INFLUENCE OF PHYSICAL ACTIVITY, SEDENTARY LIFESTYLE AND BONE BIOMARKERS ON BONE HEALTH AMONG ADOLESCENTS IN KOTA BHARU, KELANTAN

by

TEO PEY SZE

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DEDICATION

This dissertation is lovingly dedicated to my family, particularly my parents, Teo Chok Joo and Lee Kah Heng. Their endless love, support and encouragement has sustained me throughout my life. A special feeling of gratitude to my lovely sister, Teo Pey Huey, who has always being there for me throughout my entire postgraduate study. I also dedicate this work to my uncles and aunties, especially to Teo Kuek Chong, Low Gek Luang and Teo Kiok Long who believe in the pursuit of dreams and have been my best cheerleaders.

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LIST OF ABBREVIATIONS

PA	Physical activity
MVPA	Moderate-to-vigorous physical activity
SSR	Small screen recreation
Ca	Calcium
Phos	Inorganic phosphorus
Cr	Creatinine
ALP	Alkaline phosphatase
P1NP	Procollagen type I amino-terminal propeptide
OC	Osteocalcin
CTx	Collagen type I cross-linked C-telopeptide
PTH	Parathyroid hormone
BMI	Body mass index
WC	Waist circumference
WHR	Waist-hip ratio
TBF	Total body fat
%BF	Percent body fat
ARF	Android regional fat
TLM	Total lean mass
BMC	Bone mineral content
BMD	Bone mineral density
BA	Bone area
DXA	Dual energy X-ray absorptiometry
PBM	Peak bone mass

PENGARUH DI ANTARA AKTIVITI FIZIKAL, GAYA HIDUP SEDENTARI DAN PETUNJUK BIOKIMIA TULANG TERHADAP KESIHATAN TULANG DALAM KALANGAN REMAJA DALAM KOTA BHARU KELANTAN

ABSTRAK

Pencapaian jisim tulang puncak pada masa pertumbuhan adalah sangat penting untuk mengurangkan risiko keretakan osteoporosis pada kemudian hari. Pemahaman dan pengenalan faktor-faktor gaya hidup seperti aktiviti fizikal dan gaya hidup yang berkaitan dengan pertumbuhan dan pemeliharaan jisim tulang yang tinggi dalam kalangan kanak-kanak dan remaja adalah amat penting bagi memaksimakan jisim tulang puncak sewaktu tempoh pertumbuhan yang kritikal. Oleh itu, objektif utama kajian ini adalah untuk mengkaji pengaruh aktiviti fizikal, gaya hidup sedentari dan petunjuk biokimia darah tulang terhadap status kesihatan tulang yang ditentukan dengan pengukuran tenaga dwi sinar-X absorptiometri (DXA) dalam kalangan 455 orang remaja lelaki dan perempuan berbangsa Melayu dan Cina yang berumur lingkungan di antara 12 hingga 19 tahun di Kota Bharu, Kelantan. Borang soal-selidik yang telah divalidasi digunakan untuk menentukan amalan aktiviti fizikal, amalan sedentari yang berunsurkan skrin (SSR) dan corak pemakanan, manakala komposisi tubuh badan dan kekuatan otot bagi anggota atas dan bawah dinilai dengan menggunakan pengukuran antropometri, dinamometer tangan dan isokinetik. Bagi penilaian status kesihatan tulang, kandungan mineral tulang (BMC) dan kepadatan mineral tulang (BMD) bagi keseluruhan badan (TB), tulang paha proksimal (PF), tulang belakang lumbar L2-L4 (LS) dan bahagian tulang tertentu

diukur dengan menggunakan DXA. Purata umur peserta kajian adalah 15.4 ± 1.9 tahun, dan kebanyakannya (72.5%) mempunyai indek jisim tubuh (BMI) yang normal. Perbandingan mengikut jantina menunjukkan remaja lelaki mengamalkan jumlah harian aktiviti fizikal (PA) (1.5 *vs.* 1.0jam/hari; $P<0.001$) dan aktiviti fizikal sederhana kepada aktivit lasak (MVPA) (1.2 *vs.* 0.4jam; $P<0.001$) yang lebih tinggi berbanding dengan perempuan; manakala pengamalan masa SSR adalah sama di antara jantina (3.1 *vs.* 3.3jam/hari). Secara umumnya, terdapat dua-pertiga daripada remaja (63.3%) mengamalkan amalan aktiviti fizikal aktif yang rendah, ia ditentukan oleh amalan MVPA harian yang kurang daripada sejam, di mana peratusan adalah tinggi dalam kalangan perempuan (80%) berbanding dengan remaja lelaki (34%). Analisis regresi linear berganda menunjukkan umur ($P=0.012$) dan jantina ($P<0.001$) merupakan penentu secara negatif terhadap MVPA harian model yang digunakan setelah penyelarasan bagi etnik, status sosio-demografi dan pengamalan pemakanan yang diuji. Tambahan pula, umur ($P<0.001$) dan amalan sarapan pagi seharian ($P<0.05$) muncul sebagai penentu secara negatif, manakala kumpulan etnik ($P<0.01$) sebagai penentu secara positif terhadap sedentari SSR model yang digunakan. Pengaruh di antara faktor-faktor gaya hidup dengan status kesihatan tulang diuji untuk menggunakan kumpulan berdasarkan jumlah dan intensiti aktiviti fizikal harian dan sedentari SSR. Ia menunjukkan bahawa remaja lelaki yang mengamalkan jumlah dan intensiti akviviti fizikal harian yang tinggi iaitu PA$\geq$1.5jam/hari dan MVPA$\geq$1jam/hari mempunyai BMC yang lebih tinggi pada TB, bahagian inter-trochanter, dan kaki (semuanya dengan $P<0.05$), dan BMD yang lebih tinggi pada bahagian TB, PF, LS, lengan dan kaki (perkaitannya sekurang-kurangnya $P<0.01$), berbanding mereka yang mengamalkan PA dan MVPA yang rendah. Pengaruh positif secara signifikan hanya dikenalpasti di antara jumlah PA dan MVPA tinggi

dengan BMC dan BMD pada TB dan bahagian kaki dalam kalangan perempuan. Tambahan pula, lelaki yang mempunyai MVPA yang tinggi juga menunjukkan kekuatan otot genggaman tangan (P<0.01), *quadriceps* (P<0.05) dan *hamstring* (P<0.001) yang lebih tinggi berbanding dengan mereka yang mengamalkan MVPA harian yang rendah. Perkaitan secara signifikan hanya ditunjukkan di antara amalan MVPA dan kekuatan otot *hamstring* dalam kalangan remaja perempuan (P<0.01). Sebaliknya, jumlah gaya hidup sedentari hanya menunjukkan perkaitan secara signifikan dan negatif terhadap profil komposisi tulang bagi perempuan. Remaja perempuan yang mengamalkan tempoh masa SSR yang tinggi mempunyai BMD yang lebih rendah di LS (P<0.05) dan saiz tulang pada TB (P<0.05), bahagian lengan (P<0.01) dan kaki (P<0.05) berbanding dengan mereka yang mengamalkan SSR yang rendah. Petunjuk biokimia darah tulang juga menunjukkan perkaitan secara negatif dengan profil komposisi tulang bagi semua bahagian tulang yang diukur, setelah mengambil kira faktor-faktor lain seperi status pertumbuhan pubertal dan etnik. Kajian ini menunjukkan bahawa penyertaan masa dan intensiti aktiviti fizikal yang tinggi akan menghasilkan kesan yang positif terhadap profil komposisi tulang dalam kalangan remaja serta mempunyai pengaruh yang berkesan dan baik terhadap bahagian tulang yang sangat sensitif dengan loading mekanikal. Selain itu, gaya hidup sedentari juga menunjukkan pengaruh yang negatif terhadap status kesihatan tulang dalam kalangan perempuan. Oleh itu, galakan secara berterusan terhadap pengamalan gaya hidup yang aktif perlu dititikberatkan dalam kalangan remaja bagi memaksimakan pertumbuhan dan pemeliharaan jisim tulang puncak sewaktu tempoh pertumbuhan kritikal.

INFLUENCE OF PHYSICAL ACTIVITY, SEDENTARY LIFESTYLE AND BONE BIOMARKERS ON BONE HEALTH AMONG ADOLESCENTS IN KOTA BHARU, KELANTAN

ABSTRACT

Maximum attainment of peak bone mass (PBM) during the growing years is ultimately important to reduce the risk of osteoporotic fracture later in life. Understanding and identification of lifestyle factors such as physical activity (PA) and other lifestyle practices that are associated with higher bone mass accruals in children and adolescents is important in order to optimize the PBM during these critical years of growth. Therefore, the main objective of the study was to determine the influence of PA, sedentary behavioural practice and blood biomarkers of bone remodeling on bone health status, as assessed by a dual energy *X*-ray absorptiometry (DXA) in 455 adolescent boys and girls of Malay and Chinese-origins aged 12 to 19 years of age in Kota Bharu, Kelantan. Validated questionnaires were used to assess PA, sedentary small screen recreation (SSR) practice assessments, and dietary food intakes, whereas body composition and muscular strength of the upper and lower extremities were determined using anthropometry measurements, handgrip and isokinetic-dynamometers. For the bone health status, bone mineral content (BMC), bone area (BA) and bone mineral density (BMD) were assessed for total body (TB), at the lumbar spine (L2-L4), proximal femur and specific regions of interest using the DXA device. Mean age of the adolescents were 15.4 ± 1.9 years, with majority (72.5%) had a normal ranges of body mass index (BMI). Sex-specific comparisons on lifestyle practices showed that adolescent boys had significantly higher levels of

daily PA status (1.5hours *vs.* 1.0hours; $P<0.001$) and intense moderate-to-vigorous PA (MVPA) (1.2 *vs.* 0.4hours; all, $P<0.001$), compared to the girl participants. In contrast, sedentary SSR practices were similar between genders (3.1 *vs.* 3.3hours/day). In general, about two-thirds of adolescents (63.3%) had low daily active PA practice, as determined by the MVPA less than one hour per day, with higher proportion found in girls (80%) than in adolescent boys (34%). Multiple linear regression analyses showed that age ($P=0.012$) and sex ($P<0.001$) emerged as significant negative determinants on daily MVPA levels, after adjusting for ethnicity, socio-demographic status and dietary behaviours. Moreover, age ($P<0.001$) and daily breakfast consumption ($P<0.05$) emerged as negative independent determinants; whereas ethnicity ($P<0.01$) was significant positive independent determinant on sedentary SSR levels. The influence of these lifestyle factors was further examined based on duration spent on PA levels and sedentary SSR levels. It showed that participant boys with higher total PA group$\geq$1.5hours/day and MVPA group$\geq$1hour/day, respectively, had a significantly higher size-adjusted BMC of TB, intertrochanter and leg region (all, $P<0.05$) and the BMD of the TB, PF, LS, regional arm and leg region (at least, $P<0.01$) than that of those at low PA and MVPA levels. Only a significant positive influence was found between high total PA and MVPA with BMC and BMD of the TB and leg region in adolescent girls. Furthermore, boys with high MVPA levels showed significantly higher of muscle strength of the handgrip ($P<0.01$) and lower extremity strength of the quadriceps ($P<0.05$) and the hamstring strength ($P<0.001$) than those at lowest MVPA level. Only a significant positive association was found between high MVPA level and hamstring muscle strength in girls ($P<0.01$). On the other hand, sedentary lifestyle practices was also found to be negatively associated with bone health profiles assessed in girls, in which

high SSR practice showed a significantly lower lumbar spine BMD (P<0.05) and bone area of the TB (P<0.05), arm (P<0.01) and leg region (P<0.05) compared to those who only practiced low SSR level. Blood biomarkers of bone remodeling were significantly and negatively associated with all skeletal sites assessed, after adjustments for pubertal growth and ethnicity. These present results showed that higher habitual total and intense PA level could contributed to positive bone mass profiles in these adolescents, and it has profoundly influence on weight-loaded skeletal region assessed. In addition, sedentary lifestyle practices also exert a negative influence on bone health assessed in adolescent girls. Therefore, encouragement of active lifestyle practices in children and adolescents should be promoted to optimize the peak bone mass accretion during the critical years of growth.

CHAPTER 1

INTRODUCTION

1.0 Introduction of the osteoporosis

Osteoporosis is defined as a systematic skeletal disorder disease that characterized by low bone mass, deterioration of skeletal architecture and compromised bone strength, which consequently increased risk of bone fragility and susceptibility to fracture (Consensus Development Conference, 1993). Several skeletal sites such as proximal femur (hip), vertebrae (spine), and distal forearm (wrist) are regarded as most commonly reported fractures attributed to osteoporosis, in which it exerts significant clinical consequences to affected individual such as morbidity and prolonged medical healthcare and medical expenses and to some extent may cause death due to serious complications from osteoporotic-related fractures (Riggs and Melton III, 1995; Reginster and Burlet, 2006; Leboime *et al.*, 2010).

An increasing prevalence of osteoporosis is considered as emerging serious public health challenges worldwide. It is estimated that the prevalence of osteoporosis is expected to rise to threefold in next 60 years from 1990 to 2050 worldwide (Prins *et al.*, 1998; Gullberg *et al.*, 1997) and the healthcare cost is expecting to escalate rapidly. For instance, hip fractures alone accounting for almost two third of the total annual fractures expenses in USA (Ray *et al.*, 1997) and it is reported that the annual expenditures for medical treatment for osteoporotic-related fractures in 1995 is estimated to cost around $13.8 billion in the United States, which the amount was far exceeding the total expenses spent for breast and gynaecological cancers (Ray *et al.*, 1997; Hoerger *et al.*, 1999). Moreover, it is found that approximately 10% to 20%

women whom sustained a hip fracture become totally dependent on their daily living and more than 20% required a long-term nursing care for their normal daily activities (Salkeld *et al.*, 2000).

Osteoporotic fracture, especially the hip fracture, is considered to be a major public health problem and challenge in Asian countries (Lau *et al.*, 2001), with more than half of the hip fractures (3.2 million) were expected to occur in Asia in 2050 (Cooper *et al.*, 1992). The trend and prevalence of osteoporosis is expecting to increase dramatically due to increasing of the numbers of aging populations aged 65 years and above from 145 million in 1990 to 894 million in 2050 (Cummings and Melton, 2002). In a recent data by Lau (2010), it is reported that approximately 17% and 29% of all types of osteoporotic fractures, respectively, are found in the regions of the Southeast Asia and West Pacific, as compared with 35% prevalence rates in Europe regions (Lau, 2010), suggesting that osteoporosis is becoming as an alarming healthcare burden, which could lead to serious adverse clinical consequences to an affected individual and the nations (Cummings and Melton, 2002; Melton, 2000). Based on the study of the Asian Osteoporosis Study (AOS) in four countries namely, Hong Kong, Singapore, Malaysia and Thailand found that a significant increase in the prevalence of hip fracture in these countries, i.e. 639, 606, 306 and 383 per 100,000 population respectively which approaching the hip fractures incidence in Caucasian countries (Lau *et al.*, 2001), whereby the prevalence of osteoporosis is higher among women than that of their men counterparts.

1.0.1 Aetiology of osteoporosis development

Although the osteoporosis manifests itself as a disease of the elderly and postmenopausal women, whose have a low bone mass, caused by an excessive bone loss during aging (Kovacs, 2008), but there is an emerging body of evidence suggests that lower attainment of peak bone mass during critical growing years is also regarded as one of the determinant factor associated with the higher risk of osteoporotic fractures later in life (Bailey *et al.*, 1996; Hernandez *et al.*, 2003). For instance, it is found that the incidence of osteoporotic-related fractures in postmenopausal women could be delayed by 13 years with an increase in 10% of bone mass during childhood (Hernandez *et al.*, 2003). In contrast, a 10% increase in the age of menopause or a 10% decrease in the age-related non-menopausal bone loss have shown to be only delayed the onset of osteoporosis by two years (Hernandez *et al.*, 2003), which further indicating that the peak bone mass might be the most important factor in preventing osteoporosis in later life. In general, the aetiology of osteoporosis could be attributed to two main causes namely, excessive rapid bone loss during aging or lower attainment of peak bone mass (PBM) accretion during childhood and adolescence or both (Melton, 1991; Riggs *et al.*, 1991; Bailey *et al.*, 1996; Center and Eisman, 1997).

1.1 Peak bone mass (PBM)

Peak bone mass (PBM) is defined as an amount of bony tissue present at the end of skeletal maturation (Bonjour *et al.*, 1994). Approximately 90% of maximum peak bone mass is achieved at the end of adolescence growth- the age of 18 and about 25% PBM is occurred during the critical growth spurt between 2 years of peak height

velocity (Bailey *et al.*, 1997). Several non-modifiable and modifiable environmental factors have been identified that could play an important contributing factors on the maximum attainment of PBM in growing children and adolescents (Heaney *et al.*, 2000). Although it is generally agreed that non-modifiable such as genetic factor play an major role, which explaining around 80% of the total variance at a given age to the variation of maximum attainment of PBM (Guéguen *et al.*, 1995; Duren *et al.*, 2007), but other modifiable factors such as body composition (Hrafnkelsson *et al.*, 2010), hormonal status (Bonjour *et al.*, 1994), lifestyle physical activity status (Janz *et al.*, 2001; Pettersson *et al.*, 2010) and dietary factors (Vatanparast *et al.*, 2007) could also influence the full potential of genetic-determined of PBM.

1.1.1 Factors associated with PBM- Physical activity

Physical activity has found to be associated with bone health across the lifespan (Twisk, 2001; Kohrt *et al.*, 2004; Bloomfield, 2005; Boyd *et al.*, 2011). It is reported that up to 17% of the variance in bone mineral density levels is achieved by active physical activity levels in adolescent and young adults (Welten *et al.*, 1994). In addition, children who were practicing active physical activity levels had significantly higher bone mass than their counterparts of low habitual physical activity levels during two years of peak bone mass accrual (Tobias *et al.*, 2007; Janz *et al.*, 2010).

Apart from the frequency of PA, it is also showed that high intensity of mechanical loading physical activities is a major determinant of higher bone mass in children (Morris *et al.*, 1997; MacKelvie *et al.*, 2003). Based on the mechanostat theory, the

direct effect of physical activity or exercise on bone mass is mainly based on the association between the intensity of strain on bone and adaptation of bone to that particular stimulus (van Der Meulen *et al.*, 1993).

However, most studies of the influence of physical activity on bone mass accretion among apparently healthy children and adolescents are largely focused on Caucasian-origin populations, in which the intensity and duration of the habitual physical activity level may different between Caucasian children and Asian children. It is reported that the frequency and intensity of PA level of children and adolescents in the Asian regions are relatively lower than the PA levels reported in Caucasian populations (Rhodes *et al.*, 2006; Foo *et al.*, 2009). In addition, the precise elucidation of the duration, frequency, intensity as well as the magnitude of physical activity that is augmented greater bone mass accretion in growing children and adolescents still remains uncertain among Asian populations. Therefore, comprehensive understanding of various physical activity measures such as magnitude, frequency and intensity of habitual physical activity is highly required in order to determine the potential contributing factors associated with greater bone mass in these growing Asian populations.

1.1.2 Factors associated with PBM- Sedentary practices

Apart from the active habitual PA status, there is an increasing evidence suggesting that sedentary practices, also known as sedentary physiology, is associated with an adverse effects on general well-being and health status (Hamilton *et al.*, 2004; Healy *et al.*, 2008). It has been defined as the low end of physical activity continuum where

most of the changes in disease occur, in which it exerts a unique, independent and qualitatively different effects on human physiological response and health consequences, which is totally different than the physical activity (Hamilton *et al.*, 2004; Healy *et al.*, 2008).

Several epidemiological studies found that sedentary lifestyles is associated significantly with greater risk of non-communicable diseases such as type 2 diabetes (Zimmet *et al.*, 2001), coronary heart disease (Owen *et al.*, 2009), obesity (Lakerveld *et al.*, 2011) and colon cancer (Powell and Blair, 1994). In addition, sedentary livings are also found to be responsible for about one-third of deaths of those non-communicable diseases (Powell and Blair, 1994). Those study findings also stated that association between sedentary behaviour and bone mass accrual is mediated by bone resorption without any concomitant changes in bone formation (Kim *et al.*, 2003; Smith *et al.*, 2003). There is very limited information pertaining to sedentary behaviour practices on the bone health, with only a study found out that the sedentary behaviours associated with the bone mass attainment during the prepuberty among adolescents when growth may relatively independently from the sex hormones (Wang *et al.*, 2003). Therefore apart from determine the influence of physical activity and sedentary practices with bone mass accrual among adolescents, this study is also aimed to elucidate the mechanism involved between physical activity and sedentary with bone mass, whether this effect is mediated by the mechanism of bone remodeling markers of bone formation and bone resorption and/ or parathyroid hormones.

1.1.3 Factors associated with PBM- Blood bone markers

Biochemical markers of bone remodeling are also associated with the bone health especially in the osteoporosis aspect. Biochemical markers of bone remodeling is defined as the fragments of skeletal tissue proteins or enzymes specific to osteocytes released into the circulation during the bone turnover or remodeling process (Carey John *et al.*, 2006), which is divided into two different groups namely, bone resorption markers and bone formation markers. The resorption markers reflect its activity on the osteoclast which is also known as the bone resorption cells and/or collagen degradation, while the bone formation marker is an indicator involve in osteoblastic synthetic activity or postrelease metabolism of procollagen (Christenson, 1997). The occurrence of osteoporotic fractures in the elderly occurs is attributed to the higher rate of bone turnover exceeds the bone formation. Thus, bone biochemical markers for both bone formation and bone resorption are important to indicate and predict the risk of occurrence of osteoporosis among elderly and postmenopausal women (Seeman, 1994). Moreover, parathyroid hormone (PTH) is an 84-amino acid polypeptide secreted by parathyroid glands which acts as the principal modulator by response the small changes of Ca^{2+} (Rosen, 2004). Hence, PTH is important in activating the interactions between osteoclasts (bone resorption) and osteoblasts (bone formation). However, the use of biochemical markers of bone remodeling and PTH in growing children and adolescents is still limited, which mainly focused on illness children. Understanding the association between bone remodeling markers, PTH and bone mass accretion as well as whether these effects are mediated by other external factor such as physical activity and sedentary is particularly important in bone homeostasis in growing children and adolescents. To our knowledge, none of

the studies have been investigated this mechanism in Asian population especially in populations of diverse ethnicity.

1.2 Significance of the study

Several studies in last decade found out that around one-quarter of the total adulthood bone mass are gained during the 2 years peak bone mass accrual period (girls: 12.5 years and boys: 14.1 years) and almost same with the amount bone mass that people will loss in their entire adulthood (Bailey *et al.*, 1999; Bailey *et al.*, 2000). Therefore, maximum attainment of peak bone mass during growing years by increasing engagement of physical activity and reducing the sedentarism should be emphasized since the subsequent gain of bone mass will be minimal after achieving peak bone mass. As known that most of the studies of lifestyle factors on bone health are widely focused on the elderly and postmenopausal women (Lewiecki, 2008). In addition, study of Ginty *et al.* (2005) stated that most studies of bone health assessments in growing children and adolescents have not been carried-out at the very specific age group such as pre-pubertal, pubertal and post pubertal-aged of adolescents and mainly focused on adolescent girls (Ginty *et al.*, 2005). Hence, the present study subjects comprise whole range of adolescence period from early pubertal to the late stage adolescent period. In addition, other important factors such as race and sex differences are also taking into account.

There are many factors associated with physical activity and sedentary behaviour. According to the reviews of Sallis *et al.* (2000) there are five groups which found correlates of physical activity and sedentary behaviours, including demographic and

biological; psychchological, cognitive and emotional; behaviour attributes and skills; and social and cultural (Sallis *et al.,* 2000). Therefore, factor determinants contributing physical activity and sedentary practices also investigated in this present study to provide a more holistic picture and make up the important policy for promoting active lifestyles and reducing sedentary behaviour, for instance by implementing extra co-curriculum and physical education class in schools.

To date, there is limited studies have investigated the influence of physical activity, sedentary practices, parathyroid hormone and bone biochemical markers on bone mass accretion in growing children and adolescents. Therefore, the present population-based study is formulate to understand the mechanism of these factors involved in maximum attainment of bone mass accretion among these growing adolescents in Kelantan, Malaysia.

1.3 Objectives

1.3.1 Main objective

To investigate the influence of physical activity, sedentary lifestyles, and blood biochemical markers of bone remodeling on bone health status among adolescent boys and girls of Malay and Chinese aged 12 to 19 years in Kota Bharu, Kelantan.

1.3.2 Specific objectives

i. To design and develop the newly past one-year computerized Physical Activity Questionnaire (cPAQ) to assess the habitual physical activity pattern among adolescent boys and girls.

ii. To compare the anthropometric measurements, dietary intakes, physical activity, sedentary lifestyle, blood biochemical markers of bone remodelling, muscle strength and bone mass profiles between adolescent boys and girls.

iii. To examine the socio-demographic and dietary behaviours determinants of physical activity and sedentary practices.

iv. To examine the influences of physical activity on muscle strengths of adolescent boys and girls.

v. To examine the influences of physical activity on bone mass status of adolescent boys and girls.

vi. To examine the relationship between muscle strengths and bone mass status of adolescent boys and girls.

vii. To examine the influences of sedentary practices on muscle strengths of adolescent boys and girls.

viii. To examine the influences of sedentary practices on bone mass status of adolescent boys and girls.

ix. To examine the influences of physical activity and sedentary practices on body composition profiles of adolescent boys and girls.

x. To examine the relationship between biochemical markers of bone remodeling, pubertal growth status and bone mass status of adolescent boys and girls.

1.4 Research null hypotheses

i. There are no differences of the anthropometric measurements, dietary intakes, physical activity, sedentary lifestyle, blood biochemical markers of bone remodelling, muscle strength and bone mass profiles between adolescent boys and girls.

ii. There is no influence of physical activity on muscle strengths of adolescent boys and girls.

iii. There is no influence of physical activity on bone mass status of adolescent boys and girls.

iv. There is no relationship between muscle strengths and bone mass status of adolescent boys and girls.

v. There is no influence of sedentary practices on muscle strengths of adolescent boys and girls.

vi. There is no influence of sedentary practices on bone mass status of adolescent boys and girls.

vii. There is no influence of physical activity and sedentary lifestyle practices on body composition profiles of adolescent boys and girls.

viii. There is no relationship between biochemical markers of bone remodeling, pubertal growth status and bone mass status of adolescent boys and girls.

1.5 Conceptual framework

Physical activity and sedentary behaviour practices during childhood and adolescence are considered as one of the major determinants that positively associated with better health outcomes. In the present study, the main focus was to

determine the relationship of physical activity and sedentary behaviour practices and its correlate factors with general characteristics and socio-demographic status, as well as its association with bone health and body composition status in population-based adolescents aged 12 to 19 years, as illustrated by the study framework in **Figure 1.1**. Physical activity and sedentary practices in adolescents are associated with five main factors such as demographic, psychological, behavioural, social and cultural as well as inter-mediated with significant and important determinants of muscular strength, blood biochemical bone markers and parathyroid hormone by further influencing the quality, size and mass of bone accrual when peak bone mass achieved during the critical growing periods.

1.6 Definition of terminology

Osteoporosis. It is defined as the bone mineral density (BMD) as assessed by dual energy X-ray absorptiometry (DXA) as less than a 2.5 standard deviation below the normal mean (T-score < -2.5).

Bone health. It is determined by the level bone mass status, bone quality, bone size as well as the presence of skeletal deterioration of bone tissue.

Adolescents. They are defined as the young people between the ages of 10 and 19 years who are often thought as a healthy group by World Health Organization.

Physical activity. It is defined as any bodily movement produced by skeletal muscle that results in energy expenditure with more than or equal to 2.0

metabolic equivalents (METs) in which the low or light PA is defined as <3 METs and active or moderate-to-vigorous PA is ≥ 3 METs.

Sedentary practice. It refers to the low energy expenditure above the resting metabolic rate but below the expenditure of light PA with 1.0-1.5 METs.

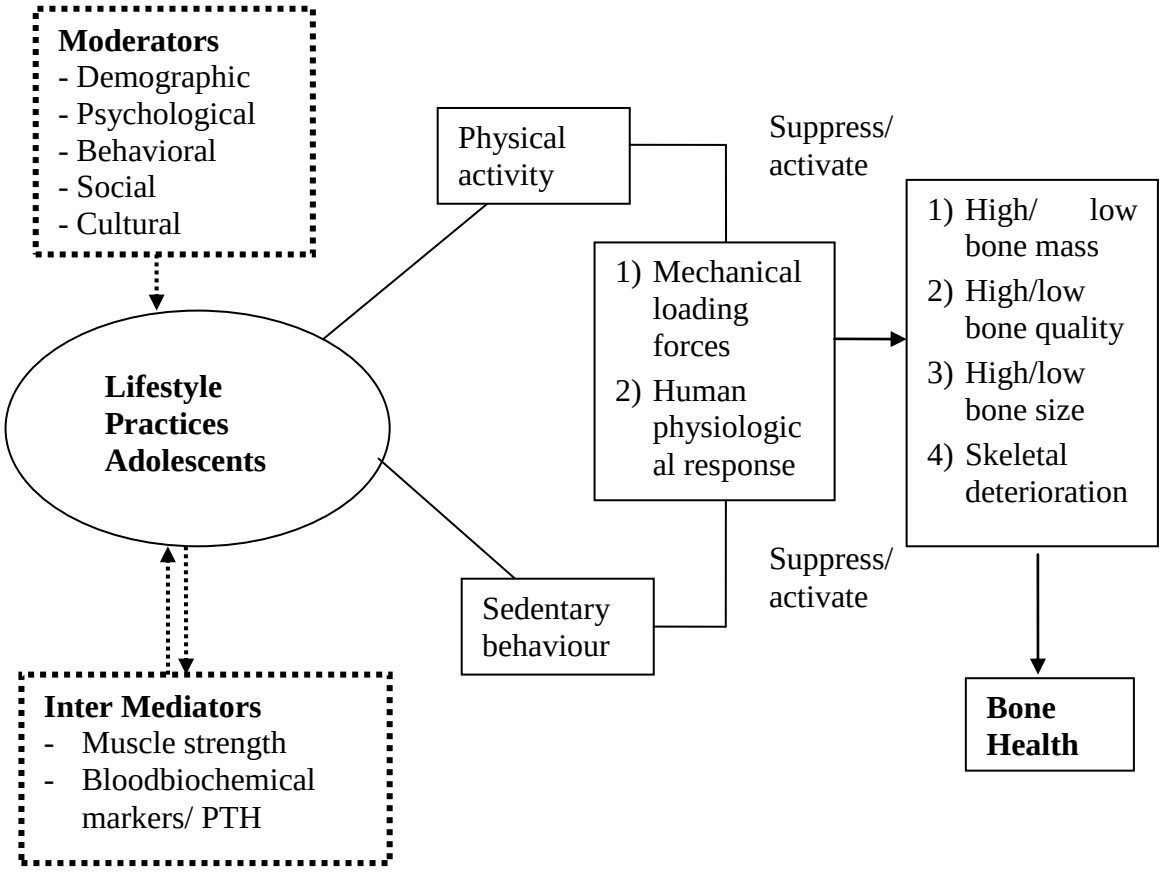

Figure 1.1 A conceptual framework of influences of physical activity on bone health status in adolescents

CHAPTER 2

LITERATURE REVIEW

2.0 Overview of osteoporosis

Osteoporosis is defined as "a systemic skeletal disorder characterized by low bone mass, micro-architectural deterioration of bone tissue and compromised bone strength, consequently increased risk of bone fragility and fractures" (WHO, 1994). Osteoporosis is considered as a "silent disease" because it is usually known when it is a bone fractures occurred and it happened without any symptoms (WHO, 1994; Lin and Lane, 2004). Operationally, it is defined as the bone mineral density (BMD), as assessed by the dual energy X-ray absorptiometry (DXA) as less than a 2.5 standard deviation (SD) below the normal mean (T-score <-2.5), whereas person with BMD more than 1.0 SD but less than or equal to 2.5SD below the mean (-1.0> T-score >-2.5) is classified as "osteopenia", or also known as low bone mass, and those with the BMD more than or equal to 1.0 SD of the normal mean T-score of the BMD is considered as normal (WHO, 1994). It has been well established that low BMD status is significantly associated with increased risk of osteoporotic fractures among postmenopausal women and elderly. For instance, a decreased in 1SD of BMD, the risk of having hip fractures is increased by 2.6-fold (Cummings *et al.*, 1993), and the two times higher risk of vertebrae fracture (Wasnich, 1993), compared to those who have their BMD of more or equal to 1SD T-score.

Osteoporosis affects over 200 million people worldwide, with significant clinical consequences, not only restricted to the immediate pain as a result of osteoporotic fracture, but it also contributes to significant increase risk of morbidity and mortality

(Riggs and Melton III, 1995; Reginster and Burlet, 2006; Leboime *et al.*, 2010). A worldwide incidence of hip fracture alone in men and women is projected to increase by 2 to 3 folds by the year of 2050 (Gullberg *et al.*, 1997). It is estimated the lifetime risk of osteoporotic fractures of the hip, vertebral and the radius are estimated to about 40%, which is equivalent to the risk of coronary heart disease (WHO, 2003). In addition, the one-in-six lifetime risk of sustaining a hip fracture in women of Caucasian-origin, which is greater than that of the risk of cancer risk (one-in-nine risk of developing breast cancer) (Melton, 2000).

The prevalence of osteoporosis is increasing among populations in Asia region, making it as one of the major public health challenges and problems in Asian populations due to advancing of aging populations. It is estimated that by 2050, the aging populations aged 65years and above will reach to approximately 894 million elderly living in Asia countries (Cummings *et al*., 2002). Moreover, it is projected that more than 50% of total hip fracture is projected to occur in Asia (3.2 million per year) by the year 2050 (Cooper *et al.*, 1992). Furthermore, 46% of all types of osteoporotic fractures are reported in the Southeast Asia and West Pacific. In addition, the estimated disability-adjusted life years lost was 24.7 million in Southeast Asia and West Pacific (34% of the world figure) (Lau, 2010). Moreover, in a regional study of Asian Osteoporosis study, it showed that Hong Kong and Singapore were among the highest rates of hip fracture, followed by Malaysia and Thailand. In addition, the prevalence of hip fracture of some Asia countries was reported to be similar to that of Caucasian populations in the United States and in United Kingdom (Lau *et al.*, 2001) (**Table 2.1**), in which elderly women and

postmenopausal women is considered at high risk of osteoporotic fracture compared to their male counterpart (Lau *et al.*, 2001; Cummings *et al*., 2002).

The common sites of osteoporotic fractures are hip, vertebra and wrist. Of all these skeletal sites, hip fractures is considered as a most serious form of osteoporotic fracture compared to fractures of any other skeletal sites such as at vertebral or wrist fractures. For instance, hip fracture increases the mortality risk by 20% during the first year of fracture. In addition, the rate of mortality within 90days among patients with osteoporotic fractures aged65years and above is unexpectedly high, in which the risk of early lethality could increase to about 6times and 4times in men and women , respectively compared to those elderly without any osteoporotic fracture (Roberts and Goldacre, 2003).

Osteoporotic fractures is required a long term health care and high health care expenses. For instance, it is estimated that approximately one-quarter of affected people are require a long-term healthcare due to long-term disability to perform their normal daily life after fractures (Jensen and Bagger, 1982; Clayer and Bauze, 1989). High cost and healthcare expenses are required such as hospitalization and long term nursing home care (Melton *et al.*, 2004; U.S Department of Health and Human Services, 2004). Similar healthcare cost burden is also reported in Asian countries.

Table 2.1 The incidence of hip fracture in four Asian countries with United States and Oxford, England (per 100,000 populations).

	Hong Kong[a]	Singapore[a]	Malaysia[a]	Thailand[a]	US[b]	Oxford, England[c]
Women (F)	459	442	218	269	535	603
Men (M)	180	164	88	114	189	114
Total	639	606	306	383	724	717
Ratio (F: M)	2.55	2.70	2.48	2.36	2.83	5.29

Source: [a]Lau *et. al*. (2001), [b]Ho *et. al*. (1993) and [c]Villa *et. al*. (2001)

For instance, it is reported that costs related to treatment and rehabilitation attributed to hip fracture is exceeded 1% of the total hospital services cost, which is approximately about HK$130 million in Hong Kong (Lau, 1997). In addition, approximately 500,000 hospital bed-nights have been occupied by osteoporotic patients annually in European Union in 1998 and it is expecting to increase to double by the year of 2050 (Delmas and Fraser, 1998).

2.0.1 Aetiology of osteoporosis

Osteoporosis is generally regarded as a disease that is manifested in postmenopausal women and elderly, as a result of excessive bone loss, leading to risk of osteoporotic fractures (Ensrud *et al.*, 1995). However, there is growing body of evidence also indicates that osteoporosis may have its origin during early stage of lifespan. it has documented that low attainment of peak bone mass (PBM) during the critical

growing years is significantly associated with greater risk of osteoporotic fractures later in life (Bailey *et al.*, 1996; Hernandez *et al.*, 2003).

In general, the aetiology of osteoporosis could be attributed to two main determinants, which is an excessive or rapid bone loss in ageing or/and low peak bone mass (PBM) accretion during childhood and adolescence (Melton, 1991; Bailey *et al.*, 1996; Center and Eisman, 1997). A growing body of evidence showing that maximum attainment of the PBM during first two decades of lifespan is regarded as an important strategy to prevent the risk of osteoporotic fractures in later life, apart from the prevention of the rapid bone loss during ageing (Bachrach and Smith, 1996; Dombrowski, 2000). It is estimated that the risk of osteoporotic-related fractures in postmenopausal women could be delayed by 13 years with an 10% increases in bone mass accrued during childhood and adolescence, whereas a 10% increase in the age of menopause or a 10% decrease in the age-related bone loss could only help to delay the onset risk of osteoporotic fractures only by two years (Hernandez *et al.*, 2003). This suggests that maximum attainment of PBM during the growing years is ultimately important factor that could help to prevent the risk of osteoporotic fractures in later life.

2.1 Bone structure and physiology

Bone is a unique and complex tissue with its main functions is to provide mechanical support for the weight bearing and locomotive activity. Skeletons is also serves as attachment sites for the muscles, ligaments and tendons, central reservoir for calcium, a protector of vulnerable internal organs and a site for haematopoiesis (Baron, 2003; Pearson and Lieberman, 2004). By fulfilling these requirements, skeletons

continually adapts to the mechanical and physiological demands placed upon it. During growth process, the skeleton maintain these functions while undergoes a dramatic changes in size and shape. Skeleton could be divided into the following five types based on the basis of shape, namely flat, short, irregular, sesamoid, and long bones. Flat bones consists of skull, scapula, mandibula, and ileum are formed by the ossification of membranes (intramembranous bone formation) independently of cartilage. Long bones such as tibia, femur and humerus are formed by the deposition of mineralised tissue preceded by cartilage analogue (endochondral bone formation or ossification) during the modelling process (Raisz, 1999). The long bones consists of two epiphyses with a midshaft (diaphysis) and a metaphysis (developmental zone) (Buckwalter and Cooper, 1995a). In growing bone, the epiphysis and metaphysis are separated by cartilage or growth plate that responsible for a longitudinal bone growth and becomes calcified at the end of the longitudinal growth after pubertal growth during adolescence (Ganong, 2003).

Bone tissue in general can be divided into two different bone components namely, cortical (or compact) and trabecular (spongy or cancellous) bone. Cortical bone is arranged in cylinders that align with the long axis and made up of dense and calcified tissue, with approximately 80 to 90% of its bone volume is made up of calcium. Trabecular bone exists as a three-dimensional lattice structure composed of an inner network of thin calcified trabeculae, with only 15 to 25% of its bone volume are made by calcium. Trabecular bone is present at the end of long bones, in vertebral bodies and nearby joint surface, and in flat bones (Khan *et al.*, 2001). In general, approximately 80% of the skeleton is cortical bone and only 20% is attributed to the

trabecular bone. Cortical bone primarily serves mechanical and protective functions; whereas trabecular bone is involved in metabolic activity (Watkins and Seifert, 2000). Bone is a connective tissue composed of cells and extracellular matrix having inorganic and organic components. On the basic level by weight, bone tissue consists of approximately 70% of mineral (or inorganic matter), about 20 to 25% of organic matrix, and remaining 5% as water. However, the major variation in the degree of mineralization in bone is depending on function within the skeletons. Major mineral (inorganic) component in bone extracellular matrix is the mixture of calcium and phosphorus in crystalline hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$], which composing of 95%, whereas the rest is composed of calcium carbonate, calcium citrate and magnesium (Seeman and Delmas, 2006). These crystals are found within the collagen fibres, that giving the rigidity and compressive strength to the skeletons (Currey, 2002).

Osteoblasts, osteoclasts and bone-lining cells are found on bone surface, whereas osteocytes permeate the mineralized interior. Osteoblasts are the fully differentiated bone-forming cells which originate from mesenchymal stem cells. The osteoblasts synthesis and secrete collagen and non-collagenous proteins that comprise the organic matrix of bone (osteoid) and subsequently mineralize the organic bone matrix (Parfitt, 2002; Baron, 2003; Seeman and Delmas, 2006). Subsequently, some osteoblasts disappear through a process of apoptosis (cell death); others differentiate into flat cells lining the bone surface (bone-lining cells) or are embedded in lacunae in the bone matrix after morphologic changes (osteocytes) (Burger and Klein-Nulend, 1999; Parfitt, 2002). On the other hand, osteocytes are osteoblasts that stopped matrix synthesis and are embedded deep within small bone cavities (osteocytic

lacunae). Osteocytes are connecting to adjacent osteocytes as well as with osteoblasts and bone-lining cells through the cytoplasmic network projecting through small canals between lacunae (as called canaliculi) in the mineralized bone matrix. This connection or communication is critical for mechno-transduction also known as mechanosensitivity of the bone (Mosekilde, 1995; Burger and Klein-Nulend, 1999). Osteoclast is a large multinucleated bone-resorbing cell that derived from the haematopietic stem cells, in which it is responsible for bone resorption and usually found in cavities on bone surfaces that known as the resorption pit (Mosekilde, 1995; Watkins and Seifert, 2000). During bone resorption process, osteoclasts secrete lysosomal enzymes, hydrogen protons and free radicals into a confined space next to bone and dissolve or degrade the bone matrix (Frost, 1987; Watkins and Seifert, 2000).

2.1.1 Bone remodeling process through the life spans

The cellular mechanisms responsible for the adaptation of bone tissue are modeling (construction) and remodeling (reconstruction) (**Figure 2.1**). Initially, modeling forms mineralized bone at developmentally determined skeletal sites during growth or acts as an adaptive response to external mechanical loading by simultaneous processes of the resorption and formation at different sites (Frost, 1987; Seeman, 2003). In growing skeleton, modeling is dominant and during this period of life, a significant change in bone shape that leading to greater bone strength (Frost, 1990). In mature skeleton during adulthood, bone remodeling process is constantly remodeled by the resorption followed by bone formation in the bone tissues, in which osteoblastic bone formation is coupled together with osteoclastic bone

resorption to restore bone loss (Buckwalter and Cooper, 1995b). Normally, the osteoblastic and osteoclastic activities are balanced in adults and remodeling.

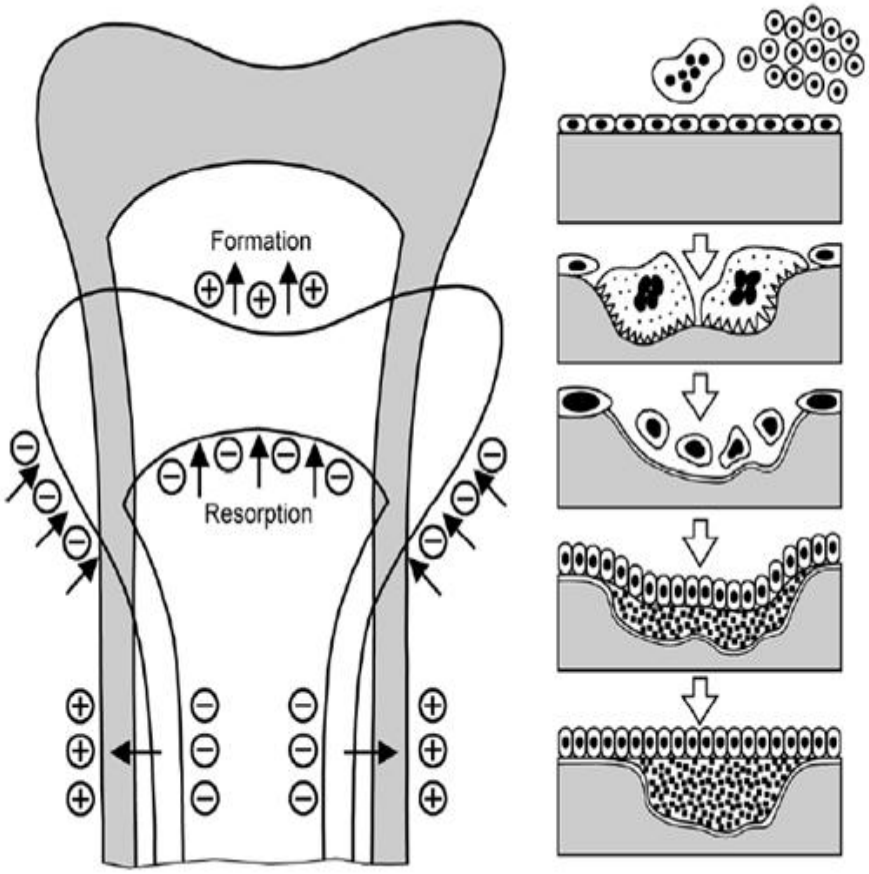

Figure 2.1 Bone modeling and remodeling. Osteoclasts break down old bone tissue and followed by osteoblasts activity, in which osteoblasts form new collagen and other matrix proteins. Then, the collagenous matrix undergoes mineralization (Adapted from Baron, 2003)

However, during aging and postmenopausal periods, processes of bone remodeling is occurs dramatically, that consequently resulting in trabecular thinning, disappearance and loss of connectivity, cortical thinning and increased intracortical porosity (Ahlborg *et al.*, 2003; Seeman, 2003).

Several blood biochemical metabolite components such as fragments of skeletal tissue proteins or enzymes specific to osteocytes are released into circulation system when bone matrix is formed and degraded during the bone remodeling process. These bone metabolites provide dynamic information on skeletal remodeling status through its metabolic activity, in which this metabolite analysis could be used to assess the biochemical markers of bone remodeling (Carey *et al.*, 2006). In general, these metabolites resulted from the bone turnover can be generally grouped into bone formation markers and bone resorption markers. Biochemical bone formation marker is used as indicator of osteoblast synthetic activity and also by-products of collagen synthesis, matrix proteins or osteoblastic enzymes. There are several bone formation markers that are commonly used such as blood osteocalcin (OC), total alkaline phosphatase (total ALP), bone-specific alkaline phosphatase (BALP) and total procollagen type I amino-terminal propeptide (P1NP). On the contrary, the bone resorption marker is used to assess the activity of osteoclast. Majority of these resorption markers are used to assess the degradation products of bone collagen and some non-collagenous proteins and osteoclast-specific enzymes (Christenson, 1997; Seibel, 2005; Vasikaran *et al.*, 2011). Several bone resorption markers that are used such as the C-terminal telopeptide of type I collagen (CTx) and N-terminal telopeptide of type I collagen (NTx) (Seibel, 2005).

Apart from the bone biochemical markers of bone remodeling, calcitropic hormones of vitamin D and parathyroid hormone (PTH) are also play a critical mediator role on skeletal development and remodeling. Vitamin D is fat-soluble and can promote calcium absorption from the intestine. Adequate vitamin D concentrations can prevent bone loss and reduce the fracture risk among the elderly (Dawson-Hughes *et*

al., 1995; Dawson-Hughes *et al.*, 1997) and musculoskeletal health and functions in growing children and adolescents (El-Hajj Fuleihan *et al.*, 2006; Foo *et al.*, 2009). The assessment of vitamin D is based on the measurement of serum 25-hydroxyvitamin D, which is considered as the main circulating metabolite form of vitamin D in the body (Lips *et al.*, 1999). Whereas PTH is defined as an 84-amino acid polypeptide that secreted by parathyroid glands in response to relatively small changes in serum Ca^{2+}, which is responsible for calcium homeostasis (Rosen, 2004). PTH synthesis is increased when low serum calcium level is sensed parathyroid glands, in which it is crucial for maintaining enzymatic process, cell membranes' stability and permeability and mineralization of newly formed bone (Kraenzlin and Meier, 2011). It acts as a potent stimulator of bone resorption during states of reduced ionized calcium availability in the blood and has biphasic effects on bone formation (Raisz, 1999). A high PTH concentrations result an acute inhibition of collagen synthesis but prolonged intermittent administration of PTH produces increased bone formation; thus, it is being explored clinically as anabolic agent (Dempster *et al.*, 1993; Frolik *et al.*, 2003). The anabolic effects of PTH are appeared to be partly site-specific, and this might due to the ability of PTH to activate mechanical loading pathways (Bakker *et al.*, 2003a). In general, process of bone modeling and remodeling is influenced by several factors such as sex, physiological growth factors, nutritional and lifestyle physical activity status, and also other hormonal status such as vitamin D, PTH, cytokines, prostaglandins and glucocortisords (Seeman and Delmas, 2006; Shapiro, 2008).