

A Study Protocol: Spinal Morphology, Physical Performance, Quality of Life and Biochemical Markers in Adults at Risk of Osteoporotic Fractures

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ABSTRACT

Older adults are at risk of osteoporotic fractures. Osteoporotic vertebral fractures are associated with a reduced cross-sectional area and muscle strength of the back extensor muscles, increased intramuscular fat infiltration and thoracic and lumbar curvature alterations. This study proposed a protocol to examine in more detail the contributions of altered spinal morphological, physical performance and biochemical markers to the risk of developing osteoporotic vertebral fractures. In this cross-sectional study, we plan

to recruit 100 adults aged 50 years and above from an orthopaedic clinic, Hospital Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia. The fracture prediction tool (FRAX) will be used to categorise high and low risk groups. Back muscle strength will be quantified using a load cell system. Thoracolumbar curvatures will be examined using an electromagnetic tracking system and intramuscular fat infiltration in the lumbar muscles will be measured using Magnetic Resonance Imaging. The Short Physical Performance Battery and JAMA dynamometer will quantify physical

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performance and the European Quality of Life Questionnaire will be used to assess self-perceived quality of life. Biochemical markers of serum C terminal telopeptide and N terminal propeptide of type I procollagen will be assessed using an enzyme-linked immunosorbent assays kit. A spine-specific model using regression analysis will be developed to predict osteoporotic vertebral fractures using the measured parameters in the present study.

Keywords: Biochemical markers, intramuscular fat infiltration, osteoporotic fracture, physical performance, spinal morphology, quality of life

INTRODUCTION

Osteoporosis is a complex chronic skeletal disorder that predisposes individuals to fractures at the hip, spinal vertebra and forearm (Leali et al., 2011). The incidence of osteoporotic fractures will rise to 3,000,000 people by the year 2021 due to the rise in proportion of older persons in society (Mithal et al., 2013) with more than half in Asia (Dhanwal et al., 2011). In 2005, the prevalence of osteoporotic fractures in Malaysia was 24.1% (Lim et al., 2005).

Osteoporotic vertebral fractures (Williams et al. 2009; Carberry et al., 2013) are the most common (Ensrud & Schousboe, 2011) with a four- to sevenfold risk of further fracture within one year (Francis et al., 2004). Symptoms of osteoporotic vertebral fractures include low-back pain, increased thoracic kyphosis (Pavlovic et al., 2013) and depression (Rauma et al., 2015), leading to poor quality-of-life (Adachi et al., 2010; Yoon et al., 2014).

Previous studies showed that an increase in the thoracic kyphosis angle was correlated to low-bone mineral density (BMD), paraspinal muscle volume and high paraspinal intermuscular adipose volume in men (Pavlovic et al., 2013; Katzman et al., 2014). An increase in muscle fat infiltration into the back muscles may be one of the causes of (So et al., 2013) osteoporotic vertebral fracture (Kim et al., 2013). Increased muscle fat infiltration is related to deterioration of back muscle strength (Visser et al., 2005) and may increase bone loss (Iki et al., 2002). The result is significant lower physical component of health-related quality of life compared with those without fractures (Sanf elix-Genov es et al., 2011).

Those with porous vertebrae had a fivefold lower mechanical strength and force (Fields, 2010) when changing activities or lifting compared with those with dense vertebrae (Holroyd et al., 2008; Woolf & Pflieger, 2011). Risk factors such as increase in age, low body mass index, menarche age, past history of fracture and falls are found to be better discriminators than BMD alone (Tsang et al., 2011). Those with osteoporotic vertebra fractures are likely to be aged 65-75, had lost height, experienced low back pain and have a history of nonvertebral fractures (Tobias et al., 2007).

Biochemical markers linked with bone remodelling including N-serum terminal propeptide of type I procollagen (sPINP) and serum Cross-linked C telopeptides of type I collagen (sCTX1) are significantly associated with risk of future osteoporotic vertebral fractures. It was found that combination use of bone markers and history of previous fractures determined osteoporotic fracture risk in post-menopausal women (Ivaska et al., 2010).

In summary, the relationship between risk of osteoporotic fractures and BMD, back extensor muscle strength and bone turnover markers in men and women has been explored in previous studies. Determinants of osteoporotic fractures could be site specific, in particular at the spine. More information is required regarding determinants of osteoporotic vertebral fractures. This information may be helpful in the prediction and prevention of osteoporotic fractures.

We established a protocol to examine the association between risk of osteoporotic fractures with spinal morphology (trunk muscle strength, cross sectional area and fat infiltration), biochemical parameters (bone resorption marker, and bone formation), physical performance and quality of life. In this study we aimed to address the following questions:

1. Is there a difference and correlation between spine morphological (intramuscular fat infiltration, cross sectional area, lumbar extensor strength, spine curvature), physical performance, quality of life and biochemical markers in adults between high and low risk individuals with spinal vertebral osteoporotic fractures?
2. Can spinal morphological, physical performance and biochemical marker parameters predict the risk of spinal vertebral osteoporosis fractures?

METHODOLOGY

Participants

A convenience sample of 100 adults aged 50 and above were recruited from the orthopaedic clinic at Hospital Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia from January 2015 to July 2016. Participants were screened for eligibility based on the inclusion and exclusion criteria. For the inclusion criteria, the participants were: males and females aged 50 and above, able to walk 3 m without a walking aid, had a history of back pain or leg pain that could not be related to spinal problems or requiring medical attention/treatment in the past 12 months, able to provide self-reported information and able to understand and provide written informed consent. Participants were excluded if they had experienced serious trauma leading to fractures and dislocations of the spine, prior surgery to the back, any known underlying pathologies such as a tumour, spinal infections, tuberculosis, any known inflammatory joint diseases and rheumatological conditions and diagnosed to have spinal deformities such as scoliosis, ankylosing spondylitis, spondylolisthesis, spondylolysis and any neurological deficits.

The study protocol was approved by the Research and Ethics Committee of Universiti Kebangsaan Malaysia (research code NN-056-2014). After providing informed consent, participants were interviewed to obtain demographic information, socio-economic status and clinical risk factors of osteoporosis. Health-related quality of life was also assessed using the EQ-5D questionnaire. Physical performance of the participants using the Short Physical Performance Battery (SPPB), dominant hand-grip strength using the JAMA dynamometer, trunk-extensor strength using a load cell and spinal curvatures using electromagnetic motion sensors was evaluated. Furthermore, participants fasting venous blood was drawn from antecubital vein by a phlebotomist. Lastly, an appointment for magnetic resonance imaging was also scheduled.

Sample Size Determination

Sample size calculation was based on the recommended procedure of continuous and categorical variables using Cochran's (1977) formula (Bartlett, Kotrlik & Higgins, 2001). Thus, the sample size required using the optimal ratio of 10 participants to each independent variable with nine independent variables as in this study and with an expected 10% drop-out rate, 100 participants were recruited.

Clinical Measures

Medical history, lifestyle and socioeconomic factors. Independent variables that were collected included demographic, socio-economic and clinical data that included age, sex, race, level of education, social and economic status, history of employment, marital status and other clinical risk factors such as age during menopause, history of falls, medication history, physical activity and past medical history including coronary heart disease, hypertension, diabetes mellitus, malignancy disease, thyroid disease and parathyroid disease, asthma, kidney disease, prostate disease, symptoms in the back and joints, history of fractures, parental fractures, glucocorticoid use, secondary osteoporosis, rheumatoid arthritis, current smoking habits, height, weight and alcohol consumption more than three units/day. BMD at the femoral neck site was obtained from the medical records. The participants were grouped into high and low risk groups using fracture prediction tool (FRAX) (Kanis, 2008). Based on the recommended cut-off point, participants with FRAX score of more and less than 10% were categorised into high and low risk of osteoporotic fractures, respectively.

Fracture risk calculations (FRAX) (<http://www.shef.ac.uk/FRAX>). Bone mass index (BMI) was automatically calculated using FRAX with femoral neck bone mineral density (Kanis, 2008). The WHO FRAX calculator was constructed and validated and then calibrated in 11 countries using primary data from population-based cohorts around the world, including centres from North America, Europe, Asia and Australia (Kanis et al., 2007). FRAX has a correspondence (κ) varied from 0.64 to 1.00 with only three items between 0.64 and 0.80 (rheumatoid arthritis, other diseases associated with secondary osteoporosis and use of oral glucocorticoids) (Kanis et al., 2007).

Bone mineral density. Participants underwent bone mineral density tests; dual energy X-ray absorptiometry (DEXA) scans at the lumbar spine and femoral neck sites, using Hologic 1000 DEXA Scanner (Hologic Inc., Bedford MA, USA). DEXA scans, were performed and analysed in accordance with the manufacturers' recommendations. DEXA has good precision (1%) and a low radiation dose (10-40 uSv) (Genant & Majumdar, 1997). Standardised procedures for participants' positioning and scan analysis were used. DEXA scanners are calibrated by a qualified technician using a phantom standard and have measurement precisions of $\leq 1\%$ for the spine and $\leq 1.5\%$ for the hip. The value of BMD at the femoral neck site was used for fracture risk calculation.

Physical performance. Individuals' physical performance was measured using SPPB (Guralnik et al., 1994). It consisted of three tests: standing balance (static), usual walking speed and timed five-times repeated chair stand and the total score ranges from 0-12, with each test contributing 0-4 points. High scores (≥ 10) suggested higher levels of function and low scores (4-6) indicated risk of functional limitations (Guralnik et al., 1995). The reliability of the SPPB ranged from 0.83 to 0.89 in large-scale epidemiologic studies (Freire et al., 2012). Low scores on the SPPB had a high predictive value of health consequences.

Dominant hand grip strength. Grip strength of the dominant hand was measured using a hand-held dynamometer (JAMAR, White Plains NY 10602, USA) as recommended by the American Society of Hand Therapists with its handle in the second position to get the most reliable and valid results (Fess, 1992). Each participant was instructed to squeeze the handle of the dynamometer as hard as possible for 5 seconds and to rest for 5 seconds. The action was performed twice. The maximum value of the two most powerful grips was recorded in kilogram. Inter-rater reliability studies of handgrip strength measured using the Jamar dynamometer was good, with ICC of 0.85-0.98 (Peolsson, Hedlund, & Oberg, 2001). Lower grip strength is associated with reduced health-related quality of life in older men and women (Sayer et al., 2006).

Biochemical parameters. A bone turnover marker of bone formation (serum N-terminal propeptide of type 1 procollagen, PINP) and a bone resorption marker (serum C-terminal telopeptide cross-links of type I collagen, CTX) were analysed as recommended by the International Osteoporosis Foundation (IOF), the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and the Malaysian Osteoporosis Group. CTX monitors progress of bone resorption independently and is a superior predictor of future bone loss (Seibel 2006). PINP is an important marker of bone matrix formation (Vasikaran et al., 2011; Hapidin, Mahmood, & Harith, 2013). It is important to collect fasting blood sample to increase the sensitivity of both tests (Qvist et al., 2002). Blood was collected in plain tubes and serum will be extracted after two hours at room temperature and centrifuged at 3000 x g for 10 min at 4°C. The serum was kept in aliquot at -70°C for no longer than 2 months prior to assay. All samples and kits used were thawed at room temperature (18-26°C) 20 minutes before analysis. A commercially available enzyme-linked immunosorbent assays kit was used to analyse these two markers (CTX1 from ELISA Immunodiagnosics Systems, UK and PINP from ELISA kit supplied by USCN Life Science Inc., China). The precision of the PINP are <10% and <12% for intra-assay and inter-assay, respectively and both inter and intra-assay imprecision of CTX1 are <10% (Hapidin et al., 2013) expressed in nanograms per millilitre.

Health-related quality of life (European Quality of Life Questionnaire EQ-5D). The Malay, English and Mandarin version of the EQ-5D quantified five life assessment domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression (Varatharajan & Chen, 2012). Participants' Likert responses were 'no problems', 'mild problems', 'moderate problems', 'severe problems' or 'extreme problems'. They rated their health status on a visual analogue

scale (EQ-5DVAS), where 0 corresponded to worst health imagined and 100 represented best health imagined (Brooks, 1996). The Malay, English and Mandarin version of the EQ-5D had reasonable test-retest reliability results ranging from 0.61 to 0.86 (Varatharajan & Chen, 2012).

Back Extensor Muscle Strength. Isometric back extensor muscle strength was measured using a load cell (LC501-200/N NEWPORT, US) connected to the upper trunk with the participants lying prone on a therapy couch. The protocol has been described in detail by Ito et al. (1996). It limits risk of lumbar hyperlordosis with a reliability of 0.94-0.96 (Shum, Crosbie, & Lee, 2010). Participants are instructed to lift the sternum off the couch with the cervical spine fully flexed. Straps will be used to secure the pelvis and knees to ensure pelvic stabilisation and that the knees are extended. Two maximum voluntary contraction (MVC) trials with a 5-second contraction and a period of rest of at least 60 seconds were given between the exertions, avoiding trunk muscular fatigue (Muller, Strässle, & Brigitte, 2010). The highest value of the two trials were recorded in Newton to obtain the MVC. A pre-written software using Matlab (version R2013a, The Mathworks, Inc., Natick, MA, USA) analysed data from the load cell.

Thoracolumbar Curvature. Thoracolumbar curvatures were tracked with an electromagnetic motion tracking device (Polhemus PATRIOT DB, US). The vertebral spinous processes at first thoracic, eight thoracic, first lumbar, fifth lumbar vertebrae levels and both the left and right PSISs were digitised. Curvature of the spine was traced using the point sensor when participants were in standing position as reported by Singh et al. (2010 & 2013). The results of this non-invasive approach provided sagittal and coronal plane measure. Furthermore, the device is portable for usage in clinical settings (Singh et al., 2010; González-Sánchez et al., 2014). Results indicated an ICC of 0.93 to assess kyphosis and 0.98 for lumbar lordosis in young and old adults (Singh et al., 2010). Another pre-written software using Matlab determined thoracolumbar curvatures (version R2013a, The Mathworks, Inc., Natick, MA, USA).

Back Muscle Cross Sectional Area (CSA) and Fat Infiltration. MRI scan using the 3.0-Tesla system (Siemens Magnetom Vision VB33A/ Avanto, Germany) measured soft-tissue contrast of back muscle CSA and fatty infiltration. MRI provides superior soft-tissue contrast without ionising radiation (Faizi et al., 2012). We measured T2-weighted axial images of the 3rd-4th lumbar vertebra spine. This section was chosen because it is at the centre of the lumbar lordosis curvature, so it could most appropriately reflect the cross-sectional area of the paravertebral muscle in the lumbar area (So et al., 2013). The 5th lumbar and 1st sacral vertebra levels were not normally considered because the axial areas were obstructed by the iliac crest and the muscular anatomy was different from the upper levels (Fortin & Battie, 2012).

Standard sequence included axial T2 TSE (TR 5000-6000msec, TE 84-100msec). For all sequences, 3-mm slice thicknesses were used. This technique has been demonstrated to be reliable with the intraclass coefficient of between 0.89-0.96 (Hu et al., 2011). Participants were required to be seated quietly for 30 min, and then lie supine on a MR imager with their hip and knees flexed to allow their normal lumbar lordosis to relax. The imaging protocol took about 10 minutes per participant. All scans were evaluated in blinded fashion with respect to clinical and

personal data by a single radiologist. All muscle measurements were determined by outlining the fascial boundary of the respective muscles and analysed using the image processing tool box, Matlab (version R2013a, The Mathworks, Inc., Natick, MA, USA).

Data Analysis

The collected data were analysed using the PASW statistic software version 18 (PASW Inc. Chicago, USA). Descriptive data analysis was used to analyse participants' demographic characteristics, biochemical parameters, thoracolumbar curvatures, trunk muscle fat infiltration and cross-sectional area, trunk muscle strength, physical functional scores and health-related quality of life scores were obtained. Values of participants with high and low fracture risks were compared using an independent-test (for normally distributed data) or the Mann-Whitney U-test (for skewed data). The statistical significance was set at $p < 0.05$. Pearson's correlation tests were used to evaluate the correlation between the independent variables. The stepwise multiple linear regression analysis was used to identify the influence of each factor on risk of vertebral osteoporotic fractures.

DISCUSSION

Various epidemiological factors have been linked to osteoporosis fractures (Kanis, 2008; Tsang et al., 2011; Liu et al., 2013). The association between vertebral osteoporotic fractures and skeletal assessment and other related risk factors has also been reported in isolation. However, the present study protocol included comprehensive measures of spinal morphology consisting of back muscle strength, cross-section area and fat infiltration as well as bone mineral density. In addition, biochemical functional parameters and quality of life measures were considered. Therefore, this study revealed for the first time a model for predicting spinal vertebral osteoporotic fractures using identifiable and functional parameters.

The fundamental scientific knowledge from this study may help in the planning of effective management strategies, prevention of recurrent osteoporotic fractures and spinal deformities in older adults. If intramuscular fat infiltration is muscle specific and difference between a high and low risk of osteoporotic fractures is demonstrated, it can be deduced that more severe impairments in spinal morphology, back muscle function, physical performance and quality of life will be expected.

The results of the study may assist in early management based on prediction models. Also, therapists will be able to tailor back-strengthening exercises for selective back muscles based on the findings of this study. This may be a basis for planning prevention of recurrent vertebral osteoporotic fractures. In summary, it will also lead to effective management strategies, prevention of recurrent osteoporotic fractures and spinal deformities in older adults to reduce the health and economic burden of the condition.

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