The cardio-metabolic profile and bone mineral density in African and Indian postmenopausal women

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I, Dr Jayeshnee Moodley, hereby submit my dissertation in partial fulfilment of the requirements for the degree of Masters in Medicine in the Department of Obstetrics and Gynaecology
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I declare that the work on which this dissertation is based is original and is my own unaided work carried out by me, under the supervision of Professor J.S Bagratee.

Neither the whole work, or any part of it, has been submitted to any other university or Examination Body.

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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH</td>
<td>Follicle stimulating hormone</td>
</tr>
<tr>
<td>LH</td>
<td>Lutenising hormone</td>
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<tr>
<td>AMH</td>
<td>Antimullerian hormone</td>
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<td>E2</td>
<td>Oestradiol</td>
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<td>TSH</td>
<td>Thyroid stimulating hormone</td>
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<td>InhB</td>
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<td>HDL</td>
<td>High density lipo-protein</td>
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<td>LDL</td>
<td>Low density lipo-protein</td>
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<tr>
<td>TG</td>
<td>Triglyceride</td>
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<tr>
<td>LOOP</td>
<td>Luteal-out-of-phase</td>
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<tr>
<td>FMP</td>
<td>Final menstrual period</td>
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<tr>
<td>BMD</td>
<td>Bone mineral density</td>
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<td>WHR</td>
<td>Waist Hip Ratio</td>
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<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>DEXA</td>
<td>Dual energy X-ray absorptiometry</td>
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<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
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<tr>
<td>CAD</td>
<td>Coronary artery disease</td>
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<tr>
<td>IALCH</td>
<td>Inkosi Albert Luthuli Central Hospital</td>
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<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
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<tr>
<td>DBP</td>
<td>Diastolic blood pressure</td>
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<td>PCOS</td>
<td>Polycystic ovarian syndrome</td>
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<tr>
<td>NOF</td>
<td>Neck of femur</td>
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<td>HRT</td>
<td>Hormone replacement therapy</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
</tbody>
</table>
## TABLE OF CONTENTS

Declaration i
Acknowledgements iii
Glossary iv
Figures and tables vii

Abstract 1

Chapter 1: Introduction and Literature review

1.1 Introduction 4
1.2 Cardio-metabolic profile of menopause 11
1.3 Bone health in the menopause 17
1.4 The relationship between cardio-metabolic profile and bone mineral density in the menopause 24
1.5 Management of the menopause
   1.5.1 Cardio-metabolic risk 33
   1.5.2 Bone mineral density 38

Chapter 2: The Study: Aims, Methods and Statistical analysis 46

Chapter 3: Results 51

Chapter 4: Discussion 71

Chapter 5: Conclusion and Recommendations 82
References

Appendices:  

<table>
<thead>
<tr>
<th>Appendix</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Appendix A: Tables and Figures</td>
<td>103</td>
</tr>
<tr>
<td></td>
<td>Appendix B: Questionnaire</td>
<td>117</td>
</tr>
<tr>
<td></td>
<td>Appendix C: Normal values</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td>Appendix D: SCORE chart</td>
<td>122</td>
</tr>
<tr>
<td></td>
<td>Appendix E: Hospital approval</td>
<td>123</td>
</tr>
<tr>
<td></td>
<td>Appendix F: Postgraduate approval</td>
<td>124</td>
</tr>
<tr>
<td></td>
<td>Appendix G: Ethical approval</td>
<td>125</td>
</tr>
</tbody>
</table>
LIST OF TABLES AND FIGURES

Table 1: Diagnosis of metabolic syndrome 14

Table 2: Fall prevention strategies 41

Table 3: Demographic profile (Mean and SD*) of African and Indian postmenopausal women 52

Table 4: Demographic profile (n and %) of African and Indian postmenopausal women 53

Table 5: Clinical profile (Mean and SD) of African and Indian postmenopausal women 54

Table 6: Clinical profile (n and %) of African and Indian postmenopausal women 55

Table 7: BMI of African and Indian postmenopausal women 55

Table 8: Biochemical profile (Mean and SD*) of African and Indian postmenopausal women 56

Table 9: Lipid profile of African and Indian postmenopausal women 57

Table 10: Bone mineral density profile of African and Indian postmenopausal women 58
Table 11: Bone mineral density profile of African and Indian postmenopausal women

Figure 1: Correlation between BMI and Total hip BMD in African and Indian postmenopausal women

Figure 2: Correlation between BMI and total hip BMD in African women

Figure 3: Correlation between BMI and total hip BMD in Indian women

Figure 4: Correlation between BMI and lumbar spine BMD in African and Indian postmenopausal women

Figure 5: Correlation between BMI and lumbar spine BMD in Indian women

Figure 6: Correlation between BMI and lumbar spine BMD in African women

Figure 7: Correlation between weight and total hip BMD in African and Indian postmenopausal women

Figure 8: Correlation between weight and total hip BMD in African women
Figure 9: Correlation between weight total hip BMD in Indian women 65

Figure 10: Correlation between weight and lumbar spine BMD in African and Indian postmenopausal women 66

Figure 11: Correlation between weight and lumbar spine BMD in African women 66

Figure 12: Correlation between weight and lumbar spine BMD in Indian women 67

Figure 13: Correlation between LDL cholesterol and lumbar spine BMD in African and Indian postmenopausal women 68

Figure 14: Correlation between LDL and lumbar spine BMD in Indian women 69

Figure 15: Correlation between LDL and lumbar spine BMD in African women 69
ABSTRACT

AIMS

To determine the cardio-metabolic risk profile and incidence of low bone mineral density in African and Indian postmenopausal women attending the IALCH menopause clinic and to determine whether there is a correlation between cardio-metabolic parameters and low bone mineral density.

METHODS

A retrospective, descriptive study involving all Indian and African postmenopausal women, above the age of 40, referred to the menopause outpatient clinic at IALCH from 01 July 2009 to 31 December 2010 was conducted.

Data was collected from the medi-com database using a structured questionnaire. Cardio-metabolic data was analysed as continuous variables and summarized using means and standard deviations. Bone mineral density was treated as a quantitative variable and correlation analysis was used to assess relationships between the variables. This was done for each race group separately. The Students T-test was used to compare cardio-metabolic variables between the two ethnic groups. SPSS version 18.0 was used to analyse data.

RESULTS

The records of 106 women were analysed (51 African and 55 Indian). In African and Indian women, the prevalence of hypertension was 54.9% vs 65.5%, the prevalence of diabetes was 31.4% vs 56.4%, the prevalence of dyslipidaemia was 17.6% vs 32.7% and the prevalence of
ischaemic heart disease was 5.9% vs 14.9% respectively. The prevalence of low bone mineral density was higher in Indian women (40%) compared to African women (23.5%). The mean body mass index (BMI) of African women was significantly higher than Indian women, (33 vs 29). There were no significant differences between African and Indian postmenopausal women regarding their lipid profile, fasting glucose, fasting insulin and thyroid profile.

The mean bone mineral density (BMD) in the hip and spine was lower in Indian women compared to African women, however the prevalence of osteopaenia and osteoporosis, as defined by T-scores, was not statistically significant.

Statistically significant positive correlations were observed between an increasing BMI and BMD (p<0.001) and increases in weight and BMD (p<0.001). A statistically significant correlation were observed between serum LDL-cholesterol values and BMD (p=0.03), where serum LDL-cholesterol values were inversely proportional to BMD. There were no significant correlations between BMD and the remaining cardio-metabolic variables (ie blood pressure; waist-hip ratio; clinical stigma of dyslipidaemia; clinical stigma of insulin resistance; cholesterol; HDL; triglycerides; fasting glucose; fasting insulin and thyroid function).

**CONCLUSIONS**

There is a high prevalence of cardiovascular risks and low BMD amongst the local menopausal population, irrespective of ethnicity. African and Indian postmenopausal women had a high prevalence of hypertension (60%), diabetes (44%), dyslipidaemia (25%) and
obesity (54%). In African women, the incidence of low BMD was 35% in the hip, 53% in the neck of femur and 55% in the lumbar spine. In Indian women, the incidence of low BMD was 55% in the hip, 67% in the neck of femur and 69% in the lumbar spine. BMI and weight showed a positive correlation with bone mineral density. Regarding the cardio-metabolic variables, an increasing LDL value was negatively correlated with bone mineral density. It thus is apparent that a screening lipid profile during the peri-menopausal years, coupled with early and appropriate lifestyle management regarding body mass index/ weight may limit the burden of morbidity in later life.
CHAPTER 1

1.1. INTRODUCTION

The term *menopause* is derived from the Greek words ‘*men*’ (month) and ‘*pausis*’ (cessation) and is defined by the World Health Organisation (1998) as “A permanent cessation of menstruation resulting from the loss of ovarian follicular activity marking the end of a women’s reproductive capacity”. The diagnosis of this hypo-oestrogenic state is made after 12 months of amenorrhea.

The mean age of menopause is approximately 50 years and 9 months (Rymer et al., 2000), with many women living longer than previously recorded.

In 2007, North American hospital statistics revealed that cardiovascular disease was the leading cause of death in postmenopausal women. (American Heart Association, Women and cardiovascular disease facts, American Heart Association, 2007). Cardiovascular risk increases in the menopause, regardless of the age of onset of menopause, and is the leading cause of mortality amongst these women (Sturdee et al., 2009).

The increased cardiovascular morbidity and mortality during the menopause may be attributed to the changing hormonal status of the menopause which renders women prone to the metabolic syndrome. In addition, women are unique as they are not only susceptible to the usual risk factors for CVD, but specific risk factors, like a history of polycystic ovarian syndrome and pre-eclampsia which, when present, doubles the background risk of a cardiac
event (Sturdee et al., 2009). Furthermore, common conditions amongst menopausal women such as hypertension, dyslipidaemia, diabetes mellitus, obesity and smoking are powerful indicators of cardiovascular events.

Osteoporosis is one of the most detrimental conditions in the elderly, affecting one third of postmenopausal women (De Villiers., 2009). Oestrogen deficiency is associated with bone loss in postmenopausal women (Bansal and McGregor., 1992), a view reinforced in earlier studies by Ohta et al (1992) which demonstrated bone loss after oophorectomy and Ahlborg et al (2001) which showed a decrease in the rate of bone loss after oestrogen replacement.

Studies by Finkelstein et al. (2008), Zhao et al. (2007) and Kadam et al. (2010) seem to favour the assumption that ethnicity and body weight determine baseline bone density and affects the rate of bone mineral loss and fracture. These disparities may be reflected by a difference in the rate of bone loss, a difference in the peak bone mass or both.

Finkelstein et al (2008) performed a longitudinal cohort study of African-American, Caucasian and Asian women participating in The Study of Women’s Health Across the Nation. This study was performed in seven sites across North America. The study reported that the average African female was found to weigh 9kg more than the average Caucasian, and up to 25-27kg more than the average Asian. In the pre-menopausal or early peri-menopausal women, lumbar spine BMD loss was accelerated in those with a low body weight. Consequently, Asian and Caucasian women demonstrated a higher incidence and prevalence of decreased bone mineral density and fracture risk.
In addition, Zhao et al (2007) evaluated the relationship between obesity and osteoporosis in more than 3000 Caucasian and Chinese postmenopausal women. The study demonstrated that bone mass was proportional to fat mass in both Asian and Caucasian women.

In a recent study by Kadam et al (2010), risk factors for low BMD were evaluated in 92 Indian postmenopausal women. The study demonstrated that both weight and BMI was proportional to BMD.

Traditionally, cardiovascular disease and osteoporosis were considered distinct and unrelated. However, studies by Ness et al (2006), Marcovitz et al (2005), Varma et al (2008) and Makovey et al (2008) suggests a pathological link between calcium metabolism, the vascular system and blood coagulation, especially in the light of shared, but independent risk factors such as dyslipidaemia, altered glucose metabolism and hypertension.

Ness et al (2006) performed a retrospective study on 1000 postmenopausal women. Women included in the study shared a similar risk profile for atherosclerosis. Women with osteoporosis or osteopaenia demonstrated a two-fold higher prevalence of atherosclerotic vascular disease than women with normal bone mineral densities.

Osteoporosis has been suggested as an indicator of cardiac disease in the postmenopausal population and a low bone mineral density appears to predict significant CAD in females. Marcovitz et al (2005) was the first study to report osteoporosis as an independant predictor of CAD in the postmenopausal population, with a five-fold higher risk of angiogram-
documented CAD in the presence of confirmed osteoporosis. Varma et al (2008) further demonstrated that the prevalence of obstructive CAD (diagnosed on angiogram following chest pain) was greater in women with osteoporosis (74%) and osteopaenia (66%) versus normal bone mineral density (45%).

To date, the many studies that have addressed this association were unable to determine whether this is as the result of an effect-effect relationship, an effect-causal relationship, chance or bias.

A survey of the literature demonstrates a lack of consensus regarding the relationship between bone mineral density and lipid profile (Makovey et al., 2008, D’Amelio et al., 2008 and Bagger et al., 2007).

The relationship between total serum cholesterol and BMD was analysed in a study by Makovey et al (2008) where 273 postmenopausal women were assessed. The study found an inverse relationship between triglyceride and LDL levels with lumbar spine and whole body BMD. In a smaller descriptive study by D’Amelio et al (2008), serum HDL levels were measured in 37 postmenopausal women with osteoporosis. These values were compared to 43 postmenopausal women with a normal BMD. HDL levels were inversely proportional to BMD. Although this data proves interesting, the sample size may impact on the reliability of such findings.
Conversely, in a prospective epidemiological study of 2662 healthy postmenopausal women, Bagger et al (2006) measured BMD, fractures and aortic calcification on an annual basis. The study demonstrated that aortic calcification was an independent risk factor for the development of osteoporosis.

While studies, like those of Makovey et al (2008), shows that a pro-atherogenic profile is associated with a favourable BMD, Bagger et al (2006) demonstrated that the rate of bone demineralization is positively associated with the rate of atherogenesis and future risk of cardiovascular events.

The link between BMD and other cardio-metabolic parameters have also been highlighted in literature (Tsuda et al., 2001, Browner et al., 1993, Jorgensen et al., 2001, Uzzan et al., 2007, Bruce and Rymer., 2009).

An earlier prospective study by Browner et al (1993) reported that low bone mineral density in postmenopausal women was associated with a higher incidence of strokes. For every standard deviation decrease in BMD in the calcaneus there was a 1.3 fold increase in cerebrovascular risk. The study concluded that low BMD is a possible predictor of the first onset of stroke in female postmenopausal women, independent of age.
Tsuda et al (2001) investigated the association between essential hypertension and low BMD. He performed DEXA scans and measured urinary calcium levels and blood pressure in elderly Japanese women. The study demonstrated that BMD was inversely correlated with systolic blood pressure in women, and thus bone health can be considered as a predictor for the essential hypertension.

In a small study by Jorgensen et al (2001), the BMD of approximately 250 Nordic patients were measured. 33 women were previously diagnosed with stroke. The study demonstrated that the BMD measured at the femoral neck was 8% lower in women who had previously had a stroke. Furthermore, women in the lowest quartile for BMD showed a four-fold greater risk per standard deviation decrease in BMD for stroke than those in the highest quartile.

A meta-analysis of 16 studies (including 3 randomized controlled trials) by Uzzan et al (2007) explored a link between statins and hip BMD. The BMD of the hip in 2971 postmenopausal women on statins were evaluated. The study concluded that statins not only played a beneficial role in decreasing atherogenesis, but were associated with decelerated bone loss.

While studies show a disparity in the prevalence of low bone mineral density in a multiethnic cohort, there are no studies in the literature that compare Indian and African postmenopausal women with regard to their cardiovascular risk profile and its relationship to BMD. This study attempts to identify and compare the cardio-metabolic risk profile and the prevalence of
low bone mineral density in Indian and African postmenopausal women and thereafter, determine whether there is a correlation between cardio-metabolic risk factors and low BMD.
CHAPTER 1

1.2 THE CARDIOMETABOLIC PROFILE OF MENOPAUSE

Cardiovascular disease (CVD) is associated with significant morbidity and mortality in the elderly, independent of age.

Before menopause, women have a favourable cardiovascular profile. This results in a 20 year delay, compared to their age-matched male counterparts, in the presentation of cardiovascular morbidity like myocardial infarction and sudden death (International Menopause Society Consensus statement, Sturdee et al., 2009). This advantage is lost in the menopause. Furthermore, women are susceptible to pre-eclampsia or polycystic ovarian syndrome, which doubles the background risk for a coronary event.

In women of a reproductive age, oestrogen has a multimodal function as a cardio-protective hormone, with both immediate and long term benefits on the cardiovascular system (Mendelsohn et al., 1999, Mendelsohn et al., 2002).

Studies by Mendelsohn et al (2002) demonstrated that the effects of oestrogen are mediated by the estrogen receptors ER-α and ER-β. The direct effects of estrogen occur through rapid non-genomic and longer-term genomic pathways. Oestrogen is responsible for a favourable lipid profile by increasing HDL-cholesterol and lowering LDL-cholesterol. These effects lead to a decrease in the total serum cholesterol concentrations, LDL concentrations, lipoprotein A (LP-a) concentrations and an increase in HDL. Blood HDL cholesterol levels are consistently...
higher and total cholesterol and LDL levels are lower in women than men. A decrease in HDL-cholesterol of 0.55 mmol/L is associated with a 40 – 50% increased CAD risk (Speroff et al., 2005).

After menopause, the risk of CAD doubles for women as the atherogenic lipids, at age 60 years, reaches levels greater than those of men (Epstein et al., 1991). The Munster heart study by Eriksson et al (1999) documented a strong association between total cholesterol and CAD in women, where CAD was three times more prevalent in women with high cholesterol values. Epstein et al (1991) demonstrated that the strongest predictor of CAD in women remains a low HDL-cholesterol. These findings by Epstein et al (1991) have not been further explored in the literature to date. Excess caloric intake and obesity decreases HDL-cholesterol and increases total cholesterol, LDL-cholesterol and TG levels.

The response of oestrogen to vascular injury and atherosclerosis remains one of the most important functions of the hormone (Morales et al., 1995, Mendelsohn et al., 1999). Morales et al (1995) suggests that the direct action of oestrogen on blood vessel walls contribute substantially to the cardio-protective and direct myocardial effects, with respect to structure and function. Oestrogen accelerates endothelial cell growth, both in-vivo and in-vitro after denudation. The vascular endothelium is also protected from the toxic effects of LDL as oestrogen inhibits LDL oxidation. Additionally, oestrogen promotes vasodilation by down-regulating the expression on angiotensin 2, the Renin-angiotensinogen system (RAS) and endothelin 1, with a resultant increase in endothelial derived NO, promoting relaxation of vascular smooth muscle (Morales et al., 1995; Rajzbaum et al., 2006). Oestrogen has further effects on the coagulation and fibrinolytic systems with hepatic gene regulation of
Antithrombin 3, Protein S and fibrinogen concentrations, resulting in an overall increase in fibrinolysis (Eriksson et al., 1999).

The aging process is “characterized by progressive endothelial dysfunction and coronary artery remodeling” resulting in a decrease in large vessel compliance (Mendelsohn et al., 2002). This is coupled with an increase in sympathetic activity resulting in an increased blood pressure during the menopause transition (Sturdee et al., 2009). The effect of hypertension in women, especially in the menopause, is both under-estimated and under-treated. Blood pressure increases with age. However, the cut-off for cardiovascular risk is unknown. In a clinical context, this translates to individuals with blood pressures deemed ‘normal’ or ‘high-normal’ being included in primary prevention programmes.

Increases in body weight and abnormal fat distribution in the menopause put the older women at risk for the metabolic syndrome. This change in body habitus results in peripheral resistance to insulin, blood pressure alterations and an atherogenic lipid profile (Carr., 2003). In North America, the overall estimated prevalence of the metabolic syndrome is 24%, higher in women (with a prevalence of 40% by age 60 years) and increases with age (Bansal et al., 1992). The prevalence of metabolic syndrome in South Africa is estimated to be 33.5% (Misra et al., 2008).
The International Diabetes Federation (IDF) proposed a definition for metabolic syndrome in 2005. This is tabulated below.

**TABLE 1: DIAGNOSIS OF METABOLIC SYNDROME**

<table>
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<th>FACTOR</th>
<th>DEFINITION</th>
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<tr>
<td>Central obesity +</td>
<td>BMI &gt;30kg/m² or waist circumference ≥88cm</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Systolic blood pressure (SBP) ≥130mmHg or Diastolic blood pressure (DBP) ≥85mmHg or Specific treatment of previously diagnosed hypertension</td>
</tr>
<tr>
<td>Reduced HDL-cholesterol</td>
<td>&lt;1.29mmol/L or specific treatment for this abnormality</td>
</tr>
<tr>
<td>Raised triglycerides</td>
<td>≥1.7mmol/L or specific treatment for this abnormality</td>
</tr>
<tr>
<td>Raised fasting plasma glucose</td>
<td>≥6.1mmol/L or previously diagnosed type 2 diabetes mellitus</td>
</tr>
</tbody>
</table>

International Diabetes Federation

Weight reduction is associated with improved insulin sensitivity, favourable lipid profiles and improved blood pressure profiles. Regular physical exercise has been documented to reduce cardiovascular risk by 75% (Mosca et al., 2007). A healthy diet during the menopausal years should include fruit, vegetables, protein and fibre. There should be judicious salt intake (<1 teaspoon per day) and cholesterol intake should be limited to <300mg daily. Calcium (1 gram
daily) and Vitamin D (800IU daily) are recommended. There is no consensus on any other food supplement (International Menopause Society Consensus statement, 2009). All individuals with features of the metabolic syndrome should be aggressively encouraged to optimize their diet and lifestyle and achieve appropriate blood pressure levels so as to minimize CVD.

In view of the multifactorial nature of cardiovascular disease, the European Society of Cardiology, the European Atherosclerosis Society and the European Society of Hypertension formulated the Systematic coronary risk evaluation (SCORE) chart in 2003 (Appendix D). Unlike the Framingham study, the SCORE chart is based on data from prospective studies and mortality statistics of individual countries. The SCORE chart allows the clinician to tailor an individual’s risk in any part of the world provided reliable national mortality information is available.

Management is targeted towards a reduction in the incidence of first or recurrent clinical events due to coronary heart disease, ischaemic stroke and peripheral artery disease in an attempt to minimise morbidity and mortality. To this end, the current guidelines address the role of lifestyle changes, the management of major cardiovascular risk factors and the use of different prophylactic drug therapies in the prevention of clinical CVD.

SCORE has proven to be a quick and effective tool for a cardiovascular death over a 10 year period in asymptomatic high and low risk women (Conroy, 2003). The SCORE chart
integrates risk factors like gender, age, smoking, systolic blood pressure and either total cholesterol or the cholesterol/HDL ratio. Low risk women (<5% risk) are offered advice on how to maintain their low risk status, which include lifestyle interventions, body weight control, blood pressure monitoring, lipid and glucose control. High risk women (≥ 5% risk) or women who will reach this level in middle age, should be given maximum attention by a multidisciplinary team (which includes a cardiologist, endocrinologist, dietician and menopause physician).

With waning ovarian function and the cessation of oestrogen production that hallmarks the menopause, cardio-protection is lost. Thus, the true burden of cardiovascular disease on age proves greater than previously recognized.
CHAPTER 1

1.3 BONE HEALTH IN THE MENOPAUSE

The internationally agreed description of osteoporosis is: “A systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture”.

The North American National Osteoporotic foundation has shown that osteoporosis affects 20 million people and results in to 1.5 million fractures per year. Locally, in the era of human immunodeficiency virus (HIV) a meta-analysis by Brown et al (2006) found low bone density in 67% of HIV positive women, with 15% having osteoporosis. This statistic translates to a more than three times greater prevalence of osteoporosis in HIV-positive women, with this being even greater in antiretroviral exposed individuals (Miller et al., 2005). The relationship between HIV and low bone mineral density has been investigated in both in-vitro and in-vivo studies. HIV was shown to have direct effects on osteoclastic activity with resultant bone demineralisation. HIV –induced chronic inflammation, resulting in chronic immune activation, was also associated with increased bone resorption. Additionally, antiretroviral therapy, namely Protease inhibitors and Nucleoside analogues showed heterogenous effects on the bone which included bone demineralisation from increased osteoclastic activity and impaired osteoblastic activity.

Both osteopaenia and osteoporosis are largely preventable sequele of the menopause. Bone health is, however, often an after-thought. Furthermore, although osteoporosis can be
effectively managed, it continues to be undertreated, in part because of inadequacies in screening and diagnostic procedures. In view of the morbid consequences of osteoporosis, fracture prevention is a paramount consideration.

Bone turnover increases during peri-menopause (Perrien et al., 2006). Bone mineral density (BMD) begins to decline substantially during the late peri-menopause, to early post-menopause (Speroff et al., 2005). Oestrogen deficiency has been identified as a major risk factor for osteoporosis in postmenopausal women.

The annual rates of loss during the late peri-menopause or early postmenopausal years are approximately 2% in the spine and 1% in the hip (Speroff et al., 2005). Over 5 years, the average woman’s BMD would decline 7–10% in the spine and 5–7% in the hip. Bone loss in the menopause is associated with approximately 50–100% higher rate of fractures (Finkelstein et al., 2008).

In accordance with the latest guidelines from the Institute of Medicine, postmenopausal women require a daily dietary intake of 1200mg elemental calcium. The dosage of supplemental calcium should be restricted to cover the shortfall between dietary intake and the dietary reference intake – approximately 500mg elemental calcium. Tang et al (2007) found that calcium supplementation, in women above 50 years old, resulted in a 12% reduction in all types of fractures, with a 24% reduction achieved if compliance on calcium was at least 80%.
A number of risk factors for low bone mineral density and fractures have been investigated in the past. Examples include age, sex, the degree of bone turnover, a history of osteoporotic fractures, lifestyle risk factors, inadequate calcium intake and little exposure to sunlight, chronic corticosteroid or anticonvulsant drug use, endocrine disorders like primary hyperparathyroidism, type 1 diabetes mellitus or hyperthyroidism, anorexia nervosa, previous gastrectomy and pernicious anaemia. A short fertile period (< 30 years) and surgical menopause were also implicated in the pathogenesis of impaired bone density (Espallargues et al., 2001).

The association between low BMI and an increased risk of fracture is well known as an adequate protein intake is needed to maintain the protein matrix in bone and the musculature that surrounds bone (De Laet et al., 2005).

Ideally, bone mineral measurements should provide diagnostic criteria, determine fracture risk and be able to monitor patients for long term follow up. In a clinical environment, bone densitometry accurately predicts osteoporosis using dual energy X-ray absorptiometry (DXA). Historically, DXA measured BMD of the hip to generate a T-score. A single BMD test has a high specificity (approximately 85%) in the prediction of fracture risk, but lacks sensitivity (less than 50% of women with osteoporosis-related fractures have a BMD T-score in the osteoporosis range) (Hough et al., 2010).

The World Health Organization (WHO) established criteria for assessing bone health and determining fracture risk. These criteria are defined by the T-score, which is the number of standard deviations (SDs) above or below the mean of the young adult group. Bone density is expressed as grams of mineral per square centimetre or grams per cubic centimetre. The T-
score is calculated by comparing the current BMD of the woman to peak BMD of a normal adult Caucasian woman (aged 20-29 years). Osteoporosis has been defined as a T-score of < -2.5 SD. Severe osteoporosis is defined in the presence of a fracture. Osteopenia is a T-score between 1.0-2.49 SD (WHO Technical report: series 921).

A Z-score compares the patient’s bone mineral density with the mean value in a population of similar age, sex, and height (Richmond., 2003). This information is useful in determining the likelihood of secondary osteoporosis due to primary or secondary metabolic bone disease, infiltrating malignancies and drug-induced decreased bone mass. Z-scores are generally used in pre-menopausal women. A low Z-score (-1.5 to -2.0) indicates a low bone mass and/or a rapid bone loss than that which is expected from an age-matched control (Hough et al., 2010).

The National Osteoporosis Foundation has stated that bone mineral measurement alone is not a good predictor of fracture risk as the test has a high specificity (85%) but low sensitivity (Hough et al., 2010). Furthermore, they found that a large proportion of fractures are demonstrated, in women who fall, outside the WHO-defined osteoporotic T-score range. This finding was highlighted in a longitudinal study by Siris et al (2004) of 140,000 women with a mean age of 64.5 years. The study relied on the self-reporting of new fractures and was conducted over a period of 12 months. 2259 women reported new fractures during 1 year, but only 6.4% had a T-score that indicated osteoporosis (–2.5 SD).

Current guidelines from the National Osteoporosis Foundation of South Africa (NOFSA) states that an integrated approach to the diagnosis and management of impaired BMD should be followed. Clinical risk factors are included in the assessment of osteoporosis-related
fractures. Non-modifiable risk factors for osteoporosis-related fractures include a personal history of fracture as an adult, history of fracture in a first-degree relative, white race, advanced age, female gender, dementia, and poor health/frailty. Modifiable risk factors include cigarette smoking, low body weight, estrogen deficiency, early menopause, prolonged premenopausal amenorrhea, low calcium intake, the use of bone toxic substances like glucocorticoids and alcohol, impaired eyesight despite adequate correction, poor health/frailty, recurrent falls, and inadequate physical activity (Hough et al., 2010).

Some of these risk factors are partially or wholly independent of BMD (Hough et al., 2010). Independent risk factors used with BMD could, therefore, enhance the information provided by BMD alone. The consideration of well-validated risk factors, with or without BMD, is likely to improve fracture prognostication and the selection of individuals at high risk for treatment.

To date, the optimal frequency of screening for osteoporosis has not been determined (van der Klift et al., 2005).

The International Society for Clinical Densitometry and the National Osteoporosis Foundation (NOF) recommends BMD testing for all women aged ≥65 years or younger postmenopausal women with additional risk factors (Lwiecki et al., 2004).
The National Osteoporosis Foundation of South Africa (NOFSA) recommends that bone mineral density screening be performed on all women after the age of 65 years (Hough et al., 2010). Furthermore, bone mineral density screening can be performed in younger women at any time in the presence of valid risk factors for an osteoporosis-related fracture. Routine follow up scans should be performed every 18-24 months. More regular scans may be indicated in conditions that are characterised by rapid bone loss like glucocorticoid-induced osteoporosis.

The WHO is currently advocating an absolute risk assessment which may help to better identify and treat women in the future – The FRAX tool. The WHO FRAX® tool evaluates the fracture risk of patients using the individual’s risks and neck of femur BMD. A 10-year probability of hip or major osteoporosis-related fracture is calculated.

The risk of fracture is calculated from gender, age, body mass index and independent risk variables like a prior fragility fracture, parental history of hip fracture, current tobacco smoking, long term use of oral glucocorticoids, rheumatoid arthritis, other causes of secondary osteoporosis and daily alcohol consumption of 3 or more units daily. In addition, femoral neck (hip) BMD, as a T-score, can be included in the calculation. This approach precludes BMD from being a primary determinant of fracture risk.

Despite the promise associated with the FRAX model, there are limitations to its use.
To date, this integrated fracture risk model has not been adjusted for local conditions and therefore is not currently applicable to a South African population. Furthermore, Vitamin D deficiency, commonly associated with osteopaenia and osteoporosis, is not included in the risk assessment tool.

Osteoporotic fractures are associated with major morbidity and impaired quality of life. With more people living to an older age, the financial and health-related costs of osteoporosis will rise in future generations (de Villiers., 2009).
CHAPTER 1

1.4 RELATIONSHIP BETWEEN CARDIOMETABOLIC PROFILE AND BONE MINERAL DENSITY

Traditionally, cardiovascular disease and osteoporosis were considered distinct and unrelated. However, in a study by Mendelsohn et al. (1999) the pathological link between calcium metabolism, the vascular system and blood coagulation was suggested.

An understanding of the cellular and molecular effects of oestrogen on both the cardiovascular system and bone allows one to appreciate the existence of a “cause-effect” and an “effect-effect” relationship between the two.

Matrix proteins, such as type 1 collagen, proteoglycan, osteopontin, and osteonectin, are present in bone and vascular matrix components. These proteins play an important role both in bone formation and in the development of atherosclerosis. Endogenous oestrogen is associated with suppression of cytokines, such as IL-1, IL-6 and TNF-alpha and upregulation of osteoprotegerin. Thus in a hypo-oestrogenic state, there is an increase in these cytokines and a decrease in osteoprotegerin, both associated with bone loss and atherogenesis (Baldini et al., 2005).

Endogenous oestrogen is seen as a cardio-protective hormone with a multimodal function. It has both immediate and long term effects on the cardiovascular system, with the long term benefits on blood vessel walls being better documented in the literature (Mendelsohn et al., 1999). Furthermore, oestrogen replacement is associated with a 35 – 50% decrease in cardiovascular risk profile (Epstein et al., 1999).
The response of oestrogen to vascular injury and atherosclerosis remains one of the most important functions of the hormone (Mendelsohn et al., 1999). Oestrogen induces vasodilation and affects the fibrinolytic-coagulation pathway, promoting fibrinolysis (Harvey, 1999). Further effects on the coagulation and fibrinolytic systems occur with hepatic gene regulation of antithrombin 3, Protein S and fibrinogen concentrations (Mendelsohn et al., 1999).

The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial examined the effects of oestrogen or oestrogen/progestin regimens on heart disease risk factors in menopausal women. The trial found that oestrogen alone or in combination with a progestin improves serum lipoprotein levels and lowers fibrinogen levels without detectable effects on insulin or blood pressure (Bush, 1995).

Oestrogen is also associated with endothelial cell growth (Morales et al., 1995). Vascular Endothelial Growth Factor (VEGF) promotes re-endothelialization, inhibiting endothelial apoptosis and enhancing the vascular system’s response to injury. This results in inhibition of smooth muscle proliferation within the vascular system and the promotion of endothelial cell growth. Additionally, 17ß oestradiol has been shown to have beneficial antioxidant effects in-vivo (Morales et al., 1995).

Mendelsohn et al (1999) found that oestrogen promotes vasodilation by down-regulating the expression of angiotensin 2, and thereby, the Renin Angiotensinogen System (RAS) and Endothelin 1. With decreases in endothelin 1, the resultant ratio between NO and endothelin...
increases. This increase allows for a greater bioavailability of endothelial derived NO, favouring relaxation of vascular smooth muscle.

Normal bone turnover involves a balance of bone resorption (by osteoclastic acidification and proteolytic digestion of old bone) and bone formation (by osteoblastic laying down of osteoid within the resorptive cavity). In older women, the bone remodeling process becomes progressively inefficient due to the hypo-oestrogenic state that characterises the menopause. Oestrogen withdrawal during menopause is associated with a protracted lifespan of osteoclasts and early osteoblast cell death resulting in bone loss (Mendelsohn et al., 1999).

Early evidence from Browner et al (1993) suggested an association between cardio-metabolic profile (which included atherosclerotic vascular disease, hypertension, dyslipidaemia and altered glucose metabolism) and low BMD. This relationship was demonstrated despite a comparable distribution of baseline cardiovascular risk factors amongst women.

Further support of this relationship was demonstrated by Barengolts et al (1998) who compared coronary calcium scores in 45 asymptomatic postmenopausal women with normal and low BMD. Coronary calcium scores were measured using electron beam computed tomography of the heart and BMD of the lumbar spine and proximal femur was measured by dual X-ray absorptiometry. The study demonstrated that oestrogen deficiency is a risk factor for osteoporosis and coronary artery disease. Furthermore, high coronary calcium scores in
patients with pre-existing osteoporotic vertebral fractures, correlated with an increased risk of coronary and aortic artery calcification and a higher prevalence of ischaemic heart disease.

Marcovitz et al (2005) was the first study to report osteoporosis as a predictor of coronary artery disease (CAD) in the postmenopausal population, with a low bone mineral density associated with significant CAD in females. Varma et al (2008) further demonstrated that the prevalence of obstructive CAD (diagnosed on angiogram following chest pain) was greater in women with osteoporosis (74%) versus osteopaenia (66%) versus normal bone mineral density (45%).

Studies performed in Denmark on postmenopausal women demonstrated an increased incidence of cardiovascular events and a two fold increase in cardiovascular mortality in patients with confirmed low bone mineral density (Von der Recke., 1999).

A further evaluation of approximately 2500 postmenopausal women (mean age, 66.5 years) with osteoporosis demonstrated that these women were at an increased risk for cardiovascular events (Tanko et al., 2005). This risk was proportional to the severity of osteoporosis at the time of the diagnosis. When compared to low bone mineral density, women with osteoporosis had a 4-fold increased risk for cardiovascular events. Furthermore, the presence of at least one vertebral fracture at baseline was associated with a 3.0-fold increase in risk. This risk was proportional to the number and severity of baseline vertebral fractures.
Bansel et al (1992) found that low calcium concentrations were associated with an up-regulation of parathyroid hormone (PTH), and a paralleled increase in tissue plasminogen activator (by osteoblasts). PTH has been likened to a hypertensive factor and is implicated in the pathophysiology of hypertension in the postmenopausal patient (Hoekman et al, 1991). Furthermore, PTH is seen to have local effects on bone demineralization and systemic effects on atherosclerotic vascular disease, hypertension and coagulopathy (Maillard et al., 1992).

This thread is further supported by a study by Browner et al (1993) were the unfavourable pattern of calcitrophic hormones (decreased Vitamin D metabolism and renal dysfunction with increased action of PTH) not only had negative implications on bone, but affected vascular reactivity.

There have also been suggestions that hypertension may be associated with low bone mineral density in the elderly, with BMD being inversely proportional to systolic blood pressure (Tsuda et al., 2001).

Low bone mineral density has been associated not only with an increased risk for stroke (relative risk of 1.3 per standard deviation below mean BMD), but has been shown to be a possible predictor of the first onset of stroke in postmenopausal women, independent of age (Browner et al (2003). Jorgensen et al (2001) demonstrated that women in the lowest quartile for BMD had a greater risk for stroke than those in the highest quartile (an odds ratio of 4.8 or an increase in odds ratio by 1.9 per standard deviation reduction in BMD).
A Swedish population-based cohort study of twins by Sennerby et al (2009) investigated the relationship between CVD and risk of hip fractures. More than 30 000 twins were followed up over a 50 year period. Following the diagnosis of peripheral atherosclerosis, there was a 3 times greater risk of a hip fracture. The risk of a hip fracture was 4 times greater following cardiac failure and 5 times greater after a stroke. The study demonstrated increased rates of hip fracture after different major cardiovascular events, and supports the hypothesis of a link between cardiovascular disease and bone health.

An additional link between cardiovascular disease and osteoporosis seems to be related to the action of some drugs, such as bisphosphonates, statins and raloxifene. Studies suggest that the mechanism of action of these drugs at cellular level may not be mutually exclusive, acting either in bone or in atherosclerotic plaque.

A meta-analysis by Uzzan et al (2007) has shown a beneficial link between statins and hip BMD. The implications thereof are that statins not only play a role in decreasing atherogenesis, but may be associated with decelerated bone loss. Varma et al (2008) gave further relevance to this by demonstrating that 86% of postmenopausal patients maintained normal BMD on statins.

A current survey of the literature demonstrates no consensus regarding the relationship between lipid profile and bone mineral density (Bagger et al., 2005, Yamaguchi et al., 2002,
D’Amelio et al., 2008, Makovey et al., 2009). Bagger et al (2005) conducted a study on the lipid profile in postmenopausal women in Denmark. The study population included postmenopausal women from the PERF study (Prospective Epidemiological Risk Factors Study). Yamaguchi et al (2002) conducted a similar study, but on Asian postmenopausal women in Japan. Both studies found that low triglyceride levels were independently associated with vertebral fractures. These studies favour the assumption that a pro-atherogenic profile is associated with a higher bone mineral density.

In a cross sectional study by D’Amelio et al (2008) on Italian postmenopausal women, a higher level of HDL cholesterol was associated with higher rates of osteoporosis in normal weighted postmenopausal women. Yamaguchi et al (2002) showed that plasma LDL cholesterol levels were significantly and inversely correlated with the absolute values of radial and lumbar BMD in Japanese postmenopausal women. Furthermore, Makovey et al (2009) conducted a study on postmenopausal Caucasian women in Sydney, Australia. They found that cholesterol levels were inversely related to BMD.

The association between low BMI and an increased risk of fracture is well known as an adequate protein intake is needed to maintain the protein matrix in bone and the musculature that surrounds bone (De Laet et al., 2005).

Zhao et al (2007) evaluated the relationship between obesity and osteoporosis in more than 3000 Caucasian and Chinese postmenopausal women. Whole body fat mass, lean mass, percentage fat mass, body mass index, and bone mass was measured in each ethnic group. The study demonstrated that bone mass was proportional to fat mass in both Asian and Caucasian
women. The findings of this study were explained by the association between high oestrogen levels and obesity, with resultant decrease in osteoclastic activity, possible increased osteoblastic activity and subsequent increased bone mass.

Finkelstein et al (2008) and Zhao et al (2007) support the assumption that ethnicity and body weight are powerful independent predictors of baseline bone density, and affected the rate of bone mineral loss and fracture risk. These disparities may be reflected by a difference in the rate of bone loss, a difference in the peak bone mass, or both (Finkelstein et al., 2002).

In a randomised controlled trial by Hyun et al (1992), women who had modest weight loss had lower bone mineral densities. Finkelstein et al (2008) demonstrated that lumbar spine bone mineral density loss was accelerated in the underweight postmenopausal women. In this study, it was demonstrated that the average African female weighs 9kg more than the average Caucasian, and up to 26 – 27kg more than the average Asian. Furthermore, Kadam et al (2010) found that Asians showed the most rapid deterioration in bone mineral density followed by Caucasians and the Africans. This may explain why osteoporosis is found to be most severe in Caucasians and Asians, and least severe in African women.

Cardiovascular disease and osteoporosis are public health problems with numerous epidemiological links and important economic consequences. These two conditions may be sustained by similar or common pathophysiological mechanisms and risk factors. However, further studies are necessary to define the relationship between the two entities more
specifically and to understand the complex interaction of similar or common risk factors and genetic or molecular determinants.
CHAPTER 1

1.5 MANAGEMENT OF THE MENOPAUSE

1.5.1 CARDIO-METABOLIC RISK

Coronary artery disease is multifactorial, with gender specific differences in the epidemiology, diagnosis, prognosis and management (International Menopause Society Consensus statement, 2009).

Adverse changes in lipids and lipoproteins are associated with the onset of menopause. Derangements in lipid profile include increases in total cholesterol, LDL and triglycerides, coupled with a clinically significant reduction in serum HDL levels (Speroff et al., 2005).

Changes in glucose and insulin metabolism that hallmark the menopause are pivotal in the pathogenesis of cardiovascular disease (Stevenson et al., 1995; Walton et al., 1993). Diabetes, alone, is associated with a four-fold increase in the incidence of cardiovascular disease (Winkler et al., 1992). An android fat deposition, associated with menopause, further promotes the metabolic derangements in lipids, glucose and insulin (Gorodeski., 2002).

In addition, the reduction in fibrinolysis and increased coagulant activity tips the balance towards a pro-coagulant environment in the menopausal years (Gorodeski., 2002).
Women should be screened for diabetes mellitus, hypertension, hypercholesterolaemia and metabolic syndrome during the menopause and be managed, where possible, by a multi-disciplinary team. Conroy et al (2003) developed the SCORE chart which estimates the ten year risk of fatal cardiovascular disease in low and high risk populations. Non modifiable cardiovascular risk factors like age, family history and ethnicity are coupled with modifiable risk factors like blood pressure, plasma cholesterol, LDL and HDL levels, diabetes or glucose intolerance, body weight and cigarette smoking. The SCORE chart is crucial in the appropriate risk stratification of the postmenopausal women which allows for the optimal intensity of patient management.

The most effective reduction in cardiovascular events is primary prevention (Conroy et al., 2003). Thus, lifestyle factors, which include a diet rich in high saturated fats, avoiding smoking and excessive alcohol intake and physical inactivity, play a pivotal role in the pathogenesis of cardiovascular disease (Gorodeski., 2002).

Body weight and central obesity is directly linked to cardiovascular risk and mortality rates with weight loss resulting in improved cardiovascular risk factors such as abdominal adiposity, elevated blood pressure, insulin resistance and high cholesterol (Gorodeski et al., 2002).

Diet and physical exercise are highly effective in reducing the incidence of metabolic syndrome and the risk of diabetes mellitus, with regular physical exercise (≥ 30 minutes on
most days of the week) decreasing cardiovascular risk by 75% (Godstein et al., 2000). A healthy diet should include the ‘five-a-day guideline of fruit and vegetables, whole-grain cereals and breads, low fat diary, lean meat and fish. Judicious salt intake (<1 teaspoon per day) and limited cholesterol intake (<300mg daily) should be highlighted (Gorodeski., 2002). The detrimental effects of smoking should be highlighted and smoking cessation strategies should be employed (Conroy et al., 2003).

In conjunction with a specialist physician, appropriate anti-hypertensives should be instituted with strict blood pressure monitoring. The target for optimal blood pressures in the non-diabetic patient is <140mmHg systolic and <90mmHg diastolic (Conroy et al., 2003). This target drops to <130mmHg systolic and <80mmHg diastolic in the diabetic or a patient with chronic renal disease (Conroy et al., 2003).

Total plasma cholesterol is a prime concern in the prevention of cardiovascular disease (De Backer et al., 2003). Target levels include <5mmol/L in the non-diabetic and <4.5mmol/L in the diabetic or women with established cardiovascular disease. Serum LDL levels should be maintained at <2.5mmol/L in the high risk population (De Backer et al., 2003).

To date there are no specific treatment goals for HLD and triglycerides, but fasting levels can be used as a marker for dyslipidaemia. The initiation of statins should be a combined decision between the cardiologist and gynaecologist. To date, there is no firm evidence that low dose aspirin or statins are as effective in women with established cardiovascular disease as they are in men (Conroy et al., 2003).
Hormone replacement therapy in menopausal women is widely accepted as the gold standard for the amelioration of distressing vasomotor symptoms in the menopause. However, oestrogen replacement has also been associated with favourable cardio-metabolic profile in both observational and randomised controlled trials (Rymer and Morris., 2000, MacLennan et al., 2001).

Total collagen declines approximately 2.1% per menopausal year over 15 years (Calleja-Aguis et al., 2009). While a decline in collagen is usually associated with troublesome skin symptomatology, the true danger lies in the effect on arterial vasculature. The arterial system is anatomically composed of the tunica intima, tunica media and tunica externa. In the menopause, there is progressive loss of connective tissue from within the tunica media. This eventuality is compounded by the associated thickening of the tunica intima by atherosclerotic plaques (Speroff et al., 2005).

Oestrogen has profound effects on connective tissue turnover, irrespective of the site, and has been shown to prevent tunica media loss. Baron et al (1998) and Sator et al (1998) have shown that oestrogen therapy users had a statistically significant greater thickness in the tunica media than those who did not (0.34mm versus 0.27mm). The mean carotid artery wall measurement was 0.76mm in the treated group and 0.70mm in the untreated group (Sator et al., 1998). Furthermore, the intima media ratio was significantly higher in the treated group (Sator et al., 1998).
Tremollieres et al (2000) noted that this protective effect of oestrogen on the tunica intima-media ratio was only found in older postmenopausal women, and unlikely to occur before age 55 years.

The effect of progestin on the vasculature is still uncertain. Liang et al (1997) has shown that progestins have no effect on tunica intima-media thickness but may have deleterious effects on arterial stiffening.

Godstein et al (2000) reported an 11% risk reduction for primary cardiovascular disease in postmenopausal women using hormone therapy compared with women who had never used hormone therapy, irrespective of duration of use (Godstein et al., 2000). This risk reduction was noted soon after initiation of treatment and sustained for up to 10 years of use.

Initiating oestrogen therapy in the immediate peri- or postmenopause is therefore believed to limit the development of atherosclerosis. However, the initiation of oestrogen therapy cannot reverse established arterial damage from pre-existing atherosclerosis (Gorodeski et al., 2002).

While alternative therapies are considered to be the safer, more natural option for the modern day women (Rees., 2009), there is limited research regarding it’s safety and benefit when compared to conventional hormonal therapies (RCOG opinion paper 2006, British Menopause Society Council statement, 2007). Examples of botanicals include phyto-oestrogens (soy and red clover), black cohosh, evening primrose, dong quai, ginseng and
many chinese herbs. The evidence regarding botanicals, vitamins and homeopathy is scant, with very little well-designed research. Furthermore, these agents are not regulated by any drug administration, resulting in various chemical compositions with unknown side effects (including malignancy) (Rees et al., 2009). With increasing concern over the anticipated detrimental effects, well designed randomized controlled trials should be performed before the clinician can safely recommend the use of an agent in the menopause.

1.5.2 BONE MINERAL DENSITY

Osteoporosis is a silent disease with little morbidity or mortality until the first fracture occurs (Sturdee et al., 2009). Undoubtedly, prevention of fractures should be the mainstay of treatment protocols.

Normal body homeostasis is regulated by the maintenance of normal serum calcium. In the event of hypocalcaemia, stores are mobilized from bone, under the action of parathyroid hormone, thus resulting in bone fragility (De Villiers., 2009). Calcium and vitamin D supplementation is required for a women to attain genetically determined peak bone mass and then maintain bone mass and strength (Tang et al., 2007). A recent meta-analysis by Tang et al (2007) with fractures as outcomes found that calcium supplementation is associated with a 12% reduction in all types of fractures in people aged 50 years. In patients with 80% compliance, fractures were reduced by 24%.
Over the recent years, vitamin D supplementation has sparked much interest and research. Vitamin D is essential to the absorption of calcium. Furthermore, the North American Menopause Society has stated that low vitamin D is associated with impaired muscle strength, more falls and higher rates of fragility fractures. Many postmenopausal women become bed-bound and, with age-related inability of the skin and renal system to produce active Vitamin D, many elderly will have grossly inadequate serum vitamin D levels (De Villiers., 2009). Vitamin D serum levels can be directly measured the blood level of 25-hydroxyvitamin D, and indirectly by observing the inverse relationship with the level of parathyroid hormone.

Current recommendations from the International Menopause Society include calcium (1 gram daily) and vitamin D (800IU daily), with no consensus on any other food supplementation.

Interventional programmes and counselling should be directed towards smoking cessation and excessive alcohol consumption. Jenkins et al (2008) found that smoking, or more specifically, the nicotinic effects of smoking, have been linked to impaired hip bone density. So too does the consumption of large amounts of alcohol. A careful history of high dose glucocorticoids should be attained and cessation of unnecessary steroid use should ensue. High dose steroid use has been demonstrated to have deleterious effects on BMD from initiation, with the peak effect attained after 6 months on treatment (de Nijs et al., 2008). This relationship is dose and duration dependant, related to age and initial BMD upon initiation of therapy.
The North American Menopause Society recommends strength training in the early menopause (North American position statement 2010: Management of osteoporosis in postmenopausal women). Strength training, done twice weekly, was associated with a 2% increase in spinal BMD (Vincent et al., 2002).

Fall prevention is pivotal in the general management of a patient with impaired BMD (Campbell et al., 2004). In a study by Campbell et al (1994) tapering or cessation of neuroleptics, sedatives and antidepressants were shown to reduce the risk of a fall by 60%. The North American Menopause Society has outlined various inexpensive measures to eliminate safety hazards in the home. These are highlighted in the table 2 below. Parker et al (2005) found that the use of hip protectors, to reduce hip and pelvic fractures in the event of a fall, have not been borne out by conclusive evidence.
Table 2: Fall prevention strategies (North American Menopause Society)

<table>
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<tr>
<th>LIGHTING</th>
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<tr>
<td>1. Provide ample lighting</td>
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<td>2. Have easy to locate light switches</td>
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<tr>
<td>3. Illuminate walkways with night lights</td>
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<table>
<thead>
<tr>
<th>OBSTRUCTIONS</th>
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</thead>
<tbody>
<tr>
<td>1. Remove clutter, low-lying objects</td>
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<tr>
<td>2. Remove raised door sills</td>
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<table>
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<tr>
<th>FLOORS AND CARPETS</th>
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<tbody>
<tr>
<td>1. Provide non-skid rugs on slippery floors</td>
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<tr>
<td>2. Repair/replace worn out carpet</td>
</tr>
<tr>
<td>3. Use nonskid floor wax</td>
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<tr>
<th>FURNITURE</th>
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<tr>
<td>1. Arrange furniture to ensure clear pathways</td>
</tr>
<tr>
<td>2. Remove or avoid low chairs and armless chairs</td>
</tr>
<tr>
<td>3. Adjust bed height if too high or too low</td>
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<table>
<thead>
<tr>
<th>STORAGE</th>
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</thead>
<tbody>
<tr>
<td>1. Install shelves and cupboards at accessible height</td>
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<tr>
<td>2. Keep frequently used items at waist height</td>
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<table>
<thead>
<tr>
<th>BATHROOM</th>
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<tbody>
<tr>
<td>1. Install grab bars in shower, bathroom, toilet</td>
</tr>
<tr>
<td>2. Use chair in shower and tub</td>
</tr>
<tr>
<td>3. Install nonskid strips</td>
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<tr>
<td>4. Elevate low toilet seat and install safety frame</td>
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<tr>
<th>STAIRWAY AND HALLS</th>
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<tbody>
<tr>
<td>1. Install handrails on both sides of stairs</td>
</tr>
<tr>
<td>2. Remove or tape down rugs</td>
</tr>
<tr>
<td>3. Repair loose or broken steps</td>
</tr>
<tr>
<td>4. Install nonskid treads on steps</td>
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North American Menopause Society Position Statement 2010
Pharmaco-therapeutic interventions available for the prevention of fractures are classified as those that inhibit bone resorption (HRT; Bisphosphonates and selective oestrogen receptor modulators - SERMS), those that stimulate bone formation (Teriparitide) and a combination of the two (like Strontium Ranelate) (Maclean et al., 2008). There are very few studies that compare the efficacy and safety of these therapies (Maclean et al., 2008). Choice of use is therefore based on the individual’s decision based on the studies for a particular drug, cost and compliance.

Oestrogen is known to inhibit osteoclastic activity and result in osteoclast apoptosis (Krassas and Papadopoulou., 2001). Oestrogen is also associated with positive effect on calcium balance (De Villiers et al., 2009).

The role of progesterone in bone turnover is still unclear but Fujimaki et al (1995) and Liang et al (2003) have shown that progesterone has an effect on bone proliferation and inhibition of bone resorption.

The Women’s HOPE study, by Lindsay et al (2002), was a two-year randomised, double-blind, placebo-controlled sub-study of the Women’s Health, Osteoporosis, Progestin, Estrogen trial, conducted at 19 centres in the United States. More than 800 post-menopausal women participated in the trial. The study demonstrated that doses as little as 0.3 mg/d oestrogen, with or without medroxyprogesterone acetate, increased BMD at the hip and spine (Lindsay et al., 2002). It is not known as to whether this finding can be associated with a reduction in fracture risk.
Following the results from the Women’s Health Initiative (WHI), long term use of HRT in the elderly became unacceptable as the risk for venous thromboembolism, cardiovascular events, stoke and breast cancer were reported as being appreciably higher (Jackson et al., 2006). The International Menopause Society suggests that HRT, at the lowest effective dose, can be used in younger menopausal women with vasomotor symptoms and a current fracture risk with replacement by another agent after the age of 60 years. HRT should not be used as the first line of therapy for osteoporosis (Sturdee et al., 2009).

Bisphosphonates have the most extensive track record in osteoporosis therapy and are widely used. They inhibit osteoclastic activity by blocking the mevalonic pathway (De Villiers., 2009) Examples include Alendronate, Etindronate, Risedronate, Ibandronate and Zoledronic acid. The level of suppression of bone turnover varies with each preparation, but the effect of osteoclastic suppression continues with all agents after cessation of use. The necessary duration of therapy is currently unknown.

Studies like those of Colon-Emeric et al (2006) recommends the cessation after 5 years of use in a patient with a T-score > -3.5 and no current risk factors for fracture. The drug has often been associated with oesophageal irritation and gastro-oesophageal reflux, thus requiring a strict protocol for ingestion (Gertz et al., 1995). Furthermore, absorption is less than 1% of the oral dose and bioavailability is easily impaired by ingestion of liquids other than plain water or by eating or drinking too soon after taking the bisphosphonate. There have also been studies linking bisphosphonates with osteonecrosis of the jaw (Woo et al., 2006).
The majority of patients taking oral bisphosphonates have a weekly or monthly dosing, with studies by Recker et al (2005) and Cooper et al (2006) showing that adherence to therapy is better, but still suboptimal, with intermittent dosing.

Raloxifene is currently the only available selective oestrogen receptor modulator. Other preparations include Lasofoxifene, Bazedoxifene and Arzoxifene. The Multiple Outcomes of Raloxifene Evaluation (MORE) study was a multi-centre, randomized, blinded, placebo-controlled trial on over 7000 women aged 31 to 80 years in 25 countries. The MORE trial by Ettinger et al (1999) demonstrated that Raloxifene was associated with increases in spine and femoral neck bone mineral density and a risk reduction in vertebral fractures. There are no significant endometrial effects, but may exacerbate vasomotor symptoms.

The Raloxifene Use for The Heart (RUTH) trial, examined the effect of Raloxifene on risk reduction for coronary heart disease in postmenopausal women (Barret-Connor et al., 2006). The study demonstrated that Raloxifene did not reduce this risk of a coronary event. Raloxifene was found to increase the risk for venous thromboembolism by 44% and fatal stroke by 49%, although no significant differences were seen in rates of death or total strokes. Raloxifene is thus used in patients with concomitant osteoporosis and breast cancer (De Villiers., 2009).

Teriparatide, a recombinant human parathyroid hormone, is a pure anabolic agent which stimulates new cortical and trabecular bone development. Teriparatide was shown to reduce
the risk for vertebral fractures by 65% and non-vertebral fractures by 53% in treatment naïve women, but was associated with concern regarding increased osteosarcoma risk in rats in a study by Neer et al (2001). To date this fear has not been substantiated in humans. Side effects are usually minimal and include headaches, nausea and muscle cramps, associated with mild hypercalcaemia. The drug is limited by its cost and method of administration (a subcutaneous daily dosing). Indications for use include patients with severe osteoporosis or the presence of new fractures despite compliance on another antiresorptive agent (Hough et al., 2010).

Strontium ranelate has a dual action in reducing bone resorption and increasing formation by acting on the RANK ligand system and calcium sensitive receptors (Chattopadhyay et al., 2007). It is packaged as a powder and taken as a daily dose in a water suspension. Studies by Meunier et al (2004) and Reginster et al (2005) have demonstrated increases in BMD with a 41% reduction in vertebral fracture risk.
AIMS

To assess the cardio-metabolic risk profile and incidence of low bone mineral density in Indian and African postmenopausal women attending the Inkosi Albert Luthuli menopause clinic and to determine whether there is a correlation between cardio-metabolic parameters and low bone mineral density.

METHODS

This study was a retrospective, descriptive audit.

After institutional ethical approval was obtained, all Indian and African postmenopausal women, above the age of 40, referred to the gynaecology menopause outpatient clinic at Inkosi Albert Luthuli Central Hospital (IALCH) from 01 July 2009 to 31 December 2010 were recruited into the study.

IALCH is a large tertiary referral hospital for the province of Kwa-Zulu Natal serving mainly an indigent population. The gynaecology menopause clinic at IALCH was formally established in June 2009. Women are referred to the menopause clinic from the surrounding regional hospitals and other outpatient clinics at IALCH (urogynaecology, general
gynaecology and other medical disciplines). Women with natural or surgical menopause are referred to the clinic.

All women, attending the menopause clinic, are assessed on the primary consultation and their demographic and clinical data are entered onto a primary assessment form. The results of biochemical and radiological investigations are entered onto this form as they are completed. All consultations at IALCH are stored in the medi-com database.

Menopause was defined as amenorrhea for more than 6 months with a serum FSH > 30IU/L or amenorrhea for more than 12 months. African or Indian postmenopausal women above the age of 40, with confirmed menopause were included in the study. Women with premature ovarian insufficiency (in women < 40 years), peri-menopausal women, patients with a Follicular Stimulating Hormone (FSH) levels < 30IU/L and women with decreased bone mineral density from pre-existing chronic disease were excluded from the study. A sample size of at least 50 women from each race group was required, as determined by a statistician.

Ethical and institutional approval was obtained from the Biomedical Research Committee, Inkosi Albert Luthuli Central Hospital and Natalia prior to the initiation of data collection.
Participant data were collected retrospectively from the IALCH medi-com database using a structured questionnaire. There was no direct patient contact and all information was kept confidential. The information required to complete the questionnaire was found on the primary assessment form.

Demographic data included age, ethnicity and years since the final menstrual period. The data analysed included the presence of menopausal symptoms, a history of hypertension, diabetes, ischaemic heart disease, hypercholesterolaemia, impaired bone mineral density or previous fragility fracture. A family history of the same parameters was assessed. A previous history of gestational diabetes, past pre-eclampsia and confirmed polycystic ovarian syndrome was assessed. Drug history, level of exercise, current smoking and alcohol consumption was included.

Clinical data included systolic and diastolic blood pressure, height and weight, abdominal and hip circumference, calculated body mass index, calculated waist hip ratio, clinical stigmata for dyslipidaemia and insulin resistance.

Biochemical investigations included a fasting lipogram (cholesterol, triglycerides, HDL and LDL), fasting glucose and insulin levels and thyroid function tests.
Radiological investigations included dual energy absorptiometry (DEXA) of the hip and lumbar spine. This provided values for total hip, neck of femur and spine bone mineral densities.

TSH was analysed using a chemiluminescent assay. Serum glucose was analysed using the Hexokinase 2 step method which produces a solution that absorbs ultraviolet light. The absorbance of the solution is proportional to the glucose concentration. Total cholesterol and triglyceride specimens were analysed using 2-point kinetic enzymatic assays. The intra- and inter-assay coefficients for TSH were 11.2% and 9.5%; 10.2% and 7.9% for fasting insulin; 6.9% and 3.4% for fasting glucose; 5.6% and 2.9% for triglycerides; 5.9% and 1.2% for cholesterol and 8.4% and 9.9% for HDL. These assay coefficients were calculated with the normal values of the respective metabolites in mind, namely 11-22.7 pmol/L for T4; 0.27-4.2 mIU/L for TSH; 3-25 mIU/ml for fasting insulin; 3.8-5.3 mmol/L for fasting glucose; <5.8 mmol/L for cholesterol; <2.83 mmol/L for triglycerides; <1 mmol/L for HDL and <2.6 mmol/L for LDL levels.

**STATISTICAL ANALYSIS**

Cardio-metabolic data were analysed as continuous variables and summarized using frequencies, percentages, means and standard deviations. Bone mineral density was treated as a quantitative variable and correlation analysis was used to assess relationships between the variables. This was done for each race group separately. The Pearson Chi² test was used to determine associations between two categorical variables. ANOVA was used to assess the
difference in means between the two ethnic groups. The Independent Students T-test was used to compare cardio-metabolic variables between the two race groups. For multiple comparisons, Bonferroni adjusted statistics was used. The significance level was set at 0.05. SPSS version 18.0 was used to analyze data.
CHAPTER 3

RESULTS

A total of 137 women attended the menopause clinic from 01 July 2009 to 31 December 2010. These included 55 African women, 61 Indian women, 18 Caucasian women and 3 Coloured women. The charts of 116 menopausal women attending the IALCH menopause clinic were analysed from 01 July 2009 to 31 December 2010. These charts comprised 55 African and 61 Indian women. Ten women were excluded from further analysis as they did not meet the inclusion criteria (6) or had missing data (4). This resulted in a sample size of 55 Indian and 51 African women in the study.

This was a retrospective chart review, negating any patient contact.

The demographic profile is displayed in Tables 3 and 4. The mean age of postmenopausal women was 60 years and 58 years for Indian and African women respectively. The mean duration after the FMP was 10 years for Indian women and 8 years for African women. There were no statistical differences between Indian and African women with regards to age and duration after FMP.

The presence of vasomotor symptoms was reported in 70.6% of African women and 61.8% of Indian women. The presence of urogenital symptoms was reported in 54.9% of African women and 61.8% of Indian women. This difference was not statistically significant. Significantly more Indian women (50.9%) used HRT preparations when compared to African
women (23.5%). Very few African women (3.9%) and Indian women (3.6%) used alternatives to HRT.

A significant number of women attending our menopause clinic had co-morbidities; 60% had hypertension, 44% diabetes, 10% ischaemic heart disease and 25% had dyslipidaemia. A previous history of pre-eclampsia and gestational diabetes was reported in 6% and 5% of women respectively. Indian postmenopausal women reported a higher prevalence of hypertension, diabetes, dyslipidaemia, ischaemic heart disease and low bone mineral density when compared to African postmenopausal women. However, there were no statistical differences for any of the risk factors in either ethnic group.

**TABLE 3: Demographic profile (Mean and SD*) of African and Indian postmenopausal women**

<table>
<thead>
<tr>
<th></th>
<th>AFRICAN (n=51)</th>
<th>INDIAN (n=55)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Mean (SD)*</td>
<td>Mean (SD)*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>58 (11)</td>
<td>60 (9)</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>Years since FMP</strong></td>
<td>8 (8)</td>
<td>10 (9)</td>
<td></td>
</tr>
</tbody>
</table>

*SD : Standard deviation
### TABLE 4: Demographic profile (n and %) of African and Indian postmenopausal women

<table>
<thead>
<tr>
<th></th>
<th>AFRICAN (n=51)</th>
<th>INDIAN (n=55)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>28 (54.9)</td>
<td>36 (65.5)</td>
<td>0.27</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>16 (31.4)</td>
<td>31 (56.4)</td>
<td>0.19</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>3 (5.9)</td>
<td>8 (14.9)</td>
<td>0.21</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>9 (17.6)</td>
<td>18 (32.7)</td>
<td>0.08</td>
</tr>
<tr>
<td>Osteopaenia/Osteoporosis</td>
<td>12 (23.5)</td>
<td>22 (40)</td>
<td>0.07</td>
</tr>
<tr>
<td>Smoking</td>
<td>7 (13.7)</td>
<td>2 (3.6)</td>
<td>0.06</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>3 (5.9)</td>
<td>1 (1.8)</td>
<td>0.27</td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Nil</td>
<td>10 (19.6)</td>
<td>22 (40)</td>
<td>0.08</td>
</tr>
<tr>
<td>- Sedentary</td>
<td>24 (47.1)</td>
<td>17 (30.9)</td>
<td></td>
</tr>
<tr>
<td>- Moderate</td>
<td>17 (33.3)</td>
<td>15 (27.3)</td>
<td></td>
</tr>
<tr>
<td>- Gym</td>
<td>0 (0)</td>
<td>1 (1.8)</td>
<td></td>
</tr>
<tr>
<td>HRT</td>
<td>12 (23.5)</td>
<td>28 (50.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HRT alternatives</td>
<td>2 (3.9)</td>
<td>2 (3.6)</td>
<td>0.93</td>
</tr>
<tr>
<td>Vitamin D supplements</td>
<td>4 (7.8)</td>
<td>6 (10.9)</td>
<td>0.59</td>
</tr>
<tr>
<td>Calcium supplements</td>
<td>29 (56.9)</td>
<td>13 (23.6)</td>
<td>0.03</td>
</tr>
<tr>
<td>Antiresorptive agents</td>
<td>2 (3.9)</td>
<td>11 (20)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

The majority of women (90%) ate a mixed diet and 68% led an inactive lifestyle. Social habits including alcohol intake and smoking were reported in 8% and 3% respectively. There were no statistical differences amongst the African and Indian women regarding diet, lifestyle and social habits.
Significantly more Indian women (20%) used antiresorptive agents compared to African women (3.9%) while significantly more African women (56.9%) used calcium supplementation compared to Indian women (23.6%).

Tables 5 and 6 illustrate the clinical profile of African and Indian women attending the IALCH menopause clinic.

**TABLE 5: Clinical profile (Mean and SD) of African and Indian postmenopausal women**

<table>
<thead>
<tr>
<th></th>
<th>AFRICAN (n=51)</th>
<th>INDIAN (n=55)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>158 (8)</td>
<td>155 (7)</td>
<td>0.12</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>84 (20)</td>
<td>69 (15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI* (kg/m2)</td>
<td>33 (7)</td>
<td>29 (7)</td>
<td>0.01</td>
</tr>
<tr>
<td>WHR**</td>
<td>0.88 (1.03)</td>
<td>0.84 (0.09)</td>
<td>0.08</td>
</tr>
<tr>
<td>SBP‡ (mmHg)</td>
<td>143 (24)</td>
<td>148 (24)</td>
<td>0.21</td>
</tr>
<tr>
<td>DBP† (mmHg)</td>
<td>77 (14)</td>
<td>81 (13)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

*BMI: Body mass Index **WHR: Waist Hip ratio
‡SBP: systolic blood pressure †DBP: Diastolic blood pressure
TABLE 6: Clinical profile (n and %) of African and Indian postmenopausal women

<table>
<thead>
<tr>
<th></th>
<th>AFRICAN (n=51)</th>
<th>INDIAN (n=55)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Xanthoma</td>
<td>10 (19.6)</td>
<td>9 (16.4)</td>
<td>0.67</td>
</tr>
<tr>
<td>Xanthelasma</td>
<td>5 (9.8)</td>
<td>7 (12.7)</td>
<td>0.64</td>
</tr>
<tr>
<td>Arcus senalis</td>
<td>2 (3.9)</td>
<td>1 (1.8)</td>
<td>0.52</td>
</tr>
<tr>
<td>Acanthosis nigricans</td>
<td>5 (9.8)</td>
<td>7 (12.7)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

The weight and mean body mass index (BMI) of African women was significantly higher in African women when compared to Indian women, with 86.3% of African women and 78.2% of Indian women having a BMI of greater than 25 (shown in Table 7). Significantly more African women had a BMI of greater than 30. There were no differences in height, WHR, SBP, DBP, clinical stigmata of dyslipidaemia or insulin resistance between African and Indian postmenopausal women.

TABLE 7: BMI of African and Indian postmenopausal women

<table>
<thead>
<tr>
<th></th>
<th>AFRICAN (n=51)</th>
<th>INDIAN (n=55)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m2)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>19-25</td>
<td>7 (13.7)</td>
<td>12 (21.8)</td>
<td>0.21</td>
</tr>
<tr>
<td>25-30</td>
<td>9 (17.6)</td>
<td>21 (38.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>&gt;30</td>
<td>35 (68.7)</td>
<td>22 (40.1)</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Table 8 demonstrates the biochemical parameters of African and Indian postmenopausal women. There were no statistically significant differences amongst African and Indian postmenopausal women with regards to the analyzed biochemical parameters.

**TABLE 8: Biochemical profile† (Mean and SD*) of African and Indian postmenopausal women**

<table>
<thead>
<tr>
<th></th>
<th>AFRICAN (n=51)</th>
<th>INDIAN (n=55)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>5.69 (1.49)</td>
<td>5.90 (0.97)</td>
<td>0.38</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>2.15 (1.44)</td>
<td>2.30 (1.31)</td>
<td>0.38</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.36 (0.33)</td>
<td>1.46 (0.41)</td>
<td>0.32</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3.20 (0.89)</td>
<td>3.37 (0.91)</td>
<td>0.36</td>
</tr>
<tr>
<td>Insulin (mIU/ml)</td>
<td>16.40 (6.30)</td>
<td>18.50 (11.60)</td>
<td>0.75</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>7.20 (2.60)</td>
<td>7.70 (2.60)</td>
<td>0.35</td>
</tr>
<tr>
<td>Thyroxine (pmol/L)</td>
<td>13.10 (2.61)</td>
<td>13.82 (2.16)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

*SD: Standard deviation
†normal values available in appendix C

Table 9 represents the lipid profile of African and Indian postmenopausal women. The majority of women had an abnormal lipid profile; 53% of African women and 73% of Indian women demonstrated abnormal cholesterol, 22% of African women and 27% of Indian women had abnormal triglyceride profiles, 82% of African women and 80% of Indian women
demonstrated abnormal LDL-cholesterol profiles and 94% of African women and 98% of Indian women demonstrated abnormal HDL-cholesterol profiles. Significantly higher rates of abnormal cholesterol levels were found in Indian women.

**TABLE 9: Lipid profile* of African and Indian postmenopausal women**

<table>
<thead>
<tr>
<th></th>
<th>AFRICAN (n=51)</th>
<th>INDIAN (n=55)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cholesterol (mmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Normal</td>
<td>24 (47)</td>
<td>15 (27)</td>
<td>0.04</td>
</tr>
<tr>
<td>• Abnormal</td>
<td>27 (53)</td>
<td>40 (73)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Triglycerides (mmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Normal</td>
<td>40 (78)</td>
<td>40 (73)</td>
<td>0.42</td>
</tr>
<tr>
<td>• Abnormal</td>
<td>11 (22)</td>
<td>15 (27)</td>
<td>0.59</td>
</tr>
<tr>
<td><strong>LDL cholesterol (mmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Normal</td>
<td>9 (18)</td>
<td>11 (20)</td>
<td>0.68</td>
</tr>
<tr>
<td>• Abnormal</td>
<td>42 (82)</td>
<td>44 (80)</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>HDL cholesterol (mmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Normal</td>
<td>3 (6)</td>
<td>1 (2)</td>
<td>0.18</td>
</tr>
<tr>
<td>• Abnormal</td>
<td>48 (94)</td>
<td>54 (98)</td>
<td>0.67</td>
</tr>
</tbody>
</table>

*normal values available in appendix C

Table 10 shows the bone mineral density (BMD) profile of both African and Indian postmenopausal women attending IALCH. BMD was determined using a dual energy x-ray absorptiometry (DEXA) scan. Statistically significant differences were demonstrated between African and Indian women with regards to total hip BMD, total hip T score, lumbar spine T score and neck of femur BMD. However, there were no statistical differences between African and Indian women when looking at the T-scores at the hip, neck of femur and lumbar spine. Though the prevalence of osteopaenia and osteoporosis was 55% compared to 35% in African women, this did not reach statistical significance (p=0.05).
TABLE 10: Bone mineral density* profile of African and Indian postmenopausal women

<table>
<thead>
<tr>
<th></th>
<th>AFRICAN (n=51)</th>
<th>INDIAN (n=55)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Total hip BMD (g/cm²)</td>
<td>0.92 (0.16)</td>
<td>-0.46 (1.14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total hip Tscore</td>
<td>0.83 (0.18)</td>
<td>-0.96 (1.37)</td>
<td>0.04</td>
</tr>
<tr>
<td>Lumbar Spine BMD (g/cm²)</td>
<td>0.93 (0.13)</td>
<td>0.88 (0.19)</td>
<td>0.15</td>
</tr>
<tr>
<td>Lumbar Spine Tscore</td>
<td>-1.22 (1.27)</td>
<td>-1.76 (1.38)</td>
<td>0.04</td>
</tr>
<tr>
<td>Neck of femur BMD (g/cm²)</td>
<td>0.77 (0.13)</td>
<td>0.72 (0.14)</td>
<td>0.03</td>
</tr>
<tr>
<td>Neck of femur Tscore</td>
<td>-0.98 (1.04)</td>
<td>-1.23 (0.97)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

TABLE 11: Bone mineral density profile* of African and Indian postmenopausal women

<table>
<thead>
<tr>
<th></th>
<th>AFRICAN (n=51)</th>
<th>INDIAN (n=55)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Total hip T score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Normal</td>
<td>33 (65)</td>
<td>25 (45)</td>
<td>0.05</td>
</tr>
<tr>
<td>• Low†</td>
<td>18 (35)</td>
<td>30 (55)</td>
<td>0.05</td>
</tr>
<tr>
<td>Neck of femur T score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Normal</td>
<td>19 (37)</td>
<td>18 (33)</td>
<td>0.87</td>
</tr>
<tr>
<td>• Low†</td>
<td>32 (53)</td>
<td>37 (67)</td>
<td>0.49</td>
</tr>
<tr>
<td>Lumbar Spine T score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Normal</td>
<td>23 (45)</td>
<td>17 (31)</td>
<td>0.10</td>
</tr>
<tr>
<td>• Low†</td>
<td>28 (55)</td>
<td>38 (69)</td>
<td>0.51</td>
</tr>
</tbody>
</table>

*WHO classification available in appendix C
† Osteopaenia and Osteoporosis
Correlations between cardio-metabolic parameters and bone mineral density (namely total hip BMD and lumbar spine BMD) were made. Clinical parameters for the cardio-metabolic profile included systolic blood pressure, diastolic blood pressure, height, weight, body mass index, waist-hip ratio, stigma of dyslipidaemia and insulin resistance. Biochemical parameters included fasting glucose, fasting insulin and fasting lipid values. Scatter plots were used to illustrate parametric correlations.

**Figure 1: Correlation between BMI and Total hip BMD in African and Indian postmenopausal women (n=106)**

BMI-total hip BMD (p<0.001)
Figure 1 demonstrates a strong positive correlation between BMI and total hip BMD (p < 0.001). This correlation was stronger in Indian women compared to African women ($r^2_{linear} = 0.522$ vs $r^2_{linear} = 0.322$), illustrated in figure 2 and 3.

**Figure 2: Correlation between BMI and total hip BMD in African women**
Figure 3: Correlation between BMI and total hip BMD in Indian women

![Image of correlation graph between BMI and total hip BMD]

Figure 4 illustrate a strong positive correlation between BMI and lumbar spine BMD ($p < 0.001$), which was more significant in Indian women than African women ($r^2_{linear} = 0.179$ vs $r^2_{linear} = 0.123$) as illustrated in figures 5 and 6.
Figure 4: Correlation between BMI and lumbar spine BMD in African and Indian postmenopausal women (n=106)

BMI-lumbar spine BMD (p<0.001)
Figure 5: Correlation between BMI and lumbar spine BMD in Indian women

Figure 6: Correlation between BMI and lumbar spine BMD in African women
There was also a positive correlation between weight and both lumbar spine (p<0.01) and total hip BMD (p<0.001), as shown in figures 7 and 10. When African and Indian women were analyzed separately (figures 8, 9, 11 and 12), Indian women demonstrated stronger correlations between weight and BMD.

**Figure 7: Correlation between weight and total hip BMD in African and Indian postmenopausal women (n=106)**

Weight-total hip BMD (p<0.001)
Figure 8: Correlation between weight and total hip BMD in African women

Figure 9: Correlation between weight total hip BMD in Indian women
Figure 10: Correlation between weight and lumbar spine BMD in African and Indian postmenopausal women (n=106)

Weight-lumbar spine BMD (p<0.001)

Figure 11: Correlation between weight and lumbar spine BMD in African women
Figure 12: Correlation between weight and lumbar spine BMD in Indian women

There were no statistically significant correlations between height and lumbar spine BMD (p=0.57) or height and total hip BMD (p=0.95).

A weak correlation was demonstrated between WHR and both lumbar BMD (p=0.06) and WHR and total hip BMD (p=0.06).

LDL exhibited a statistically significant inverse correlation to lumbar spine BMD (p=0.03), illustrated in figure 13. As LDL values increased, lumbar spine BMD decreased. This correlation was comparable amongst African and Indian women as shown in figures 14 and
15. A weak correlation was demonstrated between serum LDL cholesterol levels and total hip BMD (p=0.07).

There were no statistically significant correlations between serum HDL cholesterol or serum triglyceride levels and BMD (lumbar spine or total hip).

Figure 13: Correlation between LDL cholesterol and lumbar spine BMD in African and Indian postmenopausal women (n=106)

LDL cholesterol-lumbar spine BMD (p=0.03)
Figure 14: Correlation between LDL and lumbar spine BMD in Indian women

Figure 15: Correlation between LDL and lumbar spine BMD in African women
There were no statistically significant correlations between BMD and SBP or DBP.

Weak correlations were demonstrated between BMD and the clinical stigmata of dyslipidaemia or insulin resistance. Weak correlations were also exhibited between BMD (both lumbar spine and total hip) and abnormal fasting serum insulin, abnormal fasting serum glucose, abnormal serum thyroxine, alcohol ingestion and current smoking.
Menopause is associated with a substantially increased risk of cardiovascular events from atherosclerotic vascular disease, regardless of the age of onset of menopause. This may be attributed to the changing hormonal milieu which renders women prone to the metabolic syndrome. Furthermore, women are susceptible to risk factors like a history of polycystic ovarian syndrome and pre-eclampsia which, when present, doubles the background risk of CVD (International Menopause Society Concensus Statement: Aging, menopause, cardiovascular disease and HRT; 2009).

Additionally, osteoporosis affects one-third of postmenopausal women, resulting in significant morbidity, mortality and cost (Hough et al., 2010).

Historically cardiovascular disease and osteoporosis were considered unrelated. However, in the last decade, studies by Marcovitz et al (2005) and Varma et al (2008) have suggested that osteoporosis could be used as an independent predictor of coronary artery disease in women.

With this in mind, an understanding of the cardio-metabolic profile, and similarly an awareness of the high prevalence of low bone mineral density, is pivotal for the identification of patients at risk for a cardiovascular event and fracture.
In this study there was a high prevalence of climacteric symptoms amongst African and Indian women. This finding may be a feature of a tertiary set-up where symptomatology is elicited and treatment offered. A significantly higher proportion of Indian women (50.9%) on HRT preparations when compared to African women (23.5%). This may be attributed to more Indian women reporting, and requesting, treatment for their troublesome symptomatology.

There was a high prevalence of hypertension, diabetes, hypercholesterolemia, ischaemic heart disease and low bone mineral density amongst both African and Indian women in the study. Historically, this was not a common finding amongst African postmenopausal women. Our findings could represent a shift towards urbanisation amongst African ethnicities, with environmental factors like diet and lifestyle negatively impacting on cardio-metabolic parameters. Furthermore, one would expect a high risk profile of patients at a study site like our tertiary institution.

The majority of women attending our clinic were hypertensive. More than 50% of Indian women and almost 30% of African women were diabetic, over 30% of Indian women and 20% of African women demonstrated dyslipidaemia and the prevalence of ischaemic heart disease was low overall. The study thus demonstrated that there was a higher prevalence of the markers of cardiovascular disease in both ethnic groups, however the risk was greater in Indian postmenopausal women as compared to African postmenopausal women. This finding may be associated with a genetic predisposition for cardiovascular disease amongst Indian women.
There were no statistical differences amongst the African and Indian women regarding diet, lifestyle, smoking and alcohol intake. This finding may be attributed to the widespread urbanization amongst all South African ethnicities (Kruger et al., 2011).

In our clinic, the uptake of various menopausal therapies was evaluated. Many women used HRT and calcium supplementation during the menopause. Of significance, was that half of all Indian women and only a quarter of African women were on hormone replacement therapy. However, for calcium use, the converse was true – over 50% of African women and only 23% on Indian women were on calcium. Furthermore, significantly more Indian women were on an antiresorptive agent compared to African women. The uptake of Vitamin D supplements or alternatives to HRT was low in both African and Indian women. We anticipated that a large proportion of women in our study would be on some form of treatment or supplementation in view of the study site being of a tertiary, high risk nature. The use of antiresorptive agents was significantly higher among Indian postmenopausal women. Most women used Alendronate, a bisphosphonate. There were very few patients on Strontium Ranelate. These findings may confirm the higher prevalence of osteoporosis among Indian women, necessitating treatment with antiresorptives rather than supplementation.

The majority (82%) of African and Indian women had a BMI greater than 25. This finding seems to be in line with WHO global estimates of an increasing prevalence of obesity in developing countries, especially amongst women. African women, however, had a significantly greater weight and BMI than Indian women, with 68% of African women having a BMI > 30. Despite an expected link between increased BMI and impaired cardio-metabolic parameters, the frequency of hypertension was similar amongst African and Indian
women. Both African and Indian women demonstrated a high prevalence of abnormal fasting glucose levels and abnormal fasting insulin. This finding may represent the nutritional, demographic, epidemiological, and socioeconomic transitions occurring in developing countries, resulting in shifts in dietary and physical activity patterns and a change in ethnic-specific cardio-metabolic profiles.

In our study, abnormal lipid profiles were demonstrated in the majority of postmenopausal women, with Indian women showing greater derangements in cholesterol, triglyceride, HDL and LDL values.

Prior studies also showed this association. Mulukutla et al (2008) investigated the relationship between race and atherogenic dyslipidaemia. The study was performed on North American Caucasian and Black postmenopausal women, as well as Indian postmenopausal women from Chennai, India. He found that the prevalence of LDL and TG/HDL ratio >3 was greatest among Asian Indians and smallest among Africans. Genetic predisposition and characteristic body composition were seen as important contributors to dyslipidaemia and atherosclerosis in Indian women specifically (Misra et al., 2004).

In our study, Indian women demonstrated a higher prevalence of the markers of metabolic syndrome, and thus cardiovascular disease, despite having a lower incidence of obesity. Although a gradient relationship exists between obesity and the probability of metabolic syndrome, not all obese women have metabolic syndrome and not all women with metabolic syndrome are obese. Ruderman et al (1998) classifies Asian women as ‘metabolically obese’, with several metabolic derangements but are non-obese by conventional BMI standards. Despite a normal BMI, Indian women demonstrate a high body fat, abdominal adiposity and
thick truncal subcutaneous fat which individually, or in combination, contribute to insulin resistance, dyslipidaemia and hyperglycaemia demonstrated in the study. Thus visceral adiposity and body fat distribution correlates better with a higher prevalence of metabolic syndrome and increased cardiovascular risk than BMI. Visceral obesity in both ethnic groups was not measured in this study however, based on previous literature, it’s presence, irrespective of BMI, may explain our results regarding the biochemical and lipid profiles in Indian women. It seems likely that underlying adiposity, a predictor of metabolic syndrome, might be misclassified using BMI in the literature. With this in mind, consideration should be given to lowering BMI cut-offs for diagnosis of overweight and obesity in Indian women as opposed to current guidelines.

Bone mineral density analysis demonstrated a higher prevalence of both osteopaenia and osteoporosis among Indian postmenopausal women as compared to African postmenopausal women - at the hip, spine and neck of femur. This finding could be related to ethnic differences in the genetic make-up. Sigurdsson et al (2008) assessed the impact of genetics on bone mineral density in North American Caucasian, African-American and Hispanic postmenopausal women. The study demonstrated that genetics among different ethnicities were more important than environmental factors in the pathogenesis of low bone mineral density. Mitchell et al (2011) implicated nuclear factor κB and specific genes involved in the oestrogen endocrine pathways in the pathogenesis of osteopaenia and osteoporosis. In a North American study examining the effect of genetics on bone mineral density in the African population, Sudanese immigrants were compared to the Caucasian and Asian populations (Gong et al., 2006). The study found that 18 polymorphisms in 13 genes were associated with bone mineral density and 17 were significantly different in allele between the Sudanese population and Caucasians or Asians.
In addition, the favourable bone density reported in African women may be attributed to more African women taking calcium supplementation. Another explanation could be the relationship between BMI, ethnicity and BMD - increased BMI (specifically lean body mass) is associated with increased mechanical loading and thus plays an integral role in improved bone mass. Finkelstein et al (2008) demonstrated that body weight was a major determinant of the rate of menopausal BMD loss. Barret-Connor et al (2005) showed that body weight was influenced by ethnicity, with the highest BMD being reported in Black women. Recent literature favours the assumption that ethnicity and body weight are strong determinants of baseline bone density and influence the rate of bone mineral loss and fracture risk, which may be reflected by a difference in the rate of bone loss, a difference in the peak bone mass or both. (Finkelstein et al., 2002; Finkelstein et al., 2008; Zhao et al., 2007; Kadam et al., 2010)

This study found a strong positive correlation between body mass index and both lumbar spine and total hip bone mineral density (p < 0.01). There was also a positive correlation between weight and both lumbar spine and total hip bone mineral density (p<0.01).

Tsuda et al (2001) examined the bone mineral density in elderly Japanese women. The study found an inversely proportional relationship between systolic blood pressure and bone mineral density, with no correlation between diastolic blood pressure and BMD. In our study, there were no significant correlations between waist-hip ratio and bone mineral density or blood pressure and bone mineral density.
Furthermore, no correlations were exhibited between bone mineral density (both lumbar spine and total hip) and an abnormal fasting serum glucose; abnormal fasting insulin, abnormal serum thyroxine or the clinical stigmata of dyslipidaemia or insulin resistance.

In our study we found no correlation between social habits, which included alcohol consumption and smoking, and BMD. This finding could be the result of the small number of women who consumed alcohol or smoked in our study.

However, the relationship between social habits and BMD has been explored in earlier studies. Ganry et al (2000) and Illich et al (2002) found higher bone densities in postmenopausal women that consumed moderate quantities of alcohol. These studies postulated that alcohol increases endogenous oestrogen which has beneficial effects on bone.

Ganry et al (2000) examined the association between alcohol consumption and bone mineral density in French women aged 75 years or older. Alcohol intake was determined by a self-administered questionnaire and bone mineral density was measured at the proximal femur using dual-photon X-ray absorptiometry. Their study suggested that moderate drinking (e.g., 1-3 glasses of wine per day) is associated with an increase in trochanteric bone mineral density in elderly ambulatory women. However, the study reported detrimental effects on bone mass with higher alcohol intake.

Further to the study by Ganry et al (2000), Illich et al (2002) performed a small cross-sectional study on Caucasian women in North America. Postmenopausal women were reported as healthy and free of medications affecting bones. Alcohol consumption was
assessed by questionnaires determining frequency and amount. Bone mineral density of multiple skeletal regions and body composition were measured by dual X-ray absorptiometry. The study demonstrated that consumption of small/moderate amounts of alcohol was associated with improved bone mineral density.

Egger et al (1996) and Ilich et al (2002) examined the relationship between smoking and bone mineral density. Egger et al (1996) performed a cross-sectional study in the United Kingdom (East Hertfordshire) on postmenopausal women between the ages of 61 and 73 years. The study found that current smokers have a BMD value that was 7.7% lower than in women who had never smoked. They hypothesized that this may be due to the vaso-spastic effect of nicotine on blood vessel walls resulting in bone death and impaired mineral density. Illich et al (2002) explored the relationship between smoking and bone mineral density on North American Caucasian women (average age 61 years). A self-administered questionnaire determined a history of smoking, including number of years and packages smoked/day. The study demonstrated that past smoking was associated with bone loss in most skeletal sites.

A current survey of the literature demonstrates no consensus regarding the relationship between lipid profile and bone mineral density - while studies show that a pro-atherogenic profile is associated with a higher bone mineral density (Makovey et al., 2009; D’Amelio et al., 2008), others demonstrate that the rate of bone loss is positively related to cardiovascular events (Bagger et al., 2007).
Our study demonstrated a statistically significant inverse relationship between serum LDL cholesterol levels and lumbar spine bone mineral density (p=0.03). These findings were similar to previous studies by Makovey et al (2009) and Yamaguchi et al (2002). There was no statistically significant correlation between cholesterol, HDL cholesterol or triglycerides and bone mineral density in this study. It is possible that our small sample size did not elicit a difference, however a larger study may be able to reproduce results similar to previous larger studies.

Makovey et al (2009) examined the influence of age, menopausal status and hormone replacement therapy (HRT) on the relationship between serum cholesterol and BMD in 273 postmenopausal women in Australia. The study demonstrated a modest inverse relationship between body bone mineral density (lumbar spine and whole body) and serum total cholesterol.

In a cross-sectional study of 173 Italian women in menopause, D’Amelio et al (2008) demonstrated that HDL was significantly higher in osteoporotic patients than in controls and the risk of osteoporosis was significantly higher in women with higher level of HDL. The study concluded that a pro-atherogenic lipid profile is associated with higher bone mineral density.

An observational study by Bagger et al (2007) on 1176 Danish postmenopausal women examined the relationship between serum lipids and bone mineral density (Bagger et al., 2007). The study demonstrated that serum lipids are indirect modulators of bone mineral
density via promotion of atherosclerosis, which affects bone metabolism locally, especially when skeletal sites are supplied by end-arteries.

Yamaguchi et al (2002) evaluated the relationships between plasma lipids (total cholesterol, LDL, HDL, and triglycerides) and bone mineral density (lumbar spine, femoral neck, radius or total body) as well as the presence of vertebral fractures in 214 Japanese postmenopausal women with a mean age of 62.7 years. Their study showed that plasma LDL and HDL levels were inversely and positively correlated with both bone mineral density values at the radius and lumbar spine, respectively, while low plasma triglyceride levels were associated with the presence of vertebral fractures in postmenopausal women. The study concluded that plasma lipids are related to bone mass and bone fragility, and might be the common factor underlying both osteoporosis and atherosclerosis.

The findings of our study suggest that South African postmenopausal Indian and African women have similar presentations and profiles to women globally.

The limitations of this study were that it included patients from a tertiary institute that were ‘high risk’ by definition. These patients may have a multitude of chronic conditions, necessitating management at a tertiary hospital. Thus, this patient profile may not be applicable to the general postmenopausal population. The high rates of osteoporosis and cardiovascular disease in the population at large complicate investigations of causality. Additionally, the cause and effect remains uncertain as the exposure and disease were measured simultaneously.
The true prevalence of low bone mineral density may be skewed by the use of bisphosphonates and other treatments for osteoporosis. Similarly, the true value of specific biochemical investigations may have been altered or masked by specific medications (namely, insulin values in patients on oral hypoglycaemic agents). There are a large number of shared confounders in the study (namely age, smoking, exercise, drug use). These confounders may complicate investigations determining the association and causal link.

Although there were small numbers of African and Indian women in the sample population, we found a high prevalence of cardiovascular risk factors and low BMD amongst the local menopausal population attending a tertiary referral or high risk clinic, irrespective of ethnicity. BMI and weight showed a positive correlation with bone mineral density and an increasing LDL value was negatively correlated with bone mineral density. It thus becomes necessary that a screening lipid profile during the peri-menopausal years, coupled with early and appropriate lifestyle management regarding body mass index/weight may limit the burden of morbidity in later life.
CHAPTER 5

CONCLUSION AND RECOMMENDATIONS

Coronary artery disease and low bone mineral density are common conditions in the aging population.

Cardiovascular risk is increased in the menopause transition making it one of the leading causes of mortality amongst these women. Furthermore, statistics from the National Osteoporosis Foundation of South Africa have shown that osteoporosis affects one third of South African women above the age of 50 years, with a high prevalence of fracture-related morbidity and mortality. This makes osteoporosis, and osteoporotic fractures, one of the major public health problems to date.

Many postmenopausal women appear healthy, with no clinical features of cardiovascular disease or low bone density. However, our results demonstrated a high prevalence of cardiovascular risk factors and low bone mineral density in postmenopausal women, irrespective of ethnicity. Underlying adiposity, and not BMI, should be a predictor of metabolic syndrome.

Contemporary management of these women should include a thorough assessment of their global cardiovascular and fracture risk during the peri-menopausal years. Relevant biochemical investigations and bone density assessment should be followed by goal-directed holistic management based on the individual’s risk profile. There should be judicious follow up to ensure the initiation of treatment, were necessary.
Locally, there are no clear guidelines for the screening and assessment of cardiovascular disease and low bone mineral density in the menopause. We therefore recommend the development of screening and treatment protocols locally to assist in risk stratification and optimal management of the older women.
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APPENDIX A

TABLES AND FIGURES

Correlation between height and total hip BMD in postmenopausal women

Correlation between height and total spine in African and Indian women
Correlation between WHR and total hip BMD in postmenopausal women

Correlation between WHR and total spine in African and Indian women
Correlation between SBP and total hip BMD in postmenopausal women

Correlation between SBP and total spine in African and Indian women
Correlation between DBP and total hip BMD in postmenopausal women

Correlation between DBP and total spine in African and Indian women
Correlation between LDL and total hip BMD in postmenopausal women

Correlation between LDL and total spine in African and Indian women
Correlation between HDL and total hip BMD in postmenopausal women

Correlation between HDL and total spine in African and Indian women
Correlation between TCG and total hip BMD in postmenopausal women

Correlation between TCG and total spine in African and Indian women
Correlation between height and lumbar spine in postmenopausal women

Correlation between height and Lumbar spine in African and Indian women
Correlation between WHR and lumbar spine in postmenopausal women

Correlation between WHR and Lumbar spine in African and Indian women
Correlation between SBP and lumbar spine in postmenopausal women

Correlation between SBP and Lumbar spine in African and Indian women
Correlation between DBP and lumbar spine in postmenopausal women

Correlation between DBP and Lumbar spine in African and Indian women
Correlation between HDL and lumbar spine in postmenopausal women

Correlation between HDL and Lumbar spine in African and Indian women
Correlation between TCG and lumbar spine in postmenopausal women

Correlation between TCG and Lumbar spine in African and Indian women
## Non Parametric correlations between cardio-metabolic variables and BMD in postmenopausal women

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APPENDIX B

QUESTIONNAIRE

A retrospective audit of the cardio-metabolic profile and bone mineral density in postmenopausal women attending Inkosi Albert Luthuli Central hospital menopause clinic from 01 July 2009 to 31 December 2010

SITE: Inkosi Albert Luthuli Central Hospital

CHARACTERISTICS

Study number: _______

Age: _____ years

Ethnicity:

<table>
<thead>
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GYNAECOLOGICAL HISTORY

Years since menopause: _____ years

presence of menopausal symptoms: yes 1, no 2

... if yes:

* Vasomotor symptoms (hot flushes and night sweats) 1/0
* Urogenital complaints - vaginal dryness & itching, discomfort during coitus, prolapse 1/0
* Both 1/0

previous gynaecology pathology: yes 1, no 2

if yes...

Abnormal uterine bleeding 1/0
Infertility 1/0
Postmenopausal bleeding 1/0
Ovarian cysts 1/0
Polycystic ovarian syndrome 1/0
Other 1/0

MEDICAL HISTORY

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<tr>
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<td>Hypercholesterolaemia</td>
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FAMILY HISTORY

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<tr>
<td>Non-traumatic fractures</td>
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</tr>
<tr>
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DRUG THERAPY

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<td>Alternatives to HRT (to relieve flushes)</td>
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<td>Hormone replacement therapy</td>
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<tr>
<td>Statins</td>
<td></td>
</tr>
<tr>
<td>Calcium supplements</td>
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<td>Antihypertensives</td>
<td></td>
</tr>
<tr>
<td>IHD</td>
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</table>
Vitamin D supplements ☐ Oral Hypoglycaemic agents ☐
Calcium and Vitamin D supplements ☐ Insulin ☐
Antiresorptive drugs eg. Biphosphonates ☐ None of above ☐

**DIET**
Meat ☐ 1
Vegetarian ☐ 2

**SOCIAL**
Exercise
Nil ☐ 1 Walking ☐ 2
Sedentary ☐ 3 Gym ☐ 4

**Level of education**
Primary school ☐ 1
High school ☐ 2
Tertiary ☐ 3
Nil ☐ 4

**Employment**
Unemployed ☐ 1
Employed ☐ 2

Smoking ☐ yes 1 no ☐ 2
Alcohol ☐ yes 1 no ☐ 2

**PHYSICAL EXAMINATION**
Height (cm) _______cm
Weight (kg) _______kg
Body mass index _______kg/m^2
Abdominal circumference (cm) _______cm
Hip circumference(cm) _______cm
Waist-Hip ratio _______

Blood pressure:
Systolic _______mmHg
Diastolic _______mmHg

Stigma of dyslipidaemia 1/0
Yes ☐ 1 (specify) xanthoma ☐ xanthelasma ☐ arcus senalis ☐
No ☐ 2
Not documented ☐ 3

Insulin resistance 1/0
yes ☐ 1 acanthosis nigricans ☐
no ☐ 2
Not documented ☐ 3

**HAEMATOLOGICAL INVESTIGATIONS**

Abnormal lipid profile
yes ☐ 1
no ☐ 2
not done ☐ 3

- total serum cholesterol _______mmol/L
- fasting triglycerides _______mmol/L
- HDL _______mmol/L
- LDL _______mmol/L
Abnormal fasting glucose +/- GTT
yes  1  value:_______mmol/L
no   2
not done  3

Abnormal insulin
yes  1  value: _____iu/ml
No   2
Not done  3

Abnormal Thyroid function test
yes  1  value: _TFT___  T4(tyroxine)_____
No   2
Not done  3

Hormone levels
FSH   ___
Oestradiol ___

RADIOLOGICAL INVESTIGATIONS

<table>
<thead>
<tr>
<th>DEXA</th>
<th>g/cm²</th>
<th>T score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Hip</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck of femur</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spine</td>
<td></td>
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</tbody>
</table>
APPENDIX C
NORMAL VALUES

Lipids

**Low density lipo-protein (LDL)**
Optimal: <2.6 mmol/L
near-above optimal : 2.6 – 3.3
borderline high: 3.4 – 4.1
high: 4.1 – 4.9
very high ≥ 4.9

**High density lipo-protein (HDL)**
Favourable <1 mmol/L
High ≥ 1.6

**Triglycerides (TCG)**
Normal <2.83 mmol/L
Borderline high 2.83 – 5.65
Hypertriglyceridaemia >5.65
Pancreatitis risk >11.3

**Cholesterol**
Normal <5.18 mmol/L
Borderline high 5.18 – 6.19 mmol/L
High ≥ 6.22 mmol/L

**Fasting Glucose**
normal 3.8 – 5.3 mmol/L

**Fasting Insulin**
Normal 3 – 25 mIU/ml

**TFT**

**T4 (thyroxine)**: normal 11-22.7 pmol/L
**TSH (thyroid stimulating hormone)** normal 0.27-4.2 mIU/L
FSH in menopause
23 - 116 mIU/ml

E2 (oestradiol) in menopause
0-136 mIU/ml

BMI (body mass index)
Underweight: 10-18.5
Healthy 18.5-25
Overweight 25-30
Obese 30 – 40
Very obese 40 - 70

BMD (Bone mineral density)
Tscore +2.5 to -1.0 : normal
Tscore -1.0 to -2.49 : osteopaenic
Tscore ≥ -2.5 : osteoporotic
14 January 2011

Dr J Moodley  
Department of Obstetrics & Gynaecology  
IALCH

Dear Dr Moodley

RE: PERMISSION TO CONDUCT RESEARCH AT IALCH

I have pleasure in informing you that permission has been granted to you by the Medical Manager to conduct research on: A retrospective audit of the cardio-metabolic profile and bone mineral density in postmenopausal women attending the IALCH menopause clinic from 01 July to 31 December 2010.

Kindly take note of the following information before you continue:

1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Kindly ensure that this office is informed before you commence your research.
4. The hospital will not provide any resources for this research.
5. You will be expected to provide feedback once your research is complete to the Medical Manager.

Yours faithfully,

[Signature]

Dr M E L Joshua  
Medical Manager
APPENDIX F

POSTGRADUATE APPROVAL

07 December 2010

Professor JS Bagratree
Department of Obstetrics and Gynaecology
Nelson R Mandela School of Medicine

Dear Professor Bagratree

PROTOCOL: “A retrospective audit of the cardio-metabolic profile and bone mineral density in postmenopausal women of African and Idian origin.” Student: J Moodley, student number: 200267776. (Obstetrics and Gynaecology)

The Postgraduate Education Committee ratified the approval of the abovementioned study on 07 December 2010.

Please note:

- The Postgraduate Education Committee must review any changes made to this study.
- The study may not begin without the approval of the Biomedical Research Ethics Committee.

May I take this opportunity to wish the student every success with the study.

Yours sincerely

[Signature]

Professor SR Thomson
Dean’s Assistant: MMed Programmes
Postgraduate Education Committee

CC. Dr J Moodley
Biomedical Research Ethics Committee
Westville Campus

Postgraduate Education Administration,
Medical School Campus

Postal Address: Private Bag 27, Congella, 4013, South Africa
Telephone: +27 (0)31 260 4782  FAX: +27 (0)31 260 4723  Email: jnnitjes@ukzn.ac.za  Website: www.ukzn.ac.za

Founding Campuses:  Edgewood  Howard College  Medical School  Pietermaritzburg  Westville

- 124 -
APPENDIX G

ETHICAL APPROVAL

01 April 2011

Dr. Jayeshree Moodley
Dept. of Obstetrics and Gynaecology
Nelson R. Mandela School of Medicine
University of KwaZulu-Natal

Dear Dr Moodley

PROTOCOL: A retrospective audit of the cardio-metabolic profile and bone mineral density in postmenopausal women attending the Inkosi Albert Luthuli Central Hospital menopause clinic from 01 July to 31 December 2010.

REF: BE203/010

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application dated 12 October 2010.

The study was provisionally approved pending appropriate responses to queries raised. Your responses dated 17 January 2011 to queries raised on 06 December 2010 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full ethics approval and may begin as from 01 April 2011.

Please ensure that all information collected is anonymized and managed with full regard to confidentiality.

This approval is valid for one year from 01 April 2011. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.


BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).
The sub-committee’s decision will be RATIFIED by a full Committee at its next meeting taking place on 10 May 2011.

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

[Signature]

Professor D.R Wassenaar
Chair: Biomedical Research Ethics Committee