**Peripheral quantitative computed tomography (pQCT) measures contribute to the understanding of bone fragility in older patients with low-trauma fracture**

**Study protocol**

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**Table of Contents**

1 Introduction 4

1.1 Background 4

1.2 Rationale and research questions 5

2 Objectives 5

3 Hypotheses 6

4 Study design 6

4.1 Study type 6

4.2 Study location 6

4.3 Study population and characteristics 7

4.4 Sample size 7

5 Subjects recruitment 7

5.1 Inclusion criteria 7

5.2 Exclusion criteria 8

5.3 Recruitment methods 8

6 Study procedure 9

6.1 Informed consent 9

6.2 Bone density measurement 8

6.3 Other data to be collected 8

6.4 Study duration 10

6.5 Subjects withdrawel 10

7 Data management 10

8 Statistical methods 11

9 Ethical and governance issues 11

10 Study budget 11

11 References 12

12 Appendix 16

1. **Introduction**

**1.1 Background**

Osteoporosis is a major health problem affecting Australia’s ageing population due to the associated increased risk of fragility fractures. Fragility fractures, also known as low-trauma fractures (LTFs), are defined as fractures resulting from minimal-trauma, such as a fall from a standing height, and they are associated with significant morbidity and mortality [1].

There is a strong relationship between bone mineral density (BMD) and bone strength [2], thus using bone densitometry to predict the risk of bone fractures among patients with osteoporosis is standard practice in clinical settings. Currently, the preferred tool for measuring areal BMD is dual energy X-ray absorptiometry (DXA) due to its speed, low radiation dose, accessible measurement site, and relatively low cost [3-8]. However, marked variations in the prevalence of vertebral fractures are reported for a comparable areal BMD measured by DXA, and low diagnostic sensitivity and predictive validity for osteoporotic fractures are significant clinical limitations of this modality [9-16]. Indeed, the majority of patients presenting with low-trauma fractures have osteopenia by WHO criteria rather than osteoporosis on DXA examination, indicating the limited diagnostic sensitivity and predictive value of DXA [17].

Alternative modalities, such as quantitative computed tomography (QCT), transmission ultrasoundand magnetic resonance imaging, can also be used to assess bone strength [18, 19]. Peripheral quantitative computed tomography (pQCT) is a technique that was specifically developed for the quantitative determination of BMD in the forearm and the tibia [20]. It can offer the ability to measure volumetric bone mineral density (vBMD). As DXA is a projective technique that provides a two-dimensional representation of bone structure, the measurement of bone mineral density by DXA is an areal BMD in g/cm2 [21]. At the same time, pQCT uses three-dimensional approach to monitor bone mineral density in a given volume (vBMD in mg/cm3) [22]. pQCT can separately estimate trabecular and cortical compartments of bone [23]. This is advantageous as previous study shows cortical and trabecular structure have been associated with low-trauma fracture differentially in postmenopausal women [24]. Furthermore, pQCT can also measure bone geometry allowing estimation of bone bending strength. Geometric parameters have a strong correlation with bone failure loads [25-29]. pQCT-assessed Stress-Strength Index (SSI), which reflects the mechanical competence of human bone, is based on the calculation of such parameters and is recommended as diagnostic indicator for osteoporosis or related bone-weakening diseases [30-37]. One recent study even concludes that this mechanical competence is mostly determined by those geometric parameters rather than vBMD [38]. Thanks to its properties, pQCT may therefore provide additional information compared to DXA for the assessment of bone strength and the prediction of fracture.

T-scores are defined as the standard deviation from the young normal reference mean and DXA T-scores are the main measures for diagnosing osteoporosis or osteopenia. T-scores for DXA are well established in clinical practice [39], while T-scores for pQCT have not been established yet. Creating pQCT T-scores may contribute to the understanding of bone fragility in older patients with low-trauma fracture.

* 1. **Rationale and research questions**

Due to deficiencies of currently utilized DXA measures and the potential benefits of pQCT assessment, it is important to explore the role of pQCT in patients who have sustained LTFs. Therefore, this study will evaluate the potential utility of pQCT for the assessment of bone fragility among older patients who have sustained low-trauma fractures, by using pQCT T-scores calculated from mean and standard deviation of young healthy females obtained from our previous research.

1. **Objectives**

The objectives of this study are:

* To express the pQCT variables of low-trauma fracture patients as T-scores, using T-score scales previously obtained from studies of young women’s health (in which T scores were calculated using young women’s mean and standard deviation values for pQCT variables).
* To evaluate the potential clinical utility of pQCT for the assessment of bone fragility.

The exploratory objective is:

* To identify novel factors that may contribute to the prediction of low-trauma fracture in older patients with osteoporosis.

1. **Hypothesis**

The study is to be conducted with the hypotheses that:

* pQCT measures of bone strength and bone quality are reduced significantly in older patients with osteoporosis.
* pQCT parameters are independently associated with LTF and improve the modeling of the association with fracture compared with DXA parameters without pQCT.

1. **Study design**

**4.1 Study type**

This study will be an observational cross-sectional study on pQCT and DXA parameters in older patients with osteoporosis.

* 1. **Study location**

This study will be conducted at locations as below:

* Fracture Capture Clinic at the Royal Melbourne Hospital, City Campus.
* Other Royal Melbourne Hospital Endocrinology clinics and affiliated private practices (Victorian Endocrine Clinic and Melbourne Medical Consulting).
* Department of Medicine at Centre for Medical Research, the Royal Melbourne Hospital, City Campus.
* Bone Densitometry Unit (Bone & Mineral Medicine) at the Royal Melbourne Hospital, City Campus.
  1. **Study population and characteristics**

The study population will be subjects aged over 50 years who have sustained one or more recent LTFs. These patients will be recruited from the Fracture Capture Clinic and other clinics at the Royal Melbourne Hospital.

We will also use young adult healthy females’ T-scores variables (derived from the means and standard deviations of bone variables which have already been obtained from the Young Female Health Initiative (YFHI) study and Safe-D study). The YFHI is a comprehensive study of health in young Australian females, and the Safe-D is a Vitamin D study in females. Participants of these two studies have had pQCT scans as part of the studies. We will not have access to individual data of these two studies but only use the means and standard deviations as reference.

* 1. **Sample size**

In the absence of preliminary data we have selected an opportunistic sample of 85 subjects. Eighty-five older patients with LTF will be recruited from Royal Melbourne Hospital outpatient clinics. This sample size will be large enough to provide valuable information and is feasible based on Royal Melbourne Hospital clinic attendance rates.

1. **Subjects recruitment**
2. **Inclusion criteria**

* Aged 50 years or greater;
* One or more low-trauma fractures within the past three months;
* Informed verbal and written consent provided.

**5.2 Exclusion criteria**

* Prior diagnosis of osteoporosis;
* Prolonged (>3 months) use of osteoporosis therapy in the past 2 years;
* Prior therapy with teripatratide or strontium ranelate;
* Unstable doses of hormone replacement therapy;
* Patients with secondary causes of low bone density, e.g. hyperthyroidism, diabetes, Vitamin D deficiency, alcoholism, smoking.

**5.3 Recruitment methods**

Potential subjects presenting to the Fracture Capture Clinic and other Royal Melbourne Hospital clinics will be advised about this study and screened for eligibility if agreeable. Those meeting the eligibility criteria and interested in participating in the study will be asked to provide formal written informed consent.

1. **Study procedure**
   1. **Informed consent**

The researchers will advise the fracture group participants about the details of the study, including the objectives, methods, specific procedures and potential adverse effects and provide the approved PICF, before offering any informed consent documents. If they want to participate in this study after getting the details and having the opportunity to consider and discuss them, written informed consent will be obtained before any study procedures are undertaken.

* 1. **Bone density measurement**

Participants will attend the Bone Densitometry Unit at the Royal Melbourne Hospital for bone scans to measure bone strength, bone mineral density and content. Two imaging modalities will be used. DXA (QDR 4500A densitometer, Hologic Inc., Bedford, USA) will be used to measure hip and lumbar spine BMD as standard care, while pQCT (XCT 3000, Stratec Medical, Pforzheim, Germany) will be used to measure trabecular and cortical volumetric BMD, bone geometry and indices of bone strength at the tibia (4% and 66%) and radius forearm of the participants.

The bone scans expose participants to a very low level of ionizing radiation which poses an extremely low and unmeasurable risk to safety, and information on ionizing radiation will be provided to participants in the approved PICF.

* 1. **Other data to be collected**

This study will collect other data of the participants, including: name, date of birth, gender, height, weight, fracture history, risk factors for fracture and comorbidities. A study questionnaire will be applied to collect these data. This questionnaire is attached to this protocol.

All these data and radiological data will be kept confidentially in accordance with the National Statement on Ethical Conduct in Research Involving Humans (2007).

* 1. **Study duration**

This study is estimated to take 1.5 years including one year for recruitment and data collection:

* March – July, 2014: study preparation and application for ethical review and research governance
* August, 2014-August, 2015: participants recruitment and data collection
* August-October, 2015: statistical analysis, and paper and thesis writing
  1. **Subject withdrawal**

Withdrawal from the study may be direct or indirect (as detailed below). In the case of withdrawal, the details will be recorded in the study database, along with a reason for withdrawal where possible. Withdrawing patients would have been advised in the PICF that they may request that their data not be used. Recruitment will continue until the sample size is achieved

* + 1. **Direct withdrawal**

A participant may, at any time, advise that they no longer wish to be involved in the study. This may be through any means of communication including telephone, SMS or email. Reasons for withdrawal will be recorded in detail.

* + 1. **Indirect withdrawal**

Where a participant that does not complete a significant component of the study (i.e.one of the two imaging modalities, demographic data collection), they will be considered as withdrawn from the study.

1. **Data management**

All study data will be kept confidentially in a password-protected Microsoft Excel document. The document will be stored on a computer held in a secure location in the Department of Medicine. Only the researchers will be able to access the database. After completing the questionnaire for each participant, we will remove his/her name and code the data. All data will be stored in a un-identified format, linked to a unique identification number for each participant. Participant information is protected and will only be used to facilitate the research. Information identifying an individual will not be disclosed to any third party except as may be required by law. All data collected will be stored and backed-up every day in case of data missing. All data will be stored electronically for at least 5 years after study completion. This is in accordance with local Australian regulations.

1. **Statistical methods**

All continuous data will be tested for normality prior to data analysis. Univariable analysis will be undertaken to compare relationships between demographic and clinical factors and LTF. Continuous data (i.e. height, weight, BMI, DXA measures, pQCT measures) will be analyzed using either two-sample t-test or Wilcoxon rank-sum test and categorical data (i.e. gender, risk factors, comorbidities) using the Chi-square test. Multivariable analysis will be used to determine the correlations between low-trauma fracture risk and these factors while adjusting for the differences between groups and potential confounders. The statistical analysis will be performed using SPSS Statistics 22.0 (SPSS Inc., Chicago, IL, USA). The level of significance will be set at *p*<0.05.

1. **Ethical and governance issues**

This study will be conducted in accordance with the National Statement on Ethical Conduct in Research Involving Humans (2007) by the National Health and Medical Research Council of Australia. This national statement was developed to protect the interests of people who participate in medical research. Under the guidance of the statement, confidentiality of all study participants will be maintained except as required by law.

This study will also be conducted based on the principles and guidelines set in the Declaration of Helsinki and its subsequent amendments.

1. **Study budget**

Application fee for ethical review and research governance will be 220 dollars. The main research cost will be for performance and analysis of pQCT scans and the Bone Density Unit will fund those costs for this pilot study.

There may be some low office maintenance costs such as postage and printing. The Department of Medicine will afford such maintenance costs.

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**12 Appendix: Study Questionnaire**

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| **Peripheral Quantitative Computed Tomography (pQCT) Measures Contribute to the Understanding of Bone Fragility in Oder Patients with Low-Trauma Fracture**  **(Short Title: PQCT for Estimating Bone Fragility)**  **Study Questionnaire**  **General Information**  Name: DOB:  Gender: Height:  Weight:  **Fracture History**  Fracture date:  Cause of Fracture:    **Risk Factors [40] (Please Tick)**  Previous Fracture Parent Fractured Hip  Current Smoking Glucocorticoids Use  Rheumatoid Arthritis  Three or More Units of Alcohol Per Day  **Comorbidity**  Please specify any diagnosed condition with you: |