this consent form, you do not waive any of your legal rights.

Study Costs:

You will not be paid for participating in this study.

Confidentiality:

Your confidentiality will be respected. All forms and responses will be kept completely confidential. All forms will be coded with a number. Data will be kept in a locked filing cabinet and only used for the purpose of this research.

If you have any questions regarding this study or desire further information you may contact the supervisor

Prof.Dr .Mohammed Elfadel Mohammed at ----------

If you have any concerns about your rights as a research subject participating in this study, you may contact on Sudan University of science and Technology College of graduate studies at_____

I have read the above information and I have had a chance to ask any questions about the study and my involvement. I understand what I have to do and what will happen if i take in this study. I freely choose to take this study and l have a copy of the consent form.

Name of participant **Signature**

_____ _____

Date: /…/ 201..

إستمارة طلب موافقة

من الشخص المشارك في البحث أو من ينوب عنه

أنا الباحـث : أيمن سالم زين علوي

المؤسسة : جامعة السودان للعلوم والتكنولوجيا

القســـم : الطب النووي

المؤهل المطلوب : دكتوراه

أقوم ببحث ودراسة عن :

(تقويم هشاشة العظام في مرضى سرطان البروستات باستخدام المسح الذري والاشعة السينية).

عزيزي المشارك :

لقد تم اختيارك لتشارك في هذا البحث أنت ومعك عدد آخر من المرضى من مرضى البروستاتا الذين خضعوا لعلاج هرموني خلال فترة العلاج ..

مرضى سرطان البروستاتا للتأكد من نتوقع بمشاركتك أنت والمرضى الآخرين أن نتحصل على نتائج تفيد سلامة العظم بتقنيات بسيطة وغير مكلفة مثل الاشعة السينية ..

بتصوير عظم الحوض وجزء من العمود الفقري بواسطة الاشعة السينية . خلال هذه الدراسة سنقوم مع خلو هذا الفحص من أية مخاطر تذكر .

ونحن إذ نأمل في مشاركتك معنا في هذا البحث , نؤكد لك على سرية المعلومات و الوثائق الخاصة بك , و أنه لن يطلع عليها إلا الباحث .

ونود أن نشير كذلك إلى أن المشاركة في البحث طوعية وأن رفضك للمشاركة في البحث لا تفقدك الحق في أي فوائد من البحث ,و أنه بمشاركتك ستكون أحد المتطوعين والذين يشملهم البحث و عددهم حوالى 100مشارك متطوع .

.....

إذا كان لديك أي سؤال أو إستفسار يخص البحث , المشاركين معك في البحث , أو حقوقك كمشارك أثناء تنفيذ البحث يمكنك تقديم السؤال مباشرتا دون تردد.

موقعاً فورم إقرار موافقة المشارك في البحث

إقرار المشارك :

لقد أطلعت على المعلومات الحالية والتي تم شرحها لي وأتيح لى طرح الأسئلة عنها كيفما شئت , و قد تلقيت الإجابات الوافية عن كل الأسئلة , و أنا أقر بالموافقة على المشاركة متطوع في هذه الدراسة و أعلم بحقي في التوقف عن المشاركة في أي وقت دون أن يؤثر ذلك على حقوقي في تلقى العناية الطبية اللازمة في أي وقت لاحقاً

رمز المشارك.....

إسم المشارك: .....

توقيع المشارك

.....

رمز من ينوب عن المشارك(في حال عدم قدرة المشارك على قراءة الإقرار ويحتاج إلى من يشرح أو يترجم له)

.....

توقيع من ينوب عن المشارك شرعاً.....

عنوان من ينوب عن المشارك:.....

مع خالص الشكر لتعاونكم

توقيع الباحث: .....

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ASSESSMENT OF OSTEOPOROSIS IN PATIENTS WITH PROSTATE CANCER USING COMPUTED RADIOGRAPHY

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ABSTRACT
In this paper we assessment of osteoporosis in patients with prostate cancer using computed radiography, the Bone metastases are a common cause of morbidity in patients with prostate carcinoma. Imaging bone metastases from prostate cancer presents several challenges. The lesions are usually sclerotic and appear late on the conventional X-ray. patient's osteoporosis with prostate cancer imaging with x.ray and the images analysing by Interactive Data Language IDL software version 6.1 to measure the grey level variation of x.ray images with spine and hip examinations, data was available for 200 patients with x.ray hip and spine examinations , 100 normal and 100 osteoporosis patients with hip and spine x.ray. The results show that the mean of up normal and normal CR for hip regions was 2526.43±310.63 and 619.67±86.39, and for normal and up normal CR spine the mean was 1988±592.44 and 598.77±73.44. and by using T.Test show that there is significant difference between normal and up normal CR for hip regions. and between normal and up normal CR spine. Linear regression results show that the rate of change between normal and up normal hip decreasing, and same for normal and up normal CR spine. Conclusion: there is significant difference between normal and up normal CR for hip regions, and between normal and up normal CR spine, and the rate of change between normal and up normal hip decreasing, for normal and up normal CR spine.

KEYWORDS: Osteoporosis, prostate cancer, Computed Radiography.

INTRODUCTION
Prostate carcinoma is one of the most common cancers in men worldwide.[1,2] Bone is a preferred and sometimes the only, site for prostate cancer metastases, which occur in more than 80% of men with advanced prostate cancer.[3,4] In addition to bone metastases, bone loss resulting from previous orchiectomy or hormonal therapies that lower or block androgen activity may contribute to an increased risk of fracture, pain and other skeletal complications.[5–8] Complications from bone metastases are a major cause of morbidity in patients with prostate carcinoma, causing pain, spinal cord compression, pathologic fractures and abnormalities in serum calcium levels.[9]

There are several available methods for treatment of patients with PCa, such as active surveillance, resection, radiotherapy and androgen deprivation. Gonadotropin-releasing hormone analogs may be indicated as adjunctive therapy in the treatment of metastases or as the therapy of choice in biochemical recurrence of primary disease.[10]

From the age of 40 on, there is deterioration in bone health. Maternal family history of osteoporosis, smoking, diabetes mellitus, alcoholism and drug use. Although the risk to bone health is recognized, usually patients using GnRHaare not evaluated for osteoporosis. Often the bone mineral density (BMD) before the start of antiandrogenic therapy (ADT) is not performed and in many cases, analysis of bone health is performed only after a major adverse outcome (fracture) has occurred increase the risk of developing osteoporosis.[11-13] and bone loss resulting from previous orchiectomy or hormonal therapies that lower or block androgen activity may contribute to an increased risk of fracture, pain and other skeletal complications.[14-17] Complications from bone metastases are a major cause of morbidity in patients with prostate carcinoma, causing pain, spinal cord compression, pathologic fractures, and abnormalities in serum calcium levels.[18]

MATERIAL AND METHOD
The data collected from Radiation and Isotopes Center of Khartoum (RICK) and Antalyia Diagnostic Center, where 200 patients, used x.ray machines (philps and shemadzu), patients osteoporosis with prostate cancer imaging with spine and hip x.ray examinations analysing the image with Interactive Data Language IDL software version 6.1 to measure the grey level variation of images

with spine and hip area, data was available for 200 patients with x.ray hip and spine examinations, 100 normal and 100 osteoporosis patients with hip and spine x.ray.

And the collected variables: age, Body Mass Index, weight, height and bone scan image. x.ray, PSA and period of starting hormone therapy.

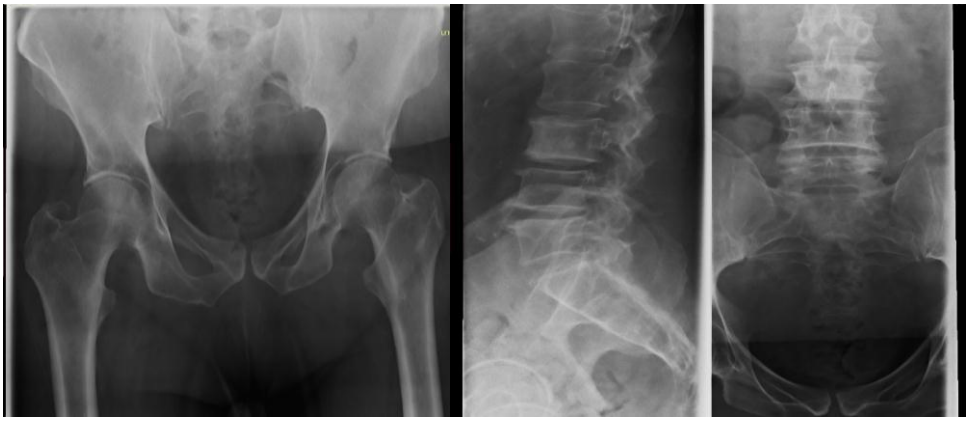

Fig: 1 Show x.ray images for up normal hip and spine

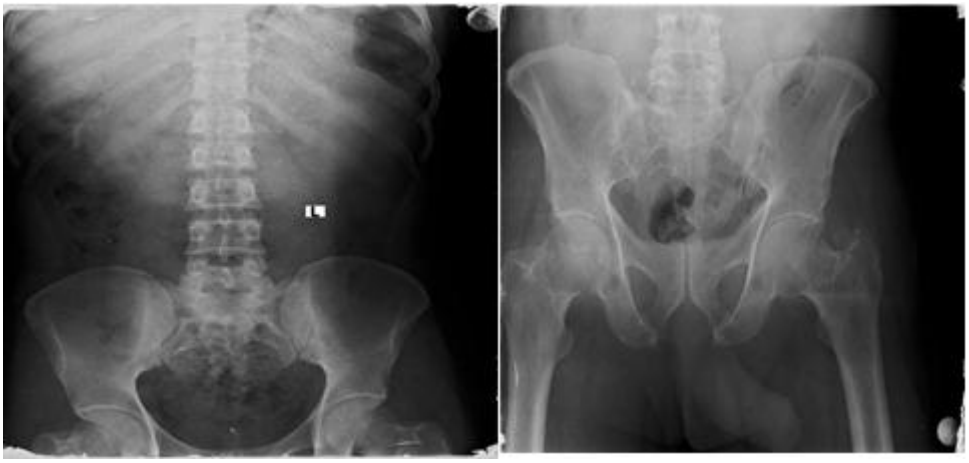

Fig: 2 Show x.ray images for normal hip and spine

RESULTS AND DISCUSSION

Table: 1 show statistical parameters for all patients

	Mean	Median	SD	Min	Max
Age	**69.43**	**70.5**	**10.52**	**45**	**89**
Period of Treatment	2.41	2	1.28	1	7
High	169.9	169.5	8.34	149	192
Weight	75.33	74	12.25	42	114
PSA	5.36	5.30	2.33	0.02	10.4
BMI	25.96	26.35	3.46	15.43	33.49
Up normal CR Hip	2526.43	2505.5	310.63	1978	3197
Up normal CR Spine	1988	1926	592.44	1245	3184
Normal CR Hip	619.67	618.5	86.39	440	760
Normal CR Spine	598.77	599	73.34	417	711

Table: 2. show paired sample for all images

Paired Samples Statistics			
		Mean	Std. Deviation
Pair 1	Up normal Hip CR	2526.43	310.63
	Normal Hip CR	619.67	86.39
Pair 2	Up normal Spine CR	1988	592.44
	Up normal Spine CR	598.77	73.34

Table: 3. show T.Test for equality of means CR normal and up normal images

		t-test for Equality of Means	
		t	P.value
Hip CR	Equal variances assumed	32.392	.000
	Equal variances not assumed	32.392	.000
Spine CR	Equal variances assumed	12.747	.000
	Equal variances not assumed	12.747	.000

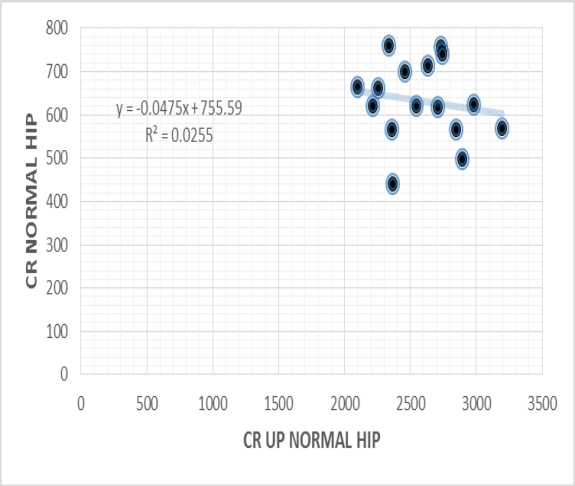

Figure: 3 show correlation between CR normal and up normal hip images

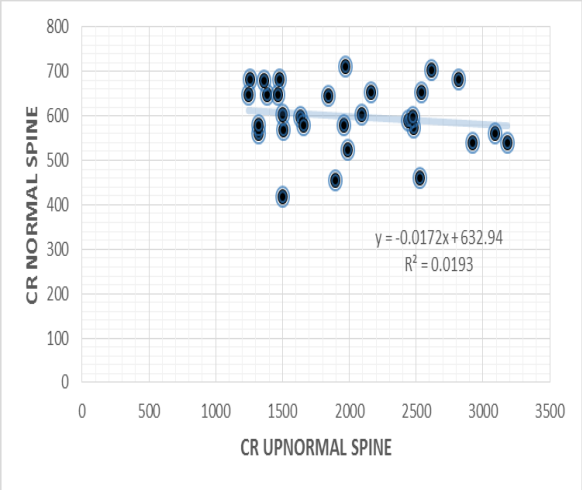

Figure 4. show correlation between CR normal and up normal spine images

DISCUSSIONS

Assessment of osteoporosis in patients with prostate cancer using computed radiography for 200 patients (100 Normal and 100 Up normal patients) and we using statistical parameters to show the data, for age the mean±SD was 69.43±10.52 and for weight, high, body mass index and PSA 75.33±12.25, 169.9±8.34, 25.96.3.46 and 5.36±2.33 respectively, **table 1** . And the values for images measurement the mean for Up normal CR for hip regions 2526.67±310.63, Up normal CR spine 1988±592.44, for Normal CR hip 619.67±86.39, Normal CR spine 598.77±73.34 **table 1.**

The mean of up normal and normal CR for hip regions was 2526.43±310.63 and 619.67±86.39, and for normal and up normal CR spine the mean was 1988±592.44 and 598.77±73.44 **table 2.**

Using show T.Test for equality of means CR normal and up normal show that there is significant difference between normal and up normal CR for hip regions **table 3.** And between normal and up normal CR spine **table 3.**

Linear regression results show that the rate of change between normal and up normal hip decreasing by 0.0475 versus one unit of up normal **fig 3.** and by rate of 0.0172 versus one unit of up normal CR spine **fig 4.**

CONCLUSION

Assessment of osteoporosis in patients with prostate cancer using Computed Radiography show that there is no significant difference between normal and up normal hip and spine regions.

And the Linear regression results in decreasing rate between normal CR hip and spine and up normal G.C for hip and spine, per one unit for normal CR versus up normal G.C spine. and estimated of *values between the normal and up normal* hip and spine calculated using the following linear equations:

CR normal hip = - 0.0475 (up normal CR hip) +755.59

CR normal spine = - 0.0172 (up normal CR spine) + 632.94

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Assessment of Osteoporosis in Patients with Prostate Cancer using Gamma Camera

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Abstract: ***Background: Prostate cancer is one of the most common diseases in the world. can primarily disseminate to the bone, causing bone metastases, which in turn can lead to death. To treat the disease, it is important to diagnose bone metastases as soon as possible. Bone metastases are diagnosed usually by bone scan imaging (Gamma Camera). However, interpretation of bone scan images is not always an easy task for physicians. One way of minimizing the risk of misinterpretation is quantitative analysis of bone scan images in order to ascertain whether they show any metastatic lesions, and if so, to what extent. The aim of the thesis was to assessment of osteoporosis in patients with prostate cancer using Gamma Camera and computed radiography (x.ray). Methods: patients osteoporosis with prostate cancer imaging with gamma camera and computed radiography (x.ray), analysing the image with Interactive Data Language IDL software version 6.1 to measure the grey level variation of images with spine and hip area, data was available for 200 patients, 100 patients with x.ray images for hip and spine and 100 for patients with bone scan using Gamma Camera. Results: The mean of up normal G.C hip and normal CR for hip regions was 630.67±92.64 and 619.67±86.39, and the mean for up normal G.C spine and normal CR spine the mean was 582.57±87.57 and 598.77±73.34. Using T.Test show that there is significant difference between normal CR and up normal G.C for hip regions (0.00). And between normal CR and up normal G.C spine (0.00).Linear regression results show that the rate of change between normal CR hip and up normal G.C hip Increasing by 0.8301. And 0.6607 for normal CR and up normal G.C spine. Conclusion: there is significant difference between normal CR and up normal G.C for hip regions, and between normal CR and up normal G.C spine, and the rate of change increasing for normal CR and up normal G.C spine.***

Keywords: osteoporosis, prostate cancer, Gamma Camera, Computed Radiography

1. Introduction

Prostate cancer is the second most common cancer in men,accounting for 1 in 9 of all new cancers, and with more than670,000 new diagnoses annually worldwide. The metastatic spreadis primarily in the skeleton (supporting the 'seed-and-soil'hypothesis described by Paget in 1889) in which lesions are oftenlocated in vertebra and ribs because of dissemination throughBatson's venous plexus. The spread in bone also follows thedistribution of adult red bone marrow, that is, skull, thorax, pelvis,spine, proximal long bones [1,2],subsequently progressing to involve adjacent cortical bone.

Preclinical models confirm that skeletal sites rich in cellularmarrow with active turnover show increased cancer localization [3]. Although predominantly osteoblastic, osteoclast activation also has an important role in the growth ofsclerotic metastases in the bone. In a study of 68 men withprostatic bone metastases who underwent surgery for stabilization of pathological fracture or impending fracture, most metastaseswere osteoblastic, but 29.1% had metastases that were osteolytic ormixed [4].

Skeletal metastases occur in approximately 90% of patientspresenting with advanced prostate cancer, and the burden of bonedisease directly correlates with survival [5,6]. After treatment of the primary site, bone isthe first site of relapse in more than 80% of cases [7]. Plain film and bone scintigraphy studies form the mainstayof detection, but they underestimate true incidence. In one autopsyseries of 1589 men with prostate cancer (47% were unsuspected), the incidence of metastatic bone disease was 90% [8].

The detection of bone metastases indicates progression to lethalprostate carcinoma [2]. At this stage, complete remissions are rare and onset of the complications of bone metastases are likely [7]. The investigation oftherapeutic interventions to slow the progression of bone diseaseand its complications make the need for accurate assessment ofdisease burden in the bone and its response to treatment offundamental importance. PSA is used widely to monitor responseto therapy, with a decrease in PSA to the normal range aftertreatment used as a predictor of prolonged response in manypatients [9]. However, PSA levels are influenced byboth soft tissue and bony disease and PSA does not always correlate with tumour burden.

The most widely used imaging modality for detection of pathologicalchanges in bone – osteoblastic activity – is bone scintigraphy. The mainclinical indication for bone-scan imaging is evaluation of metastatic disease.

The most common patient group referred for bone scans is prostate-cancerpatients who are being examined to diagnose metastatic disease. Referrals areespecially common in high-risk patients and for evaluation of treatmentresponse. Prostate cancer has a tendency to disseminate to lymph nodes andthe skeleton as the preferred organs [10].

This non-invasive nuclear-medicine imaging examination is performed using a gamma camera (Fig. 1). Whole-body bone scans are obtained three to four hours after administration of 600 MBq 99 16 m -technetium methylene diphosphonate (MDP) [11]. The scanning procedure takes about 25 minutes and the result is two two-dimensional images – an anterior and a posterior image. These two-dimensional images are usually enough to show whether there are any pathological changes in the skeleton.

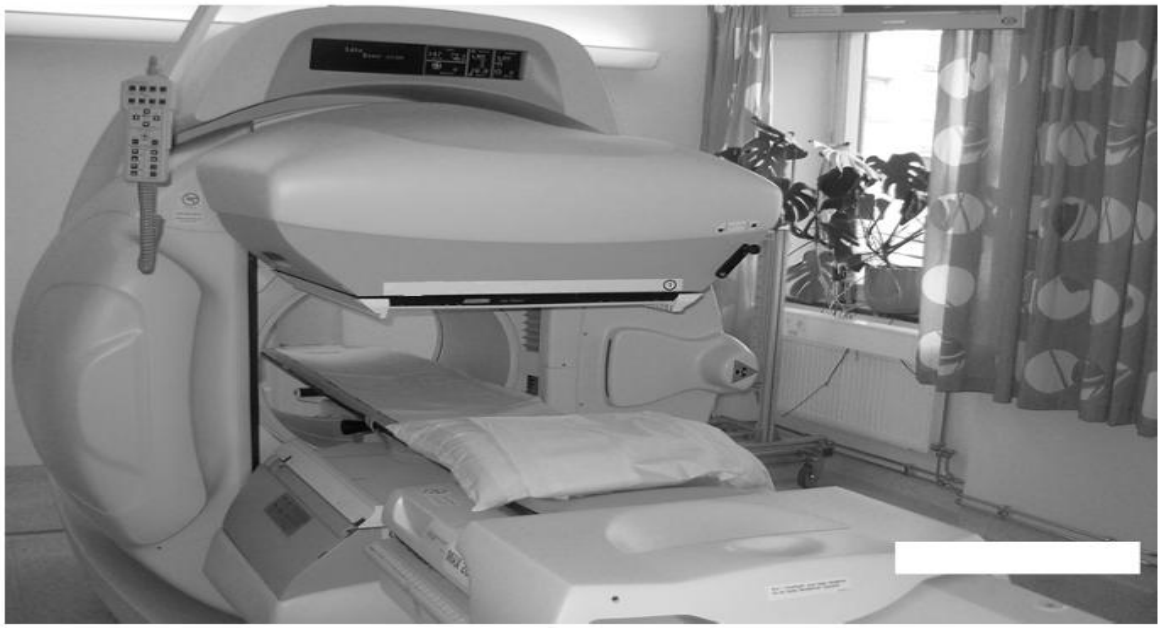

Figure 1: A gamma camera with capability to acquire planar whole-body and tomography images

2. Material and Method

The data collected from Radiation and Isotopes Center of Khartoum (RICK) and Antalyia Diagnostic Center, where 200 patients, used medical imaging system gamma camera model Mediso, and x.ray machine philps, patients osteoporosis with prostate cancer imaging with gamma camera and x.ray analysing the image with Interactive Data Language IDL software version 6.1 to measure the grey level variation of images with spine and hip area, data was available for 200 patients, 100 patients with x.ray images for hip and spine and 100 for patients with bone scan using Gamma Camera

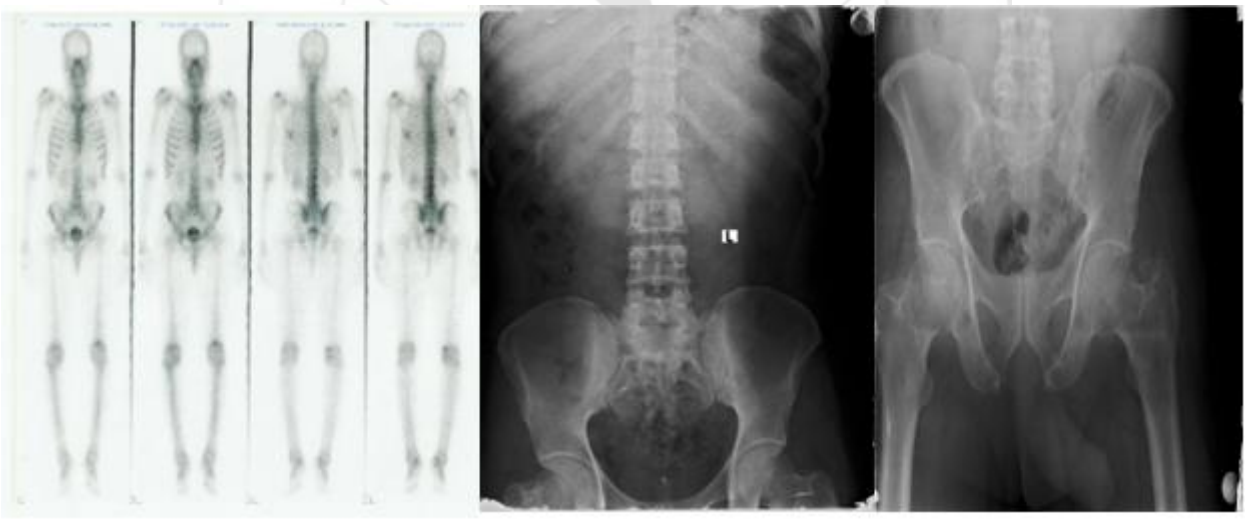

Figure 2: Bone scan using gamma camera and spine, hip x.ray examinations

And The collected variables: age, Body Mass Index, weight, height and bone scan image. x.ray images of lumber spine and hip bone (DXR), PSA, and period of starting hormone therapy.

3. Results and Discussion

Table 1: Show statistical parameters for all patients

	Mean	Median	SD	Min	Max
Age	69.43	70.5	10.52	45	89
P of T	2.41	2	1.28	1	7
High	169.9	169.5	8.34	149	192
Weight	75.33	74	12.25	42	114
PSA	5.36	5.30	2.33	0.02	10.4
BMI	25.96	26.35	3.46	15.43	33.49
Up normal G.C Hip	630.67	620.5	92.64	440	760
Up normal G.C Spine	582.57	584.5	87.57	357	711
Normal CR Hip	619.67	618.5	86.39	440	760
Normal CR Spine	598.77	599	73.34	417	711

Table 2: Show sample for all images:

Paired Samples Statistics			
		Mean	Std. Deviation
Pair 1	Up normal G.C Hip	630.67	92.64
	Normal CR Hip	619.67	86.39
Pair 2	Up normal G.C Spine	582.57	87.57
	Normal CR Spine	598.77	73.34

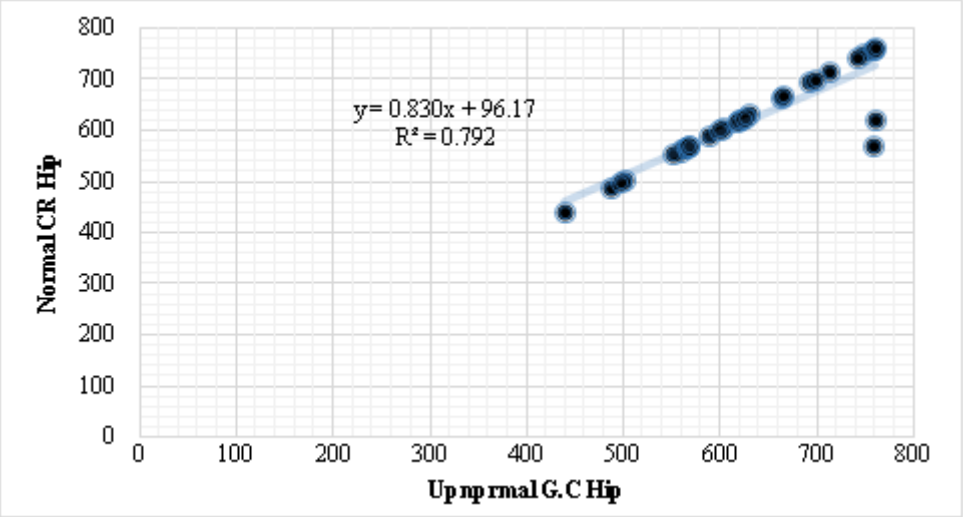

Figure 3: Show correlation between CR normal and G.C up normal for HIP images

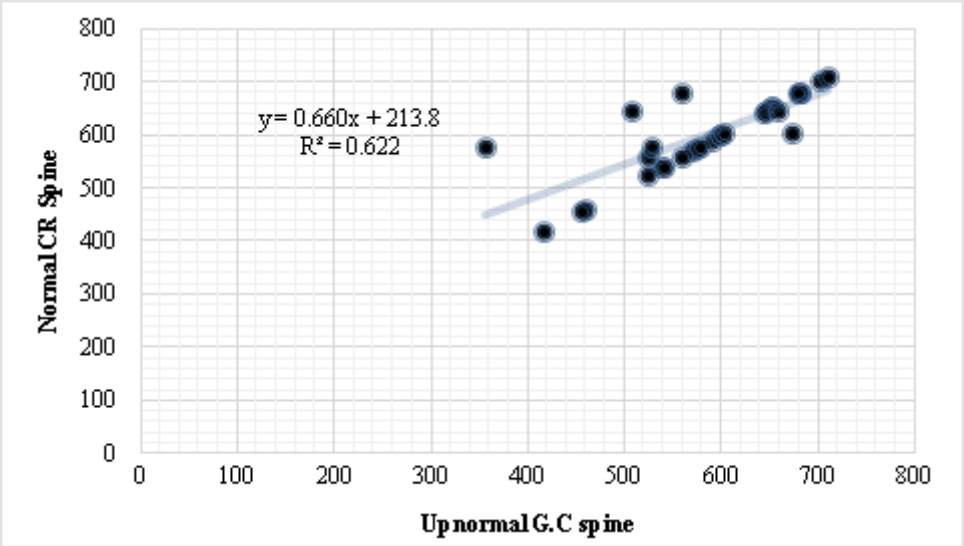

Figure 4: Show correlation between CR normal and G.C up normal for SPINE images

4. Discussions

Assessment of osteoporosis in patients with prostate cancer using Gamma Camera for 200 patients (100 Normal and 100 Up normal patients), and we using statistical parameters to show the data, for age the mean±SD was 69.43±10.52 and for weight, high, body mass index and PSA 75.33±12.25, 169.9±8.34, 25.96.3.46 and 5.36±2.33 respectively, **table 1** . And the values for images measurement the Up normal G.C for hip regions 630.67±92.64, up normal G.C spine582.57±87.57 , for Normal CR hip 619.67±86.39, Normal CR spine 598.77±73.34 **table1.**

For compare the mean of up normal G.C hip and normal CR for hip regions was 630.67±92.64 and 619.67±86.39, and the mean for up normal G.C spine and normal CR spine the mean was 582.57±87.57 and 598.77±73.34 **table2.**

Using T.Test show that there is significant difference between normal CR and up normal G.C for hip regions (0.00) **table 3.** And between normal CR and up normal G.C spine (0.00) **table 3.**

Linear regression results show that the rate of change between normal CR and G.C hip imagesIncreasing by rate 0.8301 for normal CR versus one unit of up normal G.C hip**fig 3.**and by rate of 0.6607of normal CR versus one unit of up normal G.C spine images **fig 4.**

5. Conclusion

Assessment of osteoporosis in patients with prostate cancer using Computed Radiologyand Gamma Camera show that there is significant difference between normal CR and up normal G.C hip and spine regions.

And the Linear regression results show rate of change between normal CR and up normal G.C hip was decreasing by rate 0.0475 for normal CR versus one unit of up normal G.C hip, and by rate of 0.0172 for normal CR spine versus one unit of up normal G.C spine.

And estimated of *values between the normal CR and up normal*G.C hip and spine images calculated using the following linear equations:

CR normal hip = 0.8301(up normal G.Chip) +755.59
CR normal spine = 0.6607(up normal G.C spine) + 632.94

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