A determination of normal reference ranges for bone mineral density for Indian women of varying age groups in KZN: the impact of local data on the diagnosis of osteoporosis.

BY

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DECLARATION:

Except for quotations specifically indicated in the text and such help as I have acknowledged, this dissertation is wholly my own work, and has not been submitted for any qualification at any other institution.

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DEDICATION

This dissertation is dedicated to my Husband, Harold, for his unrelenting support

And my Precious Sons, Sashan and Rishay

Who keep me humble by being who they are!

They bring me more joy than I could ever hope for!

Being your MOM is my greatest reward.

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ABSTRACT

Aim / Research questions

The aim of this research was to determine normal bone mineral density (BMD) reference ranges (means and standard deviations) for the lumbar spine, total hip and distal forearm, for Indian women of varying age groups in KwaZulu-Natal. The aim also included a comparison of the study population reference ranges with those provided by the manufacturer in order to evaluate any diagnostic implications.

Motivation

The importance of the BMD measurements is that it is recognised as the key determinant of bone strength and fracture risk and is a means of classifying osteoporosis, in terms of T-scores. The World Health Organisation (WHO) had established diagnostic criteria based on these T-scores and provides clinicians with a practical way in which to identify individuals with osteoporosis and those at risk of developing the disease. However, the calculation of T-scores depends on having appropriate population BMD reference ranges. Global variations in BMD values have been reported, however, these values have not been assessed in the Indian women in KwaZulu-Natal. In addition, BMD scanners currently use reference ranges provided by the manufacturers for the calculation of T-scores. If

these reference ranges are not an accurate representation of the population being studied, then application of the WHO criteria will have profound implications with regard to diagnosis of osteoporosis in local populations.

Methodology

Dual energy x-ray absorptiometry (DEXA) BMD measurements at the lumbar spine, total hip and distal forearm were taken on Indian women aged 20 to 66 years, using the Hologic QDR 4500 bone densitometer. The BMD reference ranges for the current study population were compared with the manufacturer's reference ranges, using the WHO diagnostic criteria.

Results / Conclusions

Significant differences between the study populations' and the manufacturer's BMD reference ranges were demonstrated. The BMD normal values for peak BMD in the Indian women in KZN were significantly different from the manufacturer's normal values at all 3 skeletal sites.

The BMD means were 0.972 g/cm^2 and 0.542 g/cm^2 at the lumbar spine and distal forearm respectively, with $p = .000$ at these sites against the Hologic Caucasian female lumbar spine and distal forearm reference data and the BMD mean was 0.863 g/cm^2 at the total hip, with $p = .000$ against the NHANES III Caucasian

female total hip reference data. BMD values in the study population were approximately 8 percent lower at the lumbar spine and total hip and approximately 4 percent lower at the distal forearm, compared to the Hologic and NHANES III Caucasian female reference databases.

The significance of these findings is that some individuals (11 to 14 percent) who were reported osteopaenic using the manufacturer's reference ranges will now be reported normal. In addition to the controversy regarding treatment strategies and its associated side effects, the undue stress and anxiety that usually accompany unexpected "abnormal" results could be avoided in these individuals.

Recommendations

It is recommended that longitudinal studies are undertaken in, not only the study population, but all the population groups of South Africa to determine BMD statuses as well as the epidemiology of osteoporosis in these populations. This will ensure accurate diagnosis of osteoporosis among these population groups. Other recommendations include re-evaluating the benefits of screening for secondary osteoporosis in the study population, re-evaluating the current recommendations for screening in the different populations, as well as investigating urban versus rural populations.

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LIST OF ABBREVIATIONS

BMD	**-**	**Bone Mineral Density**
DEXA	**-**	**Dual Energy X-ray Absorptiometry**
DUT	**-**	**Durban University of Technology**
ICSBM	**-**	**International Committee for Standards in Bone Measurement**
ISCD	**-**	**International Society of Clinical Densitometry**
KZN	**-**	**KwaZulu-Natal**
MRCSA	**-**	**Medical Research Council of South Africa**
NHANES III	**-**	**National Health and Nutrition Examination Survey III**
NIH	**-**	**National Institute of Health**
NOF	**-**	**National Osteoporosis Foundation**
NOFSA	**-**	**National Osteoporosis Foundation of South Africa**
PBM	**-**	**Peak Bone Mass**
QCT	**-**	**Quantitative Computed Tomography**
QUS	**-**	**Quantitative Ultrasound**
SA	**-**	**South Africa**
SD	**-**	**Standard Deviation**
SEXA	**-**	**Single Energy X-ray Absorptiometry**
US	**-**	**United States**
WHO	**-**	**World Health Organisation**

CHAPTER 1

BACKGROUND TO THE STUDY

"EXPERIENCING a few weeks with an immobilised broken limb, or the increasing limitations of a progressive bone illness such as osteoporosis, underscores how important the skeletal system is to our enjoyment of life"

(Shier, Butler and Lewis, 1996)

1.1 INTRODUCTION

One of the achievements of modern medicine is the increase in life expectancy. According to the World Health Organisation (WHO), older persons defined as 60 years and older are growing in numbers in virtually all countries worldwide. This trend is particularly significant in the developing countries, where it is predicted to be in excess of 700 million by the year 2020 (WHO Technical Report Series 921, 2003).

South Africa (SA) has the highest proportions of older populations within Southern Africa, with 5.6 million people older than 50 years (Kinsella and Ferreira, 1997). Population estimates for 2005 indicated that approximately 2.6 million (6%) people will be older than 60 years in SA (Kinsella and Ferreira, 1997). The Statistics South Africa mid-year population estimates for 2005 also showed that there would be approximately 600 000 Asian women residing in SA, with approximately 21% of them older than 50 years (Statistics South Africa, 2003).

The majority of the Asian (from now referred to as Indian in the text) population in SA are descendants of immigrants from India. The consensus report also indicated that KwaZulu-Natal (KZN) has the largest share of SA's total population at 9.6 million and of these there are approximately 827 000 Indians. Of particular importance to the current study, the report indicated that approximately 267 000 Indian women aged between 20 and 69 years reside in KZN and approximately 75% of the total Indian women in SA, aged 50 years and older reside in KZN (Statistics South Africa, 2003).

A grave concern with the increase in life expectancy is that it is not accompanied by a disability – free extended life. Osteoporosis is said to be one of the important causes of disability, fractures, aches and pains in old age (Kansra, 2002). According to the WHO (WHO Technical Report Series 921, 2003), osteoporosis is second only to cardiovascular disease as a global healthcare problem. Vaidya, Dholakia and Yadev (2003) further added that one in every 4 women and one in every man older than 50 years are projected to have osteoporosis.

Osteoporosis is a chronic disorder that involves a reduction in bone strength or decreased bone mineral density (BMD), thereby leading to an increased risk of fragility fracture (WHO Technical Report Series 843, 1994). Medical studies as stated by Kanis, Johnell and De Laet (2002) showed that a 50 year old woman has a similar lifetime risk of dying from complications associated with hip fractures as from breast cancer.

According to the WHO (WHO Technical Report 921, 2003), it is predicted that one out of every two women and one in eight men will suffer an osteoporosis related fracture in their lifetime. Shah (2005) added that the incidence of osteopaenia and osteoporosis increases as age advances and together with the progressive ageing of the world's population, a resultant increase in osteoporotic fractures will be evident. Furthermore, Shah (2005) reiterated that globally, 1.5 million fractures occur annually as a consequence to osteoporosis; and these result in either permanent disability, loss of independence or even death. While the fractures caused by this debilitating disease can occur at any site within the body; they are most frequent in the hip, vertebral body and distal forearm, i.e. areas in the skeleton that are rich in trabecular bone.

Globally, the highest incidence of osteoporosis occurs in the Caucasian and Asian populations, and these populations are important risk factors for osteoporosis (WHO Technical Report Series 843, 1994). Joshi, et al. (1998) further indicated that the burden of osteoporosis in the Indian scenario will be immense, as in India alone the population of postmenopausal women will be the second highest in the world by 2030, second only to China. Additionally, Indians from the Indian subcontinent have BMD values that are approximately 15% lower than those in Caucasian women (unpublished data, Shah and Savardekar as cited by Shah, 2005). An earlier study undertaken by Reddy, Mithal and Rao (2002) showed a similar variance in Indians residing in America.

A further concern is that Indians living in the Indian subcontinent are known to suffer osteoporotic fractures approximately 10 to 20 years earlier than Caucasians (Shah, 2005). Fragility fractures are a consequence to osteoporosis and early identification of individuals at risk for fractures due to increased bone loss is critical to ensure optimal management of this debilitating disease.

The magnitude of the problem of osteoporosis and its consequences in South Africa's populations is very limited and most of the available data are from the first world countries. Additionally, the statuses of BMD in the local populations of SA are very limited and in the Indian community are non-existent. The assumption that a similar variance exists in the Indian women in KZN, SA has been explored in this study. Future epidemiology studies in the local population will confirm osteoporotic fracture incidences.

A few studies have documented BMD measurements for children (Patel, *et al*. 1993) and White and Black females (Daniels, *et al*. 1995) in SA; however, there is no known evidence of BMD measurements in the Indian female population. Currently, the Bone Mineral Unit of the Medical Research Council (MRC) of SA are currently undertaking the Birth to Twenty Study, which commenced in 1990, evaluating ethnic differences in children living in Johannesburg, SA. They are also investigating post menopausal Black women, with the aim of providing an insight into the reasons for lower postmenopausal fracture rates in SA Black women.

Globally, osteoporosis ranks as one of the five most costly diseases of aging after diabetes, hyperlipidaemia, hypertension and cardiovascular disease (WHO Technical Report Series 843, 1994). In addition to the economic burden for this disease, other consequences include physical and psychosocial related issues. According to the National Institutes of Health (NIH Consensus Statement, 2000), these significantly affect the individual as well as the family and community. The statement further reported that osteoporosis is no longer considered age or gender dependent, even though it was once thought to be natural part of ageing among women.

In this light, it is desirable to identify individuals who might be at medium to high risk for osteoporosis; with the goal for initiating treatment early enough to prevent future fractures. According to Fogelman and Blake (2000), there has been remarkable progress and evolution in the diagnostic and therapeutic options for management of this disease, thereby making menopausal osteoporosis largely preventable.

Clinically BMD measurements provide such reliable quantitative evidence to assess the severity of osteoporosis and any changes in bone mass are commonly used as a surrogate for fracture risk (Cummings, *et al*. 1993). Several different techniques have been developed to measure bone mineral density at multiple skeletal sites, including the hip, spine and peripheral skeleton (Adams, 1997). These include plain film radiography, radiographic absorptiometry, single and dual photon absorptiometry, quantitative computed tomography, quantitative ultrasound, single and dual energy x-ray absorptiometry.

Dual Energy X-ray Absorptiometry (DEXA) is considered the 'gold standard' technique for assessment of BMD status, as well as monitoring osteoporosis in an individual (NIH Consensus Statement, 2000). In fact, the WHO established criteria based on DEXA BMD for the diagnosis of osteoporosis (WHO Technical Report Series 921, 2003). BMD measurements of the lumbar spine, total hip and distal forearm, using DEXA technology, were undertaken in the current study.

In clinical practice the absolute BMD values (in g/cm^2) are not normally used for assessing skeletal status and fracture risk, as they vary depending on the measuring instrument used or the skeletal site measured (Watts, 2002). Instead, they are expressed in terms of the number of standard deviations (SD) above or below the average peak BMD value (reference data) for young adults of the same sex and ethnicity. This is commonly referred to a T-score; and is used to diagnose an individual's bone status as defined by the WHO classification system for osteoporosis. BMD values are also expressed in terms of the number of SDs above or below the average age-matched normal BMD value (reference data), commonly referred to a Z-score, and assesses fracture risk relative to an individual's age (Cummings, Black and Bates, 2002).

In addition, the WHO had established the diagnostic criteria for osteoporosis based on these T-scores and not the absolute BMD values. The criteria define osteoporosis as a T-score of less than 2.5 SDs below the young adult normal mean for BMD of a skeletal site (Kanis and Gluer, 2000). Binckley, *et al*. (2002) added that this definition

depends on having BMD reference values (mean ± SD) for each skeletal site for a particular reference population. This implies that even if an inappropriate reference population is chosen, then the T-score can easily be adjusted accordingly, although highly inaccurate. In this light, the determination of reliable reference values that accurately represent the population at large is essential for the correct identification of osteoporosis from BMD measurements.

1.2 MOTIVATION FOR THE STUDY

The increasing life expectancy in many parts of the world means that women now live more than one-third of their lives after menopause, and that the number of postmenopausal women is increasing (WHO Technical Report Series 921, 2003). The changing pattern in the length of life in general emphasises the vulnerability of the elderly with particular reference to osteoporosis and its consequences, i.e. fragility fractures.

A fracture is usually the most common presentation for osteoporosis, and is often a late occurrence in this disease process. Hence, it is desirable to identify individuals who might be at moderate to high risk for fracture and low bone mass. BMD measurements provide such reliable quantitative evidence. Consequently, the determination of reliable reference values that accurately represent the population at large is essential for the correct identification of osteoporosis from BMD

measurements. Furthermore, a review of the literature shows that interracial and interethnic variations in BMD measurements exists, and have highlighted the importance of having a reliable ethnic matched reference database for accurate assessment of fracture risk. A more detailed explanation of these variances will be described in Chapter 2. No known study of this nature has been undertaken in Indian women of KZN or SA and the results of the current study will establish the presence or absence of a variance.

Currently, DEXA instruments in operation within KZN use reference ranges for measuring BMD of the spine, hip and forearm provided by the equipment manufacturers, in the absence of local reference data. This raises the question of whether the reference ranges provided by the manufacturers accurately represent of the population being studied. If there is a significant difference in the reference ranges derived from the current study and those of the manufacturers, then application of the WHO criteria will have profound implications with regard to diagnosis. These inaccuracies will give a false assessment of fracture risk, thereby misguiding the clinical management of a patient.

Moreover, there are no reference databases for the SA populations, least of all Indian women. The current study aimed to determine reference data for Indian women residing in KZN. Future studies are needed to determine accurate reference data for the other populations in South Africa. The aim of this study was to determine reference values for BMD measurements, T-scores and Z-scores for the lumbar spine, total hip and distal forearm for the Indian population within KZN and to compare the

mean BMD reference ranges for the study population with the manufacturer's reference ranges currently in use.

1.3 SUMMARY OF CHAPTERS

Chapter 2, the literature review, provides a profile of research that is related to the osteoporosis and its consequences. The role of bone mineral density testing for accurate diagnosis and therapeutic management of this disease is explained. Finally, a summary of existing research in the field is given.

Chapter 3, the methods and design, describes the study population and the inclusion and exclusion criteria that were employed for the selection of the research participants. It also describes the DEXA technique for measuring bone mineral density.

Chapter 4, the results section, documents the data analyses and results. This includes the descriptive statistics and associated inferential statistics are provided for each research question.

Chapter 5 comprises the discussion - the main trends and patterns emerging from the results are discussed. Chapter 6 highlights the significance of the results and recommendations for future research for the accurate diagnosis of osteoporosis in a South African context.

CHAPTER 2

LITERATURE REVIEW

2.1 INTRODUCTION

This chapter provides a profile of the literature related to osteoporosis and the assessment of fracture risk in a given population using bone densitometry. There are commonly four methods of assessing the prevalence of osteoporosis and fracture risk. These include simple calculated osteoporosis risk estimation (SCORE) which is a clinical assessment, as well as biochemical tests, bone densitometry and bone ashing (WHO Technical Report Series 843, 1994).

Bone densitometry is a quantitative measurement of bone mineral density (BMD) status in an individual and measurements are possible using various techniques, which include the use of x-rays, gamma rays and ultrasound. Nevertheless, dual energy x-ray absorptiometry (DEXA) is the gold standard for BMD testing (WHO Technical Report Series 921, 2003) and is the measuring tool used in the current study. The principles of DEXA scanning will be covered extensively, while the other bone densitometry tests will be covered only briefly, as they are not directly applicable to this research study.

This chapter also presents a brief review of the anatomy and physiology of the skeletal system in order to facilitate understanding of the mechanisms of pathophysiology for osteoporosis. It also describes osteoporosis and its consequences, the methods of testing used to identify individuals who have the disease, as well as those who might be at risk. The discussion leads to the importance of accurate reference values that should be used to measure BMD in an individual. It further shows that the reference data should and must be derived from the population being tested, to ensure correct epidemiological evaluation of osteoporosis and the consequent management of the disease.

Globally, research population studies have indicated that the reference data for BMD vary from the manufacturer reference values provided with the DEXA scanners and that there is a need for local population reference values to be published. This is highlighted in the discussion. The chapter ends with statements of the research aims.

2.2 ANATOMY AND PHYSIOLOGY OF SKELETAL SYSTEM

The bones of the adult skeleton comprise of two types of tissue, cortical or compact, and cancellous or spongy bone; and they form bones which are classified: long, short, flat, irregular and sesamoid (Ross and Wilson, 1985:24-26).

The bones of the skeleton are further divided into two groups:

- axial or central skeleton – which comprises the skull, vertebrae, ribs and sternum
- appendicular or peripheral skeleton – which comprises the shoulder and pelvic girdles and the upper and lower limbs (Ross and Wilson, 1985:24-26).

2.2.1 NORMAL CHARACTERISTICS OF BONE

Most bones consist of an outer cortical sheath enclosing a trabecular network of cancellous bone that contains the marrow. The cortical sheath is bounded outside and inside by the periosteal and endosteal surfaces, respectively (Shier, Butler and Lewis, 1996: 187-203). The endosteal surface of the cortical sheath is connected to the cancellous bone and consists of interconnected rods and plates. These structures maximise the strength of the bone while minimising the weight. The rods and plates of the cancellous network are preferentially oriented along the lines of mechanical strain of the bone (Tortora and Derrickson, 2006: 171-191).

In adults, 80% of the skeleton is cortical bone. However, the relative proportions of cortical and cancellous bone vary in different parts of the skeleton. For instance, in the lumbar spine, cancellous bone accounts for about 70 percent of the total bone tissue, whereas in the femoral neck and radial diaphysis, it accounts for about 50 percent and 5 percent, respectively (Shier, Butler and Lewis, 1996: 187-203).

The three measurement sites that are relevant to this study are lumbar spine vertebral bodies, proximal femur (total hip) and radius and ulna (distal forearm). These bones are high in trabecular content and any significant changes in the content leads to decreased bone strength and fragility and are the primary sites for risk of fracture with associated morbidity and mortality.

As a connective tissue, bone is highly specialised and differs from other connective tissue by its rigidity and hardness, primarily due to the inorganic salts that are deposited in its matrix (Shier, Butler and Lewis, 1996: 187-203). These properties are essential, as the functions of the skeleton include maintaining the shape of the human body, protection of the vital organs, and body movement (Resnick, Manolagas and Fallon, 2005).

In addition, bone serves as a reservoir for ions, particularly calcium, that are essential to normal fluid regulation. In fact, bone stores 99% of the total body calcium, which is made available as a response to stimuli produced by a number of hormones, particularly the parathyroid hormone, as well as vitamin D and calcitonin (Tortora and Derrickson, 2006: 186-189). The depletion of calcium from the body due to homeostatic imbalances, causes bone mass to become depleted; which in turn results in bone fragility.

2.2.2 PHYSIOLOGY OF BONE

Bone is a remarkable tissue, and is constantly undergoing change. This change not only occurs in the immature skeleton, where growth and development is apparent, but also in the mature skeleton through the constant and balanced processes of bone formation and resorption (Resnick, Manolagas and Fallon, 2005). Both the shape and structure of bone are continuously renovated and modified by the processes of modelling and remodelling (Tortora and Derrickson, 2006:182), described below.

2.2.2.1 Bone modelling

Bone modelling begins with the development of the skeleton during foetal life and continues until the end of the second decade, when the longitudinal growth of the skeleton is completed (Shier, Butler and Lewis, 1996: 187-203). In the modelling process, bone is formed at locations that differ from the sites of resorption, leading to a change in the shape or macro-architecture of the skeleton. Longitudinal growth of a typical long bone, such as the tibia, depends on the proliferation and differentiation of cartilage cells in the epiphyseal (growth) plate. Cross-sectional growth, such as the increase in girth of the radial diaphysis, occurs as new bone is laid down beneath the periosteum. Simultaneously bone is resorbed at the endosteal surface (Tortora and Derrickson, 2006: 181-182).

Bone modelling may continue, but to a lesser extent, during adult life when resorption at the end endosteal surface increases the mechanical strain on the remaining cortical

bone, leading to the stimulation of periosteal bone apposition. This phenomenon, which increases with ageing and is somewhat more pronounced in men than in women, counteracts the negative effects of bone resorption at the endosteal surface on mechanical strength (Guyton and Hall, 2006: 982-983). This explains why men have stronger bones and higher peak bone mass than women.

2.2.2.2 Bone remodelling

Bone remodelling occurs simultaneously with modelling from foetal life through to skeletal maturity, when it becomes the predominant process that occurs throughout adult life. Remodelling maintains the mechanical integrity of the skeleton by replacing old bone with new. It is a tightly coupled process where bone resorption closely parallels bone formation (Resnick, Manolagas and Fallon 2005).

Bone resorption and bone formation occur at the same place, so that there is no change in the shape of the bone. This constant process of turnover enables the skeleton to release calcium phosphate whenever the net intestinal absorption of this mineral is less than the amount excreted in urine (Tortora and Derrickson, 2006:183-186).

In the adult skeleton, approximately 5–10% of the existing bone is replaced every year through remodelling. This does not occur uniformly throughout the skeleton, but in focal or discrete sites, and is a function of a team of specialised cells called the bone

multicellular unit (BMU). This unit comprises of osteophytes, lining cells, osteoclasts (bone resorption) and osteoblasts (bone formation) (Resnick, Manolagas and Fallon, 2005).

The osteoblasts are present on the outer surfaces of bone and in bone cavities and are responsible for continuously depositing new bone. Osteoblastic activity occurs continuously in all living bones. Conversely, bone is also continually being absorbed where osteoclasts are active (Guyton and Hall, 2006:982).

In summary, the amount of bone in the skeleton at any age is the result of the quantity of bone gained during growth, from foetal development to skeletal maturity, and the loss of bone that occurs with aging.

2.2.3 PEAK BONE MASS (PBM)

Adult bone mass represents the end result of two processes; acquisition of peak bone mass (PBM) during adolescence into adulthood and maintenance of bone density during the middle and later years (Bonjour, *et al*. 1994). PBM is the amount of bone tissue present at the end of skeletal maturation or the bone modelling process (WHO Technical Report Series 843, 1994) and is often regarded as the “bone bank of the remainder of life”. Bonjour, *et al.* (1994) further added that, acquiring a “solid account” contributes to counteracting the inevitable bone loss caused by aging and other illnesses.

According to Riggs and Melton (1992), the exact age for PBM is not known, however, gradual bone loss begins in both men and women between ages 30 and 40. The age at which PBM is attained is highly controversial, and estimates of peak BMD in the different populations vary significantly. Tudor- Locke and McColl (2000) added that various cross-sectional studies have shown that bone mass peaks from late adolescence, to the third decade, extending into the fourth decade of life and even beyond. Similarly, the reason why bone formation exceeds resorption up to the peak bone mass age, followed by bone resorption exceeding bone formation is not also fully understood. Nevertheless, literature shows that PBM is influenced by genetic and heredity factors, race and ethnicity, gender, endocrine factors, and lifestyle factors that include diet and exercise.

Genetic factors are recognised as a major determinant of peak bone mass. According to Baran, *et al.* (1999a), this has been confirmed in Twin Studies, as well as studies that have shown a positive relationship between the bone mass of mothers and daughters. Understanding the role played by genetic factors has twofold benefits. The first being the discovery of genetic markers that predict osteoporotic fractures followed by the early identification of individuals at high risk and their response to treatment (Tudor-Locke and McColl, 2000) . Although an important consideration, genetic factors and its influence on bone mass were not included in the aims of this study, as this was beyond the scope of this study.

Many studies have also shown that normal PBM values are influenced by ethnicity and/ or race (population). Local (Daniels, *et al*. 1995) and international studies (Looker, *et al*. 1998) have shown that Whites (Caucasians) have lower peak bone mass than Blacks. Asian studies (Leong and Feng, 1997; Iki, *et al*. 2001; Laio, *et al*. 2003) have shown that generally, multi-ethnic Asians have lower peak bone mass than Caucasians.

In addition to ethnic differences, variances in PBM exist among the peers in a particular ethnic group. For example, BMD values in European Caucasians are exceeded by American Caucasians (Petley, *et al*. 1996; Ahmed, *et al*. 1997; Holt, *et al*. 2002; Pedrazzoni, *et al.* 2003). A study comparing Chinese, Japanese and Caucasian women performed by Wu, *et al*. (2003) also showed that bone mass varies among the different ethnic groups of Asian descent.

The Japanese Population – Based Osteoporosis Study (JPOS) is another study that showed that PBM in the same population varies from one geographical area to another, sometimes even in the same country (Iki, *et al.* 2001). Environmental and lifestyle factors seemed to be the key explanations for the differences noted. These differences were also identified in a study undertaken by Roy, *et al*. (2005) in the United Kingdom (UK), where inter-ethnic variances between Pakistani Muslim and Gujarati Hindu individuals were evident, both descendants from the Indian subcontinent.

All of the above issues around PBM raise questions of:

- whether these scenarios are applicable to the South African populations in general, but in particular reference to the current study, Indian women.
- how urbanisation and westernisation will influence PBM in the different populations in South Africa (SA), including Indian women.

The former question with specific reference to Indian women will be addressed in the current study; however the latter is an area for future research. Although the current study used the convenience sampling technique, it allowed for the heterogeneity within the Indian women. As shown by Roy, et al. (2005) inter-ethnic differences that include genetics, environmental factors and lifestyle factors do exist and should not be discounted. So the current study sample comprised of reasonable representation from the various Hindu, Muslim and Christian subgroups of Indian women in KZN, while the intention was not to compare the inter-ethnic differences.

As stated earlier, PBM is also influenced by environmental factors together with nutritional factors particularly during growth, hormonal factors and lifestyle factors which include diet and physical activities (WHO Technical Report Series 921, 2003). While the aim of the current study did not include the epidemiology of osteoporosis in the study population, some of these determinants were used to identify any aberrant results among the current study's participants.

In addition to the variances of PBM in the different populations, it is important to recognise that peak bone mass occurs:

- at different times in different individuals
- in different bones within the same individual
- in different parts of the same bone

Establishing each individual's own PBM in the different populations, for different measurement techniques and different sites by bone densitometry is ideal but not practical or feasible (Baran, *et al*. 1999b).

In this light, a patient's own PBM achieved is never available to provide their own baseline for future bone densitometer readings. This means that the BMD values obtained at a patient's first measurement has to suffice, even though it almost certainly represents a threshold below their original peak bone mass. According to Baran, *et al.* (1999b) it has become necessary to use data from age-, gender- and ethnically matched reference populations as standards for measurements of bone status for the diagnosis of osteoporosis. They further added that reference data should be based on randomly selected individuals from the target population, where mean values and standard deviations (SDs) of estimated BMD can be derived. This will be discussed later in the chapter.

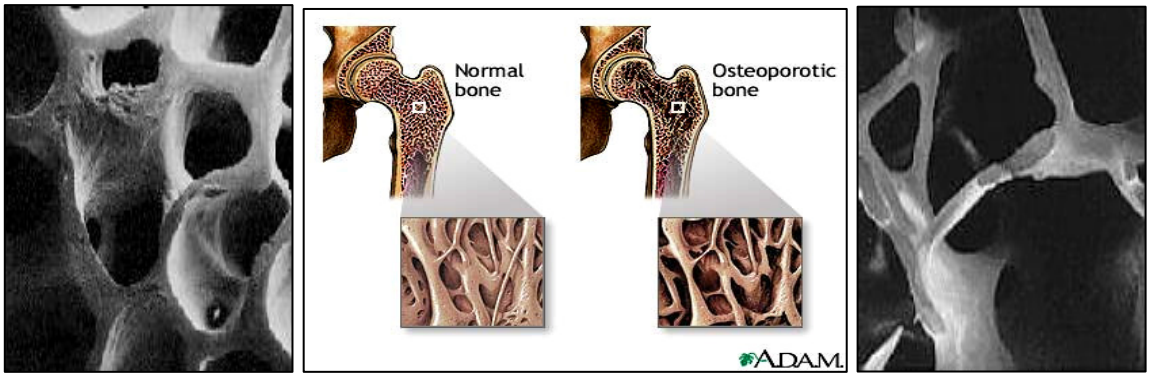
2.2.4 PATHOPHYSIOLOGY OF BONE LOSS

The maintenance of a normal, healthy, mechanically competent skeletal mass depends on keeping the process of bone resorption and formation in balance. Physiologic and pathophysiologic processes in the bone remodelling cycle contribute to changes in bone mass/density (Baron, 2002). This can occur during the stage of accelerated linear growth in adolescence, or much later in life, usually after menopause in women. Failure to match bone formation with bone resorption results in net bone loss (Resnick, Manolagas and Fallon, 2005). This is what occurs in osteoporosis, whether primary or secondary, as a result of deficiency of sex hormone, primary hyperparathyroidism, hyperthyroidism or excessive use of glucocorticoids. Osteoporosis has been classically defined in a pathogenic manner as an “uncoupling” in which resorption exceeds formation resulting in a net loss of bone (Baron, 2002).

2.3 OSTEOPOROSIS

In 1994, the World Health Organisation (WHO) defined osteoporosis as “ a skeletal disease characterised by low bone mass and micro architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture”*(*Kanis, *et al.* 1997). Simply stated, it is a skeletal disease in which bone resorption exceeds bone formation, resulting in reduced strength and quality of the

skeleton (see Figure 2.1) and a consequent increased risk of bone fracture. This thinning and weakening of the bone is a very slow and often painless process. Consequently, osteoporosis is referred to as a silent epidemic.



a) Normal Bone **b) Osteoporotic Bone**

Figure 2.1: Normal bone versus osteoporotic bone - showing the effects when bone resorption exceeds bone formation (www.nof.org; www.nlm.nih.gov)

A common misconception is that osteoporosis is always the result of bone loss. However while women and men lose bone with age, individuals who do not reach optimal (peak) bone mass during childhood and adolescence may develop osteoporosis without the acceleration of bone loss (NIH Consensus Statement, 2000). Osteoporosis is three times more common in women than in men, partly because women have a lower peak bone mass and partly because of the hormonal changes that occur at the menopause (WHO Technical Report Series 921, 2003). Oestrogen has an important function in preserving bone mass during adulthood, and bone loss occurs as oestrogen levels decline, usually from around the age of 50 years (see Figure 2.2). Additionally, women live longer than men (WHO Technical Report Series 921, 2003) and therefore have greater reductions in bone mass.

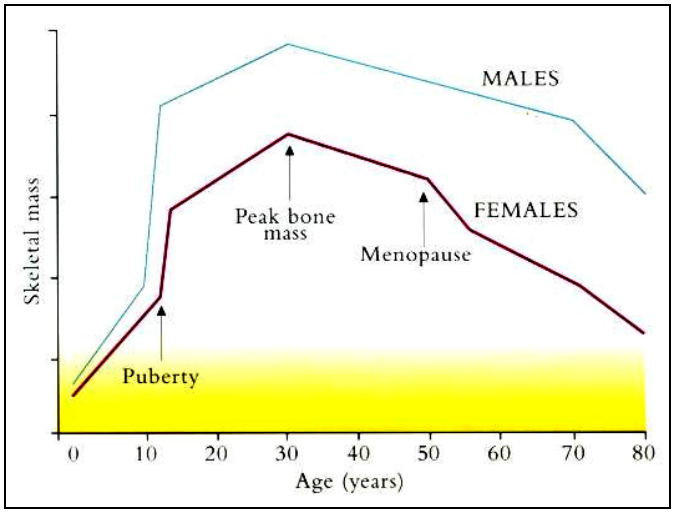


Figure 2.2: Bone mass increases in both men and women until approximately age 30 and then starts to fall. Bone loss is more pronounced in women following menopause (Baran, *et al.* 1999a).

According to WHO (2003), older persons defined as aged 60 and over are growing in numbers, in virtually all countries worldwide. The report further states that this trend is particularly significant in the developing countries. Increasing life expectancy in many parts of the world means that women now live more than one-third of their lives after the menopause, and that the number of postmenopausal women is increasing (WHO Technical Report Series 921, 2003).

In Europe the number of women over 65 years of age is projected to increase from 68 million in 1990 to 133 million in 2050, whereas in Asia the number is likely to increase from 145 million to 894 million during the same period (Cooper, Campion and Melton, 1992). In India alone, it is predicted that by 2030, the population of postmenopausal women will be the second highest in the world, second only to China (Shah, 2005).

According to Cooper, Campion and Melton (1992) aging population figures in Africa are projected to grow from 13 to 33 million by 2050. Kinsella and Ferreira (1997) added that in the face of the HIV/AIDS pandemic, this fact is overlooked. They reported that SA had the highest proportions of the elderly in 1997, "with more than 1 in 8 persons (5.6 million) aged 50 and nearly 2.9 million aged 60 and above." Kinsella and Ferreira (1997) further indicated that these aggregate figures mask the diversity of aging among the population groups. The Asians and Caucasians, who are most at risk for osteoporosis, showed the most considerable projected increases. SA Indians comprise the highest number of Asians in South Africa (1.1. million), with the highest percentages living in KwaZulu-Natal (Statistics South Africa, 2003).

The changing pattern in the length of life emphasises the vulnerability of the elderly with particular reference to osteoporosis and its consequences in fragility fractures. Kansra, (2002) added that this demographic trend alone could increase the number of hip fractures worldwide, while other important considerations include the sedentary lifestyles, decline in physical activities and the urbanisation effect of people at large.

While it is possible to distinguish between those who have osteoporosis, those who do not and those who are at risk, the clinical expression of osteoporosis (a fracture) is less easy to predict from bone density measurements alone. It is important to remember that a number of factors contribute to the probability of sustaining a fracture. These include overall bone strength, the risk of falling as well as the force of an impact (Baran, *et al.* 1999a). Osteoporosis is a multifactorial disease and a patient's clinical history, signs, symptoms and accompanying risk factors must be

considered together with BMD measurements (WHO Technical Report Series 921, 2003).

According to Baran, *et al*. (1999a) bone strength reflects the integration of 2 main features, namely bone density and bone quality, but a third component, bone geometry, is also included. Presently, bone quality and geometry cannot be quantified. Fogelman and Blake (2000) added that while there is no accurate measure of bone strength, bone density is used as a proxy measure and accounts for approximately 70 % of bone strength.

Bone mineral density (BMD) is expressed as grams of bone mineral per area (g/cm^2) or volume (g/cm^3). In an individual BMD is determined by the peak bone mass (PBM) acquired from childhood to adult and the amount of bone loss with age (Fogelman and Blake, 2000). Therefore BMD is recognised as the key determinant of strength and fracture risk. Similarly, El-Hajj Fuleihan, *et al.* (2002) have argued that BMD is a stronger predictor of fracture risk than cholesterol is a predictor of coronary artery disease and is at least as good as hypertension is a predictor of stroke.

A classification system (Table 2.1) developed by the WHO, based on T-scores (as explained on pages 60 and 86) derived from a measure of BMD means and SDs, provides clinicians with a practical way of identifying individuals with established osteoporosis and those at risk of developing the disease (Watts, 2002), with the intention of directing treatment and prevention programs towards those who are in most need (Kanis, *et al.* 1997)**.** This will be elaborated on, later in the chapter.

Table 2.1: The WHO classification of osteoporosis (WHO Technical Report Series 843, 1994).

TERM	DEFINITION
Normal	BMD not more than 1 standard deviation (SD) below the mean value of PBM in young adult women → T-score ≥ -1.0
Osteopaenia (low bone mass)	BMD of 1 – 2.5 SDs below the mean value of PBM in young adult women → -2.5 ≤ T-score ≤ -1.0
Osteoporosis	BMD of more than 2.5 SDs below the PBM in young adult women → T-score < -2.5
Severe osteoporosis	BMD of more than 2.5 SDs below the PBM in young adult women and the presence of fractures → T-score < -2.5 + #s

2.4 THE IMPACT OF OSTEOPOROSIS

According to Kanis and Pitt (1992) the United States of America (USA) data indicated that about 30% of Caucasian women over the age of 45 years have osteoporosis. Baran, *et al*. (1999a) added that approximately 54% of these women have low bone density at the lumbar spine, hip and forearm; placing them in a high risk category for future osteoporosis. Similarly Kansra (2002) indicated that on the Indian

subcontinent, 50% of Indian females and 30% males above age 65 years have osteoporosis; and that approximately 50% of Indians above age 50 years are osteopaenic.

There is insufficient known data on the incidences of osteoporosis in the South African populations, least of all the Indian female population. However, as stated previously, the incidence of osteoporosis will rise globally due to the increase in the number and proportion of elderly persons, particularly the African and Asian populations (WHO Technical Report Series 921, 2003).

The morbidity of osteoporosis arises from its associated fractures; however, the pathogenesis of fractures depends on many factors other than osteoporosis. According to the WHO, extra-skeletal factors such as the risk of falling and the force of an impact also contribute to the probability of sustaining a fracture (WHO Technical Report Series 921, 2003).

Seeley, *et al.* (1991) argued that fractures associated with osteoporosis have a clear pattern. The most common fractures are those of the hip, vertebrae and forearm. In addition, many fractures at other sites are also associated with low bone density independently of age, and are at least partly due to osteoporosis. According to Seeman (2002) although, fractures due to osteoporosis usually heal normally, they are attended by an increased risk of serious functional impairment and hospitalisation.

A study undertaken by Cooper, Campion and Melton (1992) indicated an estimated 1.3 to 1.7 million hip fractures occurred worldwide in 1990, and is expected to rise to 6.3 million by the year 2050, with the most fractures occurring among the Asians. Kanis, Johnell and Gullberg (1997) argued that this is probably an underestimate, since in many regions, hip fracture rates have increased even after age has been taken into consideration. Kanis, Johnell and Gullberg (1997) further confirmed that the total estimates worldwide could well exceed 21 million by the year 2050.

While there is insufficient documentation on the incidence of osteoporosis and its consequent fractures in the South African context, the National Osteoporotic Foundation of South Africa (NOFSA) have reported that, osteoporotic fractures in Caucasian, Asian and "mixed race" populations in this country are similar to those reported in North America and Europe (Hough, 2006).

It is of paramount importance to estimate the prevalence of osteoporosis in a given population from a public health perspective. In fact, Wolman and Hough (2003) argued that the paucity of local data on the incidence of osteoporosis and its related fractures in SA have been "a major stumbling block in the drive to prevent and manage this disease optimally".

In order to accurately estimate the incidence of this debilitating disease in the South African populations, accurate ethnic matched reference data is needed. The current study attempted to define BMD in healthy normal Indian women and to compare the study population data with the manufacturer's (Hologic®) reference data that is

currently being used for the diagnosis of osteoporosis. This will be explained further in the chapter.

Osteoporosis and its associated fractures are a major cause of illness, significant pain, disability and death and have come to be recognised as one of the most serious problems in public health (Kanis, *et al.* 1997). According to Fogelman and Blake (2000) a lifetime risk of suffering a fragility fracture is estimated to be 30 to 40 percent and these figures are comparable with lifetime risk for cardiovascular disease, thus indicating the widespread prevalence of osteoporosis. Fractures primarily of the spine, hip or forearm are usually the commonest presentations for osteoporosis. Other presentations include loss of height and stature (Figure 2.3) and developing a "hunched back" or dowager's hump" (Kanis and Gluer, 2000).

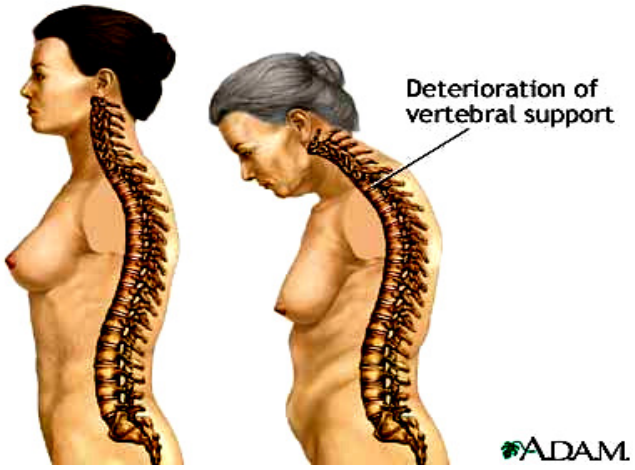


Figure 2.3: Deterioration of vertebral support leads to "dowager's hump" (www.nlm.nih.gov)

2.4.1 HIP FRACTURES

Oden, *et al.* (1998) indicated that the most serious osteoporotic fracture is that of the hip and is catastrophic with an estimated mortality rate of up to 20% during the first year following a fracture. Interestingly, these mortality rates are equivalent to that of breast cancer (Kanis, *et al*. 1997). Hip fractures (see Figure 2.4) typically result from falls, but some occur spontaneously with minimal or no trauma.

Women are more often affected than men and the incidence rates rise exponentially with age, due to gender differences which include differences in body size, as well as hormonal and metabolic influences associated with sexual development during growth (WHO Technical Report Series 921, 2003).

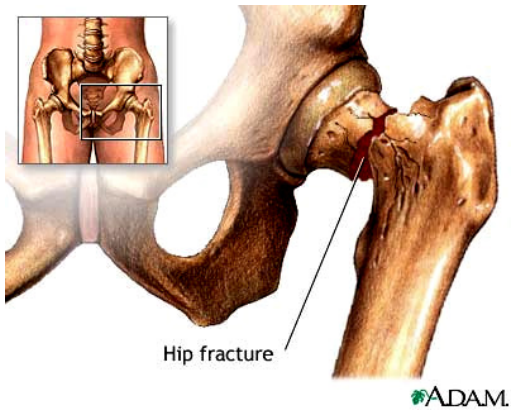


Figure 2.4: Hip fracture through neck of femur (www.nlm.nih.gov)

Hip fractures are usually painful and are associated with a high degree of morbidity and appreciable mortality (Cooper, Campion and Melton, 1992), depending in part on the patient's age, the treatment given and associated morbidity (Kanis and Pitt, 1992). Cooper, Campion and Melton (1992) further added that half of all patients permanently lose their ability to walk independently following a hip fracture. In the

USA, approximately 20% of patients with hip fractures require long-term care in a nursing home (Chrischilles, Shireman and Wallace, 1994). Similar rates are reported for many other countries. No known data on the incidence of osteoporosis and its associated fractures is evident in the South African context.

BMD measurements of the total hip, using DEXA, is the “gold standard” for determining BMD status and establishing fracture risk and osteoporosis in an individual, unless contraindicated (arthritis, prosthesis, etc). The routine total hip BMD measurements were undertaken in the study population.

2.4.2 VERTEBRAL FRACTURES

Cooper and Atkinson (1992) stated that vertebral fractures, although very insidious and mostly unreported, are particularly common in postmenopausal women with osteoporosis (see Figure 2.5). They had further explained that identifying the incidence of vertebral fractures and their attendant morbidity may be difficult because many are asymptomatic or cause too few symptoms to provoke investigation (Cooper and Atkinson, 1992).

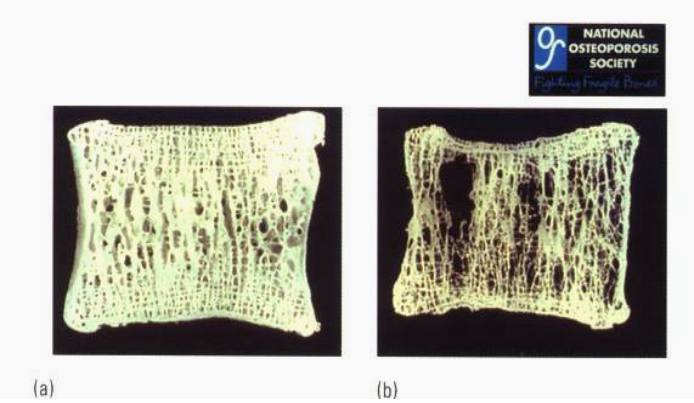


Figure 2.5: Cross-sections through normal (a) and osteoporotic (b) vertebral bodies (National Osteoporosis Society)

Vertebral fractures that come to clinical attention cause a significant decrease in the quality of life, although the impact is less than that of hip fractures. According to Kanis and McCloskey (1992), approximately 4% of women with a vertebral fracture need assistance in conducting activities of daily living. Fogelman and Blake (2000) further added that, while fractures of the spine do not usually lead to death, they do cause substantial pain and disability. Spinal deformities reduce the patient's abilities to perform simple daily activities, for example, lying on a flat bed or dressing. Quality of life becomes progressively impaired as the number and severity of vertebral fractures increases. The dowager's hump is usually the result of multiple vertebral fractures (WHO Technical Report Series 921, 2003).

BMD measurements of the lumbar spine, using DEXA, are performed routinely as a second measurement site, unless contraindicated (surgery, severe scoliosis, prosthesis, etc) and was undertaken in the study population.

2.4.3 DISTAL FOREARM FRACTURES (Colles' fractures)

Fractures of the distal forearm are common among the middle-aged and elderly and are generally caused by a fall on the outstretched hand (WHO Technical Report Series 843, 1994).

Although fractures of the wrist cause less morbidity than hip fractures, are rarely fatal and seldom require hospitalization, the consequences are often underestimated (Baran, *et al*. 1999b). Forearm fractures are painful, and usually require one or more surgical or manipulative procedures to reposition the bones, together with 4 to 6 weeks of immobilization in plaster. A significant number of patients have persistent pain and reduced function following a Colles' fracture and sometimes endure impaired daily activities (O'Neill and Roy, 2003). So, while forearm fractures increase the risk of other osteoporotic fractures in later life, mortality is not increased.

BMD measurements of the distal forearm, using DEXA, is not routinely indicated but can be used as an alternate site when measurements of the lumbar spine and total hip are contraindicated. Therefore DEXA measurements were taken at this site in the study population to determine BMD.

2.4.4 ECONOMIC CONSIDERATIONS

Osteoporosis has a significant impact on individuals, their families and society. Although bone loss is partially reversible, the micro architectural deterioration of the skeleton cannot be reversed (Baran, *et al*. 1999a). In addition to the major personal burden of this disease, the economic costs of osteoporosis are enormous.

The total cost of osteoporosis is difficult to calculate because it includes the costs of acute hospital care, loss of working days for family carers, long-term care and medication. Cost estimates are based on many assumptions, making cost comparisons between countries difficult if not impossible (Chrischilles, Shireman and Wallace, 1994). The bulk of the cost of osteoporosis is attributable to hip fractures because of the need for hospitalization and subsequent home care or nursing home care (Kanis, Johnell and Gullberg, 1997). No known data exists for the impact of osteoporosis on the South African populations.

Until recently, osteoporosis was an under-recognized disease and considered an inevitable consequence of ageing. However, as epidemiological studies have highlighted the high burden of the disease and its costs to society and health care systems, perceptions have changed. Improvements in diagnostic technology and assessment facilities over the past decade now mean that it is possible to detect the disease before fractures occur (Fogelman and Blake, 2000).

2.4.5 IDENTIFYING INDIVIDUALS AT RISK

Fractures are all late manifestations of the disease. This suggests that it is imperative that osteoporosis is diagnosed correctly prior to fracture occurrence, highlighting the need for the current research study.

Osteoporosis is a multifactorial disease and there are several well recognised risk factors as shown in Table 2.2.

While some factors are inherent risk factors and cannot be modified (example, genetics or age), some modifiable risk factors that may contribute to osteoporosis include lifestyle factors such as:

Smoking

Alcohol abuse

Excessive caffeine consumption

Excessive dietary protein consumption

Lack of dietary calcium

Lack of sunlight exposure (to generate endogenous vitamin D)

(WHO Technical Report Series 921, 2003)

Table 2.2: Clinical risks factors for osteoporosis provide a rationale for performing bone densitometry (adapted from Baran, *et al.* 1999a).

Age	Bone density declines from 30 years predominantly in postmenopausal women.
Gender	Women are more susceptible than men.
Genetics	Caucasian and Asian people are more at risk than other populations. Family history further increases this risk.
Body size	Individuals with small frame or low body mass index (<) are more at risk
Lifestyle factors	Smoking, excess alcohol, a sedentary lifestyle, inadequate diet and low calcium intake increases fracture risk
Other illnesses	Illnesses that accelerate bone loss or cause immobility can be a risk. Example, hyperparathyroidism.
Drug treatments	Several drugs influence bone metabolism, example: Cortisone therapy.
Fracture history	Previous fractures are independently correlated with the likelihood of future fractures.

Bone loss can be minimised by identifying individuals at risk and taking preventative measures where possible. This will result in fracture level reduction and preservation of the skeleton.

2.4.5.1 Age

The clinical impact of age related bone loss depends on the peak bone mass achieved while the individual is young and the subsequent rate of loss in later years. The greater the bone mass achieved in early age, the less likely the individual is to suffer from osteoporosis (WHO Technical Report Series 921, 2003). The current study measured BMD in women aged 20 to 66; as many Indian women older than 66 years did not fit the criteria for the study.

2.4.5.2 Gender

Women are more prone to osteoporosis than men. Several reasons include a lower peak bone mass, smaller skeletons and the loss of oestrogen at menopause. This loss of oestrogen has critical effects on bone density, because prior to menopause, the loss of bone is equal in both men and women (Kanis, *et al.* 1997). In addition, some women lose bone faster than others and others have an early menopause. These women become particularly vulnerable to osteoporosis in later life. He states further, that bone loss is not uniform and is greatest from trabecular bone immediately following menopause. It then gradually declines to match the bone loss from cortical bone seen in later life (Fogelman and Blake, 2000). This study was limited to women, so research questions associated with gender were not addressed.

2.4.5.3 Genetics and Race/Ethnicity

According to Riggs and Melton (1992), Caucasian and Asian individuals are more prone to osteoporosis than individuals of African (Black) descent. They indicated that this may be related to peak bone mass achieved in different race groups, where it was shown that Caucasians achieved the lowest bone mass and Black people the highest. Other studies taken among the various Asian populations (different ethnic groups) indicated that bone mass in these populations are even lower than the Caucasians (Wu, *et al.* 2003). Genetic involvement and the application of genetic factors in the identification of vulnerable patient subgroups is an area for further research in the current study population as well as other populations in SA.

2.4.5.4 Lifestyle factors

According to WHO, several lifestyle factors influence PBM and the subsequent rate of bone turnover. Inadequate nutrition, especially a low calcium intake during high bone growth periods, leads to lower PBM and therefore a greater risk for osteoporosis. Similarly, if calcium intake is inadequate in adulthood, more bone loss occurs to maintain calcium homeostasis (WHO Technical Report Series 843, 1994).

Excessive use of alcohol, particularly women, also increases the risk of osteoporosis. Additionally, cigarette smoking has toxic effects on bone cells and can cause accelerated oestrogen catabolism, thereby bringing on an earlier menopause (WHO Technical Report Series 921, 2003).

In contrast, exercise builds strong bones. While the type and frequency of exercise that will optimally increase bone mass is yet to be determined, enforced immobilisation through disease or disability, or a sedentary lifestyle, contributes to significant bone loss (WHO Technical Report Series 921, 2003).

The aim of the current study did not include evaluation of the above factors and its' influence on bone mass, however, the data was collected to validate any aberrant results that may have been evident. Further research is needed to evaluate the influence of lifestyle factors on BMD in the South Africa populations, including Indian women.

2.4.5.5. Secondary Osteoporosis

Secondary osteoporosis may be defined as bone loss caused by factors other than oestrogen deficiency and aging. It is caused by certain drug treatments or the co-existence of dietary disorders or diseases that disturb bone mineralisation or bone homeostasis (Baran, *et al.* 1999a).

Some of the drugs often associated with secondary bone loss are shown in Table 2.3. The protracted use of any of these agents may call for the regular assessment of the bone status in any individual (Baran, *et al.* 1999a).

Table 2.3: Certain drugs associated with premature bone loss and development of secondary osteoporosis (WHO Technical Report Series 921, 2003).

Glucocorticoids	Cytotoxic drugs (eg. Methotrexate)
Adrenocorticotrophin	Gonadotrophin-releasine hormone agonists
Accessive use of thyroxine	Premenopasual use of tamoxifen
Anticonvulsants used for epilepsy	Aluminium
Long term use of heparin	Vitamin D
Lithium	Cyclosporin A

In addition, endocrine, dietary and metabolic disorders, as shown in Table 2.4, are also associated with low BMD. With the wider use of bone densitometers for the measurement of BMD, higher numbers of secondary osteoporosis due to these diseases can be investigated (Baran, *et al*. 1999a).

Table 2.4: Certain clinical conditions associated with premature bone loss and secondary osteoporosis (Adapted from WHO Technical Report Series 921, 2003).

Inflammatory disorders	**Disorders associated with low body weight**	**Defects in connective tissue synthesis**
Rheumatoid arthritis Ankylosing spondylitis Inflammatory bowel disease Cystic fibrosis	Anorexia nervosa Insulin-dependent diabetes mellitus	Osteogenesis imperfecta Marfan's syndrome Homocystinuria
Bone marrow disorders	**Malabsorption disorders**	**Endocrinological disorders**
Multiple myeloma Mastocytosis Leukaemia	Coeliac disease Post gastrectomy Liver disease Total parenteral nutrition	Thyrotoxicosis Hyperparathyroidism Cushing's disease
Hypogonadism-associated disorders	**Disorders of immobilisation**	**Miscellaneous**
Athletic amenorrhea Haemochromatosis Genetic syndromes Post chemotherapy Hypopituitarism	Parkinson's disease Poliomyelitis Cerebral Palsy Paraplegia Multiple sclerosis	Pregnancy Lactation

The above conditions are not discussed further, but it must be noted that osteoporosis is a relatively common accompaniment of these disorders. The assessment of BMD status in these patients may be required as part of the overall clinical diagnosis and monitoring. Additionally, a large percentage of volunteers in the older age groups were exempted from the current study, due to the some of the disorders indicated above. This finding highlights the need for screening BMD measurements in individuals with the above conditions.

2.5 THE QUANTITATIVE ASSESSMENT AND DIAGNOSIS OF OSTEOPOROSIS

Increasing awareness and the increased scale of morbidity and mortality attributable to osteoporosis has led to a high demand globally, for the care of patients with this condition. More importantly, is to identify individuals who might be at risk for fracture (Kanis, *et al.* 1997). Together with the growing awareness of the significance of osteoporosis for public health and the development of new treatments for its prevention, there has been significant evolution of radiological techniques for non-invasive assessment of skeletal integrity. This has allowed for the early detection of osteoporosis and the assessment of increased risk for fracture (Fogelman and Blake, 2000).

The internationally agreed definition of osteoporosis is that “it is a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture” (Kanis, *et al.* 1997). According to the WHO (WHO Technical Report Series 921, 2003), this view embodies the notion that BMD (bone mass) is a critical factor in the risk for fracture. Other skeletal abnormalities also contribute to skeletal fragility, while some non-skeletal factors also affect fracture risk. The WHO (2003) further suggested that assessment of fracture risk should encompass all these factors. The diagnosis of osteoporosis by the use of BMD measurements is at the same time an assessment of a risk factor for the clinical outcome of a fracture. This section will summarise and update the extent to which this is possible in clinical practice.

2.5.1 BONE DENSITOMTERY – TECHNICAL BACKGROUND

Bone densitometry is the measurement of bone density (i.e. mineral content) by any of a variety of methods. They all rely on the difference in absorption or attenuation of x-rays, gamma rays, or sound waves by bone compared with the surrounding soft tissue (Baran, *et al.* 1999b). Several different instruments measure BMD, where central instruments measure density at the spine, hip and/or whole body and peripheral equipment that measure density at the wrist, calcaneus, finger, shin, and kneecap.

The techniques used over the past 4 to 5 decades (Figure 2.6) include:

- Conventional x-rays
    - relied on visual assessment of osteopaenia on plain film radiography
- Radiographic absorptiometry (RA)
    - uses an x-ray of the hand and a small metal wedge to calculate bone density
- Single photon absorptiometry (SPA)
    - measures the wrist (used infrequently)
- Dual photon absorptiometry (DPA)
    - measures the spine, hip or total body using isotopes
- Single energy x-ray absorptiometry (SEXA)
    - measures the wrist, heel or finger
- Dual energy x-ray absorptiometry (DEXA)
    - measures the spine, hip, forearm or total body

- Quantitative computed tomography (QCT)
    - commonly used to measure the spine, but can be used at other sites.
- Peripheral QCT (pQCT)
    - measures the wrist
- Quantitative ultrasound (QUS)
    - uses sound waves to measure density at the heel, shin bone and kneecap

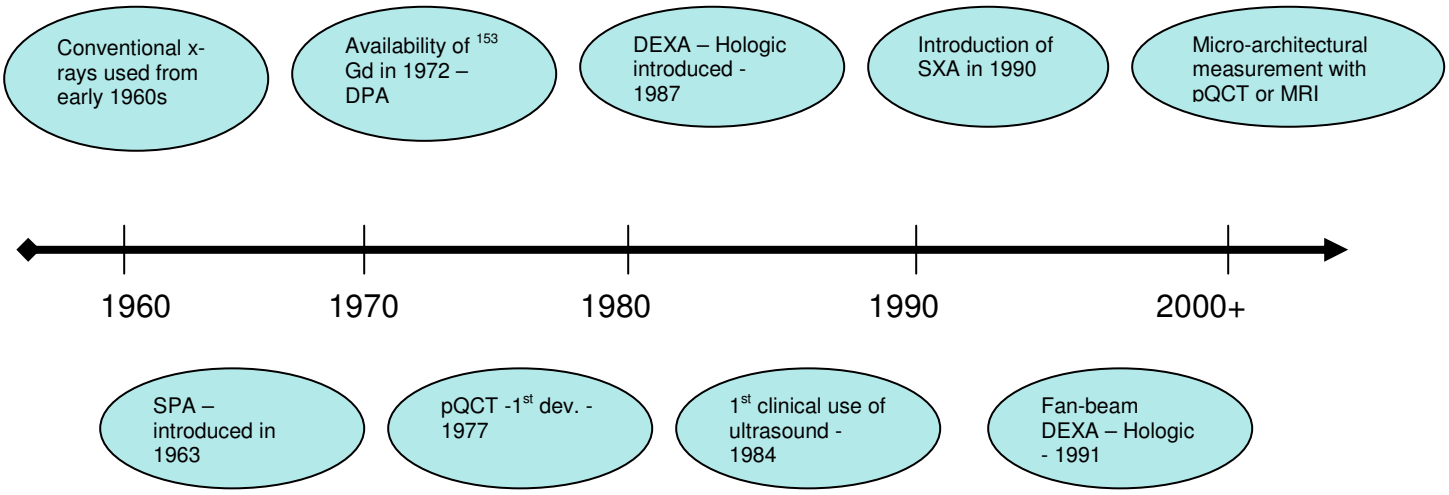


Figure 2.6: Key dates in the development of bone densitometry techniques (adapted from Baran, *et al.* 1999).

Of these, the most widely used, x-ray based assessments of BMD used today include DEXA, SEXA and QCT. Data generated using these methods is supported by biochemical tests to assess bone turnover. Together these provide a powerful armamentarium for assessing bone status and monitoring treatment (Blake and Fogelman, 1997a).

2.5.2 BACKGROUND TO BMD TECHNIQUES

As stated previously, BMD techniques can be subdivided into those that provide central measurements (DEXA, QCT) and those that measure the appendicular or peripheral skeleton (peripheral DEXA, RA, QUS and less commonly SPA and SXA). For many referring clinicians, the most readily available techniques are central DEXA and QUS. While all techniques are strongly correlated with future fracture risk at all sites, future fracture risk of the hip is best measured by DEXA BMD of the total hip (Kanis, *et al.* 1997).

Osteoporosis is common and is a primary care disease; therefore there is a need for a more simple evaluation of BMD other than DEXA, which are usually found only in large hospitals. This had caused considerable interest in the peripheral devices, such as pDEXA and QUS, because of their portability and affordability (Fogelman and Blake, 2000).

QUS for BMD measurements resulted, following the discovery that the attenuation of sound changes in relation to bone status at frequencies of > 1 MHz. According to Gluer, Jergas and Hans (1997), QUS equipment is particularly valuable for primary, low cost identification of women at risk for osteoporotic fractures. And while, QUS measurements do not use radiation and can prove to be a useful diagnostic aid, their value in monitoring treatment is not yet established (Kanis, *et al.* 1997). In contrast, its advantages include its portability, availability and affordability. Its main limitation is the application of the WHO criteria in its classification of patients (Njeh, *et al.* 1997).

QCT has been described to be the most accurate scanning technique for measuring BMD due to its advantage of determining true 3D (volumetric) BMD ($mg/cm^{3)}$, compared with 2D areal density by DEXA (Cann, 1988). Additionally, it is unique in providing separate BMD estimations of trabecular and cortical bone (Blake and Fogelman, 1997b). The major limitations are the expense, low precision and comparatively high radiation dose (Kanis, *et al.* 1997). Additionally, special purpose units that measure peripheral skeletal sites (pQCT) have overcome some of the limitations in standard QCT. Not only do these scanners use less radiation but they also occupy less space (Baran, *et al.* 1999b).

Osteoporosis can also be diagnosed by visual inspection of plain film radiographs, albeit with low sensitivity. Plain film radiography of the skeleton is a very inaccurate method of assessing the amount of bone mineral; however, any apparent loss of bone density evident is a common reason for further bone assessment. Conversely, radiographs of the spine are valuable for identifying any vertebral deformities and are sometimes incidentally discovered. This is important especially when there is no clinical evidence for the disease (WHO Technical Report Series 843, 1994).

Conventional RA was the earliest determinations of BMD; however its usefulness was limited due to its lack of sensitivity. Its main advantage is the widespread availability of conventional film radiography. There is a renewed interest in RA, facilitated by digital radiography (Baran, *et al.* 1999b), which allows improved imaging couple with analytical tools for measurement.

SPA and DPA measurements provided sufficient data predicting fracture risk, they were accompanied by many limitations. They used radioisotopes as their energy sources, which require careful handling, regulatory considerations and frequent source replacements; and these limitations were supplanted by the methods of SEXA and DEXA (Baran, *et al.* 1999b)

SEXA and DEXA measurements involve a scanning mechanism that moves the x-ray source coupled with a detector over the area of interest and measures the attenuation of x-rays at the single energy. Attenuation increases as the x-ray beam passes through an increasing thickness of tissue. Since the attenuation through minerals is higher than that of soft tissue, the slope of the attenuation curve is steeper when the beam passes through bone (Blake and Fogelman, 1997b).

In SEXA, the forearm is surrounded with a soft tissue equivalent (water bath), the attenuation curve reflects the amount of bone present. Image processing algorithms are then used to segment out the bone tissue and determine bone mass. SEXA cannot differentiate between trabecular and cortical bone, because it is an “area – projection” method (Kelly, Crane and Baran, 1994). Overall, SEXA is a popular, low-cost method for peripheral scanning with reasonable precision and in addition, a low radiation dose.

The need for homogenous soft tissue surrounding the bone is a major limitation of SEXA. According to Blake and Fogelman (1997b) measurements of the lumbar spine and hip are impossible and peripheral measurements are inconvenient. Adams (1997)

argued that this limitation can be overcome by using two energies to simultaneously scan the area of interest. Soft tissue interferences are then eliminated by mathematically processing the data using DEXA technology.

A study undertaken by Cummings, *et al.* (1993) reported that of the 8134 women aged 65 years and older whose BMD was measured with several different techniques; during a mean follow up of 1.8 years, 65 patients suffered a hip fracture. Furthermore, the study showed that with each 1 SD decrease in BMD of the hip there was an increase in the age–adjusted relative risk of hip fracture of 2.6. In contrast, measurements at the wrist and heel, using the peripheral techniques, showed significantly lower relative risks of 1.6 and 2.0 respectively (Cummings, *et al.* 1993).

Similarly, fracture studies undertaken by Marshall, Johnell and Wedel (1996) showed that BMD measurements of the hip were best at predicting hip fracture, and that the degree to which spine BMD best predicts vertebral fracture or radius BMD forearm fracture is weaker and less conclusive. These studies, together with the morbidity and more especially mortality associated with hip fractures, and the intuitive appeal for measuring the site of greatest clinical interest, has contributed to the popularity of DEXA scanning (Baran, *et al.* 1999b).

2.5.3 BMD TECHNIQUE for CURRENT STUDY – DUAL ENERGY X-RAY ABSORPTIOMETRY (DEXA)

The above discussion focused on the technical aspects of the various BMD techniques; however a comparison of their precision and accuracy provides additional information relevant to their clinical use. Each of these methods has strengths and limitations, which are summarised in Table 2.5.

Table 2.5: Comparison of the various bone mass measurement techniques (adapted from WHO Technical Report Series 921, 2003).

Method	Strengths	Limitations	Scan time (min)	Accuracy In vivo (%)	Precision In vivo (%)	Radiation dose (millirem)
SXA, pDEXA	Low radiation dose Low cost Portability	Appendicular sites only Cannot measure trabecular bone & cortical bone separately	3 – 5	3 – 8	1 – 3	~1
DEXA	Low radiation dose Multiple sites for assessment Strongest predictor for hip fracture	Cost Size	0.5 – 6 (for lateral spine)	3 – 9	1 – 2	~1 – 5
QCT	Gives true volumetric density (mg/cm3) Discriminates trabecular & cortical bone High resolution	Radiation dose Capital and running costs Competes with others uses of CT scanner Rigorous QC for follow up scans Slow	10 – 30	5 – 15	2 – 4	~50
QUS	No radiation dose Small & portable Fast & easy to use Low equipment & running costs	Limited to calcaneus, tibia and phalanges	1 – 5		2 – 3	

Fogelman and Blake (2000) indicated that DEXA scanners was introduced in 1987 and since its inception had undergone drastic improvements in scanning speed and image quality. According to WHO (2003), DEXA has established itself as the most widely used and is currently the gold standard for predicting fracture risk with bone mineral density measurements, due to its advantages of high precision and accuracy, short scan times, and stable calibration in clinical use (WHO Technical Report Series 921, 2003).

According to Kanis, *et al.* (1997) bone mineral content (BMC) is the amount of bone mineral present at a specific site of a scan. When the BMC is divided by the area or volume assessed, a BMD value is calculated. DEXA is an “area-projection” or two-dimensional method rather than a true volumetric density and is expressed in g/cm^2.

DEXA equipment allows scanning of the spine, hips, distal forearm and whole body. The lumbar spine and hips are regarded as the most important measurement sites, because they are frequent sites of fractures that cause significant impairment of quality of life and increased morbidity and mortality (Marshall, Johnell and Wedel, 1996), with the hip BMD showing to be the most reliable way of evaluating the risk of hip fracture. BMD of the lumbar spine is regarded as the optimum site for monitoring response to treatment of osteoporosis, due to the metabolically active trabecular bone in the spine (Eastell, 1998).

The fundamental principle behind DEXA is the measurement of the transmission through the body of x-rays of two different photon energy levels (Adams, 1997). The measurement of the transmission factors at these two energy levels enables the areal densities (i.e. the mass per unit projected area) of two different types of tissue to be inferred, because of the dependence of the attenuation coefficient on atomic number and photon energy (Blake and Fogelman, 1997a). In DEXA scanning, these are taken to be bone mineral (hydroxyapatite) and soft tissue.

Low-energy beams experience greater attenuation than high-energy beams, and as stated earlier, bone attenuates x-rays more than soft tissue (Blake and Fogelman 1997b). Based on this discrepancy, corrections for soft tissue can be made, which are critical due to the individual variability in soft tissue content, especially around the spine and hip (Fogelman and Blake, 2000). This scanning that occurs at two different x-ray photon energies and its principle is based on a subtraction technique, where the attenuation of bone alone is measured and the contributions of the soft tissues are eliminated (Ballinger and Frank, 2003:498-499).

In the first generation DEXA equipment (some of which are still commercially available), used a pinhole collimator (Figure 2.7a), which produced a pencil beam coupled to a scintillation detector in the scanning arm. From 1991 led by Hologic®, DEXA equipment evolved and the most significant development was the introduction of new systems that use a slit collimator to generate a fan-beam (Figure 2.7b) coupled to a linear array of solid state detectors (Adams, 1997).

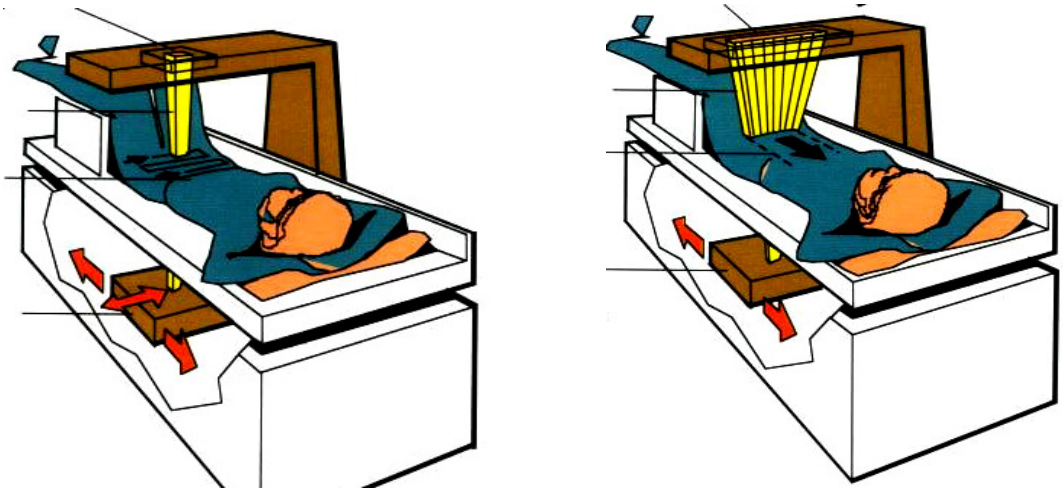


Figure 2.7: (a) Pencil beam (b) Fan-beam

Scanning geometry for DEXA (adapted from Baran, *et al*. 1999b).

Together with a higher output x-ray generator, image resolution was improved (Baran, *et al.* 1999b), scan times shortened from 5 to 10 minutes to 10 to 30 seconds for the latest fan-beam systems. In addition, there was better penetration of dense tissues such as fat and muscle and lateral spine scanning became feasible for the first time. This method of scanning also improved patient throughput (Fogelman and Blake, 2000).

According to Patel, *et al.* (1996) radiation dose to patients is higher for fan-beam systems compared with pencil beam models. Conversely, Fogelman and Blake (2000) argued that, although BMD measurements involve radiation exposure, an important ethical issue is the radiation dose to each individual is very low (1 to 10μSv.) and is comparable with the average daily dose from natural background radiation of 7 μSv. Studies undertaken by Njeh, *et al.* (1999) have further confirmed that the radiation doses to both patient and staff is negligible.

The Hologic® QDR 4500 Elite (Figure 2.8) is the bone densitometer used in the current study to measure BMD of the lumbar spine, total hip and distal forearm. It combines the superiority of fan-beam technology with a unique, value-added package of clinical, patient reporting and support software (see Appendix G).

Figure 2.8: Hologic QDR 4500 Elite (Appendix G)

2.5.4 QUALITY ASSURANCE IN BONE DENSITOMETRY

Strict instrument quality control to monitor and document instrument performance in vitro and in vivo is critical to ensure reliable and meaningful long term BMD measurements. The key parameters in bone densitometry are accuracy, precision and stability, and these are used to document the physical performance of a bone densitometer (Blake and Fogelman, 1997b). In vitro performance is assessed using phantoms and depends on instrument design and maintenance.

Accuracy measures the ability of the system to provide the same results for the bone mineral content of an object as measured by the gold standard (i.e. measuring BMD by in vitro “ashing”) or another independent method (Jayo, *et al.* 1991). Additionally, in vivo accuracy can be influenced by the ability to correct for overlying soft tissue, artefacts, spinal osteophytes and the presence of calcified aorta. In addition to the physical accuracy of the instrument, clinical accuracy is determined by quality of the reference ranges used, because clinical decision making hinges on the comparison between a patient’s BMD values with that of the reference data (Blake and Fogelman, 1997b). This will be discussed later in this section.

According to Adams (1997) in vivo aspects of quality control, such as operator errors include patient positioning and incorrect placement of regions of interest (ROIs) for bone mapping for the calculations of BMD, which in turn will yield significant errors in the BMD measured. Furthermore, other in vivo aspects of quality control include conditions that are required for a valid test, for example, avoidance of calcium supplements for 24 hours prior to the scan and not having other examinations that may require ionising radiation or contrast media beforehand. Adams (1997) maintains that the presence of calcium supplements and contrast media in the bowel (artefacts) may overly the regions of interest and may erroneously project elevated BMD values at these sites. According to Ballinger and Frank, (2003: 512-513), in vivo performance is much harder to measure and monitor. However, considerable care was taken in this study to ensure that the in vivo aspects of quality control with respect to the above were met. This is further discussed in Chapter 3 (Methodology).

Precision relates to reproducibility of a technique and reflects the ability of an instrument to produce the same results in repeat measurements. Quantitative assessment of bone yields measurements that are subject to statistical variation (Ballinger and Frank 2003:504-506). This means that when an object is measured more than once, the results will not be identical but will have a normal distribution, characterised by a mean value and a standard deviation (SD). Precision is most critical when serial measurements are performed to monitor response to therapy. Similarly, significant changes in BMD in osteoporotic individuals must be reliably measured over an interval of several years (Blake and Fogelman, 2001).

Most of the modern scanners are designed with built-in manufacturer specific programs that are used in quality control. These programs check key aspects of performance and to ensure long term stability. Hologic® uses an internal calibration system that allows correction of short term instabilities. Other manufacturer instruments rely on daily scanning of standards to provide a bone tissue equivalent calibration (Genant, Grampp and Gluer, 1994).

Densitometry instruments are also supplied with bone “phantoms” that contribute significantly to quality control. These can be measured on a daily basis and daily checks become particularly important when scanning individuals for long term follow ups. Most modern equipment are issued with instruction manuals that will provide precise and clear instructions with respect to daily and other periodic quality control checks. Additionally, the same phantom should be used every time on a given machine (Blake and Fogelman, 1997a).

The data obtained from the phantom scans should be plotted on a quality control chart as a function of time. This chart will indicate whether the system is functioning within the specifications and is stable (Ballinger and Frank, 2003:503-505). For example, the Hologic® QDR 4500 was used in the current study and with this equipment the following steps were possible:

- Autoscanning and analysis of a spine phantom.
- Daily records were updated to cumulative databases – a message is displayed when the scan is outside the set parameters. This did not occur during the course of the current study.
- Various forms of graphical representation of all scans are available in database – determine trends.
- Generation of statistical coefficients are shown – number of scans, the mean, SD and CV (which is a percentage of the SD). (Appendix G)

2.5.5 CHOICE FOR ANATOMIC SITES OF MEASUREMENT

Osteoporosis is a systemic disease; therefore bone loss occurs at all sites. It is also important to note that the patterns of bone loss may vary at different sites depending on age (National Osteoporosis Foundation, 1998). The reason for undertaking the scan, as well as the age of the patient are some of the reasons for deciding which site to measure for bone mass (Kanis, *et al.* 1997).

In the younger populations, discordance of bone mass across sites may be greatest because different sites reach peak bone mass at different times and lose bone mass at different rates (National Osteoporosis Foundation, 1998). Consequently, in these individuals, it is recommended that measurements are made at the wrist, spine or hip.

In the elderly, most bones will lose a similar net amount of bone mass, resulting in greater concordance between the sites. Additionally in this age group, hip fractures are the major concern and measurements of the hip is the most beneficial to predict hip fracture risk (Kanis, *et al.* 1997). They further argued that due to degenerative disease affecting the spine, this site is less suitable for the measurement of bone density in these age groups. Likewise those individuals who cannot undergo central measurements at spine or hip due to the presence of artefacts (for example - orthopaedic prosthesis), a peripheral measurement can be substituted (Kanis, *et al.* 1997).

As stated previously (in section 2.4), the lumbar spine, total hip and distal forearm are generally regarded as the most important BMD measurement sites, as they are the sites of the osteoporotic fractures that cause the greatest impairment of quality of life, morbidity and mortality.

According to Marshall, Johnell and Wedel, (1996) spine BMD is the optimum measurement because of its sensitivity to the changes associated with aging, disease and therapy. In contrast Adams (1997) argued that spine BMD, with advancing age, measurements are often affected by the presence of degenerative disease. This leads

to the elevated BMD values at the affected levels.

According to Kanis and Gluer (2000), most experts in bone disease have argued that hip BMD is the most useful measurement , as it is the most predictive of hip fracture and therefore the total proximal femur (total hip) should be the gold standard (Kanis and Gluer, 2000).

While literature indicated that the site of most concern must be the site that is measured, and that there is only a small advantage of measuring multiple sites, in practice when DEXA measurements are performed, BMD of the lumbar spine and the total hip are usually measured (Kanis, *et al.* 1997). In the presence of artefacts or degenerative disease that might cause an elevation in the results at any one of these sites, then measurements at the forearm, as an alternate site, can be substituted (Kanis and Gluer, 2000). For the current study, these three sites were measured using DEXA.

Table 2.6: Trabecular and cortical bone content at sites frequently used for DEXA bone densitometry (adapted from Tortora and Derrickson, 2006).

Skeletal site	Trabecular	Cortical
Spine		
Vertebral body	80 -90 %	10 – 20 %
Posterior elements	20 %	80 %
Hip		
Femoral neck	60 %	40 %
Trochanter	80 %	20 %
Intertrochanter	20 – 30 %	70 – 80 %
Ward's triangle	90 %	10 %
Forearm		
Distal	50 – 90 %	10 – 50 %
Proximal	5 – 10 %	90 – 95 %

Summary

For the current study, BMD measurements were obtained of the lumbar spine (L2 to L4), the total hip and the distal forearm, using the Hologic® QDR 4500 Densitometer. The less dominant hip was scanned to assess fracture risk in each participant, to ensure conformity when comparing reference ranges (see Appendix G). Additionally, the less dominant total hip is routinely measured, as it is assumed that the "weaker" hip is more prone to fracture. The forearm is also an alternate site for measurement when central measurements of the lumbar spine or total hip are contraindicated. A detailed description of the above procedure is given in Chapter 3, section 3.8.1. The procedure guidelines provided by the manufacturers can be seen in Appendix G.

2.6 REFERENCE RANGES, T-SCORES and Z-SCORES

Currently, all bone densitometers yield results in absolute terms (g/cm^2 or g/cm^3) or in relative terms, known as T-scores and Z-scores (Watts, 2002). As Baran, et al. (1999c) indicated, a patient's own PBM achieved at around 30 to 35 years in varying populations is never available to provide a baseline for future densitometer readings. Consequently, in the interpretation of the results obtained when assessing BMD in a patient, it is usual practice to compare them to the results of a reference population (reference ranges/data/values).

The reference ranges, which are assumed to be normally distributed are characterised by a mean and standard deviation (SD). SD scores, called T-scores and Z-scores, demonstrate the deviation of a patient's BMD values from the reference mean *(*Baran*, et al.* 1999c). According to Watts (2002), the T-score concept was developed to avoid confusion and provide a way of using a single set of numbers for all skeletal sites as well as all measuring devices, as different manufacturers' equipment produce different BMD reference values in absolute terms for the same site.

Additionally, the International Committee for Standards in Bone Measurement published equations that allow manufacturers to express their BMD values in standardised units – sBMD: mg/cm^2 to allow for clinical comparison of measurement made on different equipment (Steiger, 1995; Hanson, 1997). This standardisation equations allows for population reference databases, irrespective of which equipment

was used to obtain BMD measurements, to be adjusted for the different manufacturers, thus making T- and Z- scores derived from different manufacturers' equipment compatible (Hanson 1997). With particular reference to the current study, these equations can be adopted to generate standardised BMD reference data for the three major DEXA equipment manufacturers (Hologic, Lunar and Norland). This may mean that each manufacturer does not need to develop its own reference data.

Reference data are sometimes referred to as "normals data" and reflects the notion that reference ranges should be derived from a population not affected by the condition under study. This concept also included other conditions that might directly or indirectly lead to osteoporosis (Baran, *et al.* 1999c). Earlier studies attempted to create normals data by excluding individuals known to have low bone mass (Looker, *et al.* 1998). Approximately a decade ago, considerable effort was made to generate reference ranges by obtaining a random population sample, including all individuals (Hanson, 1997).

According to Cummings, Bates and Black (2002) the National Health and Nutrition Examination Survey (NHANES) III study is one such example, where only 20% of women had osteoporosis at the total hip, compared to 40% when the Hologic® reference database was used. The data from the NHANES III study were selected as the basis for total hip DEXA reference data, and is one of the hypothesised reference data used in the current study.

Standard deviation scores (T-scores) must be calculated based on reference data that match the ethnicity and gender of the patient. Baran, *et al*. (1999c) suggested that reference values for populations not provided by the manufacturers can be obtained by published literature that are a representation of the patients being evaluated or in its absence, be developed by further research.

According to Blake and Fogelman (1998) a study of 200 healthy young adult volunteers for each gender is required to provide statistically adequate BMD reference values for meaningful T-scores in the same population. Baran, *et al.* (1999c) added that 50 participants per 10 year age band should be recruited, from which age specific BMD reference values are estimated. The means and SDs in the 10 year age bands provide statistically adequate data for the meaningful calculation of Z-scores.

The current study attempted to provide statistically adequate BMD reference values for the young adult normal or peak bone mass age group, as well as for the 10 year age bands.

2.6.1 T-SCORES

As stated previously, the WHO classification for osteoporosis compares an individual's BMD with the young normal mean value and expresses the difference as SD scores or in relative terms. The T-score is a measure of the difference between the patient's BMD and that of a young adult population matched for gender and ethnicity and is calculated using the following formula (Watts, 2002):

$$\text{T-score} = \frac{\text{measured BMD} - \text{mean BMD}^{\text{(young adult normal)}}}{\text{SD}^{\text{(young adult normal)}}}$$

If there were a single device for measuring BMD and only one skeletal site that was measured, the absolute value in g/cm^2 would suffice. However the complexity of absolute values lies in the multiple techniques for measuring BMD as well as the many sites.

Again, it is important to remember that while T-scores are used clinically to help define osteoporosis, other risk factors other than BMD must be considered, when patient management decisions are made.

2.6.2 Z-SCORES

Watts (2002) stated that the Z-score is a standard statistical concept. The Z-score is a measure of the difference between the patient's BMD and that of healthy people matched for age, gender and ethnicity and is calculated as follows:

$$\text{Z-score} = \frac{\text{measured BMD} - \text{mean BMD}^{\text{(age matched adult)}}}{\text{SD}^{\text{(age matched adult)}}}$$

Watts (2002) further argued that the Z-score is useful in determining how an individual's BMD compares with what is the expected norm in that age group. He highlighted that if Z-scores instead of T-scores are used in the older population, the prevalence of osteoporosis will remain constant over time, giving the impression that, for example, an 80 year with a normal z-score is "normal" in terms of bone health.

2.6.3 WHO DIAGNOSTIC CRITERIA FOR OSTEOPOROSIS

As indicated earlier, the World Health Organisation (WHO) has established a set of criteria for the diagnosis of osteoporosis in adult Caucasian women (Table 2.7).

Table 2.7: Demonstrates the four general diagnostic categories as defined by WHO (WHO Technical Report Series 843, 1994).

T-score	Relative to Mean BMD	Diagnosis
≥ -1	not more than 1 SD below the mean	**normal**
< -1 to -2.5 >	more than 1SD below the mean & less than 2.5 SD below the mean	**osteopaenia/low BMD**
≤ -2.5	2.5 SD or more below the mean	**osteoporosis**
< -2.5 + f #	more than 2.5 SD below the mean with fragility fractures	**severe osteoporosis**

According to the WHO definition, the cut-off value of -2.5 identifies approximately 30 percent of postmenopausal Caucasian women as osteoporotic at the lumbar spine, total hip or distal forearm, which in turn, is approximately equivalent to the lifetime risk

of fracture at these skeletal sites. Watts (2002) argued that, while this cut-off helps clinicians to think categorically (i.e. “normal” versus “osteopaenia” versus “osteoporosis”), any system that sets an arbitrary cut-off point will inevitably “misclassify” some patients (Watts, 2002).

A further concern is that the category of osteopaenia (i.e. -2.5 ≤ T-score ≤ -1) has created at least two problems (Watts, 2002). Firstly, many individuals who are in the upper border of this range are normal. Therefore, ‘labelling’ a healthy individual as “osteopaenic” can cause undue stress and anxiety that may last a lifetime. Secondly, individuals who fall in the lower border of the same range are almost as likely to fracture as those classified in the osteoporosis range (Watts, 2002). These concerns further highlight the need for correct reference ranges to be derived from the population being tested, as this will correctly identify those who fit in the classification of osteopaenia or osteoporosis. This in turn will yield correct clinical management of these individuals.

Another significant limitation is that the WHO definition directly applies to Caucasian women. Nonetheless, osteoporotic fractures are not uncommon in non-Caucasian women, in fact, the NOF of SA indicated the osteoporotic fracture rates in the Caucasian, Asian and “mixed race” populations in this country are similar to those reported from North America and Europe (Hough, 2006)

Furthermore, both the individual practitioners and medical aids are using Bone Densitometry as important and paramount criteria for determining which patients to

treat. Regrettably, there is no densitometric definition of osteoporosis in non-Caucasian individuals resulting in clinicians measuring and diagnosing these females in the absence of these guidelines (Binkley, et al. 2002). In context to the current study, BMD measurements in the Indian women in KZN, using the Hologic® QDR 4500 bone densitometer.

If the WHO criteria are used to determine osteoporosis and fracture risk in Indian females, then it is evident that any errors in the reference data currently used, may lead to significant differences in the incidence of osteoporosis or osteopaenia when the study population reference data is applied (Fogelman and Blake, 2000). Again, it is of paramount importance that an accurate ethnic matched reference database be established for the accurate assessment of osteoporosis and fracture risk, followed by the development of adequate prevention and treatment strategies.

2.6.4 CHOICE OF REFERENCE RANGES

The reference ranges for BMD presents the average results as a function of age, sex, and ethnicity for a matched population. The reference curves (Figure 2.9) specify average BMD, and standard deviation as a function of age. Each curve applies to a specific scan type, analysis type, bone region, patient sex and ethnic group.

These reference curves used on reference database reports (Figure 2.9) provide a graphic display of a patient's results and the calculation of T and Z scores (Appendix H). Each compares a patient's scan or series of scans with the reference database.

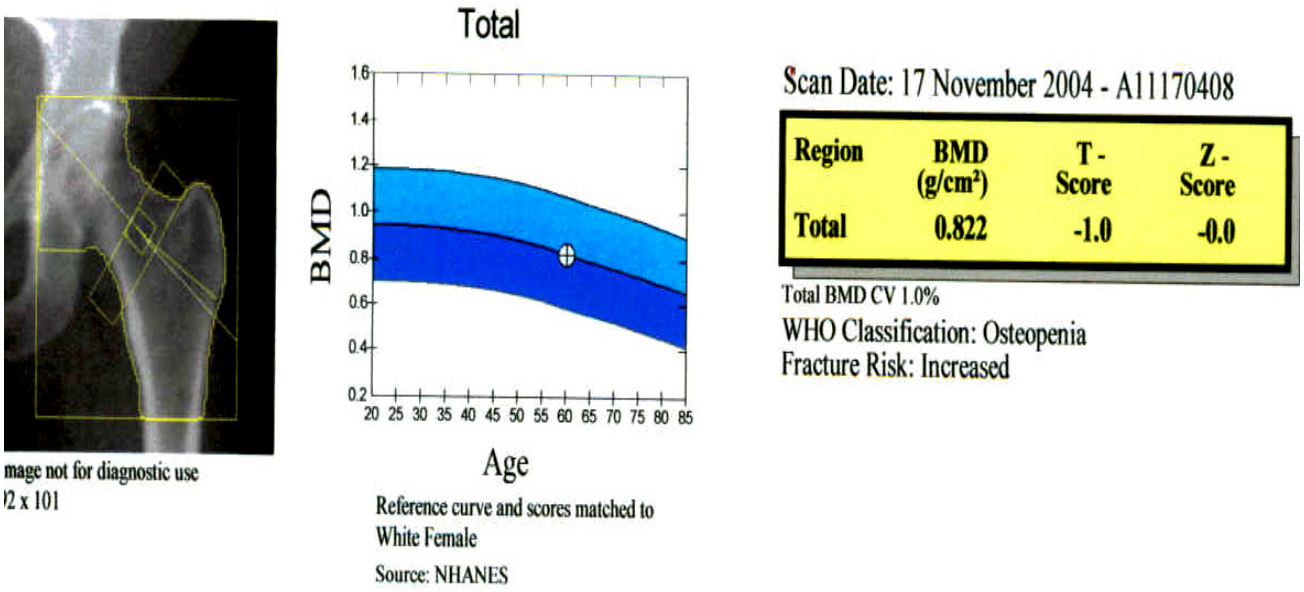


Figure 2.9: Reference curve and report for DEXA BMD

The great majority of clinical centres, both in the private and public sector, have scanning devices that use reference values provided by the equipment manufacturers. According to Faulkner, Roberts and McClung (1996) issues over the accuracy of these reference values have caused controversy in the past. This will continue to be a concern, as new devices are continually being introduced for the assessment of skeletal integrity.

Furthermore, it is uncertain whether the reference ranges supplied by the bone densitometer manufacturers can be applied to all populations, or whether different populations need to establish their own normative data (Baran, *et al.* 1999c). As can be seen in Figure 2.10, an Indian participant's BMD of the total hip was assessed for fracture risk against the NHANES III reference data, indicating increased risk. This may change when the reference values for the current study population is used.

In South Africa, least of all KwaZulu-Natal, no local reference data exists. Consequently, the manufacturer recommendation is that all populations of South Africa, irrespective of race or ethnicity, be measured against the manufacturer's Caucasian female reference values, in the absence of local population data. Conversely, the International Society of Clinical Densitometry recommended that these values apply to the United States (US) populations only and that further research is needed for populations outside the US (Binckley, *et al.* 2002).

A further implication is that the percentage of people with osteoporosis is dependent on how it is measured and compared. For example, the US NHANES III project studied a nationally representative sample of non-Hispanic White and Black, and Mexican Americans, measuring total hip BMD. Most manufacturers have replaced their femoral neck normative reference database with the NHANES III values for total hip, which has reduced the incidence of osteoporosis (Kanis, et al. 1997).

A study undertaken by Chen, *et al.* (1998), following this change, further confirmed that there was a significant decrease in the percentage of osteoporotic patients when using the total hip instead of the femoral neck reference values only. For the current study, data from measurements of the total hip was used for analyses and comparison.

The Hologic® Caucasian female young adult normal or peak BMD mean for the lumbar spine and distal forearm are 1.047g/cm^2 with a SD of 0.11. and 0.564 g/cm^2 with a SD of 0.051, respectively. The NHANES III Caucasian female young adult normal BMD

mean for the total hip is 0.942 g/cm^2 with a SD of 0.122. The manufacturer's Japanese female peak BMD reference values for the lumbar spine and total hip, although absent on the densitometer used in the current study, was 1.006 g/cm^2 with a SD of 0.115 and 0.851 g/cm^2 with a SD of 0.115 respectively. No Japanese reference data is available for the distal forearm using DEXA technology. These were the hypothesised reference values for the calculation of T-scores and can be seen in Chapter 3 in Table 3.1. The reference values for the 10 year age bands and the calculation of Z-scores are also displayed in the Table 3.1.

According to Kanis and Gluer (2000), normal reference ranges for BMD have been established and are available for many countries, among them are Holland, UK, Germany and France, Japan and China. Furthermore, many other studies have documented interethnic variations in BMD measurements (Woo, Li and Lau, 2001; Leong and Feng, 1997; Ahmed, *et al.*1997; Petley, *et al.* 1997), which in turn has led to over-diagnosis or under-diagnosis for osteoporosis in their respective populations.

Woo, Li and Lau (2001) indicated that their study population (Chinese from Hong Kong) BMD means were 0.927 g/cm^2 with a SD of 0.11 for the lumbar spine. BMD means for the femoral neck were 0.766 g/cm^2 with a SD of 0.11. With each age band, the decline in the BMD reference curve appeared steeper. The study undertaken by Ahmed, *et al.* (1997) showed similar results. The BMD means for the Caucasian women from London were 0.994 g/cm^2 with a SD of 1.22 and 0.787 g/cm^2 with a SD of 0.109 at the spine and femoral neck respectively. This finding indicated an erroneously high diagnosis of osteoporosis when the manufacturers' values (73%)

were used compared to 46% when the populations mean was used.

Other studies that used digital x-ray radiogammetry (Pande, 2002) also showed that Indian women from the Indian subcontinent had approximately 15% lower BMD than in Caucasian women. According to Pande (2002) normative reference data using x-ray radiogammetry is the only data available for Indian BMD measurements. Similar results were evident by a study undertaken by Reddy, Mithal and Rao (2002) to determine reference data for Asian Indian women living in America (as cited by Shah, 2005). It is important to note that T-scores do vary dependent on the measuring device used, and direct correlations of T-scores cannot be made between different densitometers.

Locally, a study undertaken by Daniels, *et al.* (1995) evaluated ethnic differences between South African White and Black female nurses and defined BMD in their population sample. Nevertheless, their study did not compare their population BMD measurements with the BMD reference data provided by the manufacturers. Additionally, the Medical Research Council of SA is currently undertaking a longitudinal research project, evaluating bone health in postmenopausal black women living in Soweto. The results of which, will give insight into the reasons for lower postmenopausal fractures rates in South African Black women (Medical Research Council, 2004).

Currently, no known data is evident with respect to South African Indian women.

This study attempted to define BMD in healthy Indian women and to compare the current study population reference values with the manufacturers' reference values that are presently being used for the diagnosis of osteoporosis.

One of the two major private practices in KZN measuring BMD with DEXA scanners uses the Hologic® QDR 4500. There are other medical centres that have Hologic® units, particularly in KZN. Similarly, two major hospitals in the public sector, King Edward VIII and Inkosi Albert Luthuli Central Hospital (IALCH) also use Hologic® Densitometers to measure BMD in their patients. The reference values that are currently being used to clinically diagnose their patients are those supplied by the manufacturers. In context to the current study, the similar scenario exists for Indian patients.

Currently, no known data are available regarding normal reference values for Indian women for these densitometers. Furthermore, no comparisons have been made between the reference values for the Indian female population in KZN and the manufacturer normal ranges (that are used currently), in terms of diagnostic implications.

2.7 SUMMARY AND MAIN AIMS OF STUDY

BMD of the lumbar spine and total hip by DEXA is the gold standard for the diagnosis of osteoporosis and the distal forearm is an alternate measurement site in patients with contraindications at one of these measurement sites.

The WHO classification of normal bone, osteopaenia and osteoporosis based on T-scores of > -1, between -1 and -2.5 and < -2.5 which identify patients with low, intermediate and high risk of fracture respectively, should only be applied to DEXA measurements. Although the diagnosis of osteoporosis is based on T-scores, Z-scores can be helpful in scan interpretation, especially in the elderly.

Furthermore, it is of critical importance that reference values used for the calculation of T- and Z-scores are relevant and accurate for the population concerned, taking into account gender and ethnicity.

The main research aim was to determine normal BMD reference ranges (means and SDs) for the lumbar spine, total hip and distal forearm, among Indian females of the different age groups in KwaZulu-Natal, as these values have not been previously assessed.

The second aim was to compare the study population (Indian female) reference values (means and SDs) with the manufacturer's reference values provided with the

bone densitometer and to evaluate any diagnostic implications. For the current study, the manufacturer's reference values included the Hologic® Caucasian female BMD for the lumbar spine and distal forearm and the NHANES III Caucasian female BMD for the total hip. The Asian (Japanese) values, which were derived from the Japanese population, were absent on the densitometer used during the study. However the Japanese reference values for BMD of the lumbar spine and total hip, obtained from Hologic® manufacturers, were included in the analyses. The BMD values of the distal forearm BMD for the Japanese female were not available for DEXA analyses.

The research questions addressed were:

- Do the reference values for peak BMD of the lumbar spine, total hip and distal forearm in the young adult normal population of Indian women need redefining?
- Do the T-scores for BMD of the lumbar spine, total hip and distal forearm for each participant in the Indian population vary according to the different population reference data used?
- Do the WHO classifications for the diagnosis of osteoporosis of the lumbar spine, total hip and distal forearm in the study population vary according to the reference population (Hologic® Caucasian female, NHANES III Caucasian female, Japanese female and Indian female, respectively) used?
- Do the reference values for BMD of the lumbar spine, total hip and distal forearm, as a function of age, need redefining in the Indian women in KZN?
- Do the Z-scores for BMD of the lumbar spine, total hip and distal forearm for each participant in the Indian population vary according to the different population reference data used?

CHAPTER 3

RESEARCH METHODS AND DESIGN

3.1 INTRODUCTION

A cross - sectional, quantitative study was undertaken to determine the reference values for bone mineral density (BMD) in the Indian female population of KwaZulu-Natal (KZN).

This chapter describes the research methodology that was employed in the study. The method of patient selection, data collection, and research parameters that were employed are highlighted. In addition, the reasons for the choice of research parameters, the methods of data analyses and the statistics are explained.

3.2 PERMISSION TO PERFORM THE RESEARCH STUDY

Permission letters (Appendix A) were sent to the directors of Drs Jackpersad, Rooknoodeen and Partners, the private radiology practice, situated at City Hospital in KZN, requesting permission to perform the research. The research was undertaken at this practice as the Hologic® QDR 4500 Bone Densitometer was situated there. During the study the bone densitometer was moved from the x-ray department at City Hospital to the x-ray department of the Westridge Medical Centre, another venue for

the same radiology practice. This did not directly affect the study in any way, as the equipment remained the same.

3.3 SPONSORS

The above radiology practice conceded and sponsored the use of their Hologic® QDR 4500 Bone Densitometer to undertake the BMD measurements on all the participants, using the dual energy x-ray absorptiometry (DEXA) scanning technique.

3.4 INVITATION TO PARTICIPATE

One thousand and five hundred pamphlets (Appendix B), advertising the research were distributed at the Durban University of Technology (DUT) campuses, hospitals, medical facilities in the area, and in the Durban Metropolitan area, in a concerted effort to recruit participants for the research. Intranet messages and emails were also conveyed to the staff and students of the DIT, inviting their participation.

Problems in recruiting sufficient healthy participants from certain age bands, for example the 60 to 69 year olds were anticipated. Pamphlets were then distributed to senior citizen communities, inviting participants from the older age groups. A vast majority of Indian females in the 60 to 69 age band, who responded to the invitation, did not meet the inclusion criteria for the study. Many older Indian females had endocrine disorders, arthritic disorders or a total hysterectomy. Hence, the limited

sample size in this age band.

Invitation to participate was sent out on a continual basis throughout the study, to ensure that the required numbers of participants were recruited. In addition the encountered difficulties in recruiting the 60 to 69 Indian females, the response from the 20 to 29 years age band was also relatively poor. Possible explanations for the poor responses include limited education and awareness about the disease as well as the exclusion criteria for the study, particularly in the older age groups.

3.5 PARTICIPANT INFORMATION SHEET, INFORMED CONSENT AND DATA COLLECTION SHEET

All the research participants read the participant information sheet (Appendix C). All the participants signed an informed consent form (Appendix D). These forms were designed by the researcher and approved by the Ethics Committee of the Faculty of Health Sciences, Durban University of Technology (DUT).

The data collection sheet (Appendix E) was designed to obtain as much relevant information about the participants' demographics. Furthermore, factors that could influence the results of the study, for example, smoking habits, alcohol consumption, oral contraceptives, calcium intake, frequency of load bearing exercise, menopausal status, age at menarche and age at menopause were also included on the data sheet. This data was to be used to explain any aberrant results obtained, if necessary.

3.6 RESEARCH POPULATION

Healthy female participants between the ages of 20 to 66 years of ethnic Indian origin were recruited using the convenience sampling technique. The recruitment was made in part among the DUT staff and students, hospital and other medical personnel, and the general public by pamphlet distribution as well as word of mouth, without coercion from the researcher.

A small percentage of peri menopausal and post menopausal (40 to 59 years) women volunteered for screening for osteopaenia by themselves because of their increased awareness of their health. Those volunteers who fitted the inclusion criteria were included in the data collection. In contrast, the response from the younger age bands, namely 20 to 39, was limited. It is assumed that limited education of and the awareness of osteoporosis as a debilitating disease, was the main contributing factor for reluctance to participate. While every effort was made to ensure adequate sample sizes, the 60 to 69 age band recruitment was also limited, as predicted.

Although the study used non-probability sampling, care was taken to ensure relative representation of the general population**.** These included a wide range of body sizes and lifestyle factors as well as various social and economic status groups. Following the protocol of other similar studies (Kelly, 1990; Pedrazzoni, *et al*. 2003; Roy, *et al*. 2005), participants with moderate lifestyle habits such as smoking; alcohol consumption; high, low or no calcium intake and a sedentary lifestyle were not

excluded from the study. Again, these data were to be used to explain any aberrant results obtained, if necessary.

Using a screening questionnaire (Appendix F), a cursory interview (personal or telephonic) between the researcher and the participant was used to establish those subjects who did not fit the criteria. They were excluded from the study.

3.6.1 INCLUSION CRITERIA

The criteria for individuals to be admitted to the study were:

- Indian females twenty years and older.
- individuals who were committed to following the protocol requirements as evidenced by reading and signing a written informed consent form.
- individuals who did not have any other identifiable major medical disorder, as indicated in the exclusion criteria.
- individuals who were not participating in any other investigational study involving the use of ionising radiation, or radiographic contrast studies.

3.6.2 EXCLUSION CRITERIA

The criteria for excluding individuals from the study were:

- the presence of renal, hepatic, endocrine and metabolic bone disease.

- use of hormone replacement therapy (HRT) for more than 12 months.
- menopause or bilateral oophorectomy before the age of 40 years.
- longstanding use of corticosteroids.
- not being fully ambulant.
- surgical implants to the hip and spine (prosthesis).
- all pregnant and possible pregnant women were excluded from the study.
- male participants.

3.6.3 SELECTION OF REFERENCE POPULATION

According to Blake and Fogelman (1998) a study of 200 healthy young adult volunteers of each gender is required to provide statistically adequate data for the young adult normal population for the meaningful calculation of T-scores. Additionally, Baran, *et al*. (1999) stated that 50 randomly selected individuals for each 10 year age band from a target population is sufficient to determine age-specific means and SDs. The current study was designed according to the prescribed recommendations to establish BMD means and SDs for the study population. For each 10 year age band, the sample size was anticipated to include 50 participants.

Two hundred and seventy three individuals volunteered for the study. However, only two hundred and seventeen participants from age 20 to 66 years, who were characterised as “normal” according to their answers on the questionnaire, were included in the study.

Each participant had no known risk factors for osteoporosis or metabolic disease that affects bone density, no fractures, nor received any treatment for osteoporosis or corticosteroids. None were heavy smokers or consumed more than 1 to 2 glasses of alcohol per week. None presented with a history of premature menopause or amenorrhea, nor were any of them on hormone replacement therapy.

It is important to highlight that the information by each participant was presumed to be correct in terms of their health status, as a full health assessment of each participant would have been prohibitively expensive for the study.

3.7 DATA COLLECTION

Primary data were collected over a period of eighteen months at irregular intervals, as the participants presented themselves for the study.

The primary data collected were:

- **Demographic data** including the date of birth, ethnic background, medical history, fractures history and family history of osteoporosis. This was recorded at the time of screening to ensure each participant met all the inclusion criteria.
- Age was the only **independent variable** included in the analyses.
- **Dependent variables** included the following:
    - DEXA BMD of the lumbar spine - Antero-Posterior (AP) L1 – L4
    - DEXA BMD of the total hip
    - DEXA BMD of the distal forearm

- T – scores for BMD of the lumbar spine, total hip and distal forearm
- Z – scores for BMD of the lumbar spine, total hip and distal forearm

3.8 RESEARCH PARAMETERS

The main research aim was to determine normal BMD reference ranges (means and SDs) for the lumbar spine, total hip and distal forearm, among Indian females of the different age groups in KwaZulu-Natal, as these values have not been previously assessed. This was achieved using the Hologic® QDR 4500 bone densitometer that includes an examination table, operator console and positioning aids. The QDR for Windows software interface was used to analyse the scans.

The second aim was to compare the study population (Indian female) reference values (means and SDs) with the hypothesised manufacturer's reference values provided with the bone densitometer and to evaluate any diagnostic implications. For the current study, the manufacturer's reference values included the Hologic® Caucasian female BMD for the lumbar spine and distal forearm and the NHANES III Caucasian female BMD for the total hip (Table 3.1). The Asian (Japanese) values, which were derived from the Japanese population, were absent on the densitometer used during the study. However the Japanese reference (Table 3.1) values for BMD of the lumbar spine and total hip, obtained from Hologic® manufacturers, were included in the analyses. The BMD values of the distal forearm BMD for the Japanese female were not available for DEXA analyses.

Table 3.1: BMD reference values for Lumbar Spine, total Hip and Distal forearm provided by manufacturer (Hologic®)

Age (years)	Lumbar Spine (Mean ± SD)		Total Hip (Mean ± SD)		Distal Forearm (Mean ± SD)	
	Hologic® Caucasian Female	Japanese Female	NHANES III Caucasian Female	Japanese Female	Hologic® Caucasian Female	Japanese Female
YAN/PBM	**1.047±.11**	**1.006±.115**	**0.942±.122**	**0.851±.115**	**0.564±.051**	n/a
20 to 29	**1.019 ±.11**	**0.981±.107**	**0.942±.122**	**0.850±.115**	**0.564±.051**	n/a
30 to 39	**1.047±.11**	**1.000±.118**	**0.939±.122**	**0.851±.115**	**0.557±.051**	n/a
40 to 49	**1.024±.11**	**0.979±.133**	**0.922±.122**	**0.830±.115**	**0.546±.051**	n/a
50 to 59	**0.967±.11**	**0.864±.142**	**0.886±.122**	**0.785±.115**	**0.526±.051**	n/a
60 to 69	**0.892±.11**	**0.766±.144**	**0.827±.122**	**0.727±.115**	**0.497±.051**	n/a

The research questions addressed were:

- Do the reference values for peak BMD of the lumbar spine, total hip and distal forearm in the young adult normal population of Indian women need redefining?
- Do the T-scores for BMD of the lumbar spine, total hip and distal forearm for each participant in the Indian population vary according to the different population reference data used?
- Do the WHO classifications for the diagnosis of osteoporosis of the lumbar spine, total hip and distal forearm in the study population vary according to the reference population (Hologic® Caucasian female, NHANES III Caucasian female, Japanese female and Indian female, respectively) used?
- Do the reference values for BMD of the lumbar spine, total hip and distal forearm, as a function of age, need redefining in the Indian women in KZN?
- Do the Z-scores for BMD of the lumbar spine, total hip and distal forearm for each participant in the Indian population vary according to the different population reference data used?

These research questions were addressed in Chapter 4 separately, with respect to the measurement sites, to ensure adequate presentation of the results and analyses.

3.8.1 DEXA BMD MEASUREMENTS FOR INDIAN FEMALES AGED 20 TO 66 YEARS

DEXA BMD is currently the gold standard for measuring bone density and predicting fracture risk due its advantages of high precision and accuracy (Adams, 1997). Furthermore, it is a reliable, non-invasive technique that uses short scan times, low radiation doses and stable calibration in clinical uses (Fogelman and Blake, 2000). The Hologic® QDR 4500 Bone Densitometer (Appendix G) was used to measure the absolute BMD (g/cm^2) of the lumbar spine, total hip and distal forearm in the 217 Indian women aged 20 to 66, in the current study.

3.8.1.1 Quality control and calibration

The bone density measurements were performed by the researcher to ensure consistency in technique and to minimise operator error. The protocol, using the manufacturer guidelines, remained the same for each participant.

Furthermore, daily calibration and quality control was performed with the anthropomorphic spine phantom provided by Hologic®, prior to scanning, to ensure consistency of measurements. The scanning precision was usually 1.0 % (coefficient of variance at BMD = 1.0 g/cm^2) and any deviation outside the normal would have been highlighted in the daily quality assurance report. No deviations outside the normal range occurred during the course of the study.

3.8.1.2 Participant Preparation

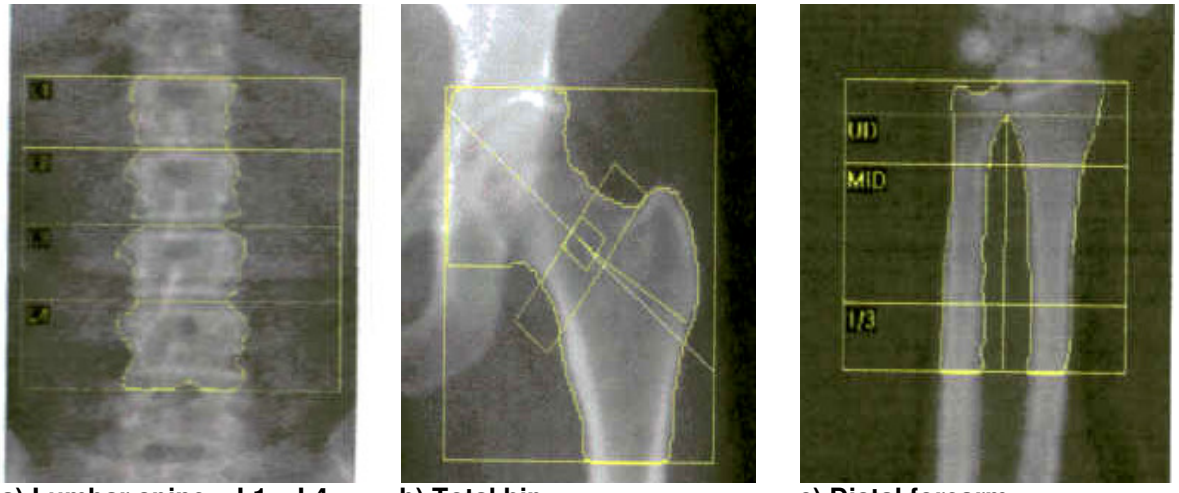
No special preparation was necessary; however a proper explanation of the procedure was given. The participants had to ensure that no calcium was taken for 24 hours prior to the scan. They were asked to inform the researcher if they had participated in any other investigational study involving the use of ionising radiation, or radiographic contrast studies. These would have delayed the procedure for approximately 2 weeks, as the results from the BMD testing could have been compromised. They were asked to wear light clothing, so they did not have to undress for the procedure. They were asked to remove any artefacts prior to scanning.

The participants read the information sheet and obtained clarification from the researcher where necessary. The entire BMD procedure and reason for the study was explained to the research participants. The participants then signed an informed consent form, which documented their agreement with the study requirements.

Each participant's height and weight was measured without shoes and in light indoor clothing using a standard electronic scale and a height attachment, respectively. The length of the forearm was also measured from the olecranon to the styloid process of the distal ulna. These measurements are standard requirement for data entry prior to scanning, as they are included in the analyses and calculations. Other details recorded included age at menarche, age at menopause (if applicable), contraceptives, daily calcium intake, weight-bearing exercise, smoking and alcohol consumption.

3.8.1.3 Measurement of BMD

Each participant was positioned for the respective scanning procedure, using the standard protocol for DEXA BMD. The sites that were measured included the antero-posterior (AP) lumbar spine (L1 – L4), the non dominant total hip and the non dominant distal forearm (Figure 3.1). According to standard protocol, the non dominant side was measured to ensure consistency, as well as to measure the "weaker' side or the site most at risk for fracture.



a) Lumbar spine – L1 – L4 **b) Total hip** **c) Distal forearm**

Figure 3.1: The 3 measurements sites for DEXA BMD in the current study.

Each participant was positioned supine on the scanning table. For the lumbar spine scans, the participants' hips and knees were flexed over a box-shaped support to flatten the spine on the table and to eliminate lumbar lordosis (Adams, 1997).

For the total hip, the participant's non dominant leg was slightly abducted and internally rotated. The positioning device provided was used to ensure that the femoral

neck was parallel to the scan table, thereby reducing foreshortening of the femoral neck. This positioning error could result in erroneous increased BMD measurements (Adams, 1997).

For the distal forearm scans, the participants were asked to sit in a chair at right angles to the table top, with the non dominant forearm resting on the table top. Each participant's distal forearm was correctly positioned, with the hand pronated and strapped in the forearm positioning device (Adams, 1997).

Following the BMD measurements that were taken at all 3 skeletal sites, the Hologic QDR software quantitatively analysed the BMD measurements for each participant at each skeletal site and a report was printed. Each report provided the participants' absolute BMD value in g/cm^2. T- and Z- scores and the resultant diagnoses as generated by the densitometer using the manufacturers' reference data (Appendix H), were also expressed.

The manufacturers' reference database is currently used for the calculations of T- and Z- scores at the different measurement sites for all the populations in South Africa, in the absence of local reference data. In this study, each participant's absolute BMD values in g/cm^2 were captured for the descriptive statistical analyses, as well as the inferential statistics derived. The T- and Z- scores calculated by the densitometer, based on the manufacturer's reference data at all 3 skeletal sites were also captured.

3.8.2 BMD MEANS AND STANDARD DEVIATIONS (SDs) OF THE LUMBAR SPINE, TOTAL HIP AND DISTAL FOREARM IN THE YOUNG ADULT NORMAL POPULATION OF INDIAN WOMEN

An individual's BMD result is expressed as an absolute BMD (g/cm^2) and/or in relative terms, expressed as T- and Z- scores.

These BMD results of the 3 skeletal sites for each participant were captured for further analyses, using the SPSS package, version 13. Means and standard deviations (SDs) for age and BMD of the lumbar spine, total hip and distal forearm were calculated for the young adult normal age group, and were taken as the reference values for the study population. The young adult normal age band for the study population (Indian female) was defined from age 20 to 48 years. The young adult normal reference values for Indian females were established by evaluating the peak bone mass in the study population for all 3 skeletal sites. BMD was virtually constant from age 20 and peaked in the 40 to 49 age band, followed by a linear decline beyond 49 years. All postmenopausal women were further excluded from this sample.

RESEARCH QUESTION: Do the reference values for peak BMD of the lumbar spine, total hip and distal forearm in the young adult normal population of Indian women need redefining?

To answer this research question the young adult normal Indian female BMD means and SDs for each measurement site were compared with the manufacturer's reference values published as Hologic® Caucasian female for the lumbar spine and distal forearm and the NHANES III Caucasian female for the total hip. Statistical

analyses and comparisons were also made with the Japanese female reference values for this age group. These values were obtained from the manufacturers although absent on the bone densitometer. The one sample t-test was used to compare the means.

These research questions were addressed in Chapter 4 separately, with respect to the measurement sites, to ensure adequate presentation of the results and analyses.

3.8.3 CALCULATION AND COMPARISON OF T-SCORES IN THE STUDY POPULATION

The T-score is used as a diagnostic interpretation of whether an individual's BMD is normal (T-score ≥ -1), osteopaenic (-2.5 < T-score < -1) or osteoporotic (T-score ≤ -2.5), according to the WHO classification for osteoporosis (WHO Technical Report, 2003). It is a measure of an individual's BMD of a measurement site compared with the young adult normal or peak bone mass mean value in a given population matched for gender and ethnicity, and is expressed as a standard deviation.

The following formula was used to calculate T-score for each participant:

$$\text{T-score} = \frac{\text{measured BMD} - \text{mean BMD}^{\text{(young adult normal)}}}{\text{SD}^{\text{(young adult normal)}}}$$

The T-scores for all 3 measurement sites were calculated separately, based on the young adult normal Indian means and SDs, to assess the departure of each participant's BMD value from the mean young adult normal or peak BMD of the Indian

population. The T-scores for the respective measurement sites, based on the Hologic® Caucasian female and the NHANES III Caucasian female reference values, were captured from the printed reports. T-scores for BMD of the lumbar spine and total hip were also calculated based on the Japanese female young adult normal means, using the above formula.

RESEARCH QUESTION: Do the T-scores for BMD of the lumbar spine, total hip and distal forearm for each participant in the Indian population vary according to the different population reference data used?

To answer the research question, T-scores for BMD of the 3 measurement sites based on the Indian female young adult normal age band were then compared with the manufacturer's Hologic® Caucasian female, NHANES III Caucasian female and the Japanese female based T-scores, using the one sample t-test.

These research questions were addressed in Chapter 4 separately, with respect to the measurement sites, to ensure adequate presentation of the results and analyses.

3.8.4 WHO CLASSIFICATIONS FOR THE DIAGNOSIS OF OSTEOPOROSIS OF THE LUMBAR SPINE, TOTAL HIP AND DISTAL FOREARM

The T-scores for the study population derived from the different population reference values were further recoded according to WHO criteria for normal bone (T-score > -1), osteopaenia (-2.5 < T-score < -1), and osteoporosis (T-score < - 2.5).

RESEARCH QUESTION: Do the WHO classifications for the diagnosis of osteoporosis of the lumbar spine, total hip and distal forearm in the study population vary according to the reference population (Hologic® Caucasian female, NHANES III Caucasian female, Japanese female and Indian female, respectively) used?

To answer the research question, the frequencies of normal bone, osteopaenia and osteoporosis in the Indian women in KZN was evaluated and compared, using the recoded values. This was done using the T-score cut-offs, as defined by the WHO criteria, determined by the study population and the manufacturer's reference values for the respective measurement sites. The results were displayed using frequency distribution tables.

These research questions were addressed in Chapter 4 separately, with respect to the measurement sites, to ensure adequate presentation of the results and analyses.

3.8.5 BMD MEANS AND SDS OF THE LUMBAR SPINE, TOTAL HIP AND DISTAL FOREARM IN THE 10 YEAR AGE BANDS

The BMD measurements for the 3 skeletal sites for each participant were captured for further analyses, using the SPSS package, version 13. This Statistical software program is manufactured by SPSS Inc, 444N. Michigan Avenue, Chicago, Illinois, USA.

Means and standard deviations for age and BMD of the lumbar spine, total hip, and distal forearm were calculated in the 10 year age bands and were taken as the reference values for the study population. The age bands were 20 to 29, 30 to 39, 40 to 49, 50 to 59 and 60 to 69.

RESEARCH QUESTION: Do the reference values for BMD of the lumbar spine, total hip and distal forearm, as a function of age, need redefining in the Indian women in KZN?

To answer this research question the means and SDs for each 10 year age band in the study population were compared with the manufacturer's reference values published as Hologic® Caucasian female for the lumbar spine and distal forearm and NHANES III Caucasian female for the total hip. Statistical analyses and comparisons were also made with the Japanese female reference values for these age bands. These values were obtained from the manufacturers although absent on the bone densitometer. The one sample t-test was used to compare the means.

These research questions were addressed in Chapter 4 separately, with respect to the measurement sites, to ensure adequate presentation of the results and analyses.

3.8.6 CALCULATION AND COMPARISON OF Z-SCORES IN THE 10 YEAR AGE BANDS OF THE STUDY POPULATION.

The Z-score is a standard statistical concept. Applied to BMD, the Z-score compares an individual with age and sex matched norms and is useful for the expression of

relative fracture risk. In contrast to T-scores, the Z-score determines how an individual's BMD compares to age-matched values rather than to young individuals peak bone mass. In other words, a low Z-score indicates whether the bone density is lower than it should be for the individual's age and sex. The following formula was used to assess Z-score for each participant:

$$\text{Z-score} = \frac{\text{measured BMD} - \text{mean BMD}^{\text{(age matched adult)}}}{\text{SD}^{\text{(age matched adult)}}}$$

The Z-scores for all 3 measurement sites were calculated separately, based on each 10 year age band means, to assess the departure of each participant's BMD value from the mean BMD of the age matched sample of the Indian population. The Z-scores for the respective measurement sites, based on the Hologic® Caucasian female and the NHANES III Caucasian female reference data, were captured from the printed reports. Z-scores for BMD of the lumbar spine and total hip were also calculated based on the Japanese female young adult normal means, using the above formula.

RESEARCH QUESTION: Do the Z-scores for BMD of the lumbar spine, total hip and distal forearm for each participant in the Indian population vary according to the different population reference data used?

To answer the research question, Z-scores for BMD of the 3 measurement sites based on the Indian female 10 year age bands were then compared with the manufacturer's Hologic® Caucasian female, NHANES III Caucasian female and the Japanese female based Z-scores, using the one sample t-test.

These research questions were addressed in Chapter 4 separately, with respect to the measurement sites, to ensure adequate presentation of the results and analyses.

3.9 ETHICAL ISSUES

The study was approved by the Faculty of Health Sciences Ethics Committee of the Durban University of Technology (DUT), KZN, South Africa.

Although BMD measurements involve radiation exposure, the radiation dose to each participant was very low (1-10 μSv.) and is comparable with the average daily dose (7 μSv.) from natural background radiation (Fogelman and Blake, 2000).

Informed written consent was obtained from all the participants. Each participant was given an information brochure, informing them of the procedure involved and indicating that they would be exposed to a minimal dose of low radiation. They were also informed that they would be able to return to normal activities following the scan.

Participant confidentiality and identification was maintained throughout the study. This was achieved using codes for the purpose of data analyses. All raw data will be securely stored for five years, until such time that it is ethically and legally permissible to destroy them.

Normal results were issued to each participant, as a record of their current BMD status. Participants with "abnormal" BMD analysis, based against the Caucasian reference database, were given the results of their scans and asked to consult with their physicians for further medical follow-up. This decision was undertaken, as currently, clinical decisions on the treatment of osteoporosis are made on all the South African populations using the manufacturer's databases as reference.

3.10 STATISTICAL ANALYSIS

Statistical Analysis was conducted using the SPSS (version 13) software programme. This Statistical software program is manufactured by SPSS Inc, 444N. Michigan Avenue, Chicago, Illinois, USA.

Various descriptive statistical techniques were used and demonstrated, via various tables and graphs and a few summary statistics including but not limited to means, proportions, percentages and standard deviations. These statistics were calculated for both the overall, young adult normal and the specific 10 year age band data for the lumbar spine, total hip and distal forearm. Descriptive statistics and frequencies were also used to display the characteristics of the study sample. These included the demographic data as well as lifestyle factors.

The inferential statistics namely hypothesis testing and confidence intervals were

used, set at the type 1 error at 5%, or mentioned differently $\alpha = 0.05$. A p value of less than 0.05 was considered a significant result and the null hypothesis was rejected. One sample t-tests using the manufacturer's specifications as the hypothesised values were performed for the young adult normal population and for each 10 year age band for the lumbar spine, total hip and distal forearm. A p value of less than 0.05 was considered significant. The null hypothesis stated that the reference values for DEXA BMD in the sample population were the same as those provided by the manufacturers in the Hologic® QDR 4500 bone densitometer. These statistics were used to answer the main aim of the research study, which was to determine new reference values.

One sample t-tests were also used to calculate the difference between the means of the T- and Z- scores of the manufacturer's reference ranges and the sample population. A p value of less than 0.05 was considered significant, and the null hypothesis would be rejected.

The T-scores were then recoded, using the WHO criteria for osteoporosis, to determine the diagnostic implications of using reference data from the study population, as well as those not derived from the study population. Frequency distribution tables were used to display the percentage differences among the manufacturer's Hologic® Caucasian female, NHANES III Caucasian female and Japanese female calculations compared to those derived using the study population.

It is important to remember that currently, the Hologic® Caucasian female and NHANES III Caucasian female reference data are used to measure osteoporosis in all the South African populations for the Hologic® bone densitometers. This recommendation by the manufacturers is based on the fact that local reference data are not available for use. The Japanese female reference data was absent on the densitometer used for the study. However comparisons were made against the Japanese female values to evaluate ethnic differences among populations of Asian descent. A further limitation with the Japanese database was that the data were categorised into 5 year age bands and not for each decade of life. The Japanese data for the distal forearm was also unavailable using DEXA technology.

CHAPTER FOUR

RESULTS

4.1 INTRODUCTION

This chapter reports the results of data analyses. The descriptive statistics for the independent variable (age) and the dependent variables (bone mineral density at the lumbar spine, total hip and distal forearm) are presented first. A sample of 131 pre menopausal participants was categorised as the young adult normal age band for peak bone mass. This was determined by exploring the bone mineral density (BMD) at the spine, total hip and distal forearm. BMD at the three sites were virtually constant between the ages 20 to 48. The data were also categorised into 10 year age bands from 20 to 29, 30 to 39, 40 to 49, 50 to 59 and 60 to 69.

The data were first explored for errors in entry and the observations are described below. Normality tests were performed for each variable to show the distribution of the data and are important criteria for using the one sample t-test for inferences. These are explained as well as demonstrated graphically. The minor outliers for the different variables did not contribute to significant differences in the analyses and were not excluded from the study. This was done to ensure a non-biased study.

Analyses relevant to each of the research questions were then presented.

The main aim of this research was to determine normal BMD reference ranges

(means and standard deviations) for the lumbar spine, total hip and distal forearm, for Indian women of varying age groups in KwaZulu-Natal, as these values have not been previously assessed.

The second aim was to compare the study population reference ranges with those provided by the manufacturer, and to evaluate the diagnostic implications thereof. They included the female Caucasian database for the lumbar spine and forearm and the NHANES III database for the total hip. The Asian (Japanese) database was not available on the Hologic® QDR 4500 bone densitometer used during the study data collection. However the Japanese reference data for the hip and spine were included in the comparative analyses.

Descriptive analyses were also performed and displayed for the other variables; these included height, weight, body mass index, age at menarche, age at menopause, and lifestyle factors. Lifestyle factors that were explored in this study were exercise, calcium intake, contraceptives, smoking and alcohol. This was done to demonstrate the characteristics of the study population and to identify or explain possible aberrant results in the study participants.

4.2 DESCRIPTIVE STATISTICS

Most of the descriptive statistics for the 217 participants used for the BMD analyses are depicted in appendices I - L. The frequency distributions of the variables are depicted using either a bar graph or a histogram with a normal curve or with tables. The measures of central tendency used are the mean and median. The range and standard deviation are the measures of variability.

4.2.1 DESCRIPTIVE STATISTICS - AGE

Descriptive statistics were performed first on all 217 participants ranging from ages 20 to 66.

The young adult normal female age band for the study population was defined as 20 to 48 years pre menopausal women, based on the peak BMD values observed at the lumbar spine, hip and distal forearm. The data were further categorised into 10 year age bands, namely, 20 to 29, 30 to 39, 40 to 49, 50 to 59, and 60 to 69. Descriptive statistics were used to establish means and standard deviations for age for the young normal adult female, as well as each of the 10 year age bands.

4.2.1.1 217 participants

The descriptive statistics for age are presented in Figure 4.1. As can be seen, the mean age for all 217 participants was 43.49 with a standard deviation of 12.27. The histogram (Figure 4.1) shows that the sample population is not normally distributed and is negatively skewed.

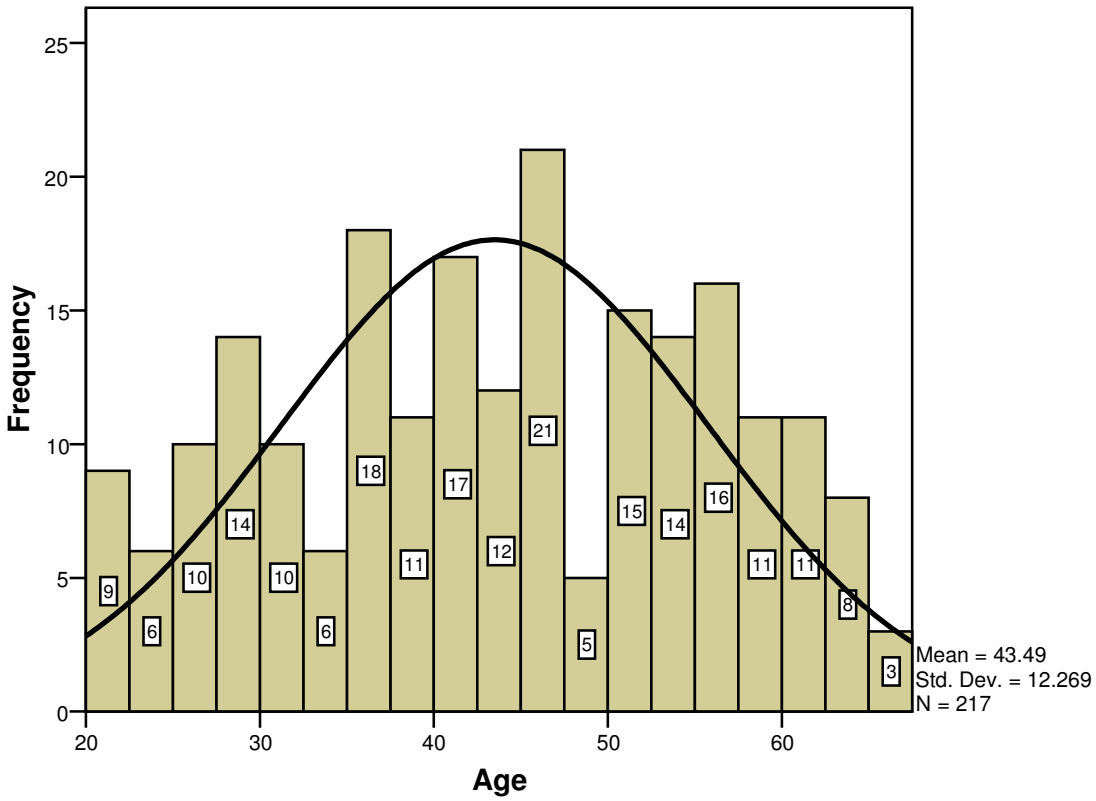


Figure 4.1: Frequency Distribution for Age - 20 to 66 years

The minimum age was 20 and the maximum age was 66.The 95% confidence interval for the mean is 41.85 (lower bound) and 45.18 (upper bound).

4.2.1.2 Young adult normal age band - 20 to 48 years

The descriptive statistics for the young adult normal age band (20 to 48 years) are presented in Figure 4.2. This age band was derived after exploring the peak bone mass measurements at the 3 skeletal sites. As can be seen, the mean age for the young adult normal study population was 35.29 with a standard deviation of 7.90.

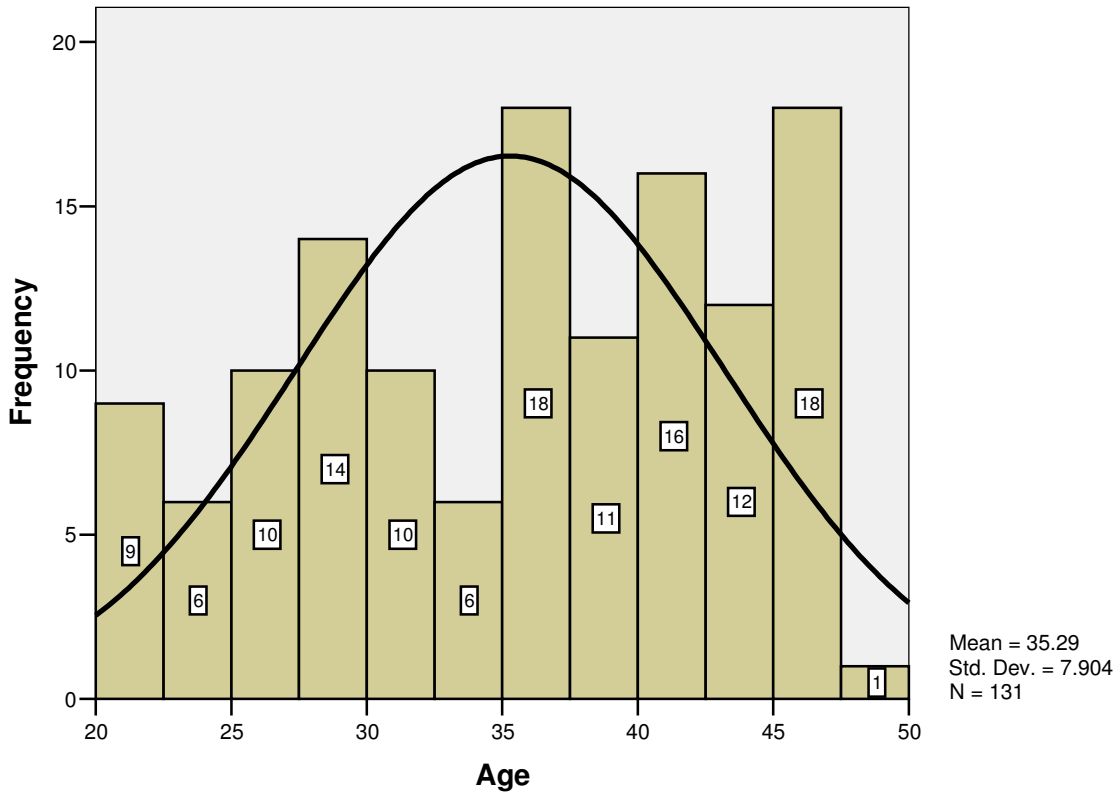


Figure 4.2: Frequency Distribution for Age - Young adult normal age band

The minimum age was 20 and the maximum age was 48. The histogram (Figure 4.2) shows that the age distribution of the sample negatively skewed. The Kolmogorov-Smirnov test also confirmed that the distribution is not normal (Appendix I).

4.2.1.3 20 to 29 age band

The descriptive statistics for the 20 to 29 age band are presented in Figure 4.3. As can be seen, the mean age for the 39 subjects was 25.38 with a standard deviation of 3.12.

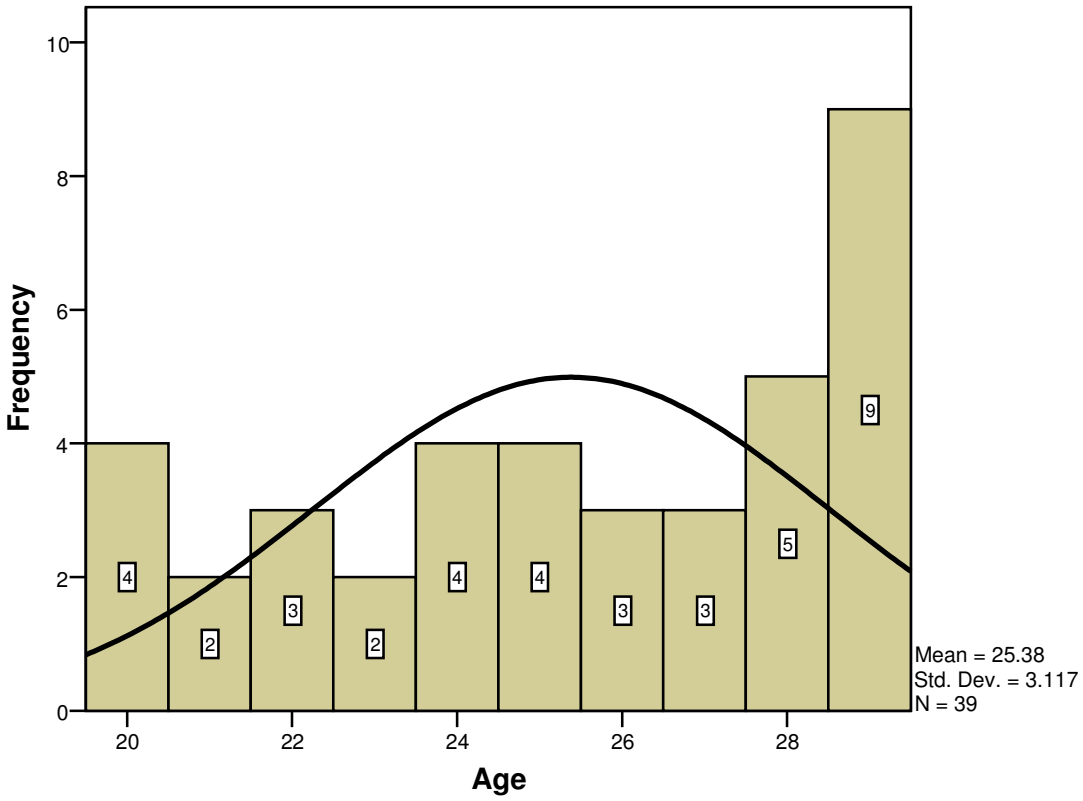


Figure 4.3: Frequency Distribution for Age - 20 to 29 years

The histogram (Figure 4.3) shows that the 20 to 29 age band distribution of the sample is slightly negatively skewed, evident by the lack of participants observed in this age band. Refer to Appendix I for normality tests.

4.2.1.4 30 to 39 age band

The descriptive statistics for the 30 to 39 age band are presented in Figure 4.4. As can be seen, the mean age for all 45 subjects was 35.09 with a standard deviation of 2.82.

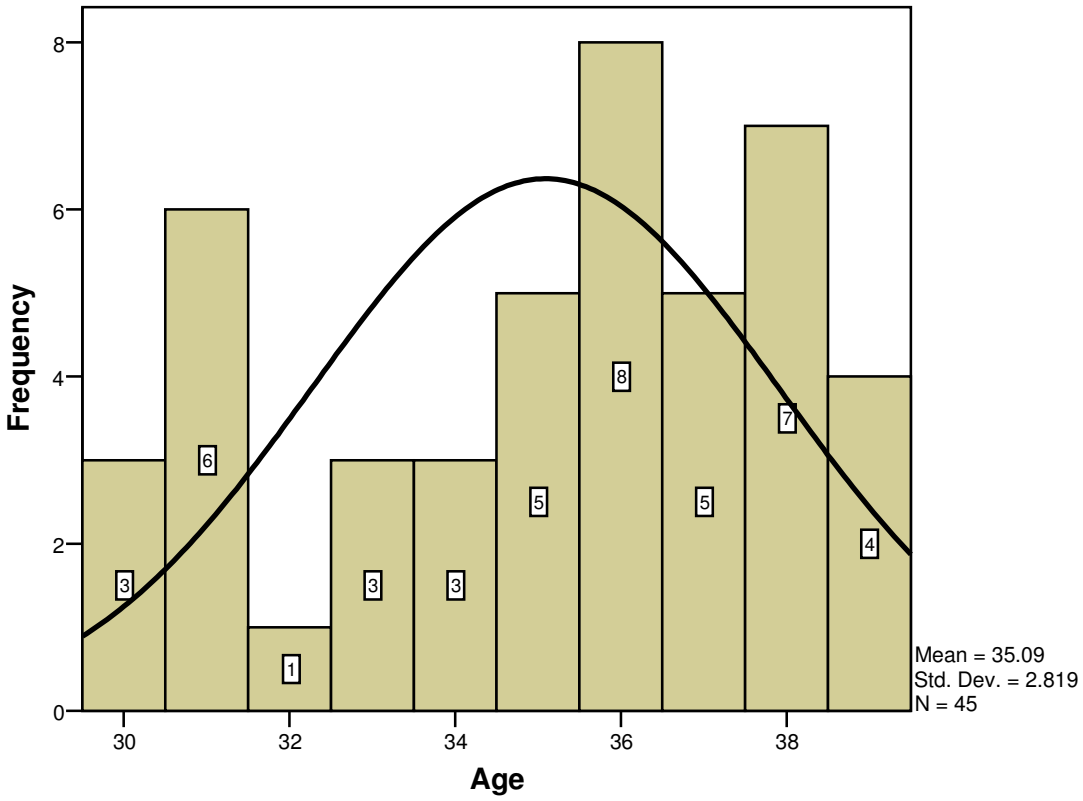


Figure 4.4: Frequency Distribution for Age - 30 to 39 years

The histogram (Figure 4.4) shows that the age distribution of the sample is slightly negatively skewed. Refer to Appendix I for normality tests.

4.2.1.5 40 to 49 age band

The descriptive statistics for the 40 to 49 age band are presented in Figure 4.5. As can be seen, the mean age for the 55 subjects was 44.18 with a standard deviation of 2.65.

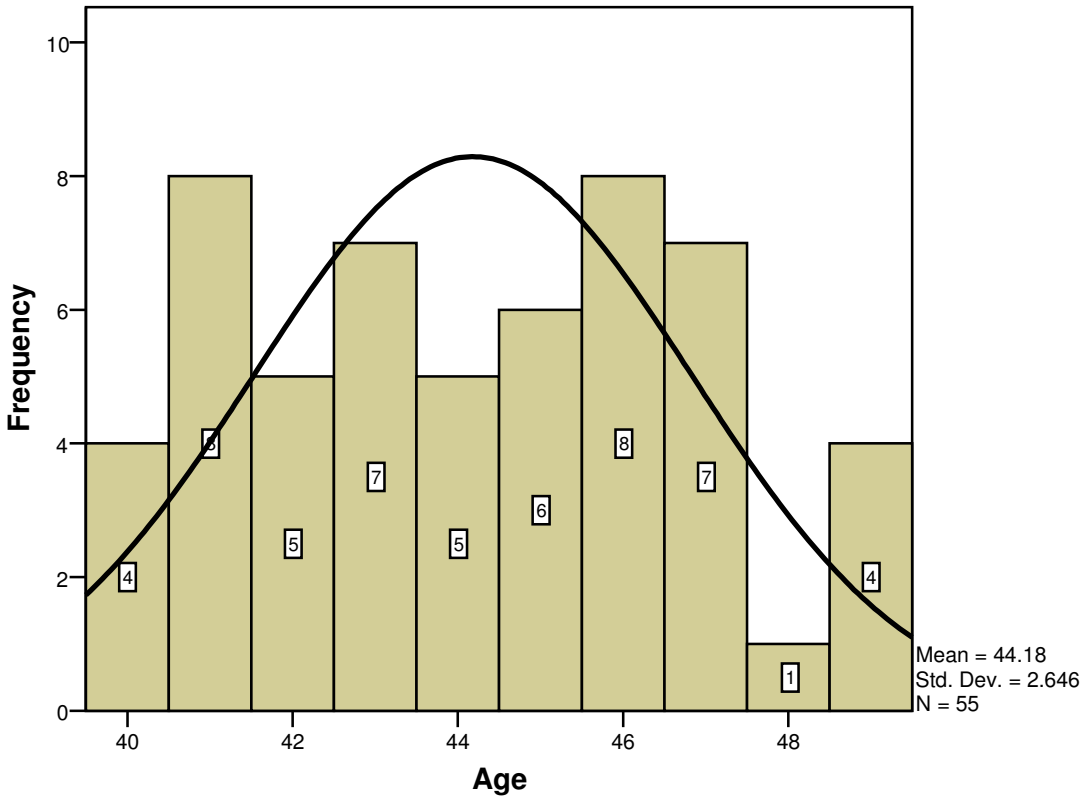


Figure 4.5: Frequency Distribution for Age - 40 to 49 years

The histogram (Figure 4.5) shows that the age distribution of the sample. Refer to Appendix I for normality tests.

4.2.1.6 50 to 59 age band

The descriptive statistics for the 50 to 59 age band are presented in Figure 4.6. As can be seen, the mean age for all 56 subjects was 54.75 with a standard deviation of 2.71.

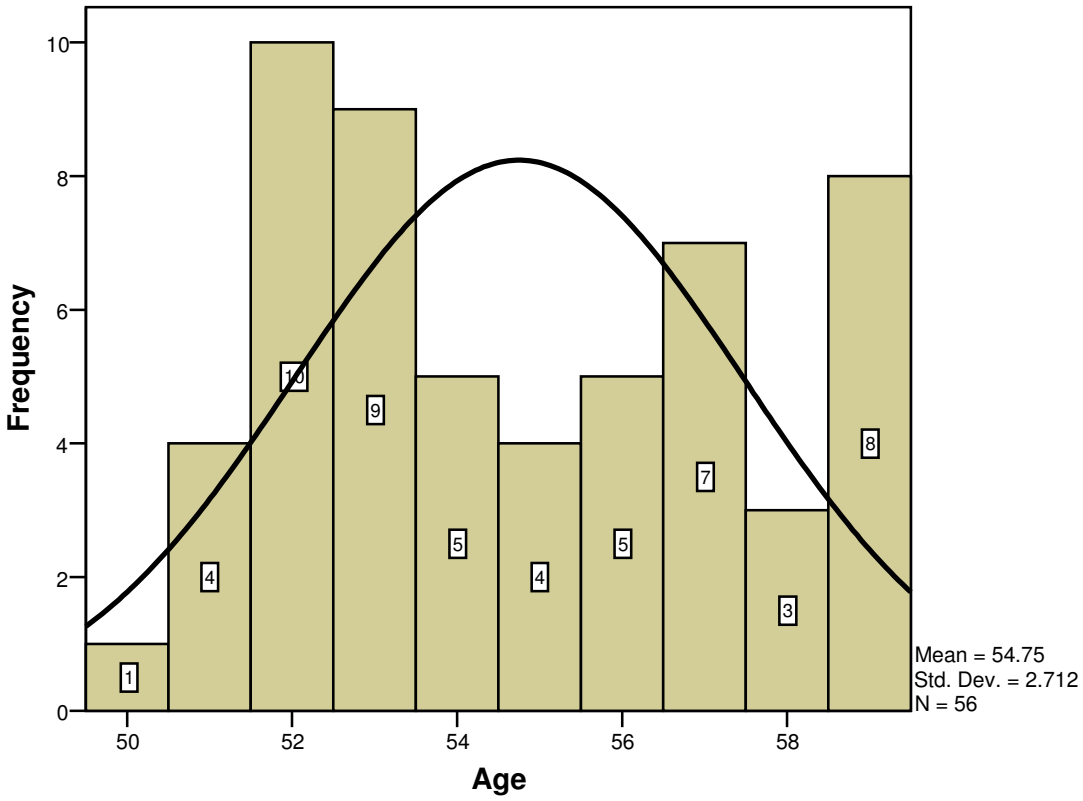


Figure 4.6: Frequency Distribution for Age - 50 to 59 years

The histogram (Figure 4.6) shows that the age distribution of the sample is positively skewed and the result for the Kolmogorov-Smirnov indicated that it is not normally distributed. Refer to Appendix I for normality tests.

4.2.1.7 60 to 69 age band

The descriptive statistics for the 60 to 69 age band are presented in Figure 4.7. This age band had a limited number of participants due to the restrictions with the inclusion criteria. The mean age for the 22 subjects was 62.36 with a standard deviation of 2.04.

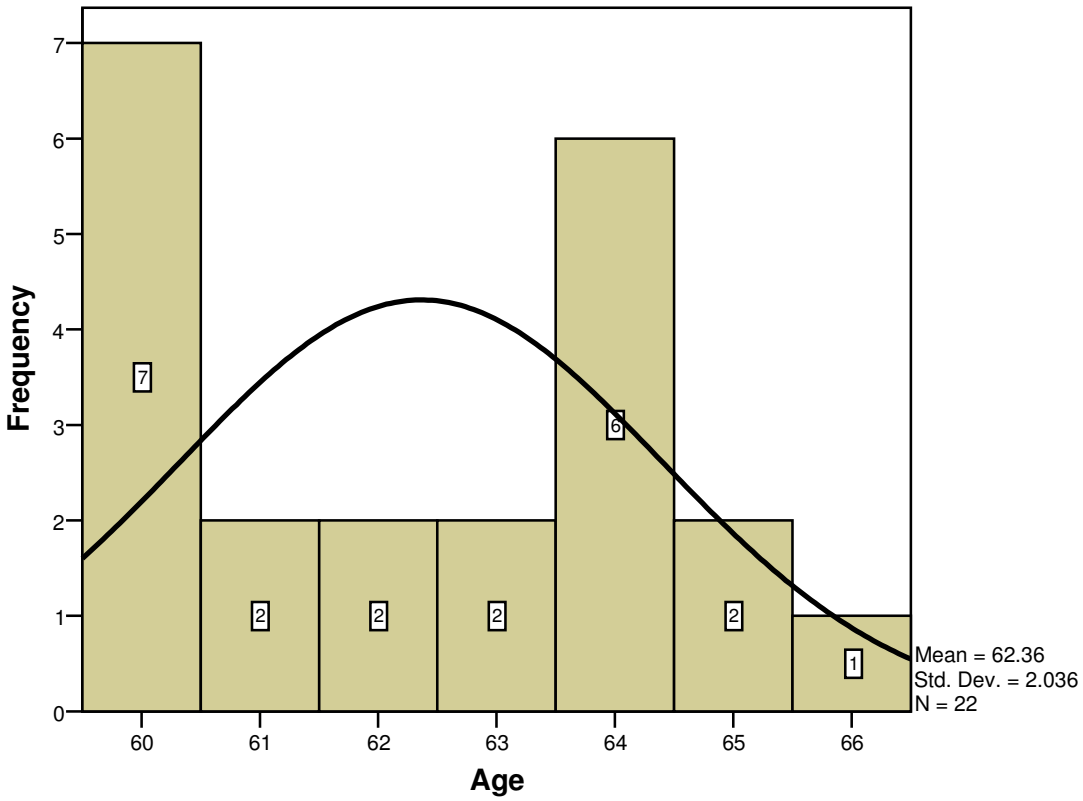


Figure 4.7: Frequency Distribution for Age - 60 to 69 years

The histogram (Figure 4.7) shows that the age distribution of the sample is slightly positively skewed. Refer to Appendix I for normality tests.

4.2.2 DESCRIPTIVE STATISTICS - BMD of the LUMBAR SPINE

The descriptive statistics for BMD measurements in g/cm^2 of the lumbar spine (L1 to L4) is presented for the young adult normal age group, as well as each 10 year age band.

4.2.2.1 Young adult normal age band – 20 to 48 years

BMD of the lumbar spine was virtually constant from age 20 and peaked in the 40 to 49 age band (Figure 4.8), followed by a decline in BMD in the 50 to 59 and 60 to 69 age bands. Post menopausal women were further excluded from the 20 to 49 age groups and a sample of 131 participants was categorised as the young adult normal age band for peak BMD of the lumbar spine. The 4 outliers evident in this age band did not significantly alter the means and SDs for the BMD of the lumbar spine and were therefore included in the analyses. This was done to ensure non-bias in the data.

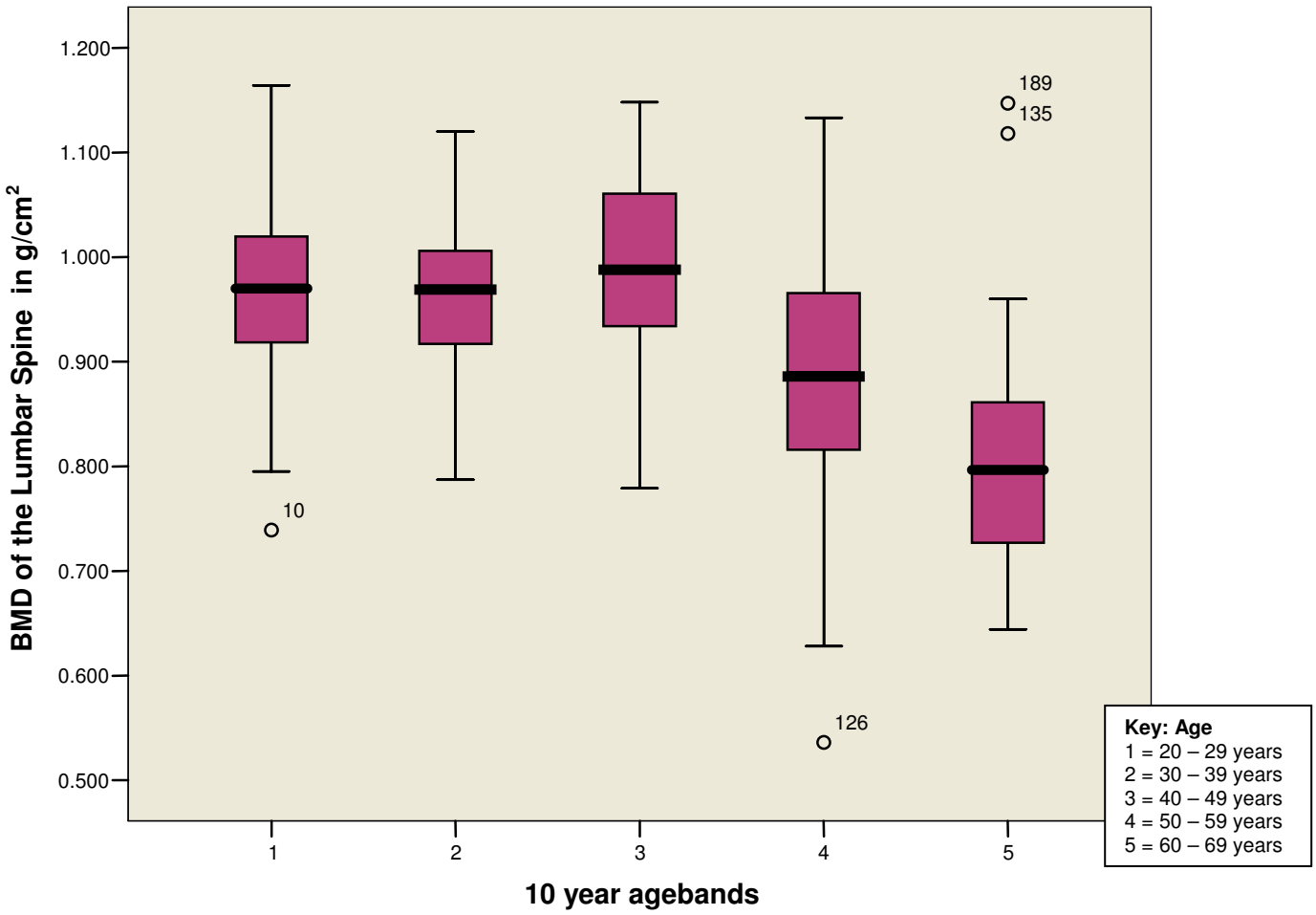


Figure 4.8: Boxplots showing BMD status at the lumbar spine in the 10 year age bands

The histogram describing the BMD values of the lumbar spine expressed in grams per centimetre squared for all 131 participants are displayed in Figure 4.9. The histogram depicts the mean BMD of the lumbar spine for the 131 participants in the peak BMD age band as 0.972 g/cm^2 with a SD of 0.083.

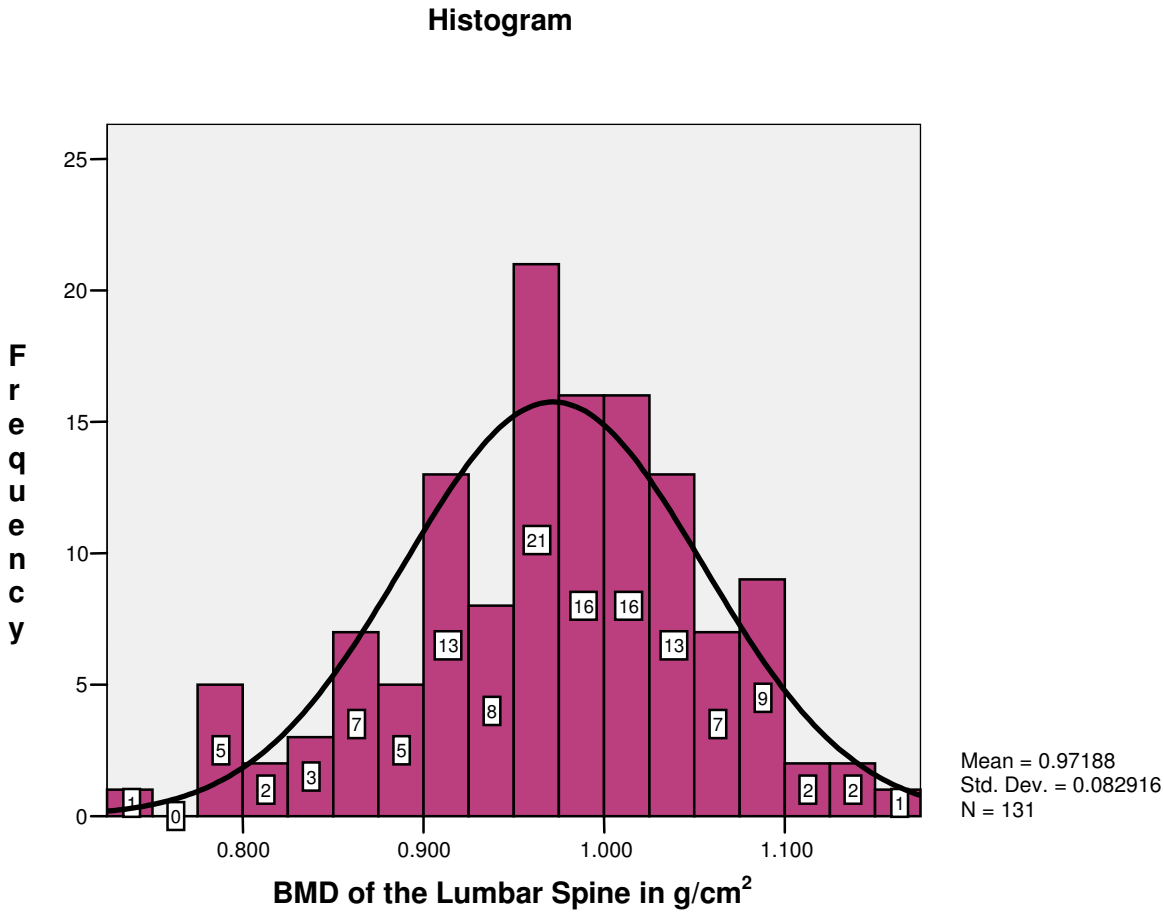


Figure 4.9: Frequency Distribution for BMD of the Lumbar Spine in young adult normal age band (20 to 48 years)

The minimum BMD of the lumbar spine was 0.739 g/cm^2 and the maximum value was 1.164 g/cm^2. The 95% confidence interval for the mean is 0.958 g/cm^2 (lower bound) and 0.986 g/cm^2 (upper bound). The histogram indicates normality. This is further confirmed by the Kolmogorov-Smirnov statistic (Appendix J). The means and SDs from this age group was used for the calculation of T-scores of the lumbar spine for each participant in the study population.

4.2.2.2 20 to 29 age band

The histogram describing the BMD values of the lumbar spine expressed in grams per centimetre squared for all 39 participants are displayed in Figure 4.10.

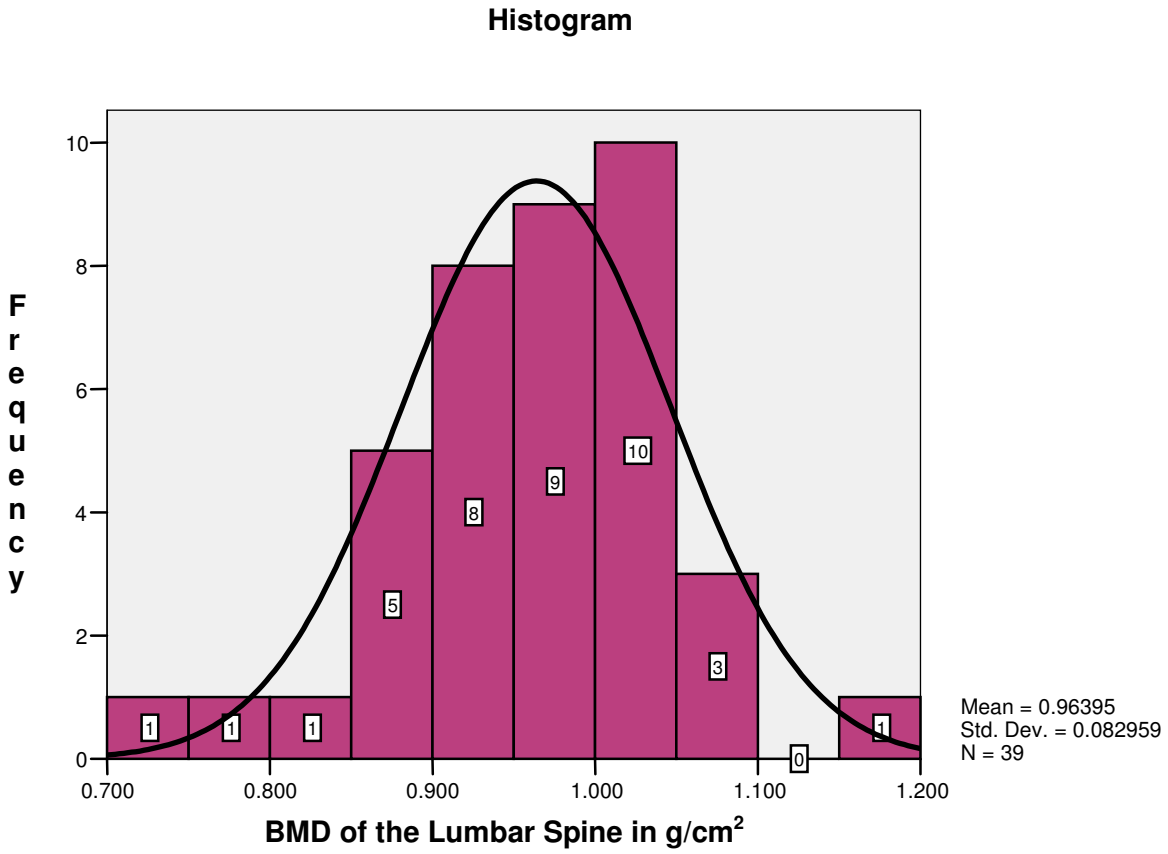


Figure 4.10: Frequency Distribution for BMD of the Lumbar Spine in the 20 to 29 age band

Figure 4.10 depicts the mean BMD of the lumbar spine for all 39 participants as 0.964 g/cm^2 with a standard deviation of 0.083. The minimum BMD of the lumbar spine was 0.739 g/cm^2 and the maximum value was 1.164 g/cm^2. The 5th percentile was 0.795 g/cm^2 and the 95th percentile was 1.086 g/cm^2. The 95% confidence interval for the

mean is 0.937 g/cm^2 (lower bound), and 0.991 g/cm^2 (upper bound). The histogram indicates normality. This is further confirmed by the Shapiro-Wilk statistic. These values can be seen in a table in Appendix J. The means and SDs from this age group was used for the calculation of Z-scores of the lumbar spine for each participant in this age band.

4.2.2.3 30 to 39 age band

The histogram (Figure 4.11) describing the BMD values of the lumbar spine for all 45 participants are displayed.

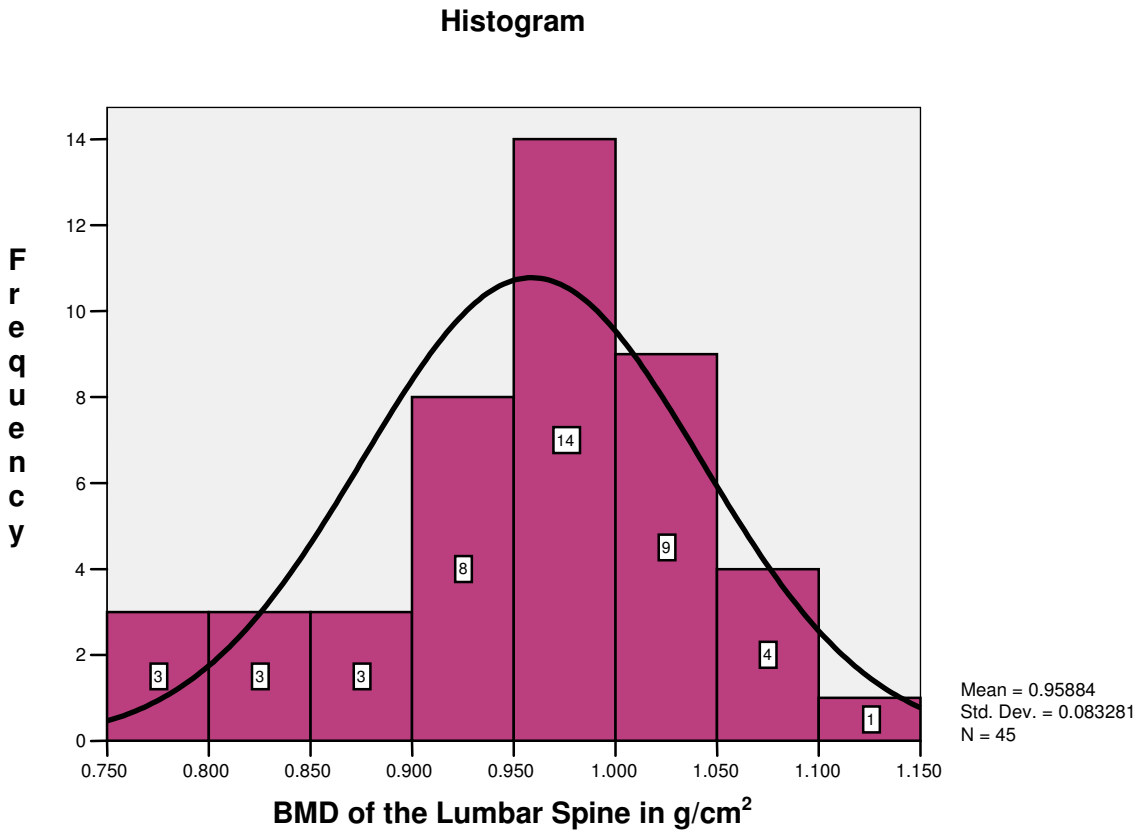


Figure 4.11: Frequency Distribution for BMD of the Lumbar Spine in the 30 to 39 age band

Figure 4.11 depicts the mean BMD of the lumbar spine for all 45 participants as 0.959 g/cm^2 with a standard deviation of 0.083. The histogram demonstrates normality. The means and SDs from this age group was used for the calculation of Z-scores at the lumbar spine for each participant in this age band.

The minimum BMD of the lumbar spine was 0.787 g/cm^2 and the maximum value was 1.120 g/cm^2. The 5th percentile was 0.794 g/cm^2 and the 95th percentile was 1.092 g/cm^2 The 95% confidence interval for the mean is 0.934 g/cm^2 (lower bound), and 0.983 g/cm^2 (upper bound). Refer to Appendix J for table demonstrating normality.

4.2.2.4 40 to 49 age band

In Figure 4.12 the BMD values for 55 participants are displayed in the histogram. The outliers in this age band did not significantly alter the means and SDs for the lumbar spine and were therefore included in the analyses. This was done to ensure non-bias in the data. The histogram is slightly negatively skewed, however the histogram demonstrates normality. Figure 4.12 depicts the mean BMD of the lumbar spine for the 55 participants in this age band as 0.989 g/cm^2 with a standard deviation of 0.086.

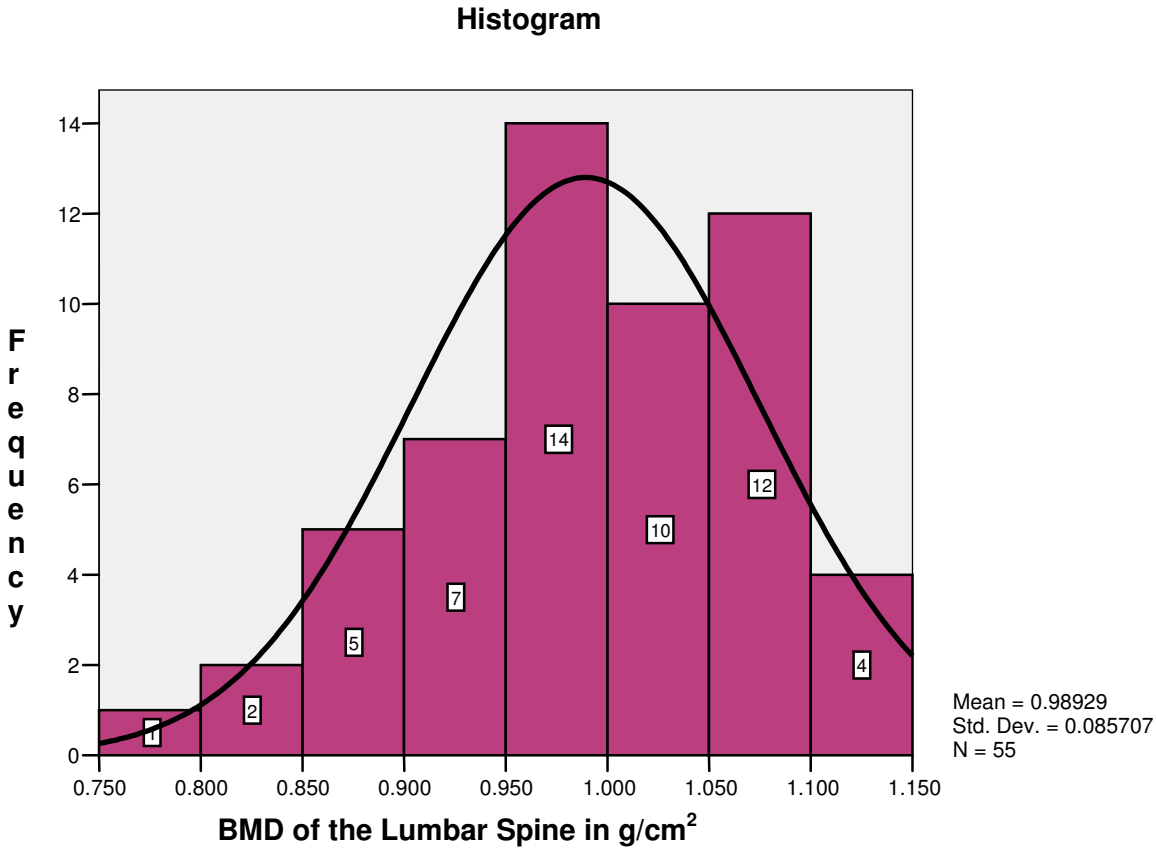


Figure 4.12: Frequency Distribution for BMD of the Lumbar Spine in the 40 to 49 age band

The minimum BMD of the lumbar spine was 0.779 g/cm^2 and the maximum value was 1.148. The 5th percentile was 0.837 g/cm^2 and the 95th percentile was 1.118 g/cm^2. The 95% confidence interval for the mean is 0.966 g/cm^2 (lower bound) and 1.012 g/cm^2 (upper bound). (These values can be seen in a table in Appendix J). The means and SDs from this age group was used for the calculation of Z-scores at the lumbar spine for each participant in this age band.

4.2.2.5 50 to 59 age band

In Figure 4.13 the BMD values for all 56 participants are displayed. The outliers in this age band did not significantly alter the means and SDs for the lumbar spine and were therefore included in the analyses. This was done to ensure non-bias in the data. Figure 4.13 depicts the mean BMD of the spine for all 55 participants as 0.889 g/cm^2 with a standard deviation of 0.12. The histogram demonstrates normality.

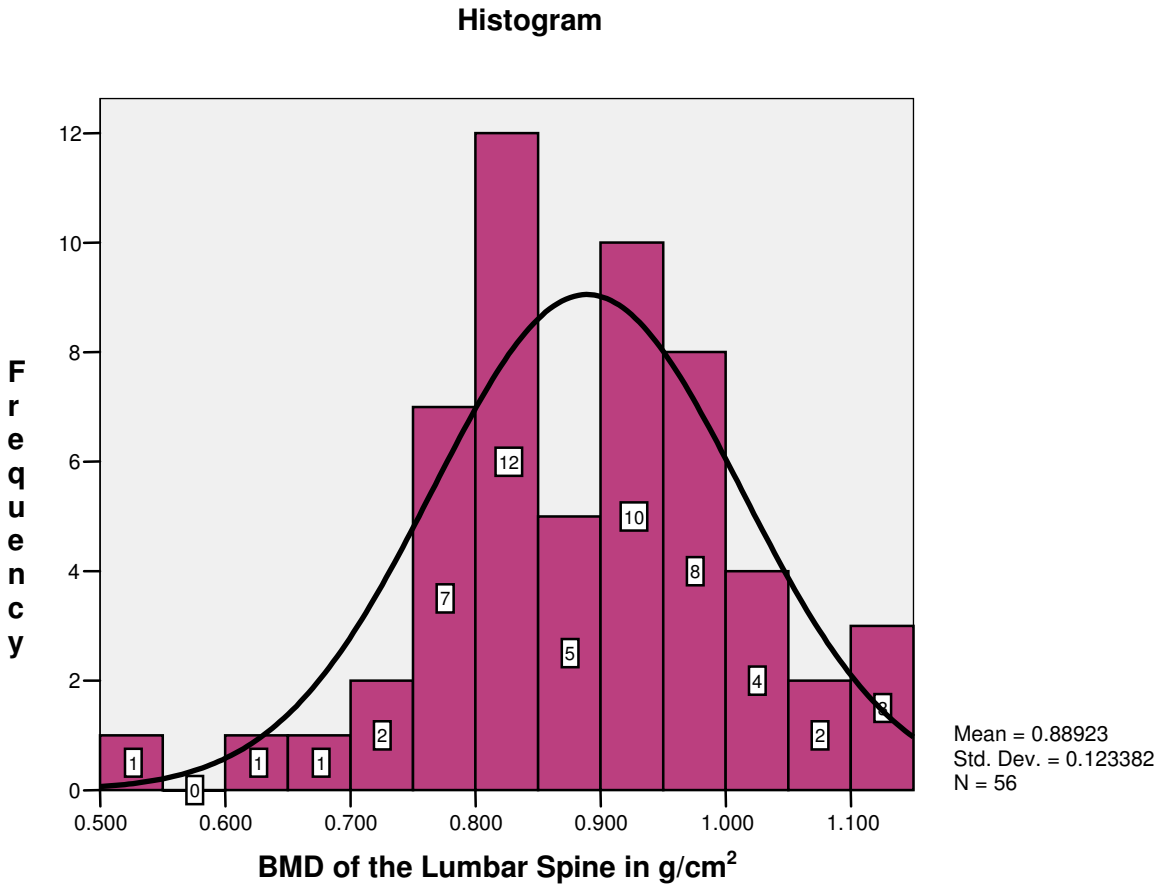


Figure 4.13: Frequency Distribution for BMD of the Lumbar Spine in the 50 to 59 age band

The minimum BMD of the spine was 0.536 g/cm^2 and the maximum value was 1.133 g/cm^2. The 5th percentile was 0.657 g/cm^2 and the 95th percentile was 1.105 g/cm^2 (these values can be seen in a table in Appendix J).

The 95% confidence interval for the mean is 0.856 g/cm^2 (lower bound), and 0.922 g/cm^2 (upper bound). The histogram is slightly negatively skewed; however the Shapiro-Wilk test shows normality (Appendix J). The means and SDs from this age group was used for the calculation of Z-scores at the lumbar spine for each participant in this age band.

4.2.2.6 60 to 69 age band

The histogram (Figure 4.14) describes the BMD values for all 22 participants in the 60 to 69 age band. The outliers in this age band did not significantly alter the means and SDs for the lumbar spine and were therefore included in the analyses. This was done to ensure non-bias in the data. The histogram is positively skewed and this is confirmed on the normality tests (Appendix J).

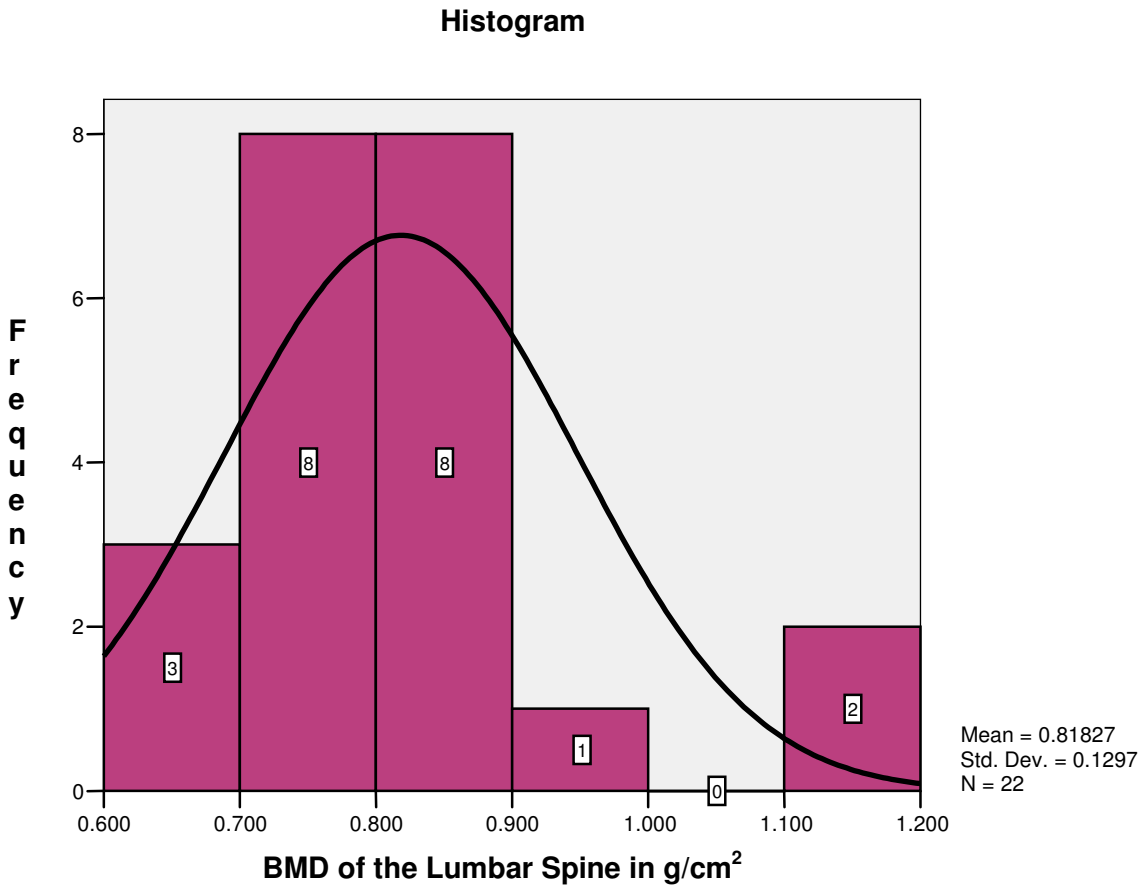


Figure 4.14: Frequency Distribution for BMD of the Lumbar Spine in the 60 to 69 age band

Figure 4.14 depicts the mean BMD of the spine for all 22 participants as 0.818 g/cm^2 with a standard deviation of 0.130. The minimum BMD of the spine was 0.644 g/cm^2 and the maximum value was 1.147 g/cm^2. The 5th percentile was 0.646 g/cm^2 and the 95th percentile was 1.142 g/cm^2 (these values can be seen in a table in Appendix J). The 95% confidence interval for the mean is 0.761 g/cm^2 (lower bound) and 0.876 g/cm^2 (upper bound). The means and SDs from this age group was used for the calculation of Z-scores at the lumbar spine for each participant in this age band.

4.2.3 DESCRIPTIVE STATISTICS – BMD of the TOTAL HIP

The descriptive statistics for BMD of the total hip will be presented for the young adult normal age group, as well as BMD of the total hip for each 10 year age band.

4.2.3.1 Young adult normal age band – 20 to 48 years

BMD of the total hip was virtually constant from age 20 and peaked in the 40 to 49 age band (Figure 4.15), followed by a decline in the 50 to 59 and 60 to 60 age bands. Post menopausal women were further excluded from these age bands and a sample of 131 participants was classified as the young adult normal age band for peak BMD of the total hip. The outliers in this age band did not significantly alter the means and SDs for the total hip and was therefore included in the analyses. This was done to ensure non-bias in the data.

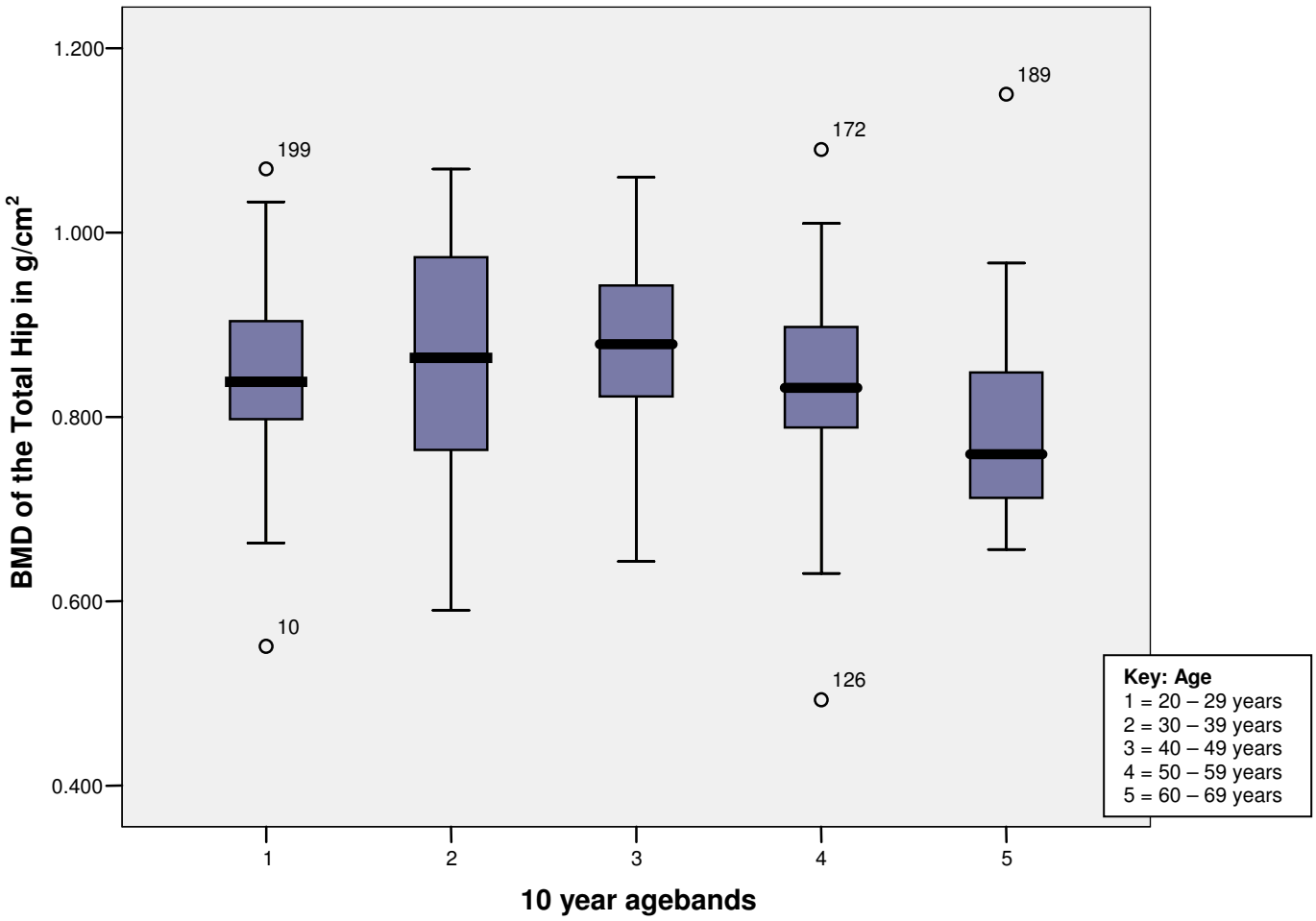


Figure 4.15: Boxplots showing BMD status of the hip in the 10 year age bands

The histogram (Figure 4.16) describes the BMD values of the total hip for the 131 participants in the peak bone mass age group.

Figure 4.16 depicts the mean BMD of the total hip for the 131 participants within this PBM age band as 0.863 g/cm^2 with a standard deviation of 0.103. The histogram is relatively normal.

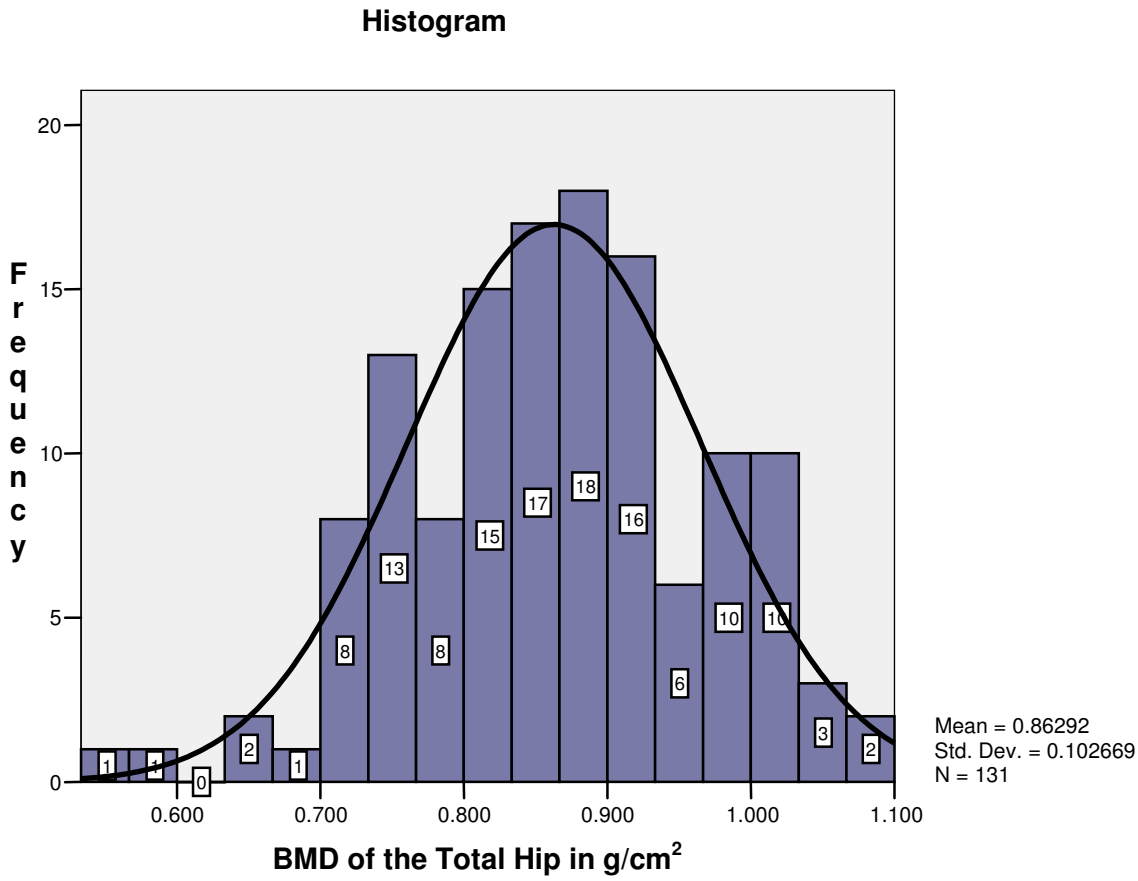


Figure 4.16: Frequency Distribution for BMD of the Total Hip in the young adult normal age band (20 to 48 years)

The minimum BMD of the total hip was 0.551 g/cm^2 and the maximum value was 1.069 g/cm^2. The 5th percentile was 0.705 g/cm^2 and the 95th percentile was 1.030 g/cm^2. The 95% confidence interval for the mean is 0.845 g/cm^2 (lower bound) and 0.881 g/cm^2 (upper bound). The Kolmogorov-Smirnov test confirms normality of data. These values can be seen in a table in Appendix K. The means and SDs from this age group was used for the calculation of T-scores of the total hip for each participant in this age band.

4.2.3.2 20 to 29 age band

The histogram (Figure 4.17) describes the BMD values for all 39 participants. The two outliers in this age band did not significantly alter the means and SDs for the total hip and were therefore included in the analyses. This was done to ensure non-bias in the data.

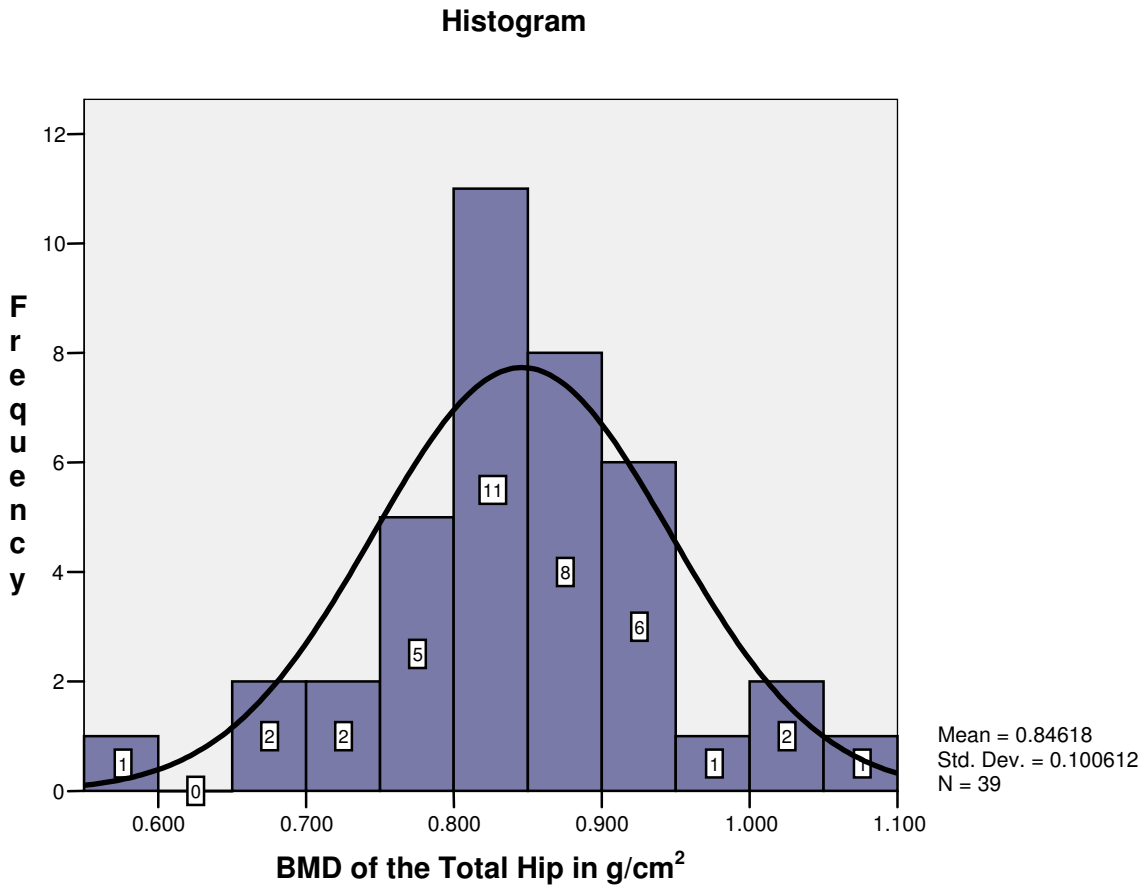


Figure 4.17: Frequency Distribution for BMD of the Total Hip in the 20 to 29 age band

Figure 4.17 depicts the mean BMD of the total hip for all 39 participants within this age band as 0.846 g/cm^2 with a standard deviation of 0.101. The histogram is relatively normal. The minimum BMD of the total hip is 0.551 g/cm^2 and the maximum value was 1.069 g/cm^2. The 5th percentile was 0.663 g/cm^2 and the 95th percentile was 1.033 g/cm^2. The 95% confidence interval for the mean is 0.814 g/cm^2 (lower bound) and 0.879 g/cm^2 (upper bound). Shapiro – Wilk test confirms normality of data. These values can be seen in a table in Appendix K. The means and SDs from this age group was used for the calculation of Z-scores of the total hip for each participant in this age band.

4.2.3.3 30 to 39 age band

There are histograms (Figure 4.18) describing the BMD values for all 45 participants are displayed. The histogram is slightly negatively skewed.

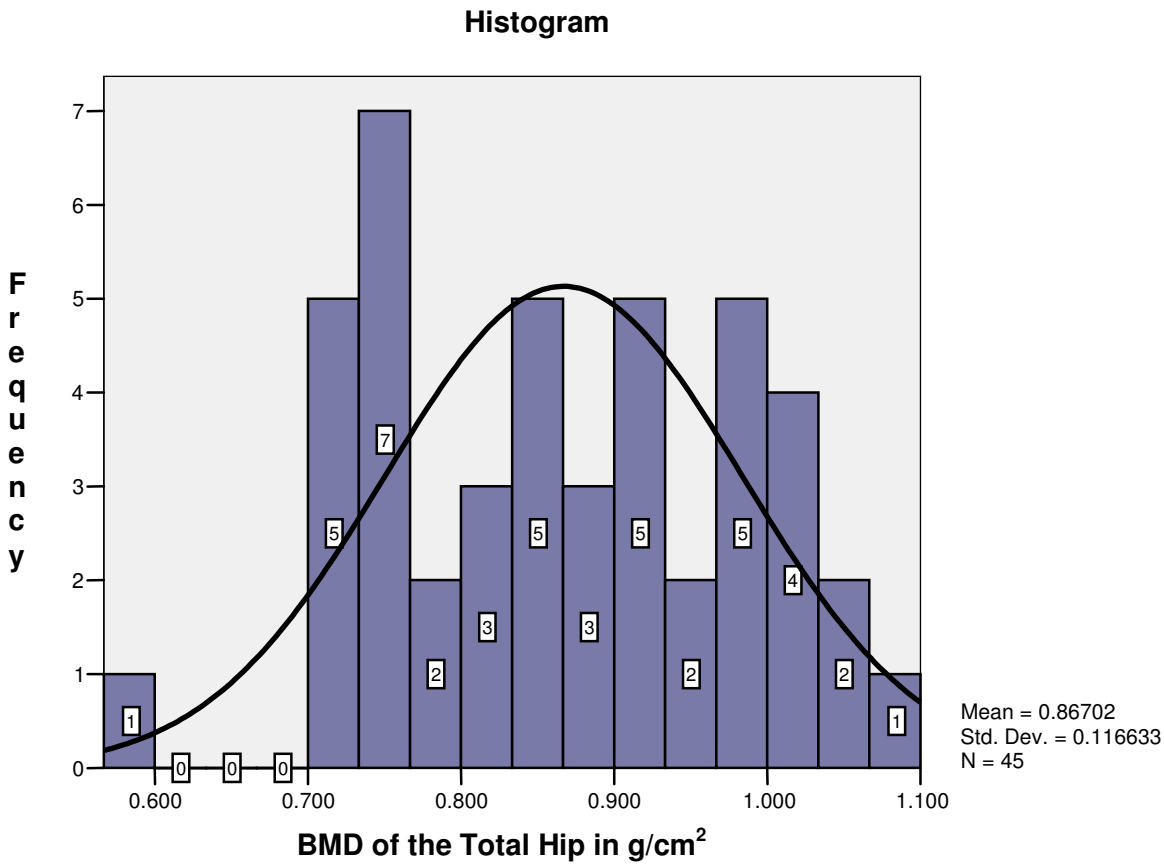


Figure 4.18: Frequency Distribution for BMD of the Total Hip in the 30 to 39 age band

Figure 4.18 depicts the mean BMD of the total hip for all 45 participants as 0.867 g/cm^2 with a standard deviation of 0.117. The minimum BMD of the total hip was 0.590 g/cm^2 and the maximum value was 1.069 g/cm^2. The 5th percentile was 0.705 g/cm^2 and the 95th percentile was 1.054 g/cm^2. The 95% confidence interval for the mean is 0.832 g/cm^2 (lower bound) and 0.902 g/cm^2 (upper bound). Refer to Appendix K for these values. The means and SDs from this age group was used for the calculation of Z-scores of the total hip for each participant in this age band.

4.2.3.4 40 to 49 age band

The histograms (Figure 4.19) describing the BMD values for all 55 participants are displayed. Figure 4.19 depicts the mean BMD of the total hip for all 55 participants as 0.878 g/cm^2 with a standard deviation of 0.089. The histogram is slightly negatively skewed; however the Shapiro-Wilk test shows a normal distribution (Appendix K).

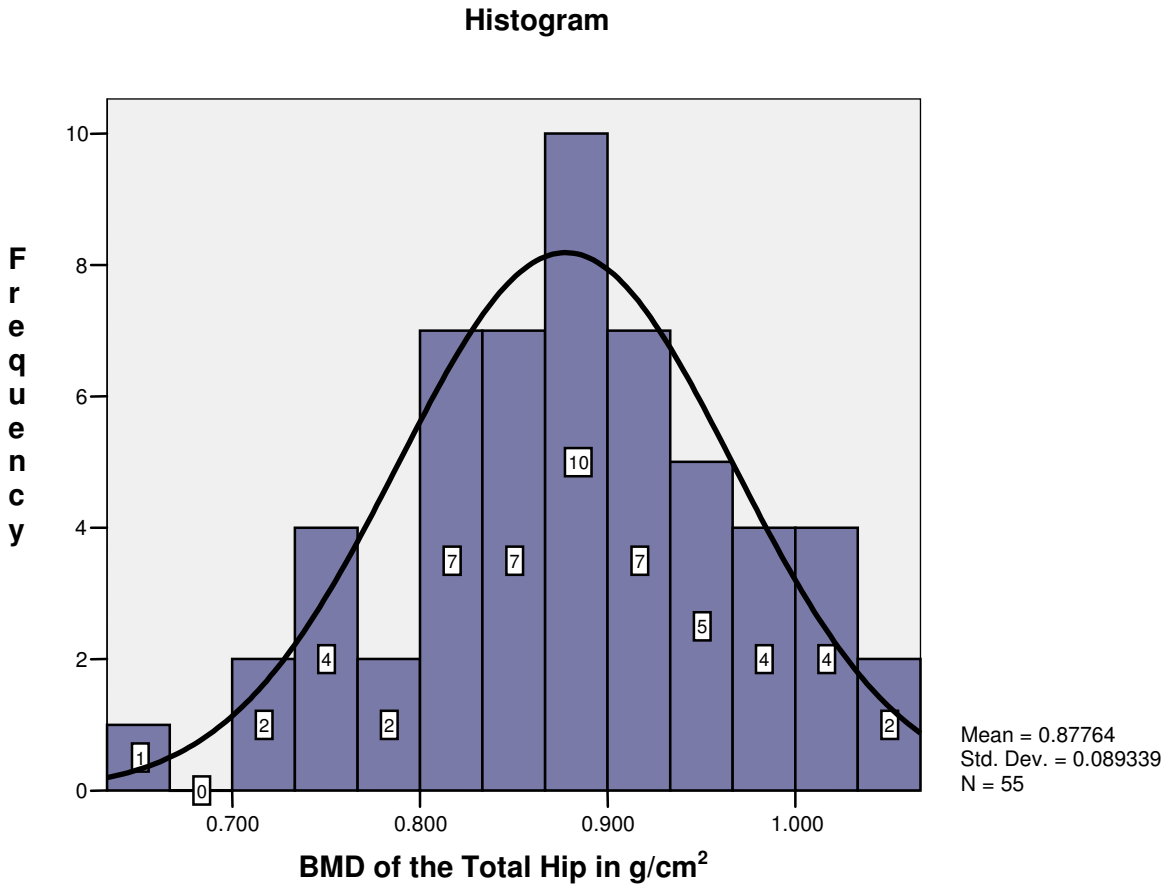


Figure 4.19: Frequency Distribution for BMD of the Total Hip in the 40 to 49 age band

The minimum BMD of the total hip was 0.643 g/cm^2 and the maximum value was 1.061 g/cm^2. The 5th percentile was 0.727 g/cm^2 and the 95th percentile was 1.031 g/cm^2. The 95% confidence interval for the mean is 0.853 g/cm^2 (lower bound), and 0.902 g/cm^2 (upper bound). Refer to Appendix K for these values. The means and SDs from this age group was used for the calculation of Z-scores of the total hip for each participant in this age band.

4.2.3.5 50 to 59 age band

The histogram (Figure 4.20) describes the BMD values for all 56 participants are displayed. The two outliers (Appendix K) in this age band did not significantly alter the means and SDs for the total hip and were therefore included in the analyses. This was done to ensure non-bias in the data.

Figure 4.20 depicts the mean BMD of the total hip for all 56 participants as 0.836 g/cm^2 with a standard deviation of 0.108. The histogram is negatively skewed, however, the Kolmogorv-Smirnov test (Appendix K) shows normality of data.

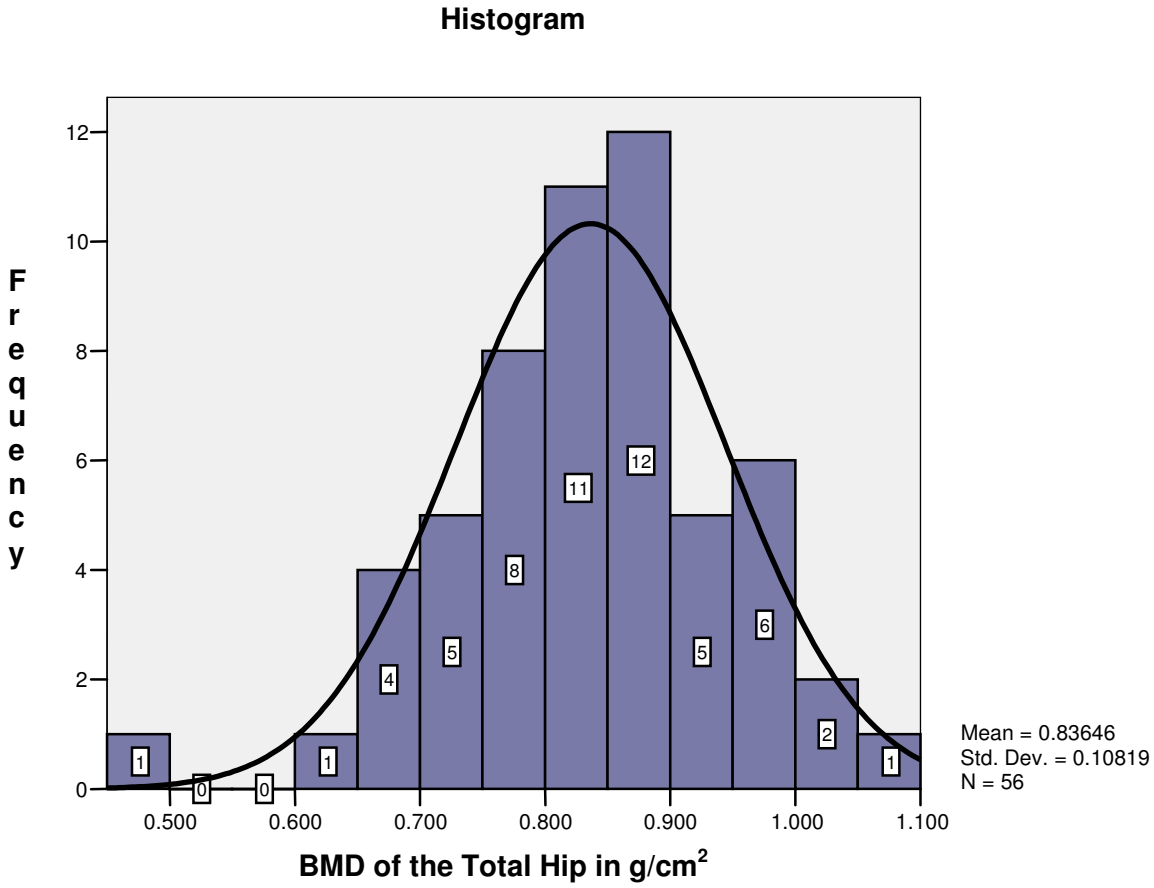


Figure 4.20: Frequency Distribution for BMD of the Total Hip in the 50 to 59 age band

The minimum BMD of the total hip was 0.836 g/cm^2 and the maximum value was 1.090 g/cm^2. The 95% confidence interval for the mean is 0.807 g/cm^2 (lower bound) and 0.865 g/cm^2 (upper bound). The 5th percentile was 0.674 g/cm^2 and the 95th percentile was 1.005 g/cm^2 (these values can be seen in a table in Appendix K). The means and SDs from this age group was used for the calculation of Z-scores at the total hip for each participant in this age band.

4.2.3.6 60 to 69 age band

The histogram (Figure 4.21) describes the BMD values for all 22 participants. The histogram has a positively skewed, and the Shapiro- Wilk test confirms that the sample is not normally distributed (Appendix K). The histogram further highlights the impact of an inadequate sample size.

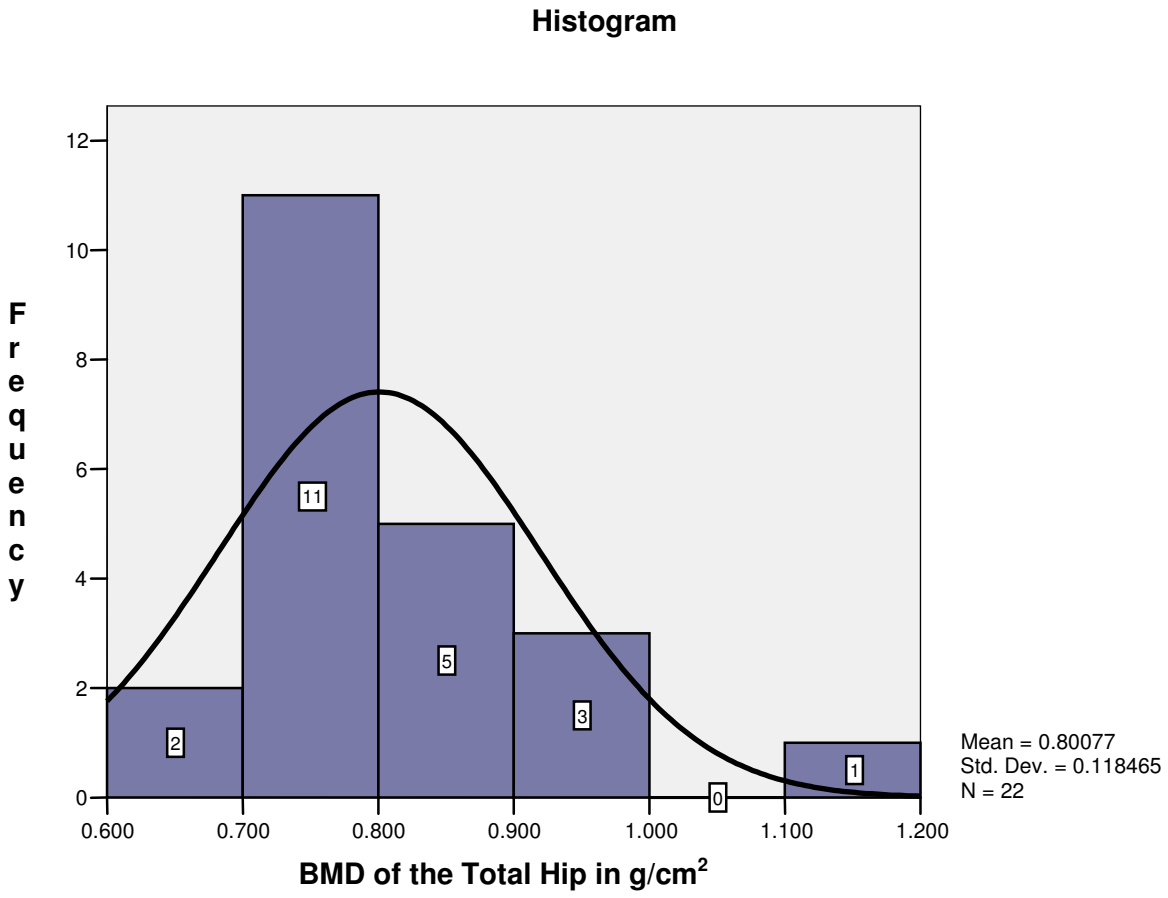


Figure 4.21: Frequency Distribution for BMD of the Total Hip in the 60 to 69 age band

Figure 4.21 depicts the mean BMD of the total hip for all 22 participants as 0.801 g/cm^2 with a standard deviation of 0.118.

The minimum BMD of the total hip was 0.656 g/cm^2 and the maximum value was 1.150 g/cm^2. The 5th percentile was 0.661 g/cm and the 95th percentile was 1.122 g/cm^2. The 95% confidence interval for the mean is 0.748 g/cm^2 (lower bound) and 0.853 g/cm^2 (upper bound). These values can be seen in a table in Appendix K. The means and SDs from this age group was used for the calculation of Z-scores of the total hip for each participant in this age band.

4.2.4 DESCRIPTIVE STATISTICS – BMD of the DISTAL FOREARM

The descriptive statistics for BMD of the distal forearm will be presented for the young adult normal age band, as well as BMD of the distal forearm for each 10 year age band.

4.2.4.2 Young adult normal age group – 20 to 48 years

BMD at the distal forearm was virtually constant from age 20 and peaked in the 40 to 49 age band (Figure 4.23), and showed a decline in the 50 to 59 and 60 to 69 age bands.

Post menopausal women were further excluded from these age bands and a sample of 131 participants was categorised as the young adult normal age band for peak BMD of the distal forearm. The three outliers in this age band did not significantly alter the means and SDs for the distal forearm and was therefore included in the analyses.

This was done to ensure non-bias in the data.

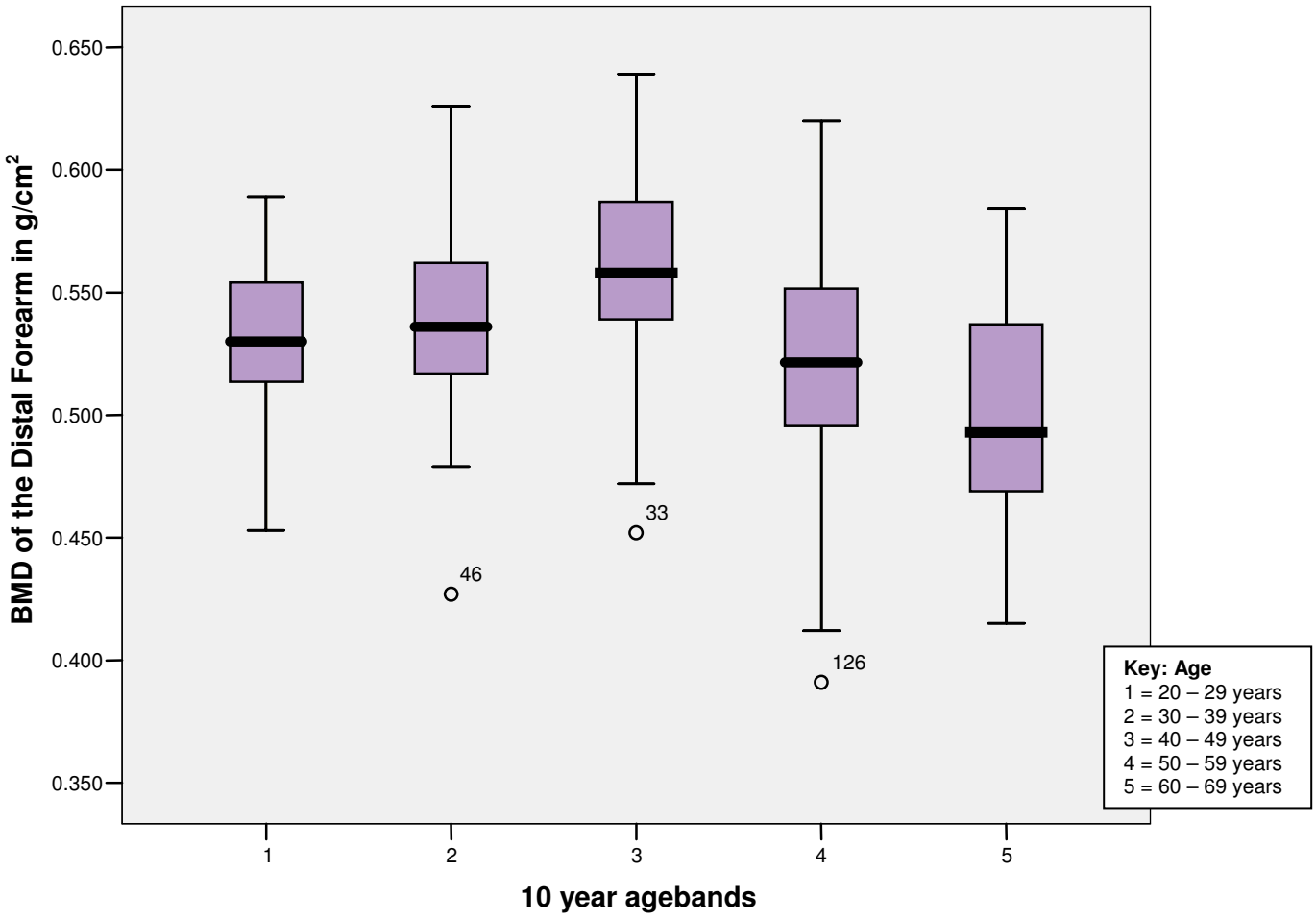


Figure 4.22: Boxplots showing BMD status at the distal forearm in the 10 year age bands

In Figure 4.23 the BMD values of the distal forearm for the 131 participants in the young adult normal age band are displayed. Figure 4.23 depicts the mean BMD of the distal forearm for the 131 participants in the young adult normal age band as 0.542 g/cm^2 with a standard deviation of 0.041. The histogram demonstrates sample normality and is confirmed by the Kolmogorov-Smirnov test (Appendix L).

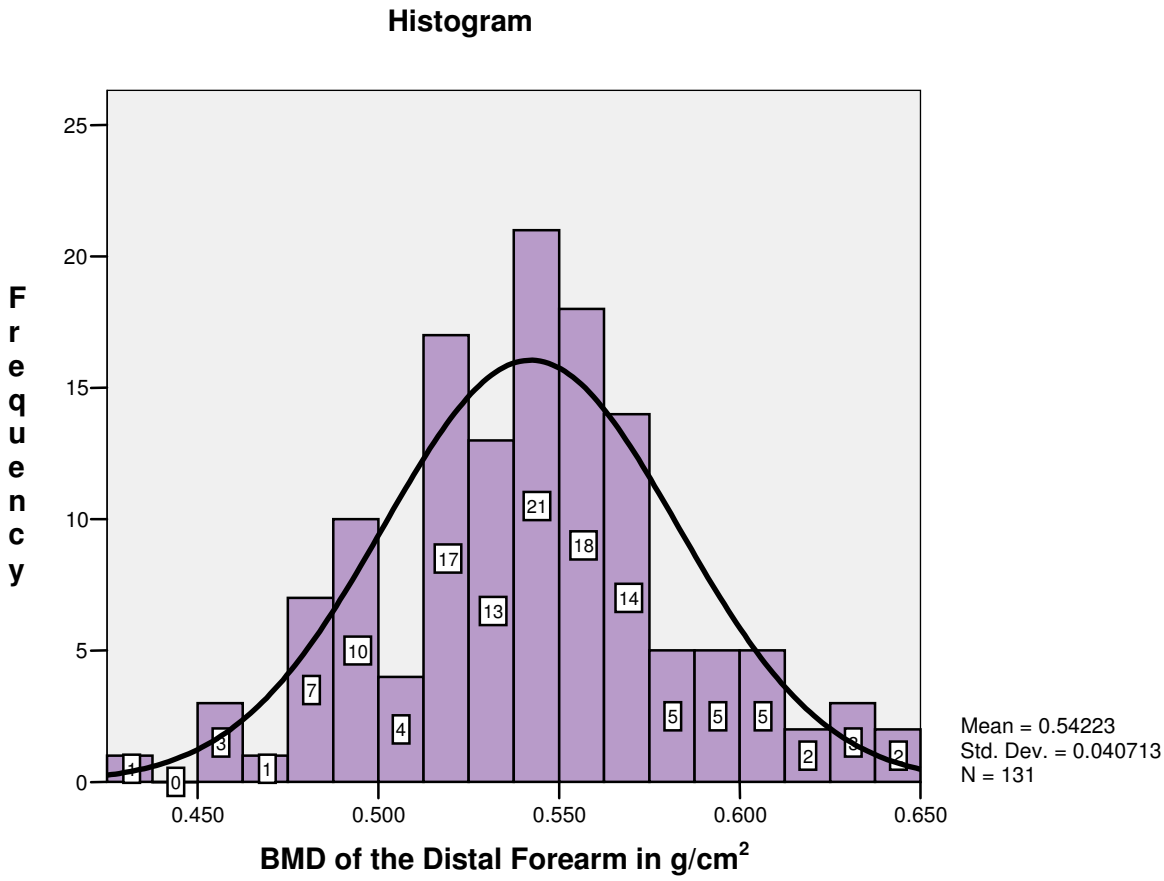


Figure 4.23: Frequency Distribution for BMD of the Distal Forearm in the young adult normal age band (20 to 48 years)

The minimum BMD of the distal forearm was 0.427 g/cm^2 and the maximum value was 0.639 g/cm^2. The 5th percentile was 0.479 g/cm^2 and the 95th percentile was 0.618 g/cm^2 The 95% confidence interval for the mean is 0.536 g/cm^2 (lower bound) and 0.550 g/cm^2 (upper bound). (Refer to Appendix L). The means and SDs from this age band was used for the calculation of T-scores of the distal forearm for each participant.

4.2.4.2 20 to 29 age band

Figure 4.24 depicts the mean BMD of the distal forearm for all 39 participants in the 20 to 29 age band as 0.529 g/cm^2 with a standard deviation of 0.031. The histogram demonstrates a slightly negative skew, whilst the Shapiro-Wilk indicates normality (Appendix L).

The minimum BMD of the forearm was 0.453 g/cm^2 and the maximum value was 0.589 g/cm^2. The 5th percentile was 0.0460 g/cm^2 and the 95th percentile was 0.573 g/cm^2. The 95% confidence interval for the mean is 0.519 g/cm^2 (lower bound) and 0.539 g/cm^2 (upper bound) - Appendix L. The means and SDs from this age band was used for the calculation of Z-scores of the distal forearm for each participant.

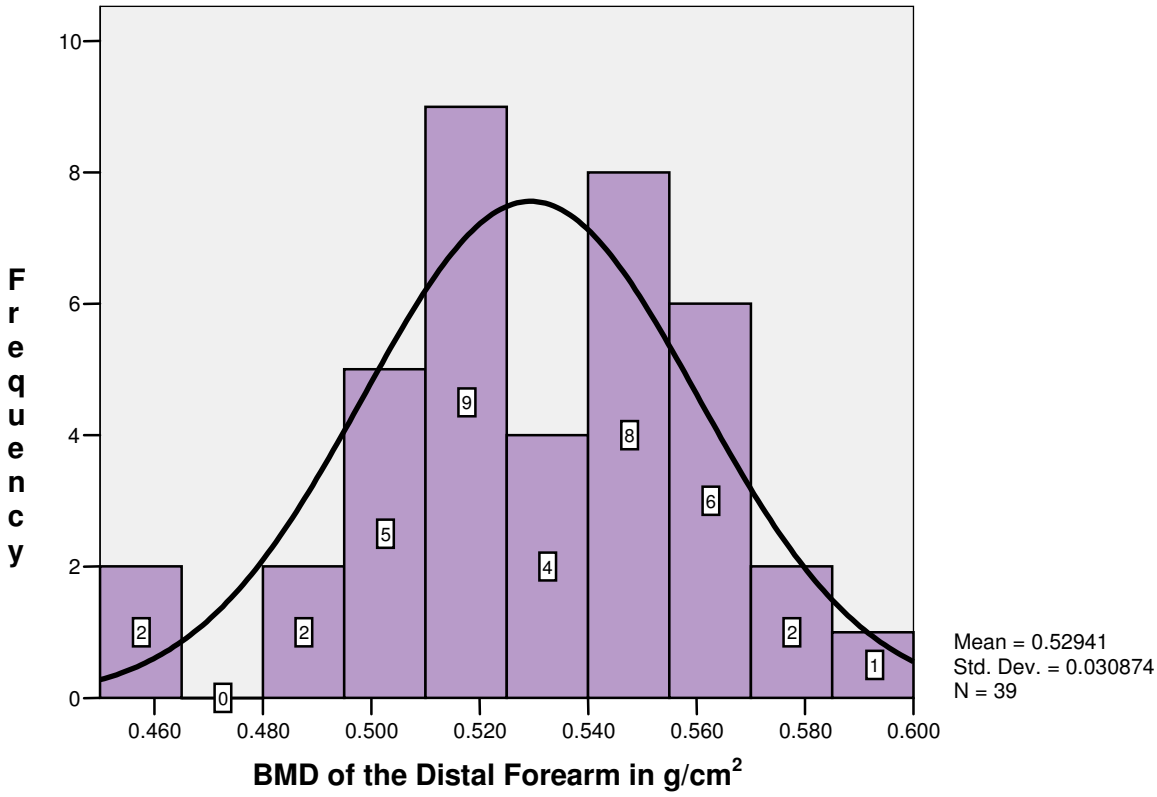


Figure 4.24: Frequency Distribution for BMD of the Distal Forearm in the 20 to 29 age band

4.2.4.3 30 to 39 age band

In Figure 4.25 the BMD values for all 45 participants in the 30 to 39 years age band are displayed. The one outlier in this age band did not significantly alter the means and SDs for the distal forearm and was therefore included in the analyses. This was done to ensure non-bias in the data.

Figure 4.25 depicts the mean BMD of the distal forearm for all 45 participants as 0.536

g/cm^2 with a standard deviation of 0.038. The histogram is slightly negatively skewed, however the Shapiro-Wilk test demonstrates normality (Appendix L).

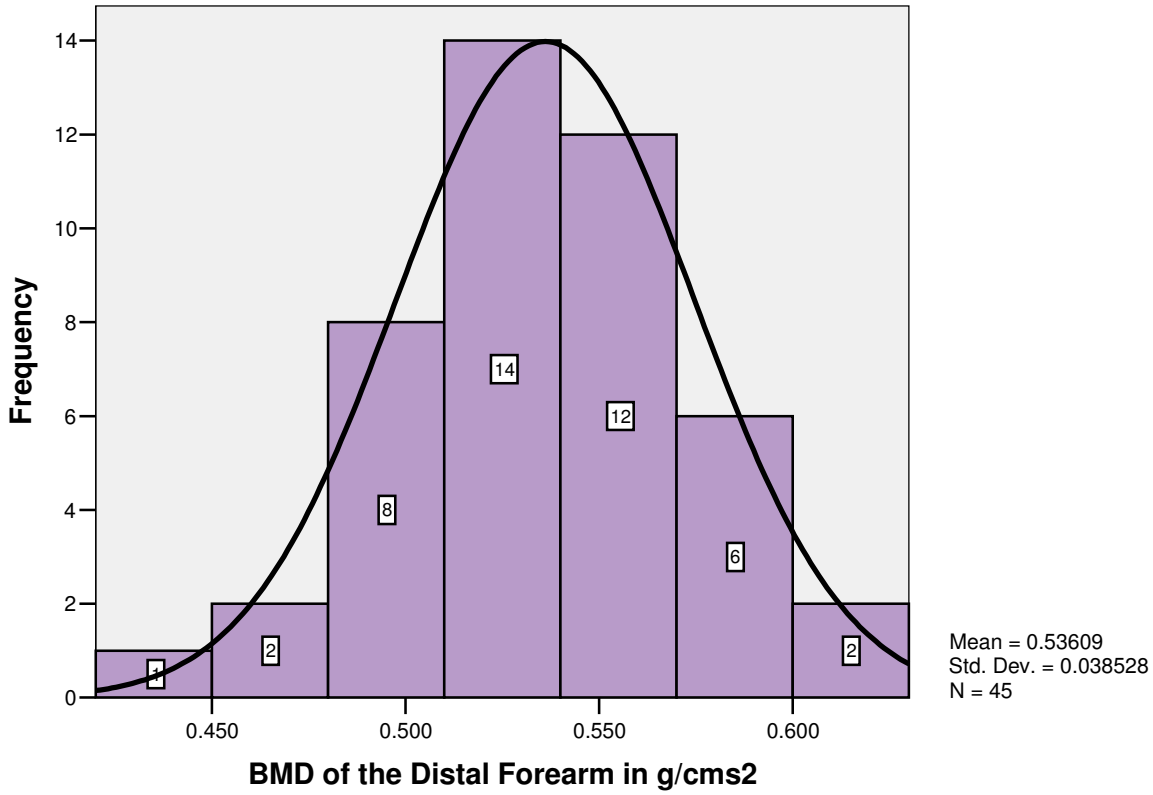


Figure 4.25: Frequency Distribution for BMD of the Distal Forearm in the 30 to 39 age band

The minimum BMD of the distal forearm was 0.427 g/cm^2 and the maximum value was 0.626 g/cm^2. The 5th percentile was 0.479 g/cm^2 and the 95th percentile was 0.599 g/cm^2. The 95% confidence interval for the mean is 0.525 g/cm^2 (lower bound) and 0.548 g/cm^2 (upper bound). Refer to Appendix L. The means and SDs from this age band was used for the calculation of Z-scores of the distal forearm.

4.2.4.4 40 to 49 age band

In Figure 4.26 the BMD values for all 55 participants in the 40 to 49 age band are displayed. The one outlier in this age band did not significantly alter the means and SDs for the distal forearm and was therefore included in the analyses to ensure non-bias in the data. The mean BMD of the distal forearm for all 55 participants as 0.558 g/cm^2 with a standard deviation of 0.043. The histogram is relatively normal.

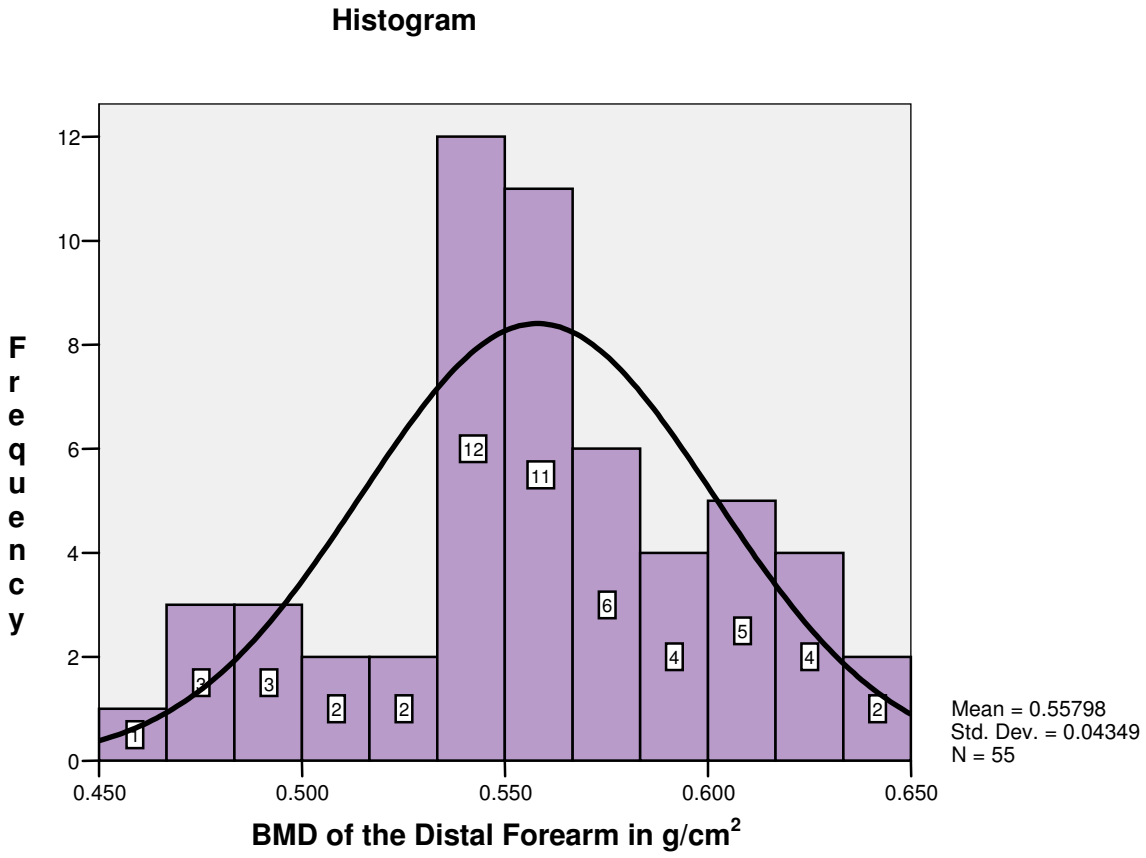


Figure 4.26: Frequency Distribution for BMD of the Distal Forearm in the 40 to 49 age band

The minimum BMD of the distal forearm was 0.452 g/cm^2 and the maximum value was 0.639 g/cm^2. The 5th percentile was 0.478 g/cm^2 and the 95th percentile was 0.634 g/cm^2.

The 95% confidence interval for the mean is 0.546 g/cm^2 (lower bound), and 0.569 g/cm^2 (upper bound). These values can be seen in Appendix L. The means and SDs from this age band was used for the calculation of Z-scores of the distal forearm for each participant.

4.2.4.5 50 to 59 age band

In Figure 4.27 the BMD values for all 56 participants in the 50 to 59 age band are displayed. The one outlier in this age band did not significantly alter the means and SDs for the distal forearm and was therefore included in the analyses. This was done to ensure non-bias in the data.

Figure 4.27 depicts the mean BMD of the forearm for all 56 participants as 0.523 g/cm^2 with a standard deviation of 0.048. The histogram is slightly negatively skewed, however the Kolmogorov-Smirnov test shows normality (Appendix L).

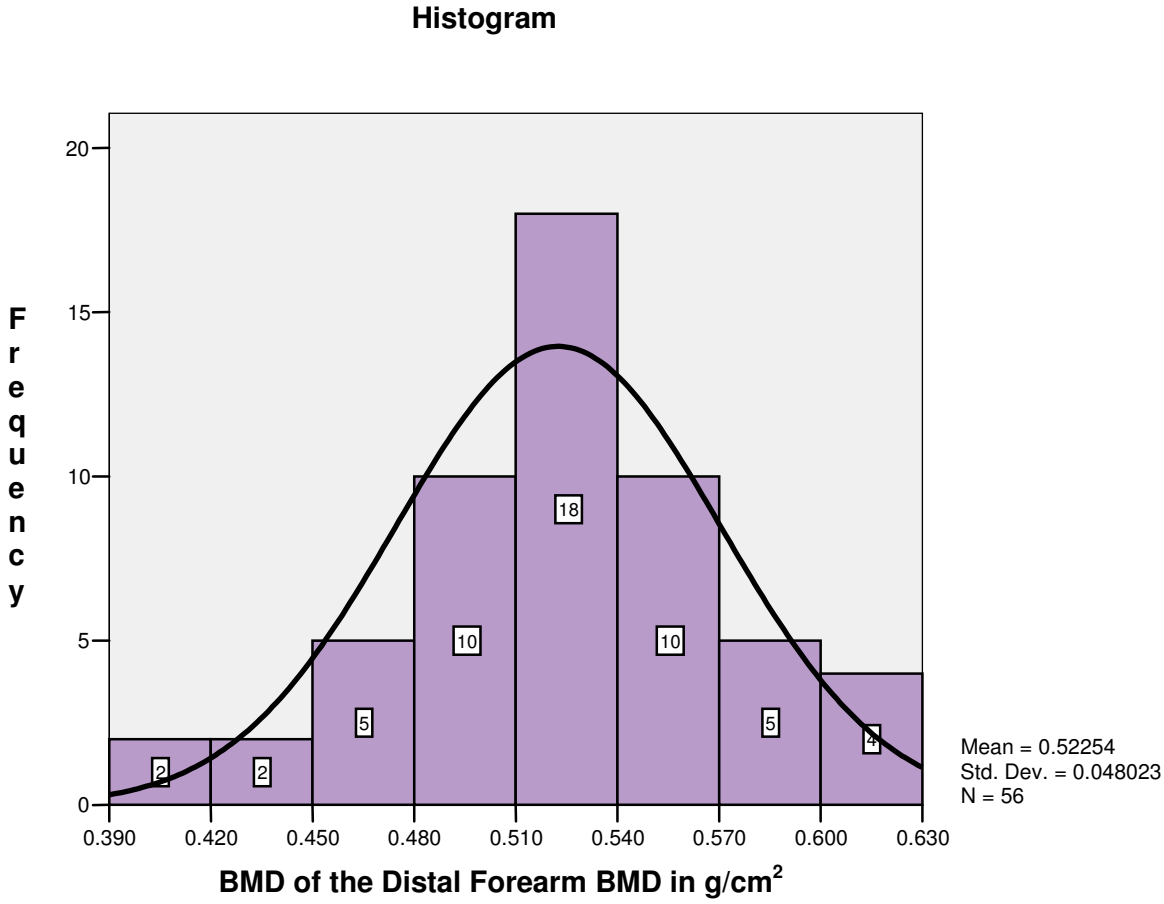


Figure 4.27: Frequency Distribution of BMD of the Distal Forearm in the 50 to 59 age band

The minimum BMD of the distal forearm was 0.391 g/cm^2 and the maximum value was 0.620 g/cm^2. The 5th percentile was 0.437 g/cm^2 and the 95th percentile was 0.603 g/cm^2. The 95% confidence interval for the mean is 0.510 g/cm^2 (lower bound) and 0.535 g/cm^2 (upper bound). Refer to Appendix L for these values. The means and SDs from this age band was used for the calculation of Z-scores of the distal forearm for each participant.

4.2.4.6 60 to 69 age band

Figure 4.28 depicts the mean BMD of the distal forearm for all 22 participants inn the 60 to 69 ageband as 0.497 g/cm^2 with a standard deviation of 0.050. The histogram is slightly positively skewed, but normality distribution is shown by the Shapiro-Wilk test (Appendix L).

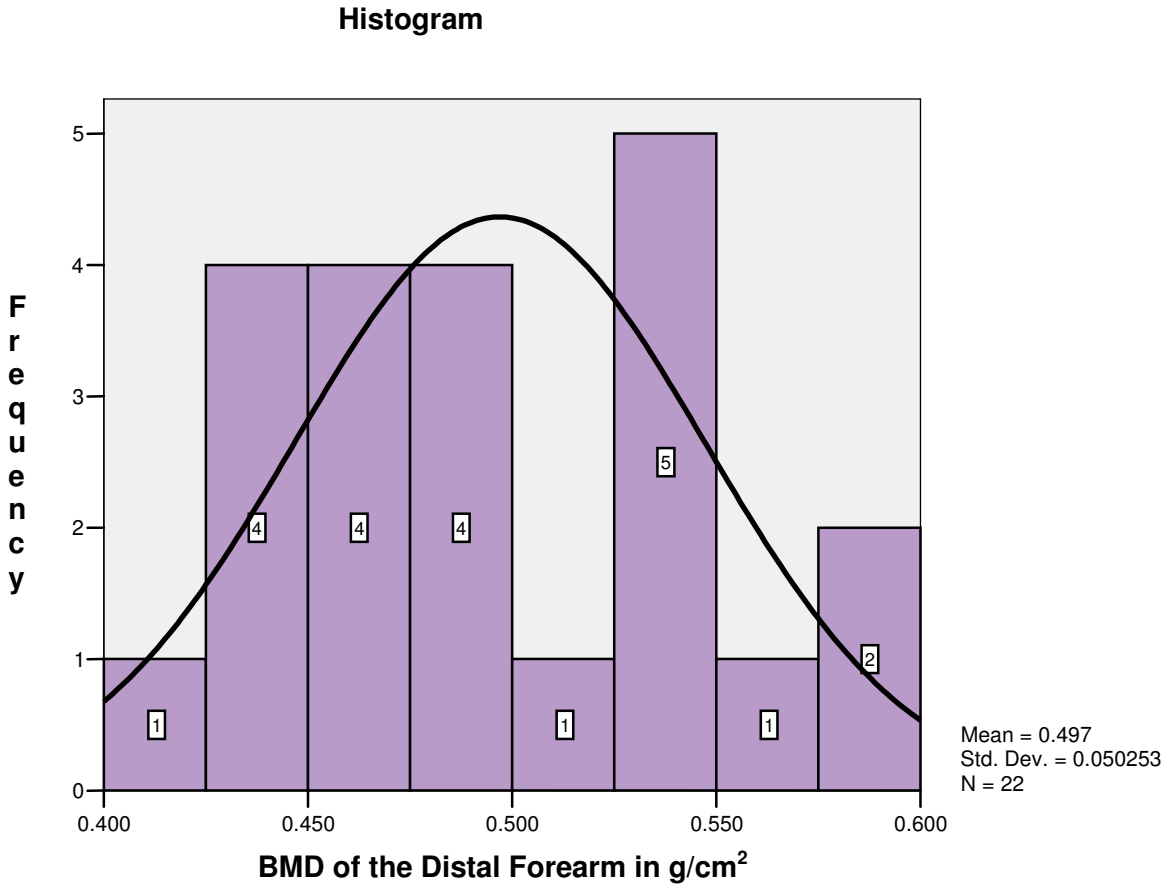


Figure 4.28: Frequency Distribution of BMD of the forearm for 60 to 69 age band

The minimum BMD of the distal forearm was 0.415 g/cm^2 and the maximum value was 0.584 g/cm^2. The 5th percentile was 0.417 g/cm^2 and the 95th percentile was 0.584 g/cm^2.

The 95% confidence interval for the mean is 0.475 g/cm^2 (lower bound) and 0.519 g/cm^2 (upper bound). Refer to Appendix L for these values. The means and SDs from this age band was used for the calculation of Z-scores of the distal forearm for each participant.

4.2.5 DESCRIPTIVE STATISTICS – DEMOGRAPHICS AND LIFESTYLE FACTORS

These descriptive data display the characteristics of the sample population (Table 4.1).

Table 4.1: Demographics and Lifestyle factors displaying characteristics of the study population

	ALL n = 217	**PBM** n = 131	**20 – 29** n = 39	**30 – 39** n = 45	**40 – 49** n = 55	**50 – 59** n = 56	**60 – 69** n = 22
	Mean ± SD	Mean ± SD	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD
Height	**157.4 ± 6**	**158.5 ± 6**	**159.9 ± 6**	**157.3 ± 6**	**158.2 ± 5**	**155.8 ± 6**	**155.1 ± 6**
Weight	**64.3 ± 12.2**	**63.5 ± 13.0**	**61.7 ±13.8**	**61.4 ± 14.9**	**66.9 ± 9.3**	**66.2 ±11.2**	**63.2 ± 10.6**
BMI	**26 ± 5.1**	**25.3 ± 5**	**24.1 ± 5**	**24.8 ± 5**	**26.8 ±4**	**27.3 ± 5**	**26.5 ± 6**
Age @ menarche	**12.6 ± 1.3**	**12.5 ± 1.2**	**12.1 ± 1.1**	**12.7 ± 1.5**	**12.6 ±1.3**	**13.0 ± 1.5**	**13.4 ± 1.3**
Age @ menopause	**48 ± 4.4**	**n/a**	**n/a**	**n/a**	**22.1%**	**15.7%**	**n/a**
Lifestyle Factors	%	%	%	%	%	%	%
Contraceptive	**17.5**	**28**	**33.3**	**42.2**	**0**	**1.8**	**0**
Daily calcium	**30**	**35**	**5.2**	**24.4**	**25.5**	**46.4**	**54.5**
Exercise	**39**	**19**	**33.3**	**37.8**	**38.2**	**48.2**	**31.8**
Smoking	**9**	**8**	**10.3**	**11.1**	**3.6**	**14.3**	**4.5**
Alcohol	**14.3**	**18**	**33.3**	**11.1**	**12.7**	**7.1**	**9.1**

Height decreased minimally with age, with the mean for the whole sample population

at 157.4cms. Weight was consistent in the 10 year age bands with a slight peak in the 40 to 59 year olds. The body mass index (BMI) is normal for the 20 to 29 and 30 to 39 age bands, however the rest of the sample population appear to be overweight with the BMI $\geq$ 25.

The mean age at menarche in the sample population was between ages 12 and 13. The mean age at menopause was 48 years, with 37.8 percent of the population being postmenopausal. It should be noted that most of the participants in the fourth and fifth decades were perimenopausal. Individuals with early menopause were excluded from the study. Only 17.5 percent of the sample population used oral contraceptives, with the majority in the premenopausal range.

Thirty percent of the total sample population consumed daily calcium, with the highest percentage of individuals in the 60 to 69 age band. Interestingly, the youngest age band (20 to 29) showed that only 5.2 percent were aware of the benefits of daily calcium supplements in their diet, highlighting the need for awareness of this debilitating disease and the importance of ensuring optimum bone mass in the early years.

Only 39 percent of the total sample population exercised regularly, the majority seem to lead a very sedentary lifestyle, with an even lower 19 percent noted in the peak bone mass age group. Notable increases for exercise and calcium intake were noted in the older age bands, highlighting that Indian women in these age groups were more concerned with their bone status.

The percentage of the sample who smoked was low, where only 9 percent are smokers and 14.3 percent of the total population are social drinkers. However the highest incidence of alcohol consumption is noted in the 20 to 29 age band, even though one-third of this group consume alcohol at a social level (< 1 glass of wine per day).

While all of these variables influence bone mass, as discussed in Chapter 2, the aims of the study did not include the epidemiology of osteoporosis in the current study population. The data is presented only to display the characteristics of the sample population and were also to be used to explain any aberrant results, if necessary. No aberrant results were evident in the study and these variables were therefore unnecessary.

4.3 INFERENTIAL STATISTICS

4.3.1 PROCEDURE 1.0

The results from the descriptive statistics were used to make inferences about the sample population (Indian females) and answer the research questions. Table 4.2 shows the means and standard deviations (SDs) for the different variables used for the inferential computations. The null hypothesis stated that the reference values for DEXA BMD in the sample population were the same as those provided by the manufacturers in the Hologic® QDR 4500 bone densitometer.

Table 4.2: Means and SDs for Age and BMD of the 3 measurements sites

	PBM (n = 131)	**20 – 29 (n = 39)**	**30 – 39 (n = 45)**	**40 – 49 (n = 55)**	**50 – 59 (n = 56)**	**60 – 69 (n = 22)**
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Age	**35.3 ± 7.9**	**25.4 ± 3.1**	**35.1 ± 2.8**	**44.18 ±2.7**	**54.75 ± 2.7**	**62.36 ± 2.0**
Lumbar spine	**0.972 ± .083**	**0.964 ± .083**	**0.959 ± .083**	**0.989 ± .086**	**0.889 ±.123**	**0.818 ± .130**
Total Hip	**0.863 ± .103**	**0.846 ± .101**	**0.867 ± .117**	**0.878 ± .089**	**0.836 ± .108**	**0.801 ± .118**
Distal Forearm	**0.542 ± .041**	**0.529 ± .031**	**0.536 ± .039**	**0.558 ± .043**	**0.523 ± .048**	**0.497 ± .05**

4.3.1.1 Research Question

Do the reference values for peak BMD of the lumbar spine in the young adult normal population of Indian women need redefining?

Test Used

One sample t-test – using the Hologic® Caucasian female and the Japanese female specifications, provided by the manufacturer, as the hypothesised values.

Sample

N = 131

Alternate Hypothesis

The reference values for peak BMD of the lumbar spine in the young adult normal population of Indian females need changing.

Assumption Testing

- The data were at the interval or ratio scale of measurement.
- The scores were normally distributed.
- The subjects appeared in only one group.

Decision Rule

If $p < 0.05$ the null hypothesis will be rejected.

Computation:

Table 4.3: One Sample t-test – BMD of the Lumbar Spine in the young adult normal population

Indian Female	N	Mean	Std. Deviation	Std. Error Mean		
BMD of the Lumbar Spine in g/cm^2	**131**	**.97188**	**.082916**	**.007244**		
	Hologic® Caucasian Female Test Value = 1.047					
	T	Df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
BMD of the Lumbar Spine in g/cm^2	**-10.370**	**130**	**.000**	**-.075122**	**-.08945**	**-.06079**
	Japanese Female Test Value = 1.006					
	T	Df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
BMD of the Lumbar Spine in g/cm^2	**-4.710**	**130**	**.000**	**-.034122**	**-.04845**	**-.01979**

Decision

The one-sample t-test shows a two-tailed significance of less than .05 (p=.000) for the BMD of the lumbar spine, which concludes that a significant difference exists between the Indian and the Japanese female BMD means at this measurement site. Inspection of the Indian and Caucasian female BMD means of the lumbar spine also indicates a significant difference ($p < .05$). This implies the alternate hypothesis will be accepted for both population comparisons. This further suggests that the calculation of T-scores of the lumbar spine will vary according to the population reference data used.

4.3.1.2 Research Question

Do the reference values for peak BMD of the total hip in the young adult normal population of Indian women need redefining?

Test Used

One sample t-test – using the NHANES III Caucasian female and the Japanese female specifications, provided by the manufacturer, as the hypothesised values.

Sample

N = 131

Alternate Hypothesis

The reference values for peak BMD of the total hip in the young adult normal population of Indian females need changing.

Assumption Testing

- The data were at the interval or ratio scale of measurement.
- The scores were normally distributed
- The subjects appeared in only one group

Decision Rule

If $p < 0.05$, the alternate hypothesis will be accepted.

Computation:

Table 4.4: One Sample t-test – BMD of the Total Hip in the young adult normal population

Indian Female	N	Mean	Std. Deviation	Std. Error Mean
BMD of the Total Hip in g/cm^2	**131**	**.86292**	**.102669**	**.008970**

	NHANES III Caucasian Female Test Value = .942					
	t	Df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
BMD of the Total Hip in g/cm^2	**-8.816**	**130**	**.000**	**-.079084**	**-.09683**	**-.06134**
	Japanese Female Test Value = .851					
	t	Df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
BMD of the Total Hip in g/cm^2	**1.328**	**130**	**.186**	**.011916**	**-.00583**	**.02966**

Decision

The one-sample t-test shows a two-tailed significance of more > .05 (p = .186) for the total hip, which concludes that there is no significant difference between the Indian and the Japanese female BMD means at this measurement site. However, inspection of the Indian and the NHANES III Caucasian female BMD means indicate a significant difference of < .05 (p = .000). This implies the alternate hypothesis will be rejected for the Japanese reference data and will be accepted for the NHANES III Caucasian female reference data. This further suggests that the calculation of T-scores will vary according to the population reference data used.

4.3.1.3 Research Question

Do the reference values for peak BMD of the distal forearm in the young adult normal population of Indian women need redefining?

Test Used

One sample t-test – using the Hologic® Caucasian female specifications, provided by the manufacturer, as the hypothesised values.

Sample

N = 131

Alternate Hypothesis

The reference values for peak BMD of the distal forearm in the young adult normal population of Indian females need changing.

Assumption Testing

- The data were at the interval or ratio scale of measurement.
- The scores were normally distributed
- The subjects appeared in only one group

Decision Rule

If $p < 0.05$, the alternate hypothesis will be accepted.

Computation:

Table 4.5: One Sample t-test – BMD of the Distal Forearm in the young adult normal population

Indian females	N	Mean	Std. Deviation	Std. Error Mean
BMD of the Distal Forearm in g/cm^2	**131**	**.54223**	**.040713**	**.003557**

	Hologic® Caucasian Female Test Value = .564					
	T	Df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
BMD of the Distal Forearm in g/cm^2	**-6.120**	**130**	**.000**	**-.021771**	**-.02881**	**-.01473**

Decision

The one-sample t-test shows a two-tailed significance of less than .05 (p =.000) for the distal forearm in the young adult normal age band. This implies that there is a significant difference between the Indian and Caucasian female BMD means at this measurement site and the alternate hypothesis will be accepted.

4.3.2 PROCEDURE 2.0

The BMD measurements of the lumbar spine and distal forearm in the Indian population were converted to T-scores using the Hologic® Caucasian, Japanese and Indian populations' young adult normal female reference data. The Japanese data for the distal forearm was not available. The BMD measurements of the total hip were converted to T-scores using the NHANES III Caucasian, Japanese and Indian populations' young adult normal female reference data.

4.3.2.1 Research Question

Do the T-scores for BMD of the lumbar spine for each participant in the Indian population vary according to the different population reference data used?

Test Used

One sample t-test – using the Hologic® Caucasian female and the Japanese female specifications, provided by the manufacturer, as the hypothesised values.

Sample

N = 217

Alternate Hypothesis

There is a significant difference in the Indian populations' T-scores for BMD of the lumbar spine, when different population reference databases are used.

Assumption Testing

- The data were at the interval or ratio scale of measurement.
- The scores were normally distributed
- The subjects appeared in only one group

Decision Rule

If $p < 0.05$, the alternate hypothesis will be accepted.

Computation:

Table 4.6: One Sample t-test – T-scores for BMD of the Lumbar Spine

		T-scores for BMD of the Lumbar Spine (L1 – L4)		
		Based on Hologic ® Caucasian female population	Based on Japanese female population	Based on Indian female population
N	Valid	217	217	217
	Missing	0	0	0
Mean		-1.0158	-.6151	-.4426
Std. Deviation		1.03344	.98851	1.36962

	Hologic ® Caucasian Female Test Value = -1.02					
Indian female T-score for BMD of the Lumbar Spine	t	df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
	6.210	**216**	**.000**	**.57738**	**.3941**	**.7606**

	Japanese Female Test Value = -.62					
Indian female T-score for BMD of the Lumbar Spine	t	df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
	1.908	**216**	**.058**	**.17738**	**-.0059**	**.3606**

Decision:

There is a two-tailed significance of .000 ($p<.05$) between the Indian female and the Hologic® Caucasian female T-scores for BMD of the lumbar spine, therefore the alternate hypothesis will be accepted for these two populations. However, the significance is slightly weaker with $p = .058$ between the Indian and Japanese female populations. This implies that the WHO classifications for the diagnosis of osteoporosis, which re based on T-scores, will vary depending on the population reference data used.

4.3.2.2 Research Question

Do the T-scores for BMD of the total hip for each participant in the Indian population vary according to the different population reference data used?

Test Used

One sample t-test – using the NHANES III Caucasian female and the Japanese female specifications, provided by the manufacturer, as the hypothesised values.

Sample

N = 217

Alternate Hypothesis

There is a significant difference in the Indian populations' T-scores for BMD of the total hip, when different population reference databases are used.

Assumption Testing

- The data were at the interval or ratio scale of measurement.
- The scores were normally distributed
- The subjects appeared in only one group

Decision Rule

If $p < 0.05$, the alternate hypothesis will be accepted.

Computation:

Table 4.7: One Sample t-test – T-score for BMD of the Total Hip

		T-scores for BMD of the Total Hip		
		Based on NHANES III Caucasian female population	Based on Japanese female population	Based on Indian female population
N	Valid	217	217	217
	Missing	0	0	0
Mean		-.7429	.0032	-.1033
Std. Deviation		.87678	.93015	1.03852

Indian female T-score for BMD of the Total Hip	NHANES III Caucasian Female Test Value = .742					
	t	df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
	9.032	**216**	**.000**	**.63674**	**.4978**	**.7757**

Indian female T-score for BMD of the Total Hip	Japanese Female Test Value = .003					
	t	df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
	-1.507	**216**	**.133**	**-.10626**	**-.2452**	**.0327**

Decision:

The two-tailed significance is 0.000 ($p<.05$) at the total hip for the Indian female and Caucasian female T-scores. A significant difference exists between the means of these two T-scores for BMD of the total hip, therefore the alternate hypotheses for the two populations were accepted. The comparison of the Indian population with the Japanese female T-scores shows a similarity ($p = .133$). These results imply that the WHO classifications for the diagnosis of osteoporosis, which are based on T-scores, will vary depending on the population reference values used, however significant.

4.3.2.3 Research Question

Do the T-scores for BMD of the distal forearm for each participant in the Indian population vary according to the different population reference data used?

Test Used

One sample t-test – using the Hologic® Caucasian female specifications, provided by the manufacturer, as the hypothesised values.

Sample

N = 217

Alternate Hypothesis

There is a significant difference in the Indian populations' T-scores for BMD of the distal forearm, when different population reference databases are used.

Assumption Testing

- The data were at the interval or ratio scale of measurement.
- The scores were normally distributed
- The subjects appeared in only one group

Decision Rule

If $p < 0.05$, the alternate hypothesis will be accepted.

Computation:

Table 4.8: One Sample t-test – T-score for BMD of the Distal forearm

		T-scores for BMD of the Distal Forearm	
		Based on Hologic® Caucasian female population	Based on Indian female population
N	Valid	217	217
	Missing	0	0
Mean		-.6083	-.2201
Std. Deviation		.89839	1.11751

	Hologic® Caucasian Female Test Value = -.608					
Indian T-score for BMD of the Distal Forearm	t	df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
	5.114	**216**	**.000**	**.38792**	**.2384**	**.5374**

Decision:

The two-tailed significance is 0.000 ($p<.05$) at the distal forearm for the Indian female and Hologic® Caucasian Female T-scores, therefore a significant difference exists between the means of these two T-score values. The alternate hypotheses for these two populations were accepted. Again, this implies that the WHO classifications for the diagnosis of osteoporosis, which is based on T-scores, will vary depending on the population reference values used.

4.3.3. PROCEDURE 3.0

Each participant's T-scores for all 3 measurement sites, based on the Indian young adult normal age band and manufacturer's young adult normal reference data, was recoded using the World Health Organisation (WHO) classification for diagnosis of osteoporosis. Frequency distributions of the WHO classifications were then explored.

4.3.3.1 Research Question

Does the WHO classification for the diagnosis of osteoporosis of the lumbar spine in the study population, vary according to the reference population (Hologic® Caucasian female, Japanese female and Indian female populations) used?

Test Used

Descriptive statistics – using a frequency distribution table

Sample

N = 217

Computation:

Table 4.9: Frequency table – WHO classification for BMD of the Lumbar Spine according to Hologic® Caucasian, Japanese and Indian female population reference data

	WHO classification for Osteoporosis - Lumbar Spine					
	Based on Hologic® Caucasian Female Reference Data		Based on Japanese Female Reference Data		Based on Indian Female Reference Data	
N Valid	217		217		217	
Missing	0		0		0	
	Frequency	Percent %	Frequency	Percent %	Frequency	Percent %
1 - Normal	**124**	**57.1**	**149**	**68.7**	**149**	**68.7**
2 - Osteopaenia	**76**	**35.0**	**61**	**28.1**	**52**	**23.5**
3 - Osteoporosis	**17**	**7.8**	**7**	**3.2**	**16**	**7.8**
Total	**217**	**100.0**	**217**	**100.0**	**217**	**100.0**

Decision:

The WHO classification for the diagnosis of osteoporosis in the Indian population varies when the reference databases differ. When using the Hologic® Caucasian female reference data to calculate T-scores; 57.1 percent of the participants had a normal report, while 35 percent suggested osteopaenia and 7.8 suggested osteoporosis. The Japanese reference data revealed that 68.7 percent of the Indian population had normal bone mass, while 28.1 percent were osteopaenic and 3.2 percent were osteoporotic. Application of the Indian female reference data for the calculation of T-scores demonstrate that, 68.7 percent of the same had normal bone mass, while only 23.5 and 7.8 percent suggested osteopaenia and osteoporosis, respectively. These results indicate that approximately 11.5 percent of the Indian

participants were erroneously reported osteopaenic against the Hologic® Caucasian female database that is currently being used to clinically diagnose osteoporosis in the same population. They have normal bone mass when measured against their own population reference data.

4.3.3.2 Research Question

Does the WHO classification for the diagnosis of osteoporosis of the total hip in the study population, vary according to the reference population (NHANES III Caucasian female, Japanese female and Indian female populations) used?

Test Used

Descriptive statistics – using a frequency distribution table

Sample

N = 217

Computation:

Table 4.10: Frequency table – WHO classification for BMD of the Total Hip according to the NHANES III Caucasian, Japanese and Indian female population reference data

		WHO classification for Osteoporosis – Total Hip					
		Based on NHANES III Caucasian Female Reference Data		Based on Japanese Female Reference Data		Based on Indian Female Reference Data	
N	Valid	217		217		217	
	Missing	0		0		0	
Valid		Frequency	Percent - %	Frequency	Percent - %	Frequency	Percent - %
1 - Normal		**143**	**65.9**	**192**	**88.5**	**174**	**80.2**
2 - Osteopaenia		**70**	**32.3**	**23**	**10.6**	**40**	**18.4**
3 - Osteoporosis		**4**	**1.8**	**2**	**.9**	**3**	**1.4**
Total		**217**	**100.0**	**217**	**100.0**	**217**	**100.0**

Decision:

The WHO classification for the diagnosis of osteoporosis of the total hip in the Indian population differs when the reference databases vary. The Japanese female reference data revealed that 88.5 percent of the study population had normal bone mass, while 10.6 and 0.9 percent were classified osteopaenic and osteoporotic, respectively. When using the NHANES III Caucasian female reference data to calculate T-scores, 65.9 percent of participants had a normal report, while 32.3 and 1.8 percent suggested osteopaenia and osteoporosis, respectively. Application of the Indian population reference data for the calculation of T-scores demonstrated that, 80.2

percent of the same had normal bone mass, while only 18.4 percent suggested osteopaenia and 1.4 percent, osteoporosis. These results indicate that while the group of osteoporotic individuals did not differ significantly, approximately 14 percent of the study population were erroneously reported osteopaenic against the NHANES III Caucasian female reference data (that is currently used to clinically) but, had normal bone mass when measured against their own population reference data.

4.3.3.3 Research Question

Does the WHO classification for the diagnosis of osteoporosis of the distal forearm in the study population, vary according to the reference population (Hologic® Caucasian female and Indian female populations) used?

Test Used

Descriptive statistics – using a frequency distribution table

Sample

N = 217

Computation:

Table 4.11: Frequency table – WHO classification for BMD of the Distal Forearm according to Hologic® Caucasian and Indian female population reference data

		WHO classification for Osteoporosis – Distal Forearm			
		Based on Hologic® Caucasian Female Reference Data		Based on Indian Female Reference Data	
N	Valid	217		217	
	Missing	0		0	
		Frequency	Percent %	Frequency	Percent %
1 - Normal		**158**	**72.8**	**164**	**75.6**
2 -Osteopaenia		**53**	**24.4**	**46**	**21.2**
3 - Osteoporosis		**6**	**2.8**	**7**	**3.2**
Total		**217**	**100.0**	**217**	**100.0**

Decision:

The WHO classification for the diagnosis of osteoporosis of the distal forearm, in the Indian female population varies when the reference databases differ. When using the Hologic® Caucasian female reference data to calculate T-scores, 72.8% of participants had a normal report, while 24.4% suggested osteopaenia and 2.8% suggested osteoporosis. Using the Indian population reference data for the calculation of T-scores, 75.6% of the same had normal bone mass, while only 20.7% suggested osteopaenia and 3.7% osteoporosis. These results indicate that approximately 11% of the study population were erroneously reported osteopaenic against the Hologic® Caucasian female reference data (that is currently used clinically) but had normal bone mass when measured against their own population reference data. These

results indicate that approximately 3% of the participants had normal bone mass when measured against the Indian female reference data, while they were diagnosed with osteopaenia against the Hologic® Caucasian female data. Although at this measurement site, it appeared as if the percentage difference was small, the T-score means showed a significant difference (see Table 4.8 on page 152).

4.3.4 PROCEDURE 4.0

The means and SDs for BMD at the three measurement sites for the 10 year age bands was used to calculate Z-scores. The Z-score predicts fracture risk and measures an individual's BMD against a reference population matched for age, sex and ethnicity. While the T-score is the score used for diagnosis of osteoporosis against the expected peak bone mass range, the Z-score does help determine the individual's BMD in relation to what is expected for that particular age group.

4.3.4.1 Research Question

Do the reference values for BMD of the lumbar spine, as a function of age, need redefining in Indian women in KZN?

Test Used:

One sample t-test – using the Hologic® Caucasian female and the Japanese female specifications, provided by the manufacturer, as the hypothesised values.

Sample:

Age bands	N =
20 – 29	**39**
30 – 39	**45**
40 – 49	**55**
50 – 59	**56**
60 – 69	**22**

Alternate Hypothesis

The reference values for BMD of the lumbar spine, as a function of age, for Indian women in KZN need changing.

Assumption Testing

- The data were at the interval or ratio scale of measurement.
- The scores were normally distributed in the different age bands, except the 60 to 69 age band.
- The subjects appeared in only one group

Decision Rule

If $p < 0.05$, the alternate hypothesis will be accepted.

Computation:

Table 4.12: One Sample t-test – Comparison of BMD of the Lumbar Spine between the Indian female, the Hologic® Caucasian female and the Japanese female populations in the 10 year age bands

10 year Age bands	Sample size (n =)	Indian Female		Hologic® Caucasian Female		Japanese Female	
		Mean BMD	SD	Test value	Sig. (2-tailed)	Test value	Sig. (2-tailed)
20 – 29	**39**	**0.964**	**.083**	**1.019**	**.000**	**0.981**	**.207**
30 – 39	**45**	**0.959**	**.083**	**1.047**	**.000**	**1.000**	**.002**
40 – 49	**55**	**0.989**	**.086**	**1.024**	**.004**	**0.979**	**.377**
50 – 59	**56**	**0.889**	**.123**	**0.967**	**.000**	**0.864**	**.132**
60 – 69	**22**	**0.818**	**.130**	**0.892**	**.014**	**0.766**	**.073**

Decision:

There is a significant difference ($p < .05$) between the Indian female and Hologic® Caucasian female BMD of the lumbar spine in the 20 to 29, 30 to 39, 40 to 49, 50 to 59 and 60 to 69 age bands, therefore the alternate hypothesis was accepted for these age bands. When inspecting the Japanese reference values, there is no difference ($p > .05$) in the different age bands except in the 30 – 39 age band, where $p < .05$. The Japanese reference ranges are not currently used in the calculation of Z-scores clinically; however, the Hologic® Caucasian female reference data is currently used. This implies that the means for the different age bands used to calculate Z- scores needs changing.

4.3.4.2 Research Question

Do the reference values for BMD of the total hip, as a function of age, need redefining in Indian women in KZN?

Test Used:

One sample t-test – using the NHANES III Caucasian female and the Japanese female specifications, provided by the manufacturer, as the hypothesised values.

Sample:

Age bands	N =
20 – 29	**39**
30 – 39	**45**
40 – 49	**55**
50 – 59	**56**
60 – 69	**22**

Alternate Hypothesis

The reference values for BMD of the total hip, as a function of age, for Indian women in KZN need changing.

Assumption Testing

- The data were at the interval or ratio scale of measurement.
- The scores were normally distributed in the different age bands, except the 60 to 69 age band.
- The subjects appeared in only one group

Decision Rule

If $p < 0.05$, the alternate hypothesis will be accepted.

Computation:

Table 4.13: One Sample t-test – Comparison of BMD of the Total Hip, between the Indian female, and NHANES III Caucasian female and Japanese female populations in the 10 year age bands

10 Year Age bands	Sample size (n=)	Indian Female		NHANES III Caucasian Female		Japanese Female	
		Mean BMD	SD	Test value	Sig. (2-tailed)	Test value	Sig. (2-tailed)
20 – 29	39	0.846	.101	0.942	.000	0.850	.814
30 – 39	45	0.867	.117	0.939	.000	0.851	.362
40 – 49	55	0.878	.089	0.922	.001	0.830	.000
50 – 59	56	0.836	.108	0.886	.001	0.785	.001
60 – 69	22	0.801	.118	0.827	.311	0.727	.008

Decision:

The Indian female BMD of the total hip differs significantly ($p < .05$) from the NHANES III Caucasian female values in all the age bands except the 60 to 69 groups ($p > .05$). This implies that the BMD in the premenopausal women of these two populations are considerably different, whereas the postmenopausal groups show some similarity. When comparing the Japanese female values, a significant difference ($p < .05$) exists in the 40 to 49, 50 to 59, 60 to 69 age bands, while the 20 to 29 and 30 to 39 age bands are similar ($p > .05$). Since the NHANES III Caucasian female reference values are the values used currently, these results suggest that the BMD mean values for total hip need changing for the accurate calculation of Z-scores in the Indian female.

4.3.4.3 Research Question

Do the reference values for BMD of the distal forearm, as a function of age, need redefining in Indian women in KZN?

Test Used:

One sample t-test – using the Hologic® Caucasian female specifications, provided by the manufacturer, as the hypothesised values.

Sample:

Age bands	N =
20 – 29	**39**
30 – 39	**45**
40 – 49	**55**
50 – 59	**56**
60 – 69	**22**

Alternate Hypothesis

The reference values for BMD of the distal forearm, as a function of age, for Indian women in KZN need changing.

Assumption Testing

- The data were at the interval or ratio scale of measurement.
- The scores were normally distributed
- The subjects appeared in only one group

Decision Rule

If $p < 0.05$, the alternate hypothesis will be accepted.

Computation:

Table 4.14: One Sample t-test – Comparison of BMD of the Distal Forearm between the Indian female and the Hologic® Caucasian female populations in the 10 year age bands

10 Year Age bands	Sample size (n=)	Indian Female Mean		Hologic® Caucasian Female	
		BMD	SD	Test value	Significance (2-tailed)
20 – 29	39	0.529	.031	0.564	.000
30 – 39	45	0.536	.039	0.557	.001
40 – 49	55	0.558	.043	0.546	.046
50 – 59	56	0.523	.048	0.526	.591
60 – 69	22	0.497	.050	0.497	1.000

Decision:

There is a significant difference ($p < .05$) between the BMD of the distal forearm in the Indian female and the Hologic® Caucasian female in the 20 to 29, 30 to 39 and 40 to 49 age bands and the alternate hypothesis is accepted. For the 50 to 59 and 60 to 69 age bands the null hypothesis is accepted, as $p > .05$. These results imply that the means that are currently being used to calculate Z-scores need changing, especially in the younger age bands.

4.3.5 PROCEDURE 5.0

The BMD measurements of the lumbar spine were converted to Z-scores, using the Hologic® Caucasian female, Japanese female and Indian female reference data in the 10 years age bands. The BMD measurements of the total hip were converted to Z-scores, using the NHANES III Caucasian female, Japanese female and Indian female reference data in the 10 years age bands. The BMD measurements for the distal forearm were converted to Z-scores using only Hologic® Caucasian female and Indian female reference data, as the Japanese female reference values were not available.

4.3.5.1 Research Question

Do the Z-scores for BMD of the lumbar spine for each participant in the Indian population vary according to the different population reference data?

Test Used

One sample t-test – using the Hologic® Caucasian female and the Japanese female specifications, provided by the manufacturer, as the hypothesised mean.

Sample

Age bands	N =
20 - 29	**39**
30 – 39	**45**
40 – 49	**55**
50 – 59	**56**
60 - 69	**22**

Alternate Hypothesis

There is a significant difference in the Indian female Z-scores for BMD of the lumbar spine, when different population reference data are used.

Assumption Testing

- The data were at the interval or ratio scale of measurement.
- The scores were normally distributed
- The subjects appeared in only one group

Decision Rule

If $p < 0.05$, the alternate hypothesis will be accepted.

Computation:

Table 4.15: One Sample t-test – Comparison of the Z-scores for BMD of the Lumbar Spine between the Indian female, Hologic® Caucasian female and Japanese female populations

10 year Age bands	Sample size (n =)	Indian Female Z-score	Z-scores of BMD of the Lumbar spine based on Hologic® Caucasian Female		Z-scores of BMD of the Lumbar spine based on Japanese Female	
		Mean	Test value	Sig. (2-tailed)	Test value	Sig. (2-tailed)
20 – 29	**39**	**0**	**-.500**	**.003**	**-.158**	**.332**
30 – 39	**45**	**0**	**-.801**	**.000**	**-.349**	**.025**
40 – 49	**55**	**0**	**-.316**	**.018**	**.077**	**.577**
50 – 59	**56**	**0**	**-.707**	**.000**	**.178**	**.117**
60 – 69	**22**	**0**	**-.670**	**.005**	**.363**	**.105**

Decision:

On inspection of the Hologic® Caucasian female Z-score comparisons, a significant difference ($p < .05$) is evident in the 20 to 29, 30 to 39, 40 to 49, 50 to 59 and 60 to 69 age bands and the alternate hypothesis is accepted for these age bands.

The comparisons with the Japanese female Z-scores show no significant difference in all the age bands except the 30 to 39 age band and the alternate hypothesis is accepted for this age band. The null hypothesis is accepted at the $p > .05$ significance for the remaining age bands.

4.3.5.2 Research Question

Do the Z-scores for BMD of the total hip for each participant in the Indian population in vary according to the population reference data?

Test Used

One sample t-test – using the NHANES III Caucasian female and the Japanese female specifications, provided by the manufacturer, as the hypothesised mean.

Sample

Age bands	N =
20 - 29	**39**
30 – 39	**45**
40 – 49	**55**
50 – 59	**56**
60 - 69	**22**

Alternate Hypothesis

There is a significant difference in the Indian female Z-scores for BMD of the total hip, when different population reference data are used.

Assumption Testing

- The data were at the interval or ratio scale of measurement.
- The scores were normally distributed
- The subjects appeared in only one group

Decision Rule

If $p < 0.05$, the alternate hypothesis will be accepted.

Computation:

Table 4.16: One Sample t-test – Comparison of the Z-scores for BMD of the Total Hip between the Indian female, NHANES III Caucasian female and Japanese female populations

10 year Age bands	Sample size (n =)	Indian Female Z-score	Z-scores of BMD of the Total Hip based on NHANES III Caucasian Female		Z-scores of BMD of the Total Hip based on Japanese Female	
		Mean	Test value	Sig. (2-tailed)	Test value	Sig. (2-tailed)
20 – 29	**39**	**0**	**-.785**	**.000**	**-.033**	**.829**
30 – 39	**45**	**0**	**-.590**	**.000**	**-.139**	**.355**
40 – 49	**55**	**0**	**-.364**	**.010**	**.414**	**.003**
50 – 59	**56**	**0**	**-.406**	**.015**	**.448**	**.004**
60 – 69	**22**	**0**	**-.215**	**.331**	**.642**	**.007**

Decision:

There is a significant difference ($p < .05$) between the NHANES III Caucasian female and the Indian female populations Z-scores for BMD of the total hip in the 20 to29, 30 to 39, 40 to 49 and 50 to 59 age bands, therefore the alternate hypothesis is accepted for these age bands. The 60 to 69 age band shows no significant difference ($p > .05$) in the same population, and the null hypothesis is accepted.

On inspecting the Japanese comparisons, no difference ($p > .05$) is evident in the 20 to 29 and 30 to 39 age bands, and the null hypothesis is accepted. However a significant difference ($p < .05$) exists in the remaining age bands and the alternate hypothesis is accepted for the 40 to 49, 50 to 59 and 60 to 69 age bands.

4.3.5.3 Research Question

Do the Z-scores for BMD of the distal forearm for each participant in the Indian population in vary according to the population reference data?

Test Used

One sample t-test – using the Hologic® Caucasian female specifications, provided by the manufacturer, as the hypothesised mean.

Sample

Age bands	N =
20 - 29	**39**
30 – 39	**45**
40 – 49	**55**
50 – 59	**56**
60 - 69	**22**

Alternate Hypothesis

There is a significant difference in the Indian female Z-scores for BMD of the distal forearm, when different population reference data are used.

Assumption Testing

- The data were at the interval or ratio scale of measurement.
- The scores were normally distributed
- The subjects appeared in only one group

Decision Rule

If $p < 0.05$, the alternate hypothesis will be accepted.

Computation:

Table 4.17: One Sample t-test – Comparison of the Z-scores for BMD of the distal forearm between the Indian female and Hologic® Caucasian female populations

10 year Age bands	Sample size (n =)	Indian Female Z-score	Z-scores of BMD of the Lumbar spine based on Hologic® Caucasian Female	
		Mean	Test value	Sig. (2-tailed)
20 - 29	**39**	**0**	**-.678**	**.000**
30 - 39	**45**	**0**	**-.419**	**.008**
40 - 49	**55**	**0**	**.235**	**.090**
50 - 59	**56**	**0**	**-.068**	**.664**
60 - 69	**22**	**0**	**.000**	**1.000**

Decision:

There is a significant difference ($p < .05$) between the Indian female and Hologic® Caucasian female population Z- scores in 20 to 29 and 30 to 39 age bands and the alternate hypothesis is accepted for these age bands. A weaker significance ($p = .090$) is evident in the 40 to 49 age band and no significant difference ($p > .05$) is evident in the 50 to 59 and 60 to 69 age bands. The null hypothesis is accepted for the 40 to 49, 50 to 59 and 60 to 69 age bands.

CHAPTER FIVE

DISCUSSION

5.1 INTRODUCTION

The data collected are presented in Chapter 4 in the form of text, tables and figures. The principal trends and patterns in the data are discussed below with reference to the aims of the study as defined in Chapter 2. The limitations or pitfalls in the study are also highlighted, together with recommendations for future research.

5.2 THE RESEARCH QUESTIONS ADDRESSED IN THIS STUDY

The main aim of the current study was to define new normal reference ranges for bone mineral density (BMD) testing using dual energy x-ray absorptiometry (DEXA) or Indian women in KZN. The second aim was to compare these reference ranges with those provided by the manufacturers and to evaluate whether a significant difference exists between them. Currently for the Hologic bone densitometers, all South African populations are measured for BMD against the Caucasian female database (Hologic® and NHANES III reference values) provided with the unit, irrespective of ethnicity or race. Although the Japanese reference data was absent on the densitometer used in the study, these values were also considered in the comparisons to evaluate inter-ethnic variations among populations of Asian descent.

5.3 POPULATION STUDIED

Two hundred and seventy three volunteers presented for this study. From this sample, only 217 participants met the inclusion criteria and were included in the statistical analyses. Most of the participants were excluded due to endocrine related disorders (in particular, thyroid related disorders) among the other exclusions for the current study. This raises the question of incidence of thyroid related disorders in the whole Indian female population. Furthermore, it highlights the need for screening for osteoporosis in Indian women, as osteoporosis is a secondary disease to thyroid dysfunction (Armstrong and Wastie, 1998: 321-322). Cummings, Bates and Black (2002) have added that "finding and treating these conditions might decrease a patient's risk of fractures." They further argued that the chance of finding a secondary cause of low BMD in patients, especially in primary care settings is unknown, and that the value of testing for secondary causes has not been adequately studied (Cummings, Bates and Black, 2002).

Of the 217 participants who were measured for DEXA BMD at the lumbar spine, total hip and distal forearm, a small percentage of participants were classified osteopaenic and osteoporotic using the manufacturer's reference data. Consistent with the ethical guidelines governing this study, these individuals were informed of their "abnormal" results and were recommended to seek further medical advice. This recommendation was based on the fact that, currently the diagnosis and therapeutic management for osteoporosis, especially among Indian women, is made using the manufacturer's reference data. On inspection of the reference data from the current study for the

classification for these participants, the percentage of osteopaenic individuals changed considerably. Little or no change was noted in the category of osteoporotic individuals. However, some individuals still appeared to have low BMD using the current study's reference data. These will be highlighted later in this chapter.

The above finding suggests that there are a percentage of Indian women in the KZN population with unrealised abnormal BMD. It raises the question of whether screening procedures should be routinely performed. Internationally, the recommendation for diagnosis of osteoporosis should be made on an individual basis, considering all other factors that can contribute to this disease. The South African Department of Health supports this notion of selected screening of the population, and recommends a case finding approach that is based on identifying patients with generally accepted clinical risk factors (South African Department of Health, 2001)

The WHO criteria for mass screening for early detection of a disease as defined by Wilson and Jungner, 1968 (cited in Mazanec, 2004) are as follows:

1. The condition should be an important health problem.
2. There should be an accepted treatment for patients with recognised disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognisable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.

7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding should be economically balanced in relation to possible expenditure as a whole.
10. Case-finding should be a continuing process and not a "once and for all" project (Wilson and Jungner, 1968 as cited in Mazanec, 2004).

The "test" in criteria 5 - DEXA BMD, is the "gold standard" for the diagnosis of osteoporosis and assessment of fracture risk in a given individual. However, as stated in criteria 6, the test should be acceptable to the population being tested. Currently, the heterogeneous populations in South Africa are being measured for BMD against reference data provided by the manufacturers, in the absence of local databases.

In context to this study, the Indian female population in KZN are being currently measured against the Hologic® Caucasian female database (reference values) for the lumbar spine and distal forearm and the NHANES III Caucasian female database (reference values) for the total hip, for the Hologic QDR 4500 bone densitometer.

In addition, the WHO diagnostic criteria for osteoporosis which are based on healthy postmenopausal Caucasian women using DEXA measurements, are being widely used to establish osteoporosis in non- Caucasian women and men. Furthermore, the WHO criteria are defined by T-scores which should be derived from the appropriate population.

Although the International Society for Clinical Densitometry (ISCD) in their position statement declared that T-score adjustments should not be made on race when measuring non-Caucasians, they added that this recommendation only applied to the United States of America and that other populations should develop their own databases for accurate BMD measurements (Binckley, *et al*. 2002). The South African Department of Health have also expressed concerns that "extrapolations of the WHO criteria to other populations assessed with different techniques and different sites should be cautioned against diagnosis of low BMD, namely osteoporosis, osteopaenia and/or identifying of persons at risk of future fractures" (South African Department of Health, 2001)

The above statements reiterate the need for reliable ethnic matched reference data for the accurate measurement of BMD for the diagnosis of osteoporosis in any given population, either for mass screening or individual diagnostic purposes.

A grave concern with population screening for osteoporosis in KZN and South Africa is one of cost, especially in the shadow of the HIV/AIDS pandemic and its associated opportunistic infections. However, in addition to the huge impact osteoporosis has on individuals and their families, there is a huge economic association. According to Baran, *et al*. (1999a) the projected healthcare costs of osteoporosis–related fractures worldwide are approximately 60 billion US dollars per year. Mazanec (2004) indicated that osteoporosis and its associated morbidity and mortality with respect to fractures seriously qualifies for "screening as a societal health problem of enormous and increasing magnitude." He added that "despite clearly meeting the tenets for a

condition meriting aggressive screening and treatment, osteoporosis still remains under-recognised and under-treated." Further research in a South African context, may be valuable in determining the benefits of screening for osteoporosis in the different populations.

More importantly in mass screening for osteoporosis, is the classification of patients who have osteopaenia (-2.5 >BMD < -1 SD below the mean for young adults). In addition to the controversy regarding treatment strategies and its associated side effects, patients endure undue stress and anxiety that usually accompany unexpected abnormal results. This has greater ramifications if an individual patient is erroneously classified as osteopaenic due to inaccurate testing tools or reference values. Additionally, this misclassification of osteopaenia in patients unduly increases the financial burden on the health services.

In contrast, mass screening has the potential to detect a disease or condition much earlier than the actual presentation of the disease, as is the case with osteoporosis. Additionally, therapeutic management of the disease is initiated earlier and complications are reduced.

Currently, there is a paucity of local statistics on the incidence of osteoporosis and its consequences in the South African context. Further research is warranted on the epidemiology of the disease and its consequences with respect to the different ethnicities and population groups in the country. Once this is done, the benefits of population screening for osteoporosis should be re-evaluated.

5.4 NORMAL PEAK BMD REFERENCE DATA FOR INDIAN FEMALES USING DEXA TECHNOLOGY

In the current study, the research participants aged 20 to 66 had BMD measurements taken at the lumbar spine (vertebral levels L1 to L4), non dominant total hip and non dominant distal forearm using the DEXA scanner. It was hypothesised that the normal range for peak BMD in the study population would differ from the normal manufacturer's Hologic® and the NHANES III Caucasian reference databases currently being used, as well as the Japanese female reference values for the respective skeletal sites.

Bone mineral density for all 3 skeletal sites in the study population showed an incline from age 20 and was virtually constant up to age 49, but showed a peak in the fourth decade after which a steady decline was evident (see Chapter 4 and page 184). The young adult normal population for this study was thus defined as pre-menopausal women aged 20 to 48, with a mean age of 35. The study undertaken by Pedrazzoni, *et al*. (2003) showed similar findings, where the BMD in Italian women was constant between age 20 to 49, followed by a linear decline after age 50.

In contrast, a study by Gurlek, Bayraktar and Ariyurek (2000) showed that BMD peaked in the second decade in the Turkish population. Another study undertaken by Ravishankar (2000), as cited in Jadeja and Rema, (2005); involving 289 Indian women living in India, between 20 to 84 years of age, showed that peak BMD was reached in the third decade after which a slow decline was noted.

As stated in Chapter 2, the age at which peak bone mass is attained is highly controversial, and estimates of peak BMD in the different populations vary significantly. According to Tudor-Locke and McColl (2000) various cross-sectional studies have shown that bone mass peaks from late adolescence, to the third decade, extending into the fourth decade of life (as can be seen in the current study), and even beyond. Pedrazzoni, *et al*. (2003) confirmed that longitudinal studies are more apt at predicting peak BMD in a target population as opposed to cross-sectional studies and are able to show slight pre-menopausal decreases of BMD. This study was cross-sectional in nature and showed lower peak bone mass values than those provided by the manufacturer.

The BMD normal values for peak BMD in the Indian women in KZN were significantly different from the manufacturer's normal values at all 3 skeletal sites. The BMD means were 0.972 g/cm^2, 0.863 g/cm^2 and 0.542 g/cm^2 for the lumbar spine, total hip and distal forearm respectively, with a $p = .000$ at all 3 sites against the Caucasian lumbar spine and distal forearm reference data and the NHANES III total hip data. BMD values in the study population were approximately 8 percent lower at the lumbar spine and total hip and approximately 4 percent lower at the distal forearm, compared to the Hologic® Caucasian and NHANES III female reference databases.

Other studies that used digital x-ray radiogammetry (Pande, 2002) also showed that Indian women from the Indian subcontinent had approximately 15 percent lower BMD than in Caucasian women. According to Pande (2002) normative reference data using x-ray radiogammetry is the only data available for Indian BMD measurements. Similar

results were evident by a study undertaken by Reddy, *et al.* (2002) to determine reference data for Asian Indian women living in America (as cited by Shah, 2005). It is important to note that T-scores do vary depending on the measuring device used, and direct correlations of T-scores cannot be made between different densitometers. This would explain the slight differences in the results obtained from the current study to the study undertaken by Pande (2002).

It is also important to note that globally, normative reference data using DEXA in the Indian population is not available in any of the DEXA densitometers. The significance of the results from this study implies that new BMD reference values for DEXA in the Indian women of KZN need to be considered for interpretation of BMD for osteoporosis. A similar study is in progress (duration 2002 to 2006) in India, aiming to generate reference values from 100 healthy men and women between 20 to 30 years of age, as well as to assess the prevalence of osteopaenia and osteoporosis in the Indian population, using 1500 subjects (Shah, 2005). It will be interesting to compare the reference data generated in India with the values obtained from the current study.

Other studies, as discussed in Chapter 2, have shown that Asians of other ethnic origins have lower BMD than Caucasians. The primary reason for this discrepancy between the race groups seems to be bone geometry and bone size (Bhudhikanok, *et al*. 1996; Marquez, *et al*. 2001; Wu, *et al*. 2003). While the aims of the current study did not include epidemiology of osteoporosis in Indian women, it can be assumed that one of the primary reasons for the racial differences in peak bone mass between the Indian women in KZN and the Caucasian women from the USA is one of bone

geometry and bone size. According to the literature, bone size directly influences bone mass, which in turn further questions the accuracy of the reference values currently being used to measure BMD status in an individual. However, other key determinants of peak bone mass should not be excluded.

Previous studies (Tobias, et al. 1994; Daniels, *et al*. 1997; Mehta, et al. 2004; Roy, *et al*. 2005) have shown that populations with smaller skeletal size do have lower BMD, but that this comparative difference disappeared with adjustments for height. However, Alekel, *et al*. (2002) argued that the validity of these adjustments to accurately reflect true BMD has not been established and may not be practical for assessing individual risk.

Other studies (Liao, *et al*. 2003; Alver, *et al*. 2005) have indicated that racial and ethnic differences in BMD continue, sometimes even after the adjustment for skeletal size is taken into consideration. Adjustments for height were not considered for this study, as it was not one of the aims of the study. However, based on the statements above, an important consideration is skeletal size and its consequent bone mineral status in the Indian women. The result being the obvious consequence that osteoporosis and low BMD is over-diagnosed in persons of petite body stature, when the means of the reference populations are calculated from values of large and small people.

More studies have shown that inter ethnic variances exist in the same populations or races. Caucasian studies undertaken by Petley, *et al*. (1996) and Ahmed, *et al*. (1997)

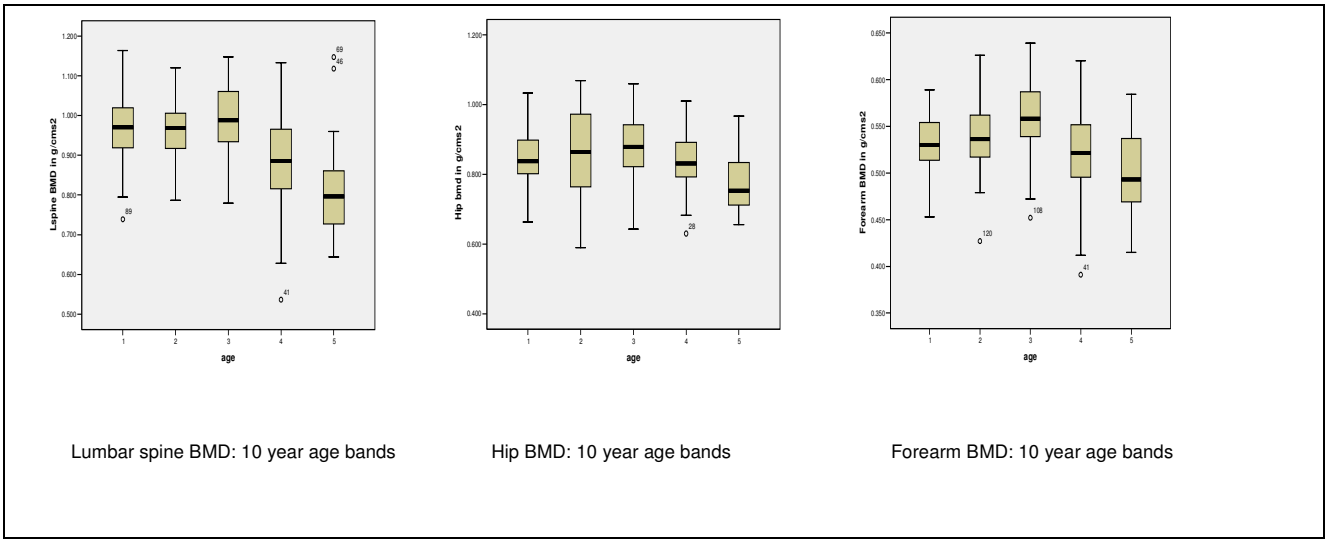
have shown that Europeans have lower BMD than their American peers, and that local reference data is needed in their populations for the accurate diagnosis of osteoporosis. Another study by Sundberg, *et al.* (1997) indicated that variances exist between urban and rural subgroups of the same ethnic population Asian studies undertaken by Wu, *et al*. (2003) and Liao, *et al*. (2003) have also shown that BMD differences exist in inter- ethnic populations of Asian descent..

The above implies that an available Asian database does not necessarily mean that it is appropriate for use against another Asian population group. To this end, the Indian female reference data determined in this study were compared with the Japanese reference data available and showed considerable differences, with a $p < .05$ evident at the lumbar spine. Similarities in the data were evident at the total hip ($p = .186$). No data is available for distal forearm measurements using DEXA. Presently in the clinical environments in KZN, DEXA BMD is measured at 2 skeletal sites or more. This implies that the Japanese database cannot be applied to Indian women in KZN.

5.5 NORMAL BMD REFERENCE DATA FOR THE 10 YEAR AGE BANDS FOR INDIAN WOMEN USING DEXA TECHNOLOGY.

In the current study, the research participants aged 20 to 66 years had BMD measurements taken at the lumbar spine (L1 to L4), non dominant total hip and non dominant distal forearm using the DEXA scanner. Similarly, it was hypothesised that the normal range for BMD in the 10 year age bands would differ from the normal manufacturer's values currently being used, as well as the Japanese values for the respective skeletal sites.

BMD for the 3 skeletal sites for the study population in the 10 years age bands showed an incline up to the fourth decade followed by a linear decline (as shown in Chapter 4. and see Figure 5.1) that was evident in the 50 to 66 years old Indian women of KZN. This finding could be due to the cross-sectional design of the study, which can impair the detection of menopause related changes in bone. However, the effect of menopause in the study population is evident in the decrement in the 10 year age bands.



Lumbar spine BMD: 10 year age bands

Hip BMD: 10 year age bands

Forearm BMD: 10 year age bands

Figure 5.1: Trends for BMD in the 10 year age bands (Larger graphs are available in Chapter 4.)

This trend is in keeping with the globally expected decline in BMD following menopause. Similar age bands trends were evident in the Italian study by Pedrazzoni, *et al*. (2003) and others, which showed BMD at the respective measurement sites being virtually constant from age 20 and peaking in the 40 to 49 age band.

The difference between this study population data and the manufacturer's Hologic® Caucasian female data for the lumbar spine and distal forearm and the NHANES III Caucasian female data for the total hip vary between the age bands. For the lumbar spine, only the 40 to 49 age band values showed similarity. Interestingly, BMD "peaked" in this age band (40 to 49) in the study population, compared to the Caucasian women, where peak bone mass was established in the 30 to 39 age band. At the total hip, significant differences are evident between the pre-menopausal

women in the study and manufacturer's population data, whereas some similarity is indicated in the postmenopausal groups. BMD in the study population is approximately 8 to 10 percent lower than the Caucasian and NHANES III population in the respective age bands.

These differences noted in the study population may be attributable to frame size, lifestyle factors, genetic and biologic factors and socio-economic considerations. Cross-sectional data is limited in providing adequate answers to the impact of these factors on bone mineral status and longitudinal studies are needed to evaluate epidemiology of osteoporosis in not just the Indian women in KZN, but throughout the heterogeneous populations of South Africa considering gender as well.

The means and standard deviations for the 10 year age bands in the study population were used to calculate Z-scores, which compares an individual with age matched norms. As indicated by Watts, (2002) Z-scores are very useful in determining how an individual's BMD compares with what is expected, however its use in the older population is limited. Cummings, Bates and Black (2002) added that as BMD declines with age, T-scores are usually consistently lower than Z-scores following age 40 years and this difference increases with age. This means that an 80 year old with a normal Z-score will be considered "normal" in terms of bone health; however the T-score will give an indication of bone loss with age.

While T-scores are useful for determining prevalence of osteoporosis, Z-scores are useful for the expression of relative fracture risk with respect to age matched peers. A Z-score of < -1 means that an individual has 2.5 times the risk of fracture at one's

given BMD when evaluated against one's age matched peers (National Osteoporosis Foundation, 1998). A low Z-score is also a very useful guide to detecting secondary causes for osteoporosis (Watts, 2002).

5.6 CALCULATION OF T- and Z-SCORES and IMPLICATIONS OF THE WHO CLASSIFICATION BASED ON NEW DATA

The young adult normal BMD means in Indian women at all 3 skeletal sites were lower than those used by the manufacturer. The SDs for the young adult normal BMD were also lower than those used by the manufacturer. This leads to important differences in the calculation of the T-score and the subsequent classification of women according to the WHO criteria. The mean T-score computed with the Indian women reference data was on average 0.6 SD higher at the lumbar spine than that estimated with the manufacturer's Caucasian, resulting in a greater proportion of women being classified as osteopaenic (35% versus 23.5%). The classification for osteoporosis did not change at this site. The mean T-score computed at the hip showed similar SD differences than that estimated with the NHANES III reference data. As a result the proportion of women classified osteopaenic (32.3% versus 18.4%) and osteoporotic (1.8% versus 1.4%).

Clinically, BMD measurements are taken at the lumbar spine and total hip to assess BMD status in a given patient. The results from the study indicate that 11 to 14 percent of individuals have been misclassified as osteopaenic. As indicated by Watts, (2002) applying a medical label of "osteopaenia" to a healthy person can create at

least two problems. Individuals who are in the upper part of this borderline range are usually perfectly normal and yet will experience undue considerable lifelong anxiety. This is compounded when the classification is erroneous. Additionally, those individuals in the lower part of the range are almost or more likely to fracture than those classified osteoporotic, and may even be candidates for therapeutic intervention.

At the distal forearm, the mean T-score computed with the Indian women reference data was on average 0.4 SD higher than that estimated with the manufacturer's Caucasian range, resulting in a slightly greater proportion of women being classified as osteopaenic (24.4% versus. 21.2%).

Clinically, the distal forearm is used as an alternate site when the lumbar spine or total hip cannot be measured due to artefacts or surgery. Interestingly, the differences noted at this site are considerably lower compared to the other sites. Lifestyle factors apart from genetic factors may have some influence on these differences noted.

The research aims did not initially include evaluating Z-scores in the study population, however evaluation of the Z-scores computed using the study population reference data varied compared to those computed using the manufacturer' reference ranges. While at certain age bands, similarities in the Z-scores were evident, there are significant differences for other age bands. This means that new reference data is needed for the 10 year age bands to accurately interpret an individual's BMD status matched for age, gender and ethnicity.

CHAPTER SIX

CONCLUSIONS AND RECOMMENDATIONS

6.1 INTRODUCTION

The data in this study represents the first comprehensive investigation of bone mineral density (BMD) values of Indian females in KwaZulu-Natal (KZN), using the Hologic® QDR 4500 bone densitometer.

Investigations of the BMD of the lumbar spine, total hip and distal forearm were performed on 217 healthy Indian female volunteers. The main finding was evidence that new normal ethnic matched reference ranges are needed for the accurate diagnosis of osteoporosis in local populations. The results from this study have added to the global evidence that BMD varies in different populations and that individual populations should construct and use their own reference range T-scores in DEXA to ensure accurate diagnosis of osteoporosis and development of adequate prevention and treatment strategies.

6.2 CONCLUSIONS AND SIGNIFICANCE

The main aim in this study was to determine the normal reference data for BMD for Indian females in KZN. Significant differences are evident between the study population BMD values and the current manufacturer values being used. The new reference ranges are significantly lower than the current values being used, which

insinuate that a high percentage of individuals previously reported as osteopaenic or having increased fracture risk; actually have normal bone mass when measured against their own reference population data.

An Indian young adult normal reference database for DEXA BMD has been established for the lumbar spine, total hip and distal forearm, albeit an inappropriate sample size. The reference ranges at all 3 measurement sites are significantly different from current normative data reported by the manufacturer. This has significant impact on an individual's classification based on the WHO criteria.

For the 10 year age bands, DEXA BMD at all 3 measurements sites are different to the current reference data reported by the manufacturer, however to a lesser extent for certain age bands. New consistent reference ranges should be adopted across the 10 year age bands, for accurate calculations of Z-scores and accurate expressions of fracture risk.

This study used non-probability sampling and the sample sizes were limited, which in turn implies that there is a possibility that the results cannot be generalised to Indian female population. Conversely, the results do reiterate that individual populations should use their own reference data for DEXA measurements in order to avoid misdiagnosis of osteopaenia and osteoporosis based on another population's reference data. Furthermore, a low BMD is not necessarily indicative of increased risk of fracture in a given population; and this approach might decrease unnecessary patient anxiety and errors concerning treatment.

6.3 SUMMARY OF CONTRIBUTIONS/RECOMMENDATIONS

- The most significant finding to emerge from this thesis is that new normal reference ranges for DEXA BMD of the lumbar spine (0.972 g/cm^2 ± .083), total hip (0.863 g/cm^2 ± .103) and distal forearm (0.542 g/cm^2 ± .041) for DEXA BMD measurements have been established. As a result of these differences in the means and SDs, T- and Z-scores are also significantly different than those currently derived using the manufacturer's reference data. The application of the WHO criteria for assessing prevalence of normal bone, osteopaenia and osteoporosis shows considerable classification differences which are dependent on the population reference data used.
- The aim of this study was to establish reference data using the Hologic QDR 4500. There are other densitometers currently available in South Africa using DEXA technology and they yield BMD values in a given individual. However, the International Committee for Standards in Bone Measurement (ICSBM) have published equations that allow different manufacturers to express their BMD values in consistent standardised units (sBMD: mg/cm^2). The absolute BMD reference ranges obtained from this study population can be compared and applied to the other manufacturers of DEXA technology, like the Lunar and Norland bone densitometers, using these standardised equations.

6.4 LIMITATIONS OF THE STUDY

The main limitation of this study lay in the selection procedure for the participants, who were all volunteers. They were all ambulatory and presumed healthier than the general public, as determined by the screening questionnaire. The screening questionnaire by itself was another limitation, as the information gathered from each participant was presumed to be truthful. Furthermore, the exclusion criteria in the study were used because they are widely quoted as risk factors for osteoporotic fractures instead of their inherent validity. This may have contributed to bias in the reference population used.

While the reference values derived should be from a population not affected by the condition under study, using too many exclusion criteria may result in a database that is not a true representation of the population. The NHANES III study is one such study that used random sampling including all individuals to reduce bias in the samples. The exclusion criteria in the current study did considerably affect the sample size in the 60 to 69 age band. For example, all those who had total hysterectomy or bilateral oophorectomy were excluded; however, all those included were postmenopausal anyway.

Sample size was an additional limitation. Ideally, a sample of 200 healthy participants from the young adult normal or peak bone mass and 50 participants in each 10 year age band should have been recruited. On the other hand, the similarity of the results obtained from the current study with other studies that used different criteria (Pande,

2002; Reddy, *et al.* 2002; Alver, *et al.* 2005; Roy, *et al*. 2005) support the general conclusions of this study.

Another concern was the convenience sampling technique used. The study population were recruited from the volunteers who responded to the advertisements. Ideally they should have been randomly sampled and drawn from a greater geographical area. This would have ensured a more accurate representation of the Indian population at large.

Use of WHO classifications for determining the categories of BMD status, even though these guidelines were established for Caucasian women and may not be entirely applicable to non-Caucasian women and men of all ethnicities. Larger epidemiological studies need to be performed to determine more accurate BMD cut-offs in Indian women, especially since they have lower BMD values and also present with increased bone loss earlier than Caucasians. It has been highlighted that the peak incidence of osteoporosis in India may afflict Indians 10 to 20 years earlier than in most Western countries, at age 50 to 60 (Lau, *et al*. 2001). Future studies will also indicate whether similar trends are present in the South African Indian population.

6.5 FUTURE RESEARCH

This study will serve as a basis for further research and recommends that the following investigations be undertaken:

- Changing the research design to include a more geographic representation for this particular ethnic group, as well as a larger sample size.
- Since fracture risk is not dependent solely on BMD, but also factors such as risk of falling and bone geometry and size, longitudinal studies are imperative to define a separate algorithm of future risk assessment of fracture based on the BMD for Indian women
- Similar comparative investigations in the other population groups in South Africa and evaluating the diagnostic implications in these populations.
- Investigating urban versus rural populations and evaluating the transition from rural to urban lifestyles and its influence on BMD. Also within same ethnic groups, widely differing environmental backgrounds and lifestyle factors exist. Comparative studies of BMD to evaluate homogenous sub-groups.
- Epidemiology studies assessing incidence of osteoporosis in the South African context as well as relationship between BMD and fracture risk, prevalence of fragility fractures and its associated implications in the different racial and ethnic populations are needed.

- Re evaluating the benefits of screening measures for secondary osteoporosis with respect to endocrine disorders, gastrointestinal disorders, cortisone therapy, as well as metabolic side effects of highly active anti-retroviral therapy (HAART) on bone.
- Re evaluating the recommendations for screening in the different populations, as “one size does not fit all” with respect to prevalence and occurrence of osteoporosis in the different populations.

6.6 CONCLUDING STATEMENTS

Significant differences in DEXA BMD reference values of the lumbar spine, total hip and distal forearm are evident in the Indian women of KwaZulu-Natal, compared to the reference values being currently used. When assessing BMD status in these women, use of the correct population reference range is imperative, to ensure accurate diagnosis for osteopaenia and osteoporosis. Currently, DEXA BMD is the “gold standard” and will remain a useful diagnostic tool for measuring BMD and assessing fracture risk in a given individual. However, new references values for the study population and the other local populations need to be included in the Hologic® QDR 4500 reference databases used in South Africa.

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Appendix

A

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Appendix I

Appendix J

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Appendix L

APPENDIX A

DURBAN UNIVERSITY of TECHNOLOGY

Directors of: Drs Jackpersad, Rooknoodeen and Partners
C/O City Hospital Radiology Department
Lorne Street
Durban, 4001

30 October 2003

Dear Doctor Jackpersad

Our verbal correspondence (08/09/03) has reference.
Your sponsorship for the DEXA scans and permission for performing them in your department is greatly appreciated.

The proposed title of my dissertation is A determination of the normal reference ranges for bone mineral density for Indian women of varying age groups in KZN: the impact of local data on the diagnosis of osteoporosis.
The study population will be determined using convenience sampling and only consists of subjects who fit the inclusion criteria.

As I have stated previously, the aim of the study is to define BMD reference values for different age groups when measuring BMD using DEXA. Currently, your patients are being diagnosed against a Caucasian database for osteoporosis. Other studies undertaken internationally and nationally have indicated interethnic variances in bone mass and no data is currently available for Indian females - which form the bulk of the patients presenting to your departments.

My proposal has been reviewed by the Department of Radiography and approved by the Research Committee of the Faculty of Health Sciences, at the Durban Institute of Technology. Appropriate ethical approval has been obtained. Experts in the field will supervise the project internally and externally.
The results from this study will have a direct benefit to your Department, as the values determined can be the 'new reference ranges' against which all your future patients can be measured – a reliable, accurate ethnic matched reference database.

I am aware of the cost implications for these scans and will therefore supply my own paper and ink cartridges and 'stiffy' disks for recording the data for this study.

DURBAN UNIVERSITY of TECHNOLOGY

I expect to collect my data from October 2003 to September 2004.
I would possibly be spending 2 – 3 days per week collecting data.
During this time, I will be able to complement your staff quota, and will undertake to assist in any way possible.

Your support is greatly appreciated. Please could you supply me with a written letter confirming your permission and sponsorship.

Yours sincerely

_____

Roshnee Sunder
Lecturer: Department of Radiography - DIT
TEL: 031-2042508 (W)
031-5636424 (H)
Cell: 0827849101
email: roshs@dit.ac.za

_____

Mrs S Naidoo (Internal Supervisor)
Master of Applied Science
Tel: 031 – 2042450 (w)
email: nalenen@dit.ac.za

APPENDIX B

DURBAN
UNIVERSITY *of*
TECHNOLOGY

CALLING ALL INDIAN LADIES 20 YEARS & OLDER

RESEARCH ON OSTEOPOROSIS

Should you meet the RESEARCH CRITERIA, you will qualify for a
FREE DEXA BMD scan
the most accurate
way to test
your bone strength

CONTACT:
ROSH SUNDER
DEPARTMENT OF RADIOGRAPHY
DURBAN INSTITUTE OF TECHNOLOGY
TEL: 031 – 2042508
031 – 5636424
CELL: 0827849101

APPENDIX C

DURBAN UNIVERSITY of TECHNOLOGY

Department of Radiography

Participant information letter

Title:

A determination of the normal reference ranges for bone mineral density for Indian women of varying age groups in KZN: the impact of local data on the diagnosis of osteoporosis.

Dear participant:

Thank you for volunteering to participate in my research project. Approximately 250 volunteers will be included in this study.
I am a M.Tech. in Radiography student and I am performing a study on bone strength. You will be required to have a DEXA BMD scan that is a special type of x-ray test used to measure the calcium content of the bone. The three areas that will be measured are your spine, hips and forearm. Your scan information will help determine normal values for this population and provide you with a baseline BMD scan measuring your bone strength.

You will also be required to fill in a simple questionnaire, outlining personal details and medical history prior to the scan. This will also determine whether you fit the criteria for the project.

How to prepare for this study

You do not need to starve for the scan, but try not take any calcium supplements (if applicable) for at least 24 hours prior to your appointment.
You should wear light, comfortable clothing avoiding belts, buttons and zippers.

Procedure

You may be asked to undress and wear a hospital gown. Your height and weight will be measured and documented. You will then be required to lie on the padded scan table with a x-ray generator below and an imaging device (detector) above you. Scans will be performed at the spine and hips.
During the examination of your spine, your legs will be supported on a padded box to flatten you lower spine and pelvis. For the hips, your feet will be placed in a special brace that helps rotate and support your hip inward.
In both instances the detector passes over the area of interest. During this time, the DEXA machine sends a thin, invisible beam of low-dose x-rays through your bones. The amount of radiation used is extremely small. Images are generated onto a computer, where special software compute the data and display the information on the monitor.
The whole procedure should be complete in 30 minutes.

Risk/ Discomfort

DEXA bone densitometry is a simple, non-invasive procedure. The table is wide open and claustrophobia is not an issue. You should feel no pain and there is no risk or discomfort. You may be asked to hold a certain position, while the arm of the machine passes over your body taking measurements. It is important that you remain as still as possible during the procedure to ensure a clear useful image.
The radiation dose that you will receive from this scan is comparable to the radiation you receive from the sun and is therefore negligible.

Benefits

DEXA bone density testing is the most accurate method available for the diagnosis of osteoporosis. It is also considered an accurate and precise predictor for fracture risk. However, a reliable ethnic reference database is needed to ensure accurate diagnosis.
The results from this study will establish a reliable ethnic database for measuring in bone mineral density in the Indian population and to further medical knowledge about osteoporosis.
If your results indicate an abnormality, then you would be advised to seek further medical attention.

Confidentiality

Your personal details will be excluded from data analyses and data presentation. (Codes will be used for each research participant.)
Please be aware that you are free to withdraw at any time during the research

Cost to participant

There is no cost to the research participant. All measurements will be performed at no cost.

Voluntary participation / withdrawal

You have rights as a research volunteer. Participating in this study is completely at your own will and you are free to withdraw from this study without a penalty.
You will not be forced to take part in this study for any reason. The researcher will answer any questions that you may have, at any time.

DURBAN UNIVERSITY of TECHNOLOGY

Ethics approval

The Ethics Committee, of the Faculty of Health Sciences at the Durban Institute of Technology, has approved this study.

Contact details:

Researcher: Rosh Sunder (Student Number: 18601614)
Lecturer: Department of Radiography
Faculty of Health Sciences
Durban University of Technology
TEL: 031-2042508 (W)
031-5636424 (H)
0827849101
email: roshs@dit.ac.za

Supervisor: Mrs S. Naidoo
Master of Applied Science
Senior Lecturer: Department of Radiography
Faculty of Health Sciences
Durban University of Technology
Tel: 031-2042450 (w)
email: nalenen@dit.ac.za

You will be required to sign an informed consent sheet.

PLEASE FEEL FREE TO CONTACT THE RESEARCHER IF YOU HAVE ANY CONCERNS OR QUERIES.

APPENDIX D

DURBAN UNIVERSITY of TECHNOLOGY

Informed Consent Form

I,…… hereby voluntarily
print name
Consent to participate in the research entitled:

A redefinition of the normal reference ranges for bone mineral density for Indian women of varying age groups in KZN: the impact of local data on the diagnosis of osteoporosis.

Conducted by:

Name of researcher: **----------**Name of supervisor:----------

Name of co-supervisor----------

Please circle the appropriate answer

1 Have you read and understood the research information sheet? Yes / No

2 Have you had an opportunity to discuss the study? Yes / No

3 Have you had an opportunity to ask questions regarding this study? Yes / No

4 Who have you spoken to?……

5 Have you received satisfactory answers to your questions? Yes / No

6 Have you received enough information about the study? Yes / No

7 Do you understand that you are free to withdraw from this study

a) at any time and

b) without having reason for withdrawing? Yes / NO

8 Do you agree to voluntarily participate in this study? Yes / No

9 Do you agree not to discuss this research project with any of the other research participants? Yes / No

If you have answered No to any of the above questions, please obtain the appropriate information before signing.

Please print in block letters

Participant Name:…… **signature** ……Date…….

Witness Name …… **Signature**…….Date……

APPENDIX E

DURBAN UNIVERSITY of TECHNOLOGY

PARTICIPANT DETAILS

NAME: _____ AGE: _____

ID: _____ DATE OF BIRTH: _____

DATE OF MENOPAUSE: _____ DATE OF MENARCHE: _____

HEIGHT: _____ WEIGHT: _____

ARE YOU ON ANY CONTRACEPTIVES?

YES	NO

_____

DO YOU EXERCISE?

IF YES, HOW OFTEN?

YES	NO

_____

DO YOU TAKE CALCIUM SUPPLEMENTS

IF YES, HOW MANY/DAY?

YES	NO

_____

APPENDIX F

DURBAN UNIVERSITY of TECHNOLOGY

SCREENING QUESTIONNAIRE

Thank you for offering to participate in this study.

You will be required to answer the following questions to determine whether you fit the inclusion and exclusion criteria:

1. Do you know what osteoporosis means?	YES / NO
2. Are you or do you think you might be pregnant?	YES / NO
3. Do you suffer from any renal conditions?	YES / NO
4 . Do you suffer from any hepatic conditions?	YES / NO
5. Do you suffer from any endocrine disorders?	YES / NO
6. Do you suffer from any renal conditions?	YES / NO
7. Have you had a bilateral oophorectomy (ovaries removed)?	YES / NO
8. Do you use hormone replacement therapy?	YES / NO
9. Have you ever been told you that you might be osteoporotic ("weak bones")?	YES / NO
10. Are any of your family members osteoporotic ("weak bones")?	YES / NO
11. Have you or any family member sustained a fracture due to "weak bones'?	YES / NO
12. Are you fully ambulant?	YES / NO

Inform the researcher of the following if you:

- ✓ have had a barium examination or
- ✓ have been injected with contrast media for an x-ray examination or radio-isotope scan

IF YES - YOU MIGHT HAVE TO WAIT 10-14 DAYS BEFORE HAVING THIS TEST. THIS IS SO THAT THERE IS NO INTEREFERENCE WITH YOUR BMD SCAN.

APPENDIX H

DURBAN UNIVERSITY of TECHNOLOGY

DRS JACKPERSAD, ROOKNOODEEN & PARTNERS

CITY HOSPITAL
X-RAY DEPARTMENT

Incorrect race!!!

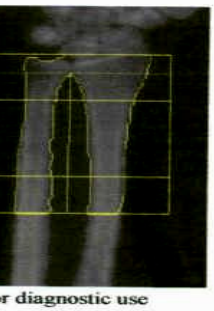
031/3652111 Fax: 031/3652198

[redacted]
eptember 1944

Sex: Female
Ethnicity: White
Menopause Age: 45

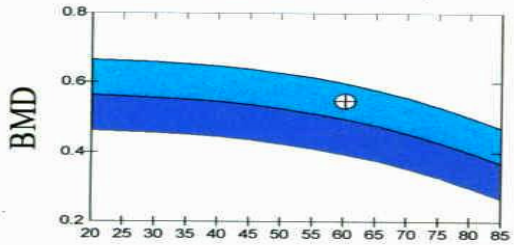
Height: 152.6 cm
Weight: 60.4 kg
Age: 60

hysician: Research



r diagnostic use

Total (Radius + Ulna)



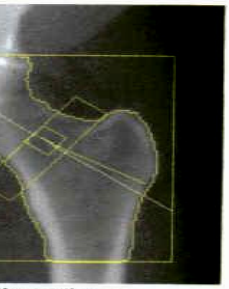
Reference curve and scores matched to White Female
Source: Hologic

Scan Date: 17 November 2004 - A11170409

DXA Results Summary:

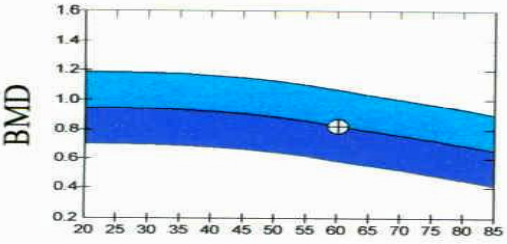
Radius + Ulna	BMD (g/cm²)	T - Score	Z - Score
Total	0.548	-0.3	1.0

Total BMD CV 1.0%
WHO Classification: Normal
Fracture Risk: Not Increased



iagnostic use

Total

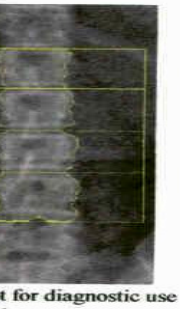


Reference curve and scores matched to White Female
Source: NHANES

Scan Date: 17 November 2004 - A11170408

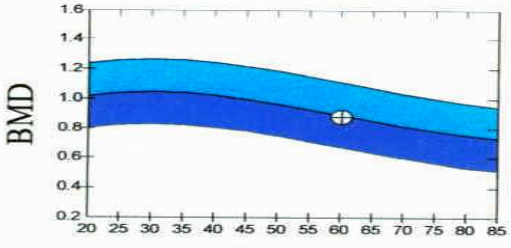
Region	BMD (g/cm²)	T - Score	Z - Score
Total	0.822	-1.0	-0.0

Total BMD CV 1.0%
WHO Classification: Osteopenia
Fracture Risk: Increased



t for diagnostic use
6

L1-L4



Reference curve and scores matched to White Female
Source: Hologic

Scan Date: 17 November 2004 - A11170407

Region	BMD (g/cm²)	T - Score	Z - Score
L1-L4	0.879	-1.5	-0.1

Total BMD CV 1.0%
WHO Classification: Osteopenia
Fracture Risk: Increased

HOLOGIC

APPENDIX I - Descriptive statistics for AGE

Age - 20 to 66 years (All participants)

Descriptives

			Statistic	Std. Error
Age	Mean		43.49	.833
	95% Confidence Interval for Mean	Lower Bound	41.85	
		Upper Bound	45.13	
	5% Trimmed Mean		43.57	
	Median		44.00	
	Variance		150.520	
	Std. Deviation		12.269	
	Minimum		20	
	Maximum		66	
	Range		46	
	Interquartile Range		20	
	Skewness		-.101	.165
	Kurtosis		-1.035	.329

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Age	.092	217	.000	.967	217	.000

a. Lilliefors Significance Correction

Age 20 to 48 years – young adult normal

Descriptives

			Statistic	Std. Error
Age	Mean		35.29	.691
	95% Confidence Interval for Mean	Lower Bound	33.92	
		Upper Bound	36.66	
	5% Trimmed Mean		35.46	
	Median		36.00	
	Variance		62.469	
	Std. Deviation		7.904	
	Minimum		20	
	Maximum		48	
	Range		28	
	Interquartile Range		13	
	Skewness		-.248	.212
	Kurtosis		-1.080	.420

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Age	.093	131	.007	.952	131	.000

a. Lilliefors Significance Correction

Age 20 to 29 years

Descriptives

			Statistic	Std. Error
Age	Mean		25.38	.499
	95% Confidence Interval for Mean	Lower Bound	24.37	
		Upper Bound	26.40	
	5% Trimmed Mean		25.48	
	Median		26.00	
	Variance		9.717	
	Std. Deviation		3.117	
	Minimum		20	
	Maximum		29	
	Range		9	
	Interquartile Range		5	
	Skewness		-.384	.378
	Kurtosis		-1.174	.741

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Age	.158	39	.015	.897	39	.002

a. Lilliefors Significance Correction

Age - 30 to 39 years

Descriptives

			Statistic	Std. Error
Age	Mean		35.09	.420
	95% Confidence Interval for Mean	Lower Bound	34.24	
		Upper Bound	35.94	
	5% Trimmed Mean		35.15	
	Median		36.00	
	Variance		7.946	
	Std. Deviation		2.819	
	Minimum		30	
	Maximum		39	
	Range		9	
	Interquartile Range		5	
	Skewness		-.439	.354
	Kurtosis		-1.008	.695

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Age	.160	45	.005	.917	45	.003

a. Lilliefors Significance Correction

Age - 40 to 49 years

Descriptives

			Statistic	Std. Error
Age	Mean		44.18	.357
	95% Confidence Interval for Mean	Lower Bound	43.47	
		Upper Bound	44.90	
	5% Trimmed Mean		44.15	
	Median		44.00	
	Variance		7.003	
	Std. Deviation		2.646	
	Minimum		40	
	Maximum		49	
	Range		9	
	Interquartile Range		4	
	Skewness		.101	.322
	Kurtosis		-1.035	.634

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Age	.118	55	.056	.946	55	.016

a. Lilliefors Significance Correction

Age - 50 to 59 years

Descriptives

			Statistic	Std. Error
Age	Mean		54.75	.362
	95% Confidence Interval for Mean	Lower Bound	54.02	
		Upper Bound	55.48	
	5% Trimmed Mean		54.74	
	Median		54.00	
	Variance		7.355	
	Std. Deviation		2.712	
	Minimum		50	
	Maximum		59	
	Range		9	
	Interquartile Range		5	
	Skewness		.218	.319
	Kurtosis		-1.261	.628

Tests of Normality

	Kolmogorov-Smirnov [a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Age	.169	56	.000	.920	56	.001

a. Lilliefors Significance Correction

Age - 60 to 69 years

Descriptives

			Statistic	Std. Error
Age	Mean		62.36	.434
	95% Confidence Interval for Mean	Lower Bound	61.46	
		Upper Bound	63.27	
	5% Trimmed Mean		62.30	
	Median		62.50	
	Variance		4.147	
	Std. Deviation		2.036	
	Minimum		60	
	Maximum		66	
	Range		6	
	Interquartile Range		4	
	Skewness		.086	.491
	Kurtosis		-1.490	.953

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Age	.198	22	.024	.870	22	.008

a. Lilliefors Significance Correction

APPENDIX J – Descriptive statistics for BMD of the Lumbar Spine

BMD of the Lumbar Spine - 20 to 48 years (young adult normal age band)

Descriptives

			Statistic	Std. Error
Lspine BMD in g/cms2	Mean		.97188	.007244
	95% Confidence Interval for Mean	Lower Bound	.95755	
		Upper Bound	.98621	
	5% Trimmed Mean		.97375	
	Median		.97600	
	Variance		.007	
	Std. Deviation		.082916	
	Minimum		.739	
	Maximum		1.164	
	Range		.425	
	Interquartile Range		.106	
	Skewness		-.345	.212
	Kurtosis		.027	.420

Tests of Normality

BMD in g/cm^2	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Lumbar Spine	.069	131	.200 *	.988	131	.289
Total Hip	.050	131	.200 *	.988	131	.340
Distal Forearm	.050	131	.200 *	.992	131	.673

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

BMD of the Lumbar Spine - 20 to 29 years

Descriptives

			Statistic	Std. Error
Lspine BMD in g/cms	Mean		.96395	.013284
	95% Confidence Interval for Mean	Lower Bound	.93706	
		Upper Bound	.99084	
	5% Trimmed Mean		.96593	
	Median		.97000	
	Variance		.007	
	Std. Deviation		.082959	
	Minimum		.739	
	Maximum		1.164	
	Range		.425	
	Interquartile Range		.105	
	Skewness		-.370	.378
	Kurtosis		.790	.741

Tests of Normality

BMD in g/cm^2	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Lumbar Spine	.084	39	.200*	.983	39	.817
Total Hip	.098	39	.200*	.974	39	.507
Distal Forearm	.084	39	.200*	.975	39	.535

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

BMD of the Lumbar Spine - 30 to 39 years

Descriptives

			Statistic	Std. Error
Lspine BMD in g/cms2	Mean		.95884	.012415
	95% Confidence Interval for Mean	Lower Bound	.93382	
		Upper Bound	.98386	
	5% Trimmed Mean		.96002	
	Median		.96900	
	Variance		.007	
	Std. Deviation		.083281	
	Minimum		.787	
	Maximum		1.120	
	Range		.333	
	Interquartile Range		.099	
	Skewness		-.382	.354
	Kurtosis		-.332	.695

Tests of Normality

BMD in g/cm^2	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Lumbar Spine	.099	45	.200 *	.969	45	.277
Total Hip	.103	45	.200 *	.964	45	.166
Distal Forearm	.074	45	.200 *	.987	45	.900

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

BMD of the Lumbar Spine - 40 to 49 years

Descriptives

			Statistic	Std. Error
Lspine BMD in g/cms2	Mean		.98929	.011557
	95% Confidence Interval for Mean	Lower Bound	.96612	
		Upper Bound	1.01246	
	5% Trimmed Mean		.99121	
	Median		.98800	
	Variance		.007	
	Std. Deviation		.085707	
	Minimum		.779	
	Maximum		1.148	
	Range		.369	
	Interquartile Range		.145	
	Skewness		-.300	.322
	Kurtosis		-.527	.634

Tests of Normality

BMD in g/cm^2	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Lumbar Spine	.066	55	.200 *	.980	55	.472
Total Hip	.049	55	.200 *	.990	55	.927
Distal Forearm	.099	55	.200 *	.978	55	.425

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

BMD of the Lumbar Spine - 50 to 59 years

Descriptives

			Statistic	Std. Error
Lspine BMD in g/cms2	Mean		.88923	.016488
	95% Confidence Interval for Mean	Lower Bound	.85619	
		Upper Bound	.92227	
	5% Trimmed Mean		.89227	
	Median		.88600	
	Variance		.015	
	Std. Deviation		.123382	
	Minimum		.536	
	Maximum		1.133	
	Range		.597	
	Interquartile Range		.152	
	Skewness		-.259	.319
	Kurtosis		.273	.628

Tests of Normality

BMD in g/cm^2	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Lumbar Spine	.061	56	.200 *	.985	56	.698
Total Hip	.094	56	.200 *	.980	56	.473
Distal Forearm	.074	56	.200 *	.984	56	.653

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

BMD of the Lumbar Spine - 60 to 69 years

Descriptives

			Statistic	Std. Error
Lspine BMD in g/cms2	Mean		.81827	.027652
	95% Confidence Interval for Mean	Lower Bound	.76077	
		Upper Bound	.87578	
	5% Trimmed Mean		.80976	
	Median		.79650	
	Variance		.017	
	Std. Deviation		.129700	
	Minimum		.644	
	Maximum		1.147	
	Range		.503	
	Interquartile Range		.141	
	Skewness		1.197	.491
	Kurtosis		1.582	.953

Tests of Normality

BMD in g/cm^2	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Lumbar Spine	.144	22	.200 *	.900	22	.030
Total Hip	.197	22	.027	.865	22	.006
Distal Forearm	.123	22	.200 *	.958	22	.458

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

APPENDIX K – Descriptive statistics for BMD of the Total Hip

BMD of the Total Hip - 20 to 48 years (young adult normal age band)

Descriptives

Hip bmd in g/cms2	Mean		.86292	.008970
	95% Confidence Interval for Mean	Lower Bound	.84517	
		Upper Bound	.88066	
	5% Trimmed Mean		.86470	
	Median		.86400	
	Variance		.011	
	Std. Deviation		.102669	
	Minimum		.551	
	Maximum		1.069	
	Range		.518	
	Interquartile Range		.135	
	Skewness		-.234	.212
	Kurtosis		-.061	.420

Tests of Normality

BMD in g/cm^2	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Lumbar Spine	.069	131	.200 *	.988	131	.289
Total Hip	.050	131	.200 *	.988	131	.340
Distal Forearm	.050	131	.200 *	.992	131	.673

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

BMD of the Total Hip - 20 to 29 years

Descriptives

Hip bmd in g/cms2	Mean	.84618	.016111
	95% Confidence Interval for Mean	Lower Bound .81356	
		Upper Bound .87879	
	5% Trimmed Mean	.84814	
	Median	.83800	
	Variance	.010	
	Std. Deviation	.100612	
	Minimum	.551	
	Maximum	1.069	
	Range	.518	
	Interquartile Range	.117	
	Skewness	-.385	.378
	Kurtosis	1.298	.741

Tests of Normality

BMD in g/cm^2	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Lumbar Spine	.084	39	.200 *	.983	39	.817
Total Hip	.098	39	.200 *	.974	39	.507
Distal Forearm	.084	39	.200 *	.975	39	.535

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

BMD of the Total Hip - 30 to 39 years

Descriptives

Hip bmd in g/cms2	Mean		.86702	.017387
	95% Confidence Interval for Mean	Lower Bound	.83198	
		Upper Bound	.90206	
	5% Trimmed Mean		.86802	
	Median		.86400	
	Variance		.014	
	Std. Deviation		.116633	
	Minimum		.590	
	Maximum		1.069	
	Range		.479	
	Interquartile Range		.211	
	Skewness		-.129	.354
	Kurtosis		-.848	.695

Tests of Normality

BMD in g/cm^2	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Lumbar Spine	.099	45	.200 *	.969	45	.277
Total Hip	.103	45	.200 *	.964	45	.166
Distal Forearm	.074	45	.200 *	.987	45	.900

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

BMD of the Total Hip - 40 to 49 years

Descriptives

Hip bmd in g/cms2	Mean		.87764	.012047
	95% Confidence Interval for Mean	Lower Bound	.85348	
		Upper Bound	.90179	
	5% Trimmed Mean		.87871	
	Median		.87900	
	Variance		.008	
	Std. Deviation		.089339	
	Minimum		.643	
	Maximum		1.060	
	Range		.417	
	Interquartile Range		.123	
	Skewness		-.201	.322
	Kurtosis		-.050	.634

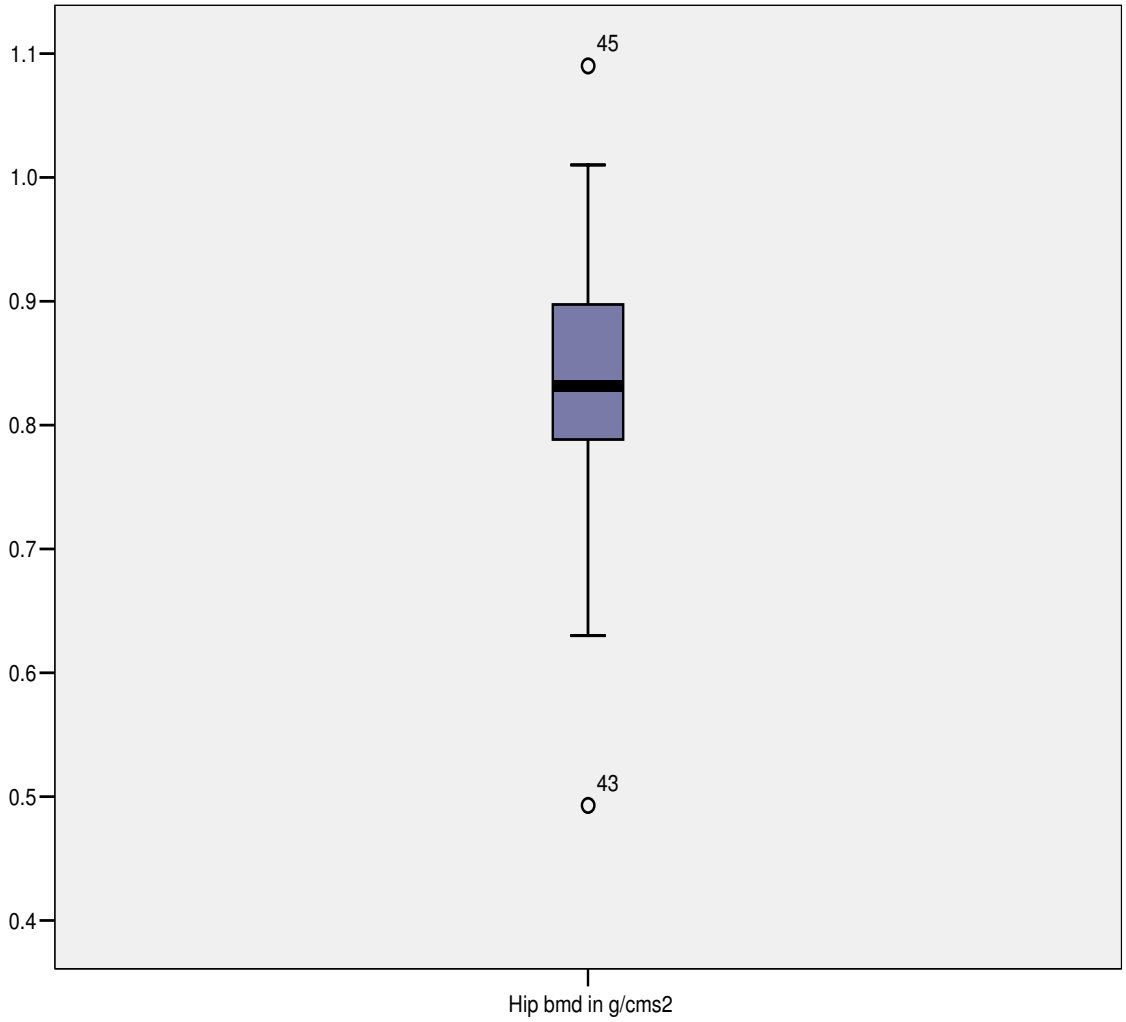
Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Lspine BMD in g/cms	.066	55	.200*	.980	55	.472
Hip bmd in g/cms2	.049	55	.200*	.990	55	.927
Forearm BMD in g/cr	.099	55	.200*	.978	55	.425

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

BMD of the Total Hip - 50 to 59 years



BMD of the Total Hip - 50 to 59 years

Descriptives

Hip bmd in g/cms2	Mean		.83646	.014457
	95% Confidence Interval for Mean	Lower Bound	.80749	
		Upper Bound	.86544	
	5% Trimmed Mean		.83868	
	Median		.83150	
	Variance		.012	
	Std. Deviation		.108190	
	Minimum		.493	
	Maximum		1.090	
	Range		.597	
	Interquartile Range		.114	
	Skewness		-.378	.319
	Kurtosis		.906	.628

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Lspine BMD in g/cms2	.061	56	.200*	.985	56	.698
Hip bmd in g/cms2	.094	56	.200*	.980	56	.473
Forearm BMD in g/cm	.074	56	.200*	.984	56	.653

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

BMD of the Total Hip - 60 to 69 years

Descriptives

Hip bmd in g/cms2	Mean	.80077	.025257
	95% Confidenc Lower Bound	.74825	
	Interval for Mea Upper Bound	.85330	
	5% Trimmed Mean	.79019	
	Median	.75950	
	Variance	.014	
	Std. Deviation	.118465	
	Minimum	.656	
	Maximum	1.150	
	Range	.494	
	Interquartile Range	.140	
	Skewness	1.441	.491
	Kurtosis	2.239	.953

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Lspine BMD in g/cms2	.144	22	.200*	.900	22	.030
Hip bmd in g/cms2	.197	22	.027	.865	22	.006
Forearm BMD in g/cm	.123	22	.200*	.958	22	.458

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

APPENDIX L – Descriptive statistics for BMD of the Distal Forearm

BMD of the Distal Forearm - 20 to 48 years (young adult normal age band)

Descriptives

	Kurtosis		[illegible]	[illegible]
Forearm BMD in g/cms2	Mean		.54223	.003557
	95% Confidence Interval for Mean	Lower Bound	.53519	
		Upper Bound	.54927	
	5% Trimmed Mean		.54200	
	Median		.54400	
	Variance		.002	
	Std. Deviation		.040713	
	Minimum		.427	
	Maximum		.639	
	Range		.212	
	Interquartile Range		.049	
	Skewness		.031	.212
	Kurtosis		.130	.420

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Lspine BMD in g/cms2	.069	131	.200*	.988	131	.289
Hip bmd in g/cms2	.050	131	.200*	.988	131	.340
Forearm BMD in g/cm	.050	131	.200*	.992	131	.673

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

BMD of the Distal Forearm - 20 to 29 years

Descriptives

Forearm BMD in g/cms	Mean		.52941	.004944
	95% Confidence Interval for Mean	Lower Bound	.51940	
		Upper Bound	.53942	
	5% Trimmed Mean		.53059	
	Median		.53000	
	Variance		.001	
	Std. Deviation		.030874	
	Minimum		.453	
	Maximum		.589	
	Range		.136	
	Interquartile Range		.041	
	Skewness		-.455	.378
	Kurtosis		.005	.741

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Lspine BMD in g/cms2	.084	39	.200*	.983	39	.817
Hip bmd in g/cms2	.098	39	.200*	.974	39	.507
Forearm BMD in g/cms2	.084	39	.200*	.975	39	.535

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

BMD of the Distal Forearm - 30 to 39 years

Descriptives

Forearm BMD in g/cms	Mean		.53609	.005743
	95% Confidence Interval for Mean	Lower Bound	.52451	
		Upper Bound	.54766	
	5% Trimmed Mean		.53635	
	Median		.53600	
	Variance		.001	
	Std. Deviation		.038528	
	Minimum		.427	
	Maximum		.626	
	Range		.199	
	Interquartile Range		.051	
	Skewness		-.194	.354
	Kurtosis		.445	.695

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Lspine BMD in g/cms2	.099	45	.200*	.969	45	.277
Hip bmd in g/cms2	.103	45	.200*	.964	45	.166
Forearm BMD in g/cm	.074	45	.200*	.987	45	.900

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

BMD of the Distal Forearm - 40 to 49 years

Descriptives

Forearm BMD in g/cms	Mean		.55798	.005864
	95% Confidence Interval for Mean	Lower Bound	.54622	
		Upper Bound	.56974	
	5% Trimmed Mean		.55867	
	Median		.55800	
	Variance		.002	
	Std. Deviation		.043490	
	Minimum		.452	
	Maximum		.639	
	Range		.187	
	Interquartile Range		.051	
	Skewness		-.208	.322
	Kurtosis		-.150	.634

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Lspine BMD in g/cms	.066	55	.200*	.980	55	.472
Hip bmd in g/cms2	.049	55	.200*	.990	55	.927
Forearm BMD in g/cm	.099	55	.200*	.978	55	.425

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

BMD of the Distal Forearm - 50 to 59 years

Descriptives

Forearm BMD in g/cms	Mean		.52254	.006417
	95% Confidence Interval for Mean	Lower Bound	.50968	
		Upper Bound	.53540	
	5% Trimmed Mean		.52373	
	Median		.52150	
	Variance		.002	
	Std. Deviation		.048023	
	Minimum		.391	
	Maximum		.620	
	Range		.229	
	Interquartile Range		.059	
	Skewness		-.267	.319
	Kurtosis		.330	.628

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Lspine BMD in g/cms2	.061	56	.200*	.985	56	.698
Hip bmd in g/cms2	.094	56	.200*	.980	56	.473
Forearm BMD in g/cms2	.074	56	.200*	.984	56	.653

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

BMD of the Distal Forearm - 60 to 69 years

Descriptives

Forearm BMD in g/cms	Mean		.49700	.010714
	95% Confidence Interval for Mean	Lower Bound	.47472	
		Upper Bound	.51928	
	5% Trimmed Mean		.49668	
	Median		.49300	
	Variance		.003	
	Std. Deviation		.050253	
	Minimum		.415	
	Maximum		.584	
	Range		.169	
	Interquartile Range		.076	
	Skewness		.061	.491
	Kurtosis		-.974	.953

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Lspine BMD in g/cms2	.144	22	.200*	.900	22	.030
Hip bmd in g/cms2	.197	22	.027	.865	22	.006
Forearm BMD in g/cms2	.123	22	.200*	.958	22	.458

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

QDR® 4500 *Elite*

When Performance Counts

HOLOGIC®

QDR® 4500 Elite

The standard of value and efficiency for the private practitioner

The QDR 4500 Elite combines the superiority of fan-beam technology with a unique, value-added package of clinical, patient reporting, and support software. It delivers high-performance imaging and bone density measurement with unsurpassed precision and low patient dose. The Elite protects your investment from obsolescence with a modular design that easily accommodates upgrades and enhancements as the technology advances and your practice grows.

The intuitive, user-friendly *QDR for Windows* operating system guides operators step-by-step through the patient examination process. With just a single click, operators can access quality control, patient data entry, scan acquisition and analysis, report generation, and archiving functions. Subsequent screens provide an automatic, guided flow through each process, enhancing patient throughput under real clinical conditions.

In just 30 seconds or less, Elite's fan-beam x-ray completes hip, AP spine and forearm scans with uncompromised precision and image quality and low patient dose. That's nearly *five times faster* than the fastest pencil-beam system takes to produce similar, clinically-meaningful scans. Faster scanning lets you accommodate more patients in your busy schedule and contributes to your potential for practice growth.

in clinical bone densitometry

QDR 4500 Elite features . . .

- **Modular, fan-beam DXA technology** scans spine, hip and forearm
- Advanced computer system and printer, **modem, SuperDisk drive** and **CD ROM**
- *QDR for Windows* operating system with flexible navigation and multiple reporting options
- **Dual-Hip™ Analysis** automatically moves table and C-arm into position for measurement of opposite hip to help identify lowest BMD site
- **NHANES Reference Database** complies with standardization guidelines
- **One Time™ Auto Analysis** automatically and reliably identifies region of interest and delivers expertly analyzed hip and AP spine scans in less than five seconds
- **Internet** access-ready
- **Fracture Risk Indication** with World Health Organization criteria
- **Context Sensitive Help** provides an overview and virtual "walk through" of the QDR 4500 Elite's operation and capabilities
- **Practice Development Guide** helps you promote your bone densitometry services to patients and referring clinicians

QDR® 4500 *Elite*

QDR® for Windows®

QDR for Windows enhances performance by putting the power and ease of a Windows-based operating system at your fingertips. Distinct icons and logical screen design makes navigating the system interface and workflow highly intuitive and user-friendly.

Access all QDR quality control, scanning, analysis, reporting and archiving functions by just clicking the appropriate on-screen button. Subsequent screens and help menus walk you through each process. *QDR for Windows* reduces the operator learning curve and makes it easy to train new operators on the job.

QDR for Windows features . . .

- Flexible navigation to accommodate diverse workflow
- Complete data compatibility with DOS-based QDR systems
- Multiple reporting options that can be configured to your specific needs
- Enhancements to simplify connection with and integration of other information systems

Windows is a registered trademark of Microsoft Corp.

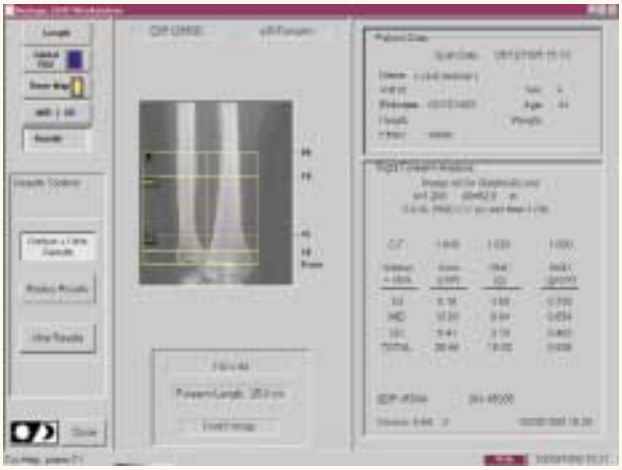
Clinical Applications

Proximal Femur

The Elite performs hip BMD evaluations in as little as 10 seconds. It can measure five separate regions of interest, including a Ward's triangle (lowest density)—determined by an automatic search along the entire femoral neck. Typical hip precision=1.0% (total hip). Displays a higher resolution single-energy image with one key stroke—a feature possible with fan-beam technology.

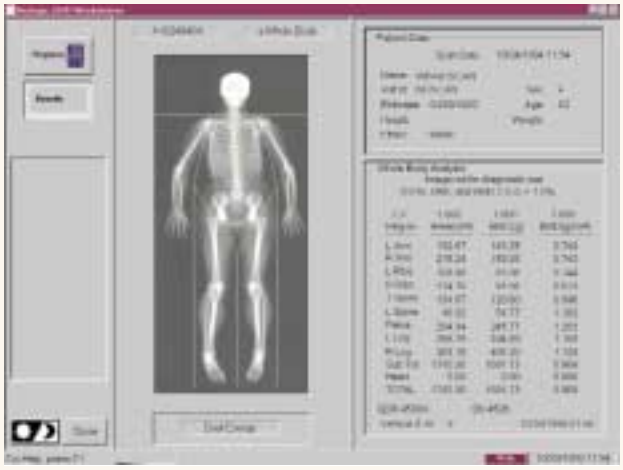
Lumbar Spine

Lumbar vertebrae represent one of the most important sites of interest for bone mineral assessment due to the presence of high-turnover trabecular bone. The Elite provides unmatched precision for lumbar spine studies with scanning times as rapid as 10 seconds. Spine precision is better than 1.0% (C.V. at BMD=1.0g/cm^2). Displays a higher resolution single-energy image with one key stroke—a feature possible with fan-beam technology.



Forearm

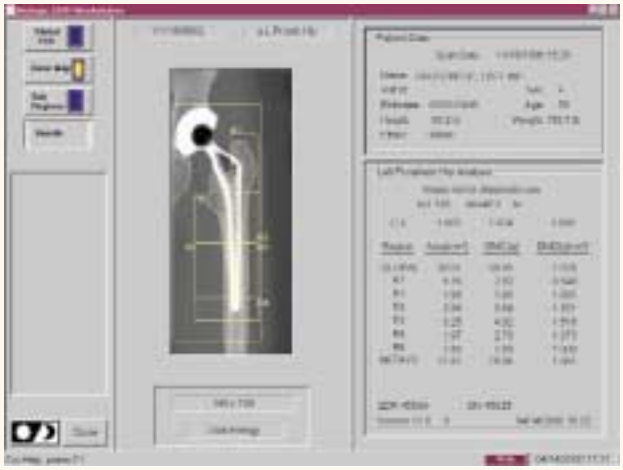
A 30-second forearm scan performed on the Elite produces simultaneous assessments of 1/3, mid- and ultra-distal regions. Elite can scan and analyze the radius and ulna, either separately or combined.



Whole Body/BMD Analysis

The QDR 4500W and 4500A models can evaluate BMD of the entire skeleton and report on up to 10 continuously adjustable regions of interest. Region markers can be angulated for correct anatomical placement. Typical precision for whole body scans is 0.75% (total region CV at BMD = 1.0 g/cm^2).

Optional body composition analysis software enables evaluation of fat mass, lean mass and total mass for the entire skeleton and for individual sub-regions. Both BMD and body composition can be derived from a single whole body scan.



Prosthetic Hip

Bone resorption around a hip prosthesis can eventually contribute to loosening of the implant device. Monitoring changes in the bone surrounding the prosthesis provides clinicians with pertinent information regarding bone status and the viability of the implant.

The QDR Prosthetic Hip software option employs a special algorithm that automatically identifies and removes the influence of a metal prosthesis to produce precise BMD measurements. The display can be switched from a dual- to single-energy image for viewing the implant without rescanning.

Optional

Scan Comparison

This feature can be used in all QDR scan modes. The above example shows a current hip exam displayed and compared simultaneously with a previous baseline study. Scan comparison automatically replicates regions of analysis, minimizing operator involvement and performance time.

QDR® 4500 Elite

Value-Added Features

QDR OnePage Report

Combine image, scan, analysis, and reference curves in a concise, easy-to-read, visually impressive, single-page report. Choose from several preformatted templates and customize your choice with your clinic's name, address, and phone number to save time and materials.

Standard Patient Report with Reference Values

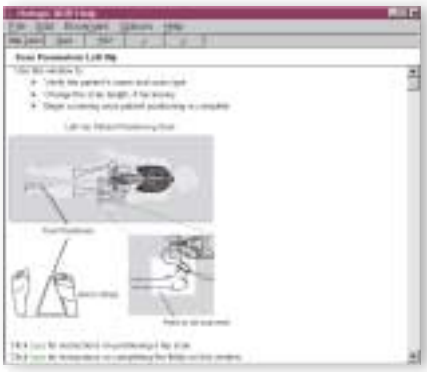
Rate of Change Report

Reference Values
The extensive online database of reference values included with *QDR for Windows* simplifies interpretation of studies. Hip reference data are based on NHANES in compliance with standardization criteria.

Rate of Change
Trend Reports provide an easy method to compare annualized rates of change. Significant changes in bone mineral status are automatically and clearly noted on the report.

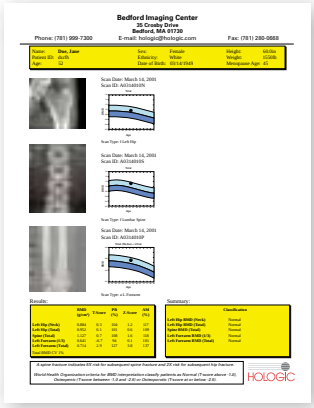
Context Sensitive Help

The text and graphics in *QDR for Windows* Help Menu provide an overview and virtual "walk through" of Elite's operation and capabilities. A single click on a topic button produces instructions on scanning, analysis, and data management.

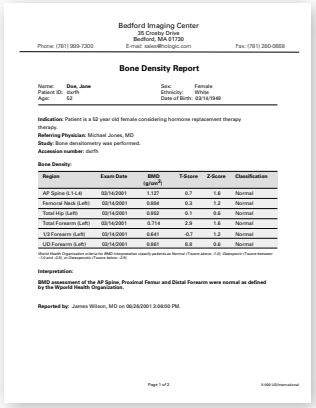


Physician's Report Writer (Optional)

The most advanced interpretation and e-reporting solution for DXA. With the click of a button, produce a comprehensive electronic report. Includes BMD results, plus physician's interpretation in a customizable, Microsoft Word® format for electronic distribution and printing.



OnePage Dx Report



Interpreting Report

Practice Development Guide

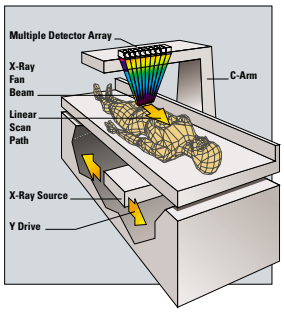
The Practice Development Guide helps you raise public awareness and take full advantage of Elite's practice-building potential. Two CDs include ready-to-print marketing and patient education materials and tips on how to use the available array of marketing and media options to maximize the return on your investment of time, resources, and capital.

The QDR 4500 Advantage

Technological Leadership

Hologic pioneered DXA technology with the introduction of the first DXA system in 1987. Since then, Hologic has developed four generations of bone densitometers— including the first fan-beam system—all of which are completely data compatible to protect your investment and make upgrades easy.

Fan-Beam Technology



Hologic's fan-beam bone densitometers image across the entire width of a region of interest, eliminating the need for scanning in the slower, rectilinear pattern required by pencil-beam systems. Fan-beam scans faster without compromising precision or safety. The QDR 4500's optimal x-ray energies (100/140 kVp) penetrate a wider range of patients to produce better quality images. Also, fan-beam technology supports high-resolution, single-energy image display for optimal visualization of demineralized bone without additional patient scanning.

Convenience and Reliability

Each QDR unit comes with an anthropomorphic spine phantom, used for quality control. This assures consistently accurate measurements without the need for waterbaths to perform calibration procedures.

The QDR 4500's patented Automatic Internal Reference System— comprised of a rotating calibration drum— automatically maintains pixel-by-pixel calibration without operator involvement and assures long-term precision and compatibility between all QDR systems.

Unsurpassed Precision

Hologic QDR systems surpass the precision of competitive systems where it really counts—on real patients, especially those with low bone density. The chart below compares hip and spine precision values of pre- and post-menopausal women scanned on a QDR fan-beam system and our competitor's fan-beam and pencil-beam systems.

Comparison of Precision (C.V.) Between HOLOGIC QDR and Competitive Systems

	Region of Interest/ Pre-/Post-Menopausal	HOLOGIC Fan-Beam System[1]	Competitive Fan-Beam System[2]	Competitive Pencil-Beam System[2]
SPINE	Pre-Menopause	0.7%	1.9%	0.8%
	Post-Menopause	1.2%	1.8%	2.1%
FEMUR (Neck)	Pre-Menopause	2.0%	2.1%	2.2%
	Post-Menopause	1.9%	2.9%	2.4%

1Fuerst T, Osteo. Int. Vol 6 (S1), page S370, 1995.
2Lang T. Presented at 11th International Bone Densitometry Workshop (Gleneden Beach, OR, Sept. 1995).

Other Exclusive HOLOGIC Features

- **Patient Rescan** makes obtaining the perfect scan easy. With the push of a button, operators can interrupt scanning to adjust the image on screen, eliminating the need to reposition patient on table. This exclusive feature saves time and assures patient comfort.
- **Reanalysis**—QDR systems store scan information as raw data that can be repeatedly reanalyzed—even a year or more later—without rescanning.
- **Scoliotic Spine Analysis** tailors vertebral BMD assessment to the unique curvature of patients with scoliosis.
- **Automatic Bone Mapping** calculates the soft tissue and bone map of any scan without operator involvement.
- **Automatic Locate** feature internally records and monitors the location of patient data saved to a storage media, eliminating the need to log patient data. This program displays the disk and location where data were archived.

HOLOGIC®

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