Association between Risk Factors of Osteoporosis and Bone Mineral Density in Women of Different Ethnic Groups in a Malaysian Hospital

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ABSTRACT
Risk factors of osteoporosis need to be identified for prevention of osteoporosis. However, studies on the risk factors of osteoporosis in the Malaysian population are lacking. The study aimed to determine the relationship between potential risk factors of osteoporosis and hip BMD of postmenopausal women in a Malaysian tertiary hospital setting. A cross-sectional study was carried out on 76 postmenopausal women, who were scheduled for Dual-energy X-ray Absorptiometry (DXA) scan at UKM Medical Centre (UKMMC) from February to May, 2014. Interview sessions using structured questionnaire were conducted to obtain information on social demographic and potential risk factors of osteoporosis. The DXA scan results of the hip BMD for all the respondents were recorded to determine the association between the potential risk factors of osteoporosis and hip BMD. In this study, 44.7% of patients had normal hip BMD measurement (T score ≥-1.0), while 55.3% had low hip BMD measurement (T score ≤-1.0). Ethnically, among those who had low hip BMD measurement, 62% were Chinese, 26% were Malay, 10% were Indian and 2% were other ethnic groups. There were significant association between hip BMD with parity (p = 0.049), daily habitual tea consumption (p = 0.022), duration of sleep (p = 0.021) and Body Mass Index (BMI) (p = 0.041). There were no significant association (p>0.05) between hip BMD and family history of osteoporosis, lifestyle activities and smoking. Parity, habitual tea consumption and BMI were positively associated with hip BMD, whereas duration of sleep was negatively associated with hip BMD among postmenopausal women in UKMMC.

Key words: Osteoporosis, bone mineral density, risk factors

INTRODUCTION
Osteoporosis is defined as a progressive metabolic bone disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with increased risk of bone fragility and fracture (Leali et al., 2011). In the year 2000, 9 million osteoporotic patients worldwide suffered from fracture in which 1.6 million were hip fractures, 1.7 million were forearm fractures and 1.4 million were vertebral fractures (Johnell and Kanis, 2006).

The prevalence of osteoporosis was 24.1% among middle aged or elderly women (Lim et al., 2005). In addition, 30% of postmenopausal women suffered from osteoporosis (Bock and
Felsonberg, 2008). The major cause is the sudden drop of estrogen due to menopause, the main hormone which restrains bone resorptive activities of osteoclasts (Riggs and Melton III, 1986). The incidence of osteoporosis and its fracture complication is lower in men as testosterone level declines gradually with aging, thus enabling testosterone to maintain bone mass directly or alternatively, it could be converted to estrogen to influence bone remodeling (Chin and Ima-Nirwana, 2012).

DXA is the gold standard measurement for the diagnosis of osteoporosis as it gives an accurate and precise estimation of BMD (Levis and Altman, 1998). The World Health Organization (WHO) has defined osteoporosis as BMD of 2.5 standard deviations or more below the standard reference for maximum bone mineral density of young adult female (WHO., 1994). BMD could also be used to predict fracture risk (Black et al., 1992). The patient’s risk profile for osteoporosis is crucial in deciding whether they are indicated for BMD measurement which will in turn influence the management of osteoporosis (MOS., 2012).

Osteoporosis is known as one of the most important health problem affecting the elderly. Malaysia is a developing country in South East Asia with rising number of elderly people because of increasing life expectancy (Clayle and Bauze, 1989). Osteoporosis weakens the bones and exposes its sufferers to fracture. The common sites of fracture are the wrist, hip and spine. Hip fractures are associated with high morbidity and mortality rate of up to 20% in the first year after fracture. The majority of those who survived were disabled and only 25% resumed normal activities (Jensen and Bagger, 1982). Patients with hip osteoporotic fracture experienced long term morbidity including chronic pain, deformity and disability. Indirect morbidities include depression, self-isolation, low self-esteem and loss of independence. Osteoporotic fractures were reported to have great impact on society in terms of morbidity and mortality (Oka et al., 2006). Besides, the cost involved in the diagnosis and management of osteoporotic fracture is another great concern affecting health care policy planning (Woratanarath et al., 2005). The risk factors of osteoporosis need to be identified and managed properly for the prevention of osteoporosis and its related osteoporotic fracture. Careful consideration should be taken when conducting studies on the risk factors of osteoporosis as they may vary according to the population, gender, ethnicity and type of fractures (Cummings and Melton, 2002; Nguyen et al., 1996).

In Malaysia, the incidence of osteoporosis is not up to date. There was a report that the incidence of hip fractures among individuals above 50 years of age in 1997 was 90 per 100,000 population (Lee and Khir, 2007). These hip fractures were more likely contributed by osteoporosis. There are three major ethnic groups in Malaysia; Malay (55%), Chinese (25%) and Indian (10%) with different background and lifestyles. Currently, there has been no study to examine the local risk factors of osteoporosis in the Malaysian population.

Based on the Malaysian Clinical Practice Guidelines on the Management of Osteoporosis in 2012, the risk factors of osteoporosis can be categorized into non-modifiable and modifiable risk factors (MOS., 2012). According to the Asian Osteoporotic Study, there are many lifestyle factors that are associated with osteoporosis including a sedentary lifestyle and cigarette smoking (Lau et al., 2001).

There were no previous studies which determine the risk factors of osteoporosis related to the local social or lifestyle behavior in Malaysia. We had to do an educated assumption on several risk factors that are relevant to Malaysian modern lifestyles in which this study will focus on. These include having less number of children, high Body Mass Index (BMI), poor sleep pattern, sedentary lifestyle and smoking. Family history of osteoporosis is another risk factor which can be influenced by the different ethnic background of Malaysia. Other than that, we also include tea drinking as several studies have shown its association with osteoporosis and Malaysia being one of the top tea drinking countries.
This study aimed to determine the relationship between potential risk factors of osteoporosis and hip BMD among postmenopausal women who were referred for DXA scan in UKM Medical Centre. Identification of the risk factors unique to the local context is important to plan strategies for prevention of osteoporosis and its fracture complications.

MATERIALS AND METHODS

This cross sectional study was conducted in UKM Medical Centre (UKMMC), an academic teaching hospital affiliated with Universiti Kebangsaan Malaysia (UKM), one of the public higher education centers. It is located in Kuala Lumpur, the capital city of Malaysia.

Data collection was carried out from February to May of 2014 after obtaining ethical approval from UKM ethical committee. Patients scheduled for DXA scan by the clinicians were screened for eligibility to participate in the study. A total of 76 respondents who fulfilled the inclusion criteria (natural postmenopausal Malaysian women, aged >50 years old) agreed to participate in the study. The exclusion criteria for participation in the study are related to factors that are able to modify bone density which included intake of certain drugs (corticosteroid, heparin, anticonvulsant, immunosuppressant, thiazolidinedione), diagnosed with endocrine diseases (hyperthyroidism, hyperparathyroidism or Cushing’s syndrome), chronic diseases (renal impairment, liver cirrhosis, malabsorption, asthma, rheumatoid arthritis or some inflammatory diseases), malignancy, osteogenesis imperfecta and premature menopause (less than 45 years old). Consent was taken and interview sessions were carried out using structured questionnaire. The questionnaire was designed to collect information on social demographic data and selected modifiable risk factors (daily habitual tea consumption, active smoking; daily lifestyle activity, BMI, duration of sleep) and non-modifiable factors (family history of osteoporosis, parity). All the information provided by the respondents was treated as confidential.

The respondents were then allowed to continue with their DXA scan session and their hip BMD measurements were recorded. Data collected were keyed into SPSS version 2.0. The association between risk factors of osteoporosis and hip BMD measurement by DXA scan were analyzed using chi-square and Wilcoxon rank sum test.

RESULTS

A total of 76 respondents were included in the study. Sixteen (21.1%) respondents were below the age of 60, 38 (50.0%) were between 61 to 70 years old, 19 (25.0%) were between 71 to 80 years old and 3 (3.9%) were more than 80 years old (Fig. 1).

Among the ethnic groups, the majority of patients referred for DXA scan in UKMMC were Chinese, which comprised of 45% of respondents, followed by Malay (42%), Indian (10%) and other ethnic (3%) (Fig. 2a).

Among the respondents, 34 (45%) had normal hip BMD (T score >-1.0), while 42 (55%) had low hip BMD (T score <-1.0) (Fig. 2b). Among those respondents who had low hip BMD, 62% were Chinese, 26% were Malay, 10% were Indian and 2% were other ethnic (Fig. 2c).

Association between hip BMD measurement and parity, habitual tea consumption, duration of sleep and BMI among postmenopausal women in UKMMC: A total of 19 (45%) respondents with parity of 2 or less had low hip BMD compared to only 8 (24%) respondents with parity of 2 or less had normal hip BMD. The risk of low hip BMD was increased 2.68 times in respondent with 2 or less children compared to those with 3 or more children (Table 1).
Fig. 1: Age group of respondents who were referred for DXA scan in UKMMC

![Age Group Chart]

Fig. 2(a-c): (a) Prevalence of ethnicity, (b) Hip BMD and (c) Percentage of low hip BMD according to ethnicity among respondents who were referred for DXA scan in UKMMC

![Ethnicity and BMD Charts]

About 11 (26%) respondents who never drink tea had low hip BMD compared to only 1 (3%) with normal hip BMD. There was a significant relationship between habitual tea consumption with
Table 1: Association between hip BMD with parity, daily habitual tea consumption and duration of sleep

<table>
<thead>
<tr>
<th>Risk factor and variables</th>
<th>Bone density of hip</th>
<th></th>
<th></th>
<th>X²</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>n = 42</td>
<td>%</td>
<td>Normal</td>
<td>n = 34</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2</td>
<td>19</td>
<td>45</td>
<td>8</td>
<td>24</td>
<td>27</td>
</tr>
<tr>
<td>≥3</td>
<td>23</td>
<td>55</td>
<td>26</td>
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<td>49</td>
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<tr>
<td>Daily habitual tea consumption</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11</td>
<td>26</td>
<td>11</td>
<td>32</td>
<td>22</td>
</tr>
<tr>
<td>No</td>
<td>20</td>
<td>48</td>
<td>22</td>
<td>65</td>
<td>42</td>
</tr>
<tr>
<td>Never</td>
<td>11</td>
<td>26</td>
<td>1</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Duration of sleep (h)</td>
<td></td>
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<td></td>
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<tr>
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<td>13</td>
<td>31</td>
<td>14</td>
<td>41</td>
<td>27</td>
</tr>
<tr>
<td>6-7.9</td>
<td>17</td>
<td>40</td>
<td>19</td>
<td>56</td>
<td>36</td>
</tr>
<tr>
<td>≥8</td>
<td>12</td>
<td>29</td>
<td>1</td>
<td>3</td>
<td>13</td>
</tr>
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</table>

Table 2: Association of hip BMD with body mass index

<table>
<thead>
<tr>
<th>Hip BMD</th>
<th>N</th>
<th>Mean rank</th>
<th>Sum of rank</th>
<th>W</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Normal</td>
<td>34</td>
<td>44.26</td>
<td>1505.00</td>
<td>513.0</td>
<td>0.041</td>
</tr>
<tr>
<td>Low</td>
<td>42</td>
<td>33.83</td>
<td>1421.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>76</td>
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</table>

Hip BMD measurement by DXA scan among the respondent in the study (p = 0.022). Daily habitual tea consumption was protective against low hip BMD among postmenopausal women in the study (Table 1).

A total of 12 (29%) respondents who sleep 8 h and more had low hip BMD compared to only 1 (3%) with normal hip BMD. There was a significant relationship between the duration of sleep with hip BMD among respondents in the study (p = 0.021). Based on the finding of this study, the risk of getting low hip BMD was 12 times higher in postmenopausal women with duration of sleep of 8 h and more (Table 1).

Most respondents with normal hip BMD had higher BMI. This was evidenced by the higher sum of rank of 1505 compared to 1421 (Table 2). There was a significant relationship between BMI and hip BMD (p = 0.041). Hence, postmenopausal women with high BMI tend to have normal BMD (Table 2).

**Association between hip BMD and daily physical activity, smoking status and habitual of carbonated drink consumption among postmenopausal women in UKMMC:** A total of 26 (62%) respondents with daily physical activities of less than 30 min had low hip BMD compared to 26 (76%) respondents with daily physical activities of 30 min or more which had normal hip BMD. However, there was no significant relationship between daily physical activity with hip BMD measurement (p = 0.219) (Table 3).

A total of 17 (40%) respondents with positive family history of osteoporosis had low BMD, while 10 (29%) respondents with positive family history of osteoporosis had normal BMD. There was no significant relationship between family history of osteoporosis with hip BMD (p = 0.529) (Table 3). About 40 (65%) respondents who never smoke had low hip BMD while 34 (100%) respondents who never smoke had normal hip BMD. There was no significant relationship between smoking status with hip BMD (p = 1.000) (Table 3).
Table 3: Association of hip BMD with daily physical activity, family history of osteoporosis and smoking status

<table>
<thead>
<tr>
<th>Risk factors and variable</th>
<th>BMD</th>
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<tr>
<td></td>
<td>Low</td>
<td>Normal</td>
<td>Total</td>
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<td>Daily physical activity (min)</td>
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<tr>
<td>&lt;30</td>
<td>16</td>
<td>38</td>
<td>8</td>
<td>24</td>
<td>24</td>
<td>32</td>
<td>1.845</td>
<td>0.219</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30</td>
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<td>62</td>
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<tr>
<td>Positive</td>
<td>17</td>
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<td>10</td>
<td>29</td>
<td>27</td>
<td>36</td>
<td>1.392</td>
<td>0.529</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Never smoke</td>
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<td>95</td>
<td>34</td>
<td>100</td>
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<td>1.540</td>
<td>1.000</td>
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<td>100</td>
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<td>1</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Active smoker</td>
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<td></td>
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</table>

DISCUSSION

This study has discovered several positive associations between specific risk factors of osteoporosis and hip BMD in a Malaysian hospital population. The risk factors studied were shown to be associated with osteoporosis which include cigarette smoking (Lau et al., 1998), low body mass index (Ravn et al., 1999), family history of osteoporosis (Fleming, 1992) and reduced sunlight exposure (Stillman et al., 1986).

As expected the Chinese ethnic in Malaysia has the highest percentage of low BMD. This was consistent with the ethnic distribution of hip fracture incidence published in 2007 (Lee and Khir, 2007). The risk of osteoporosis for Chinese ethnic also appeared to be higher in the United States as studies reported that the BMD values of immigrant Chinese women were lower than Caucasian women (Lauderdale et al., 2003; Babbar et al., 2006). It was postulated that immigrant Chinese in America are at higher risk of osteoporosis due to poor nutrition in childhood, have thin body habitus and have difficulty accessing medical care because of finances, lack of insurance, language and distrust of the medical system.

There is a positive association between parity and hip BMD, in which normal hip BMD is associated with higher parity. Our results were in accordance with several studies (Streeten et al., 2005; Kauppi et al., 2011; Michaelsson et al., 2001). The reason behind the positive association between parity and BMD level is that serum estrogen levels remained elevated throughout pregnancy, thus exerting protective effects on bone from osteoporosis. Furthermore, estrogen improves neuromuscular performance, muscle strength and hence prevention of hip fracture (Sipila et al., 2006; McEwen, 1999). During pregnancy, there is increased dietary calcium and maternal intestinal calcium absorption to provide adequate calcium requirement for fetal bone mineralization, without any net loss in maternal bone mineral density (Ritchie et al., 1998). The maternal intestinal calcium absorption is increased as the result of increased 1, 25-dihydroxy vitamin D level during pregnancy.

Malaysia is one of the main tea-drinking countries, ranked at 87th in the world with the annual per capita tea consumption of 0.80 kg (FAO, 2012). Habitual tea drinkers can be defined by tea consumption of 120 mL per day or more for at least a year (Yang et al., 2004). Based on the levels of fermentation, tea can be categorized into green (non-fermented), oolong (partially fermented)
and black (fermented) teas. Tea contains thousands of chemical compounds that may affect the human body in many aspects, including bone metabolism. In the present study, a significant positive association was found between habitual tea consumption with hip BMD level. When compared with non-habitual tea drinkers, habitual tea drinkers had significantly greater hip BMD level.

Several studies have reported similar positive association between habitual tea consumption and BMD level (Grosso et al., 2014; Hegarty et al., 2000; Hoover et al., 1986). Other studies verified that tea has protective effects against hip fracture (Kanis et al., 1999; Hillier et al., 2000). These beneficial effects may be contributed by the high concentrations of fluoride, flavonoids and phytoestrogen in tea. These chemical compounds have been shown to promote BMD (Wu et al., 2002). In terms of anti-oxidant activity, green tea has high content of catechin, another subgroup of flavonoid, which may promote BMD level in postmenopausal women. Epigallocatechin-3-gallate, one of the green tea catechin, has stimulatory effects on osteogenesis of mesenchymal stem cells (Chen et al., 2005). In addition, isoflavonoids (subgroups of flavonoids) has weak estrogenic effect which was beneficial in maintaining BMD of estrogen-deficient postmenopausal women (Hernandez-Avila et al., 1993; Miskec, 1993). Habitual tea consumption of any type of tea exhibited positive correlation with BMD (Wu et al., 2002).

There are limited studies regarding the association between sleep duration and BMD level. Our study showed that the risk of getting low hip BMD was 12 times higher in postmenopausal women who slept more than 8 h. This showed that longer duration of sleep was associated with lower hip BMD. Kim et al. (2014) reported significant association between prolonged sleeping duration and lower hip BMD in elderly Korean women. In another study, Kobayashi et al. (2012) showed that middle-aged and elderly Japanese adult who slept longer have higher risks of osteoporosis. These two studies on Asian subjects were consistent with the findings of our study. In contrast, Fu et al. (2011) showed that decreased sleep duration was associated with lower BMD especially in middle aged or elderly Chinese women.

Kobayashi et al. (2012) hypothesized that longer duration of sleep adversely affected BMD via reduced daily mechanical loading due to inactivity and lower light-induced estrogen levels due to limited light exposure. Excessive amount of sleep (decreased activity) could reduce biomechanical forces on the bone, resulting in signals being sent for bone elimination due to the lower requirement for bone mass (Riggs and Melton III, 1995).

In terms of BMI, our study showed that postmenopausal women with higher BMI have normal hip BMD. Other studies have reported positive relationship between body weight and BMD (Chen et al., 1997). The femoral BMD was positively correlated with BMI in middle aged or elderly women (Kirchengast et al., 2001). Women with low BMI (16-23) had up to 12% lower baseline hip and spine BMD as compared to those with high BMI (27-40) (Ravn et al., 1999). In another study, bone loss among women weighing less than 60 kg was more pronounced than those weighing more than 70 kg (Nguyen et al., 1998). In fact, weight reduction accelerated the rate of bone loss in postmenopausal women (Felson et al., 1993). Based on these studies, BMI was shown to play an important role in the regulation of bone mass.

It was hypothesized that these positive relationship was contributed by mechanical (gravitational) forces on bone by weight loading, which had been shown to increase bone mass (Glauber et al., 1995). Obese postmenopausal women have more adipose tissue which could convert androstenedione to active estrogen. Besides that, the aromatase present in adipocytes could convert testosterone to estradiol or estrone, which in turn restrains bone reabsorption (Rosen and Bouxsein, 2006).
Family history is a recognised risk factor for osteoporosis (Kanis et al., 2004; Van der Voort et al., 2001). It was reported to be a significant, independent risk factor for osteoporosis in US women (Robitaille et al., 2008). However, we could not find any association between family history and BMD level in our subjects. The low reporting of osteoporosis in family members by our subjects could be due to lack of knowledge and awareness of osteoporosis, impaired memory, or an insufficient availability of screening methods for the detection of osteoporosis among family members (Ribeiro et al., 2000; Yu and Huang, 2003).

Smoking could be categorized into current or active smoker, past or ex-smokers and non-smoker (Howard et al., 1998). We found no association between smoking and BMD level. However, our result could be biased as there were only one active smoker and one ex-smoker. The low smoking rate in Malaysian women is likely due to traditionally unacceptable habit by Malaysian culture and religious factors (Egger et al., 1996; Manaf and Shamsuddin, 2008).

In our study, we could not find any significant association between daily physical activities and BMD level. Similar finding was reported by Coupland et al. (1999), in which there was no significant association between BMD and total physical activity. Hagberg et al. (2001) reported that only moderate physical activity was significantly associated with BMD level. Since we only measure normal daily activities, the intensity may not be high enough to exert mechanical loading on the bone.

The limitation for our study was the short time duration which resulted in a low number of participants. This could have affected some results to be negative. However, this preliminary Malaysian population data have yielded many positive insights and will serve as a stepping stone for future larger studies.

CONCLUSION

In conclusion, parity, habitual tea consumption, duration of sleep and BMI were associated with low BMD in our local postmenopausal population. These information would be useful for prevention of osteoporosis in the local context to keep in check fragility fracture cases.

ACKNOWLEDGMENTS

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REFERENCES


