Upper Limb Bone Health: Cadaveric, imaging and clinical studies with special emphasis on Peripheral Quantitative Computed Tomography

By

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Abstract

Introduction

Osteoporotic fractures are a major health care problem. A radial fracture is an important risk factor for osteoporosis that should initiate the assessment of bone health.

Purpose

1) To validate pQCT measures of bone in aged cadaveric radii.
2) To examine side-side differences in radial bone variables after disuse.
3) To test a novel intervention for secondary prevention of osteoporosis after an index radial fracture.

Methods

Study Design: *Part I:* Parts IA and IB are descriptive cadaveric studies. *Part 2:* Cross-sectional observational studies of bone response to disuse; *Part 3:* Part 3A is a 6-month intervention of secondary prevention of osteoporosis following a fragility fracture. Part 3B uses a questionnaire to ascertain barriers to investigation after fracture.

Participants: *Part I:* Cadaveric specimens from women (73 to 88 years) for Parts IA and IB. *Part 2A:* Women (52-87 years) who sustained a distal radius fracture and *Part 2B:* women and men (52 to 79 years) who had suffered a stroke. *Part 3A:* Women and men (50-90 years) with a fragility fracture; and *Part 3B*: physicians in British Columbia.

Results *Part I:* With different pQCT acquisition-analysis protocols, total bone area varied by 3-34%; cortical area varied by 3-30% and total content by 6-45% from a criterion standard. Total bone content of the distal radius explained between 74 and 81% of bone strength. *Part 2:* There was a significant decrease in bone strength in participants who had upper limb disuse because of stroke or fracture. *Part 3:* A patient and physician intervention improved bone health investigation rate by a factor of 3.1 times (RR) after fragility fracture. BC doctors reported few barriers to investigating osteoporosis.

Summary: Peripheral QCT acquisition and analysis protocols significantly influenced outcome variables. Patients do not have "normal" bone strength after fracture or stroke. In particular, there is an increased risk for non-dominant radial fractures to have lower bone strength and be associated with poorer limb function, compared with a dominant radial fracture. Physicians report no barriers to investigation after a fragility radial fracture and a systematic intervention may best address secondary prevention of osteoporosis.

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List of Nomenclature and Abbreviations

Term	Definition
Absolute Risk (AR)	Incidence of a disease in a population. Can indicate the magnitude of risk but does not account for the unexposed population for comparison.
Accuracy	Test of the proximity of outcome to a criterion standard. Many tests do not have a criterion standard for comparison.
Bone Mineral Content (BMC)	The amount of mineral contained within a defined area or volume (g)
Areal Bone Mineral Density (aBMD)	The ratio of BMC to the projectional area of bone (g/cm^2).
Basic Multicellular Unit (BMU)	Discrete packet of bone cells (osteoblasts and osteoclasts) responsible for bone remodeling. There are distinct units for cortical and trabecular bone.
Bone Health	The state of the contributing factors to the mechanical competence of bone, such as mineral content, structure and modeling-remodeling rate, resulting in the optimal function of the skeleton for mechanical, metabolic, and protective tasks.
Bone Mass	Amount of bone mineralisation in a cross-section or structure. Can be BMC or BMD.
Bone Material Properties	Properties of the material that compose bone; includes the amount and degree of tissue mineralization.
Bone Mineral Density (BMD)	The amount of bone mineral contained within a specific area or volume (g/cm^2).
Bone Strength	Ultimate failure load of bone
Bone Strength Index (BSI)	Similar to SSI and accounts for bone strength as the product of cortical area and cortical density.
Bone Structural Properties	Properties of bone structure that contribute to the overall strength of a bone including its size, shape and distribution of material.
Coefficient of Variation (C^{RMS} -%CV)	A measure of variation between measurements. Calculated as the standard deviation/mean *100.
Cortical Area (CoA)	Cortical bone area contained within a defined ROI (mm^2)
Cortical Content (CoCNT)	Amount of cortical bone mineral within a defined ROI (mg)
Cortical Density (CoD)	Cortical mineral content divided by the cortical volume contained within a specific ROI (mg/cm^3)
Cross-Sectional Area (CSA)	Bone, marrow and space contained within a defined ROI (mm^2)
Cross-Sectional Moment of Inertia. (CSMI)	In a bone cross-section, the distance of bone mass from the neutral axis of bending. The further the material from the axis of rotation, the greater the moment and the larger the resistance to deform or fail.
Effect Size (ES)	Magnitude of difference between two treatments or observations independent of sample size. It is the standard difference between two means.
Ex vivo	Removal of tissue/organ from an organism for investigation.
In vivo	Within a living organism (animal or human); investigations using living participants.
Odds Ratio (OR)	Estimation of the relative risk in a case-control study
Partial Correlation Coefficients	Calculation of the strength of relation between variables for normally distributed data with the effect of covariates removed.
Primary Care Physician (PCP)	First contact for health care and usually the family or general physician.
Range of Motion (ROM)	Available range of movement at a joint. Active, passive or torque.
Region of Interest (ROI)	Region of bone selected for analysis.
Relative Risk (RR)	Incidence of disease, but the risk in the exposed group is compared

	with the risk in the unexposed group.
Section Modulus (Z)	Strength prediction of the subperiosteal surface. A measure of the distribution of material within a section of bone (cm^3).
Sensitivity (True Positive Rate)	The ability of a screening test to identify correctly individuals who will fracture or have a disease. It is the proportion of true positives among all individuals who fracture or have disease.
Spearman Rank Correlation Coefficients (r)	Calculation of the strength of relation between variables for non-normally distributed data (non-parametric).
Specificity (True Negative Rate)	The ability of a screening test to identify correctly individuals who will not fracture or have a disease. It is the proportion of true negatives among all individuals who did not fracture.
Standard Error the Estimate (SEE)	Distribution of residuals around the regression line and is the average error of prediction.
Stress-Strain Index (SSI)	pQCT-derived strength index that includes bone geometry and cortical volumetric density in the calculation (mm^3).
Total Area (ToA)	Total bone area contained within a defined ROI (mm^2) (includes cortical, trabecular bone, marrow, and space).
Total Content (ToCNT)	Total content of bone mineral within a defined ROI (mg) (includes cortical, trabecular bone, marrow, and space).
Total Density (ToD)	Total density (total mineral content divided by the total area mg/cm^3) contained within a specific ROI (includes cortical, trabecular bone, marrow, space).
Trabecular Area (TrabA)	Trabecular bone area contained within a defined ROI (mm^2).
Trabecular Content (TrabCNT)	Trabecular content of bone mineral within a defined ROI (mg).
Trabecular Density (TrabD)	Trabecular density (Trabecular mineral content divided by the Trabecular area mg/cm^3) contained within a specific ROI (mg/cm^3).
Volumetric Bone Mineral Density (vBMD)	When measured by pQCT is expressed as mg/cm^3. pQCT technology provides a volumetric mineral density and DXA generates aBMD.
Voxel (volumetric element)	Three dimensional digital measurement unit that is used to describe image resolution with pQCT.
Wilcoxon Signed Rank Test	Comparison of paired samples for non-parametric data.

PREFACE: PUBLICATIONS AND ABSTRACTS ARISING FROM THIS THESIS

Sections of this thesis have been published as multi-authored papers in refereed journals that are listed below. Details of authors' contributions are provided where relevant.

PUBLICATIONS

1. ASHE MC, Khan KM, Guy P, Janssen P, McKay HA. WristWatch: Distal Radial Fractures as a Marker for Osteoporosis Intervention. *Journal of Hand Therapy* July-September 2004
Authors' contributions: Maureen Ashe was responsible for the original ideas behind the paper, analysis and presentation of findings, and writing and editing of the original paper. Karim Khan and Patti Janssen provided critical review during planning and data collection and reviewed the draft manuscripts. Pierre Guy and Heather McKay stimulated discussion of results and provided editorial assistance. Patti Janssen provided ongoing statistical consultation throughout data analysis. This paper reported radial fracture data only.

2. ASHE MC, McKay HA, Guy P, Janssen P, Khan KM. Improving Osteoporosis Management in "At Risk" Fracture Clinic Patients (Letter). *Journal of the American Geriatrics Society* IN PRESS April 2005.
Authors' contributions: Maureen Ashe was responsible for the original ideas behind the paper, analysis and presentation of findings, and writing and editing of the original paper. Karim Khan and Patti Janssen provided critical review during planning and data collection and reviewed the draft manuscripts. Pierre Guy and Heather McKay stimulated discussion of results and provided editorial assistance. Patti Janssen provided ongoing statistical consultation throughout data analysis.
This letter outlined results of the intervention using patients with either radial or humeral fractures. (Some overlap of data as noted in the letter).

3. ASHE MC, Khan KM, Guy P, Janssen P, McKay HA. Fragility fractures and Osteoporosis Investigation. *British Columbia Medical Journal 2004 Volume 45 No.10 ; 506-509.*
Authors' contributions: Maureen Ashe was responsible for the original ideas behind the paper, analysis and presentation of findings, and writing and editing of the original paper. Karim Khan and Patti Janssen provided critical review during planning and data collection and reviewed the draft manuscripts. Pierre Guy and Heather McKay stimulated discussion of results and provided editorial assistance. Patti Janssen provided ongoing statistical consultation throughout data analysis.

4. ASHE MC, Liu-Ambrose T, Khan KM, McKay HA. Reliability of Peripheral Quantitative Computed Tomography: Cadaveric and Clinically Relevant Studies. *Journal of Clinical Densitometry*. IN PRESS
Authors' contributions: Maureen Ashe was jointly responsible with Teresa Liu-Ambrose for the original ideas behind the paper, analysis, presentation of findings, writing and editing of the original paper. Heather McKay and Karim Khan provided critical review during planning and data collection and reviewed the draft manuscripts.

5. ASHE MC, Khan KM, Guy P, Liu D, McKay HA. Improving the Accuracy of pQCT for Evaluating the Aged Human Radius. Submitted *Osteoporosis International*
Authors' contributions: Maureen Ashe was responsible for the original ideas behind the paper, analysis and presentation of findings, and writing and editing of the original paper. Heather McKay and Karim Khan provided critical review during planning and data collection and reviewed the draft manuscripts. Danmei Liu and Pierre Guy provided engineering and orthopaedic consultation throughout the investigation and data synthesis.

6. ASHE MC, Fehling P, Eng JJ, Khan KM, McKay HA. Bone Structural Adaptation to Chronic Disuse following Stroke: Implications for Rehabilitation. Submitted *Journal of Musculoskeletal and Neuronal Interactions*.
Authors' contributions: Maureen Ashe was responsible for the original ideas behind the paper, analysis and presentation of findings, and writing and editing of the original paper. Janice Eng and Pat Fehling were key editors on this paper. Heather McKay and Karim Khan provided consultation regarding the methodology, stimulated discussion of results and provided critical review during planning and data collection and reviewed the draft manuscripts.

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ABSTRACTS

1. **ASHE MC**, Khan KM, Guy P, Janssen P, McKay H . WristWatch: Distal Radial Fractures as a Marker for Osteoporosis Intervention. American Society of Hand Therapists Annual General Meeting October 2003.
2. **ASHE MC**, Khan KM, Guy P, Janssen P, McKay H. WristWatch: Distal Radial Fractures as a Marker for Osteoporosis Intervention. Canadian Orthopaedic Association June 2004.
3. **ASHE MC**, Khan KM, Guy P, Janssen P, McKay H. WristWatch: Improving osteoporosis management in at risk fracture clinic patients. Orthopaedic Research Society 5th Combined Meeting Banff October 2004.
4. **ASHE MC**, Khan KM, Guy P, White N, McKay H. Variability of pQCT Measurement at the Distal Forearm: Influence of voxel size, Region of Interest and Analysis Software. American Society of Bone and Mineral Research Seattle October 2004
5. Fehling PC, **ASHE MC**, Eng JJ, McKay H. Side-side Differences in Bone Strength in a Chronic Stoke Population: a pQCT Study. American Society of Bone and Mineral Research, Seattle October 2004
6. **ASHE MC**, Fehling PC, Eng JJ, McKay H. Bone Structural Adaptation to Chronic Disuse following Stroke: A pQCT Study. Canadian Physiotherapy Association Annual General Meeting Victoria, BC 2005
7. **ASHE MC**, Khan KM, Davis, JC, Guy P, McKay H. Bone and Muscle Adaptation after a Wrist Fracture: A pQCT Study. European Calcified Tissue Society and International Bone and Mineral Society; Geneva, Switzerland June 2005.
8. **ASHE MC**, Khan KM, Guy P, McKay H. Accuracy of the pQCT in Assessing the Older Osteoporotic Distal Radius. European Calcified Tissue Society and International Bone and Mineral Society; Geneva, Switzerland June 2005.

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"We must have perseverance and above all, confidence in ourselves. We must believe that we are gifted for something." Madame Marie Curie.

Upper Limb Bone Health: Cadaveric, imaging and clinical studies with special emphasis on Peripheral Quantitative Computed Tomography

1 Introduction

Osteoporosis is a major health problem characterised by fragility fractures. These fractures occur, in part, because bone becomes compromised over time, that is, they decrease mineral mass, become thinner at the cortical shell and thus, become weaker so that there is a susceptibility to fracture. A fragility fracture is a disruption in bone structure resulting from a minor to moderate force or trauma; a fracture sustained from a standing height or less (1). Fragility fractures are a hallmark of osteoporosis and account for the majority of the $1.3 billion annual Canadian costs attributed to osteoporosis (2).

Osteoporosis can arise without obvious cause ('primary osteoporosis') or in association with medical conditions (e.g., hyperthyroidism), following the use of certain medications, space flight or short- or long-term immobilisation ('secondary osteoporosis'). A fragility fracture, in particular a distal radius fragility fracture, is a sentinel event in the course of osteoporosis and is a signal that warrants clinical investigation of bone health (3-9). The radial fragility fracture also provides an excellent model to investigate bone structural and material adaptation with disuse. In Part I of this thesis, I conducted novel tests of the accuracy of the state-of-the-art peripheral quantitative computed tomography (pQCT) instrument. This was particularly important in the setting of osteoporotic bone as the limited pQCT validation studies previously reported by the manufacturer were conducted with healthy, younger participants. I collected pQCT data in cadaveric radial specimens and compared these to the criterion standards of histomorphometry and ashing, and tested the capabilities of pQCT-derived bone parameters to predict bone failure as measured by biomechanical testing.

In Part 2, I sought novel insights into bone structural changes that occur with inactivity. Using a cross-sectional study design, I investigated (i) bone mass and bone geometry in patients who had suffered a distal radius fracture, and (ii) side-side differences in the radius in a group of participants who had suffered a stroke.

As a clinician, I am interested in translating knowledge to improve patient outcome. Low trauma radial fracture (fall from a standing height or lower) is diagnostic of osteoporosis but 80% of such patients are not assessed for this significant medical condition (10). Therefore, in Part 3, I tested a novel intervention to improve health care delivery services to a population at increased risk of osteoporosis (aged, fragility fracture). I also investigated physician's attitudes to osteoporosis investigation following a fragility fracture to understand the reasons for any 'gap in care' that may exist. The term 'gap in care' refers to the difference between the number of patients who are appropriate and eligible for osteoporosis assessment/treatment and the number who are receiving it. Taken together, Part 3 research seeks to contribute to more effective clinical pathways for the secondary prevention of osteoporosis. Figure 1-1 outlines the potential contribution of my thesis to the development of improved management of osteoporosis.

To précis, this thesis aims to: (I) test the accuracy of pQCT for older compromised bone, (II) extend the description of bone after disuse, and (III) test a low-cost intervention to improve delivery of health care to a population at high risk of osteoporotic fracture. There is synergy and benefit, both scientific and economic, to answering the various research questions together.

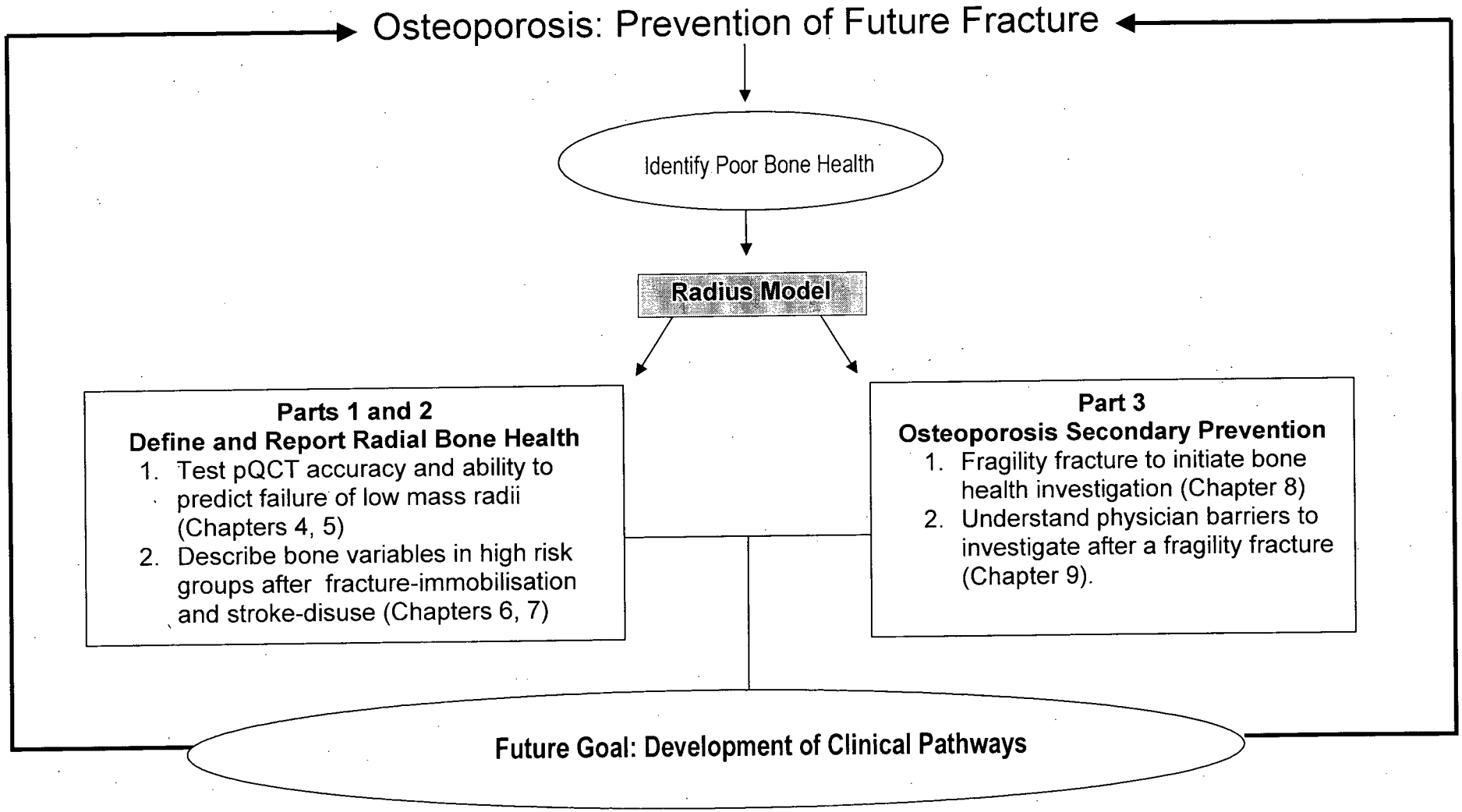


Figure 1-1. Overview of thesis highlighting the relations between studies and the potential contribution to bone health.

2 Literature Review and Background

In this chapter, I summarise key background information related to each of my studies. I begin by describing normal bone health including anatomy and physiology. I outline and compare bone-imaging technologies used to investigate the radius with a particular emphasis on peripheral quantitative computed tomography. Next, I detail musculoskeletal information related specifically to the radius including fracture epidemiology, healing and the changes that occur with aging and activity/inactivity. I conclude this chapter by reviewing clinical applications of the distal radius as a model to improve bone health in people at risk for osteoporosis and fragility fractures.

2.1 Overview of Bone

Before describing bone itself, I highlight commonly used techniques to describe bone from a molecular level to whole bone.

2.1.1 Multimodal Description of Bone

Evaluation of bone occurs in a multitude of ways depending on the level of investigation— from the molecular level to whole bone. Each level of investigation provides important data to help understand and describe bone deterioration compared with healthy bone. For example, at an organ level, bone is measured anatomically for geometric properties such as length or diameter. Its intimate relation to other tissues (e.g. muscle, tendon) is described. Biomechanical testing for material and structural properties of bone are measured using whole bone or smaller bone sections. Urine and blood analyses yield biochemical bone markers to quantify rate of bone turnover. Mineral content, area/volume and density can be quantified non-invasively with imaging technologies. Histomorphometry is used at the tissue and cellular level to provide an in-depth understanding of bone, while molecular histology is a new technique to isolate genes for coding, location and report the intensity of gene expression. Table 2-1 provides a summary of various levels at which bone can be studied and the most common investigations used at present. In this thesis, I investigate bone at a tissue and whole bone level. I use imaging technology to ascertain mineral density and structural properties. I use histomorphometry, ashing and biomechanical techniques to investigate the accuracy of an imaging device – peripheral quantitative computed tomography (pQCT).

Table 2-1. Summary of bone assessment by the modality used at different bone levels.

Bone Level	Modality	Outcome Parameter
Molecular	•Molecular histology	•localisation and intensity of gene expression of systemic and local biomolecules
Cellular	•Histomorphometry	•cell type, amount and distribution
	•Markers of Bone Metabolism	•bone formation and resorption markers
Tissue	•Histomorphometry	•amount of tissue type; degree of mineralisation, cross-sectional area •bone microarchitecture (cross-sectional area and separation of bone compartments)
Whole Bone	•Non-invasive imaging	•mineralisation, bone geometry (cross-sectional area and separation of bone compartments), bone strength
	•Biomechanical testing of strength	•failure load
	•Gross Anatomy	•relation to other tissues, biological variation
	•Anthropometric measures	•length, mass

2.2 Bone: Anatomy and Physiology

In this section, I discuss basic bone anatomy and physiology including the arrangement of bone from the cellular to the whole bone level. I conclude this section with a description of the basic bone remodeling sequence.

2.2.1 Bone Anatomy

Bone is a composite material consisting primarily of connective tissue embedded in an inorganic complex intertwined to provide a structural framework. At a microscopic level, bone is extremely well organized into organic and inorganic components. It consists of approximately 70% mineral, 22% protein and 8% water with the relative proportions defining the mechanical properties. The main mineral component (inorganic) consists of 95% hydroxyapatite [$CA_{10}(PO_4)_6(OH)_2$] impregnated with 5% impurities. Type 1 collagen makes up 98% of the organic phase. Within the collagen fibrils are gaps called "hole zones" which are thought to be the commencement of mineralization (11).

Bone cells include osteocytes, osteoblasts, osteoclasts and bone lining cells; all with diverse functions. Osteoblasts (OB) or building cells are primarily responsible for making new cells and governing metabolism. Among other things, OB have estrogen receptors and are intimately involved in bone remodeling. In contrast, osteoclasts (OC) or clearing cells remove old bone. There is a close relation or coupling that occurs with OB and OC. For example, in trabecular bone (spongy, sporous structure made up of a series of rods and plates), OC create Howship's lacunae followed by OB action for new bone formation. In cortical bone (dense outer layer of bone), an OC group of cells known as the "cutting cone" remove old or damaged bone to commence the remodeling sequence (12). I discuss bone remodeling in more detail in Section 2.3.1. Table 2-2 summarizes the differences between osteoblasts and osteoclasts.

Table 2-2. Comparison of the basic features and functions of osteoblasts and osteoclasts (12).

	Osteoblasts (OB)	Osteoclasts (OC)
Basic Features	•Produces bone matrix (collagen and ground substance) •Found in clusters of 100-400 at bone forming sites •Alkaline phosphatase is abundant (serum index of bone formation) •Parathyroid hormone (PTH) present •Express receptors for estrogen, 1, 25 dihydroxy-Vitamin D in their nuclei •Over time becomes a flat lining cell or osteocyte	•Active agents in bone resorption multinucleated •In trabecular bone OC creates areas of resorption known as Howship's lacuna •Numerous OC create a cutting cone in cortical bone that "drills" through to remove old or damaged bone
Function	OB are responsible for bone formation. Endocrine, paracrine and autocrine factors control OB function. For example estrogen, PTH, vitamin D, glucocorticoids and growth hormones all act on OB.	OC stimulate bone resorption. Although OC do not have PTH receptors, stimulated indirectly via OB to commence bone resorption.

Another important cell in bone biology is the osteocyte. These cells are abundant in the mineralized matrix and although their function is poorly understood, it is thought that they play an active role in the process of mechanotransduction; bone response to mechanical stimuli (exercise) or the lack thereof (immobilisation, disuse) with structural adaptation to meet the required demands. Bone lining cells are also involved in maintaining bone integrity. Parfitt refers to bone lining cells as "gatekeepers", responsible for activation of the remodeling sequence (13). I expand on bone remodeling and mechanotransduction later in section 2.4.1. Figure 2-1 is an image of human cortical bone from the midshaft of a radius from a 76 year old women assessed using histomorphometry. Note the oval shaped Haversian canal inside the osteon; this canal or passageway is found within cortical bone and contains blood vessels and connective tissue. Together, Haversian canals form a network within bone and is called the Haversian System. The small dark coloured oval shapes scattered throughout the image are osteocytes. The exact composition of the cement sheath or lines is still unknown. It is thought to be what remains of osteoid after a basic multicellular unit or BMU (where bone modeling and remodeling takes place) has eroded old bone and replaced it with new bone (14). Cement lines are also the site of large concentrations of osteopontin (15), a bone protein involved in remodeling that binds osteoclasts to mineralized matrix.

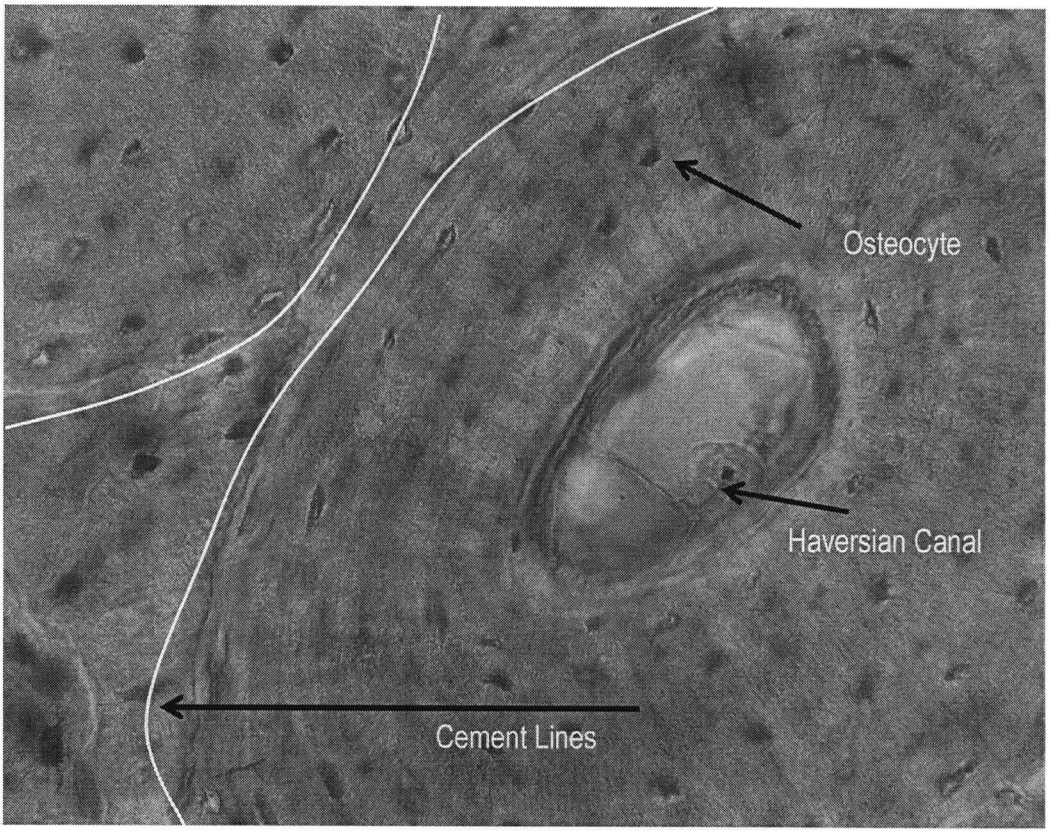


Figure 2-1. Digital image of a human osteon. Note the osteon separated from a neighbouring osteon by cement lines. The small dark ovals are osteocytes – bone cells involved in the process of mechanotransduction.

The skeleton is composed of two distinct parts: axial (vertebrae, pelvis, and flat bones) and the appendicular (long bones). In this thesis, I discuss appendicular bones only. Long bones are classified into three parts: epiphysis, metaphysis and diaphysis. The epiphysis is the growth centre of ossification and is present at both ends of the long bone. The diaphysis or shaft comprises the majority of the bone, while the metaphysis lies between the epiphysis and the diaphysis. The word metaphysis is derived from the Greek word "meta" meaning after and "physis" meaning growth; the area that lies after the growth centers—the epiphysis. It is at the metaphysis that remodeling takes place during growth and development, and it is the prime location for the majority of distal radius fractures.

Whole bone is composed of two types of tissue— woven and lamellar. Woven bone is considered immature and is found in the embryo, the newborn, fracture callus and in certain metaphyseal parts of growing bone. Lamellar bone is mature and organized, while woven bone is composed of course-fibered tissue without any uniformity of arrangement. There are more cells in woven bone per unit volume than in lamellar bone. In engineering terms, woven bone has isotropic mechanical characteristics. When it is tested under load, it responds the same regardless of the force direction, because of its random orientations. Conversely, lamellar bone is highly organized and as a result, it exhibits anisotropic properties. That is, the response of tissues to a load depends on the direction of the applied force. With anisotropic properties, the greatest resistance to applied loads occurs when the force is parallel to the longitudinal axis of the collagen fibers. I expand on biomechanical properties of bone in Section 2.5.

Bone tissue is organized into trabecular and cortical bone. Trabecular bone (also referred to as cancellous bone) is a series of rods and plates that provide a cushion for absorbing force, in addition to its metabolic and storage capacities. It exists in ~20% of the skeleton and can be found in the distal ends of long bones (e.g. distal radius, tibia etc.) pelvis, or the vertebrae. The other 80% of the skeleton consists of cortical bone. Cortical bone is present in the shafts of long bones and provides structure and stability to the skeleton. The distribution of trabecular to cortical bone can vary. As an example, the radius is composed of approximately 50-68% trabecular bone at the distal end but only 0.6-6.8% at the midshaft (16). Figures 2-2 and 2-3 are photographs of slices taken from the distal radius of a 76-year-old woman. Figure 2-2 is at the distal site where there is an abundance of trabecular bone, while Figure 2-3 is the cortical midshaft region displaying very little trabecular bone.

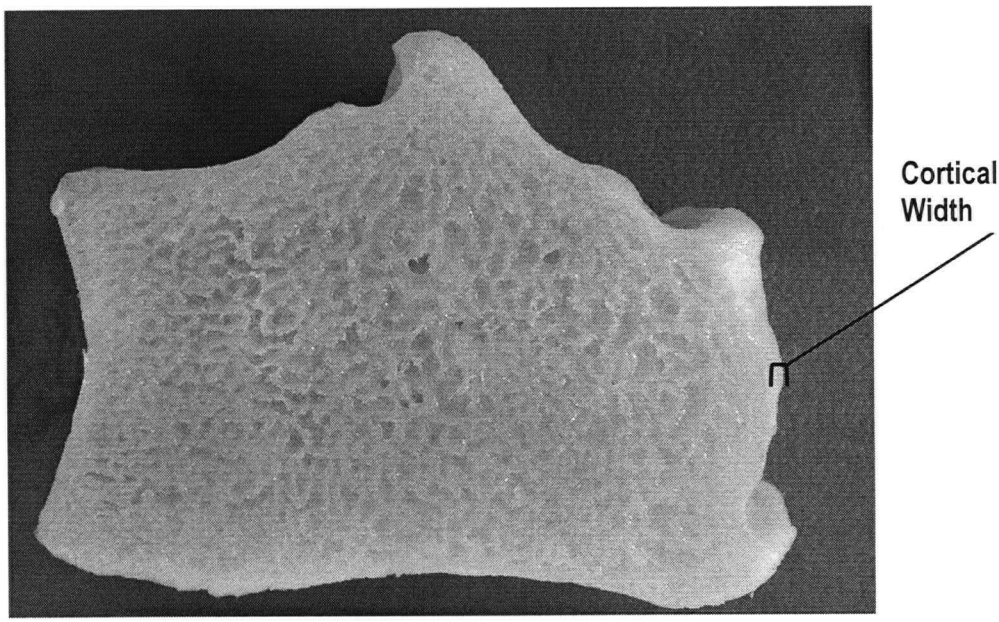


Figure 2-2. A section taken of the 4% site of the distal radius (mostly trabecular bone) from a 76-year-old-woman. Note the abundance of sponge-like trabecular bone and only a thin cortical shell.

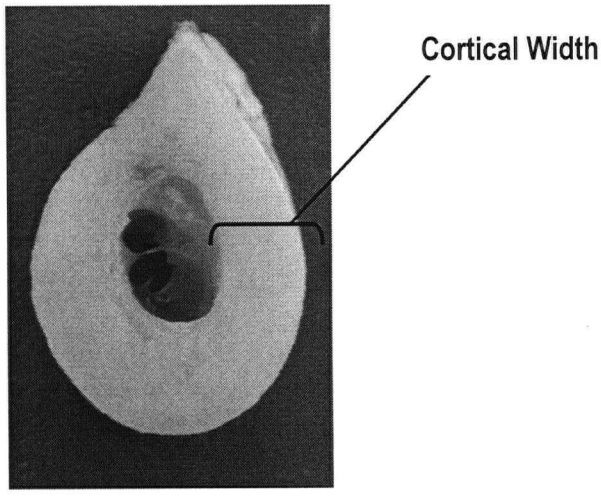


Figure 2-3. A section of bone taken from the midshaft of a radius from a 76-year-old woman. Note the solid cortical bone and distinct lack of trabecular bone. Fatty bone marrow originally occupied the centre. The cortical width (also reported as cortical thickness) is highlighted.

Cortical bone has two different surfaces – endosteal and periosteal. The endosteum is in contact with the inner surface and bone marrow. Lining cells reside here; they are metabolically active and are involved in bone remodeling. On the outside of bone is the periosteum and it is composed of two layers. The outer shell is composed of undifferentiated fibroblast-like cells and is in direct contact with muscle and fascia. The inner layer of the periosteum (also known as the cambrium) contains fibroblast-like cells (progenitors of osteoblasts) and osteogenic cells intertwined within a vast network of nerves and microvascularity. Figure 2-4 is a digital image of a histomorphometric section of cortical bone from a 76-year-old woman. There are a number of layers or bone envelopes that progress from the outside of cortical bone to the inside of the cortex. Table 2-3 highlights these layers and their main functions.

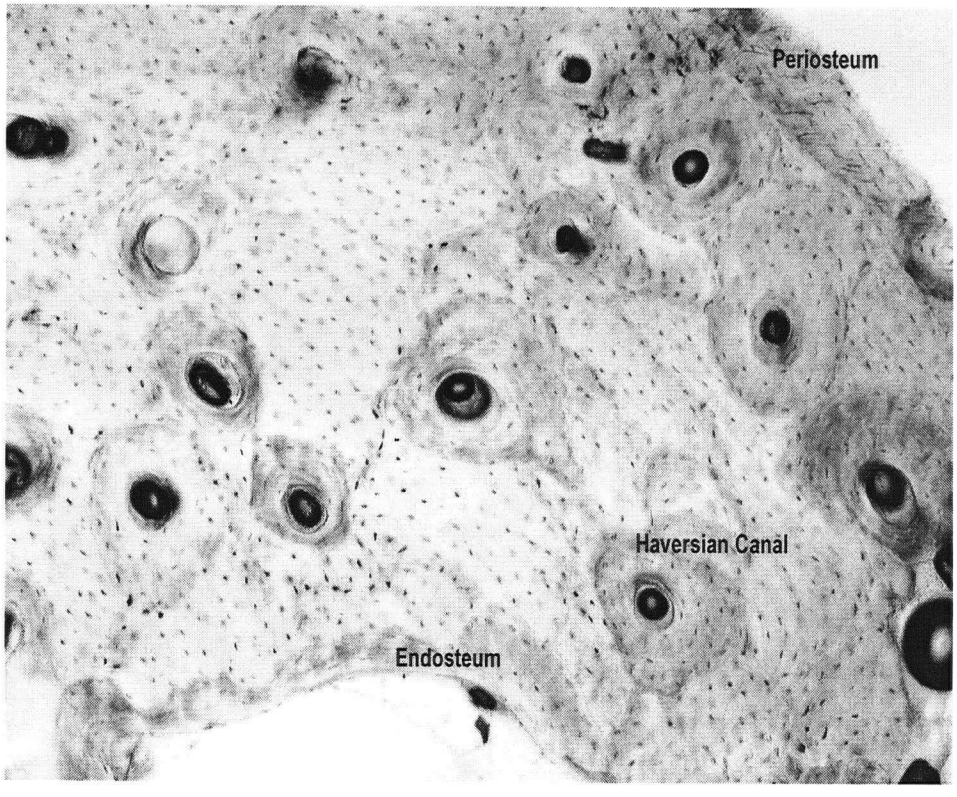


Figure 2-4. Histomorphometric section of cortical bone from a 76-year-old woman. Note the periosteal and endosteal surfaces.

Table 2-3. Table of cortical bone layers and their description.(17)

Bone Envelopes			Description
Periosteum	(outside of bone surface)	Bone Gain	Fracture healing and remodeling
Haversian			Cortical thinning
Cortical-endosteal			Connects trabecular bone to the cortex. Trabecularisation of cortical bone. Expands throughout life.
Endosteum	(next to bone marrow)	Bone Loss	Interface with bone marrow

Estrogen plays a dominant role in bone remodeling. There are more alpha-Estrogen (α-Estrogen) receptors observed in cortical bone osteoblasts and osteoclasts adjacent to the periosteum (18) compared with the endosteum. In addition, the periosteum is more mechanically sensitive to strain (19). Environments where forces on bone are reduced (aging, disuse and spaceflight) impact on bone geometry. Specifically, the endosteal or inner surface is hypothesized to control the degree of cortical bone thinning and trabecularisation of cortical bone, whereas the periosteum is responsible for periosteal apposition. The relation between resorption and apposition should, in theory, dictate overall bone strength (20-24).

During puberty, bones from girls are hypothesized to be modeled to a greater extend by increased endosteal apposition (creating a thicker cortical shell) whereas bones from boys increase bone strength primarily through periosteal apposition (larger area). By the time peak bone mass is reached, young men have larger bones and young women have relatively thicker cortical shells, in theory, to prepare for childbirth and lactation (25). Figure 2-5 is a basic illustration of the structural adaptation across aging by gender. I discuss bone adaptation to aging in Section 2.5.3.

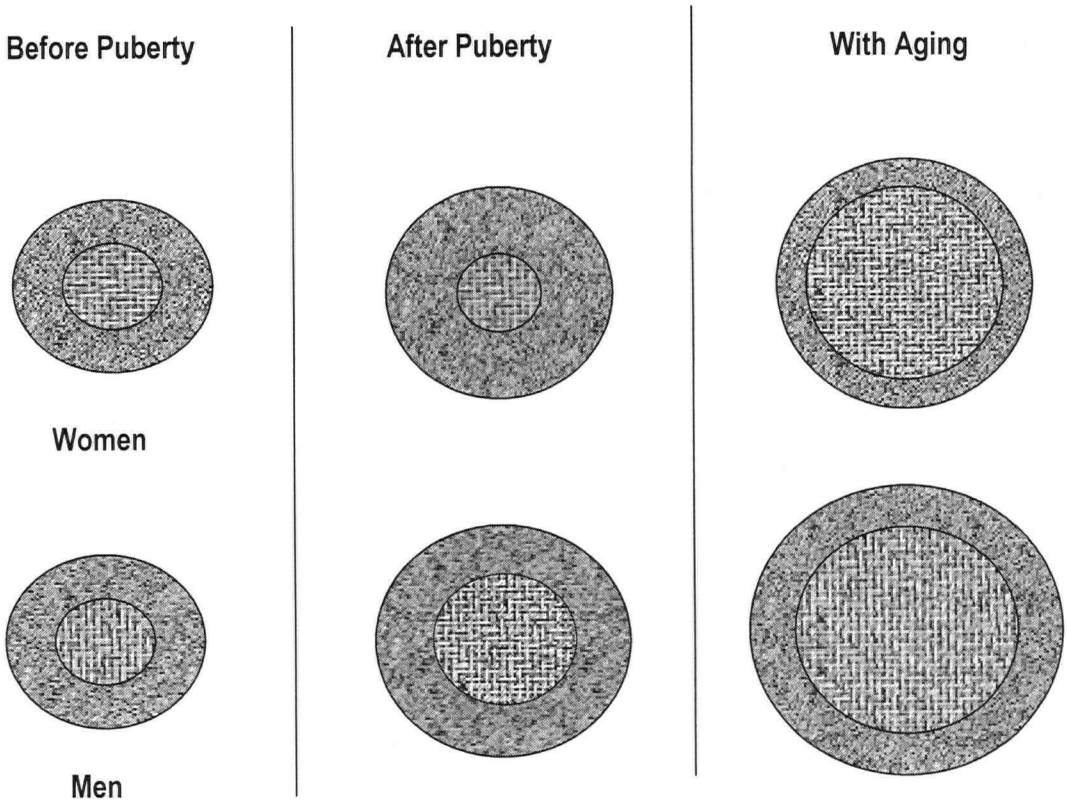


Figure 2-5. Hypothesis of bone growth and development by gender. This illustration represents the cortical shaft of long bones from women and men. Prior to puberty girls and boys have similar bone cross-sectional area and cortical thickness. Following puberty, boys/men exhibit larger bones whereas girls/women have also increased the size of the bone but the magnitude is less than the boys; there is a thicker cortical shell. With aging, men and women both experience periosteal apposition and endosteal resorption, but as a result of the lower peak bone accrual, women have generally smaller bones with thinner cortices that are more susceptible to fracture (24,25).

2.3 Bone Physiology

As mentioned previously, bone has three main functions that are vital to living organisms— to provide structural support, to house the hematopoetic system and to contribute to metabolic processes. The non-mechanical functions of bone include the regulation of calcium homeostasis and bone marrow. Bone is involved in the steady state target value for plasma free calcium and for correcting deviations from target values; it functions as a reservoir for sodium and acts as a buffer for hydrogen ion regulation. In this thesis, I do not discuss the metabolic functions of bone.

2.3.1 Bone Modeling

Bone formation commences in utero and continues through adolescence until skeletal maturity is reached. Bone modeling occurs during growth and development to maximize the required demands of the growing skeleton (26-28). During this time, bones are shaped until maturity is reached. After peak bone mass and skeletal maturity are attained, bone mass remains relatively constant in both genders until midlife (29). The knowledge that peak bone accrual (highest gain in peak bone mineral content) occurs in youth, highlights why osteoporosis has been labeled a childhood disease. If an inadequate amount of bone is laid down during crucial time periods in adolescence, there is less bone that can be lost later in life such as during the menopause.

2.3.2 Bone Remodeling

In this section, I discuss bone remodeling. Specifically I summarise the events that occur in cortical and trabecular bone and briefly review mechanotransduction and the mechanostat theory. I discuss bone remodeling with periosteal apposition in the adult skeleton in Section 2.5.3.

In contrast to bone modeling, bone remodeling is the process whereby there is a continual removal of old or damaged bone and replacement with new bone to accommodate biological aging and microarchitectural deterioration. On average, adults replace 5-10% of bone annually; although accelerated bone removal (without reciprocal replacement) can occur in environments such as diminished estrogen associated with the menopause or inactivity (30,31).

The basic multicellular unit or BMU is where bone modeling and remodeling takes place. A BMU is a discrete packet of cells responsible for bone remodeling and is found in both cortical and trabecular bone.

Bone remodeling is a surface event and it occurs in periosteal, endosteal, Haversian and trabecular bone. In cortical bone there are initiator cells collectively known as "cone cutting" that begin the process of removing old bone. The head of the cone contains approximately nine osteoclasts, while the trailing cells (up to 2000) are progenitors for osteoblasts to lay down new bone (13). The elongated cylinder of the cutting cone is approximately 2 mm (2000μm) long and 200μm wide. A cortical BMU has an average lifespan of 6-12 months and travels 20-40μm per day as it burrows along the long axis of the bone (13). Once the old or damaged bone is removed, OB start the bone formation process. If the coupling of formation-resorption is dysfunctional, (i.e. more bone is removed than is being replaced) bone becomes porous and strength is compromised (13).

In trabecular bone, remodeling occurs at Howship's lacunae and is temporally faster than in cortical bone. According to Parfitt (13,32), trabecular bone remodels in a 5 stage process that includes: quiescence, activation, resorption, reversal and formation. The sequence of events causes a downward erosion of the old bone that is replaced by new bone. Trabecular bone remains in the quiescence phase until the remodeling sequence is initiated. After activation of osteoclasts and the resorption of bone, the reversal phase initiates bone formation. The resorption phase lasts approximately 2-4 weeks. The osteoid or new bone material is first synthesized, and then mineralized (13,32). The formation phase lasts 4-6 months. Under ideal conditions, bone removal and formation work in synergy. Later in Section 2.5.4, I discuss what happens when the coupling is interrupted as in an estrogen-depleted environment (menopause) and during periods of inactivity or disuse.

2.4 Mechanotransduction and the Mechanostat Theory

In this section, I expand on the process of how bone cells communicate to activate the bone remodeling sequence. I also discuss the mechanostat theory that may control this process.

2.4.1 Mechanotransduction

At a cellular level, bone responds to mechanical loading or unloading (recorded as strain) by changing its rate of turnover. This process of converting mechanical energy into an electrical signal is the process of mechanotransduction (33) and osteocytes are considered to be the key mechanosensory cells. There are four stages to mechanotransduction: mechanocoupling, biochemical coupling, transmission of the biochemical signal and bone cell response. In the mechanocoupling phase, mechanical energy is

transformed into a useable form via alternating fluid flow in the membranes (canuliculi) of the osteocytes. The biochemical coupling involves the transfer of information using the release of calcium and the transformation of bone lining cells into osteoblasts. The last stage involves an effector cell to initiate cells to commence bone remodeling (34). In this way, mechanical stimulation and/or the lack thereof (disuse immobilisation) can affect the rate of bone formation or cause an uncoupling of this sequence.

2.4.2 Bone Turnover: The Mechanostat Theory

The mechanostat theory as proposed by Harold Frost (35) states that bone has a set level of mechanical stimulation that it requires to initiate/cease the bone cycle of absorption/formation, and there is an "optimum" range of bone strain. The mechanostat is analogous to a thermostat; and the mechanostat "set-point" can theoretically be raised or lowered by a number of biological processes such as the estrogen depletion associated with the menopause, aging, stroke and disuse (36). The mechanostat is dependent on strain [or in humans, microstrain (με)].

Strain (ϵ) is a dimensionless parameter that measures the deformation of the bone in response to an applied load. It is the change in length of the bone or object divided by the original length (37), and is measured using a strain gage. Bone response to mechanical loads depends on strain magnitude, distribution and rate. Frost suggests that strain magnitude or the minimal effective strain (MES) thresholds are determined by mechanical stimuli (38). When the strain *magnitude* on bone is above the MES range, intrinsic-bone signals send messages to commence bone modeling (MES modeling) when the strain magnitude is below the MES range, remodeling occurs (MES remodeling). Specifically, strains between 1500 με and 3000 με are thought to promote bone modeling; below this strain level bone is remodeled. Strains above 6000 με can result in microdamage and fracture (39,40). Strain *distribution* refers to the way that strain as a stimulus is presented. If the load is imposed in the same way, bone accommodates to the stimulus. Conversely, any strain deviations from the "norm" is seen as an error and bone cells respond. This is known as the error-strain distribution hypothesis (41). Finally strain *rate* refers to the manner which an external load is applied. For example, a continuous or static strain provides a consistent but low-level load.

Much has been gained from animal research that investigated the mechanical loading and unloading of bone. In non-destructive loading of bone, με are thought to be dose dependent (high intensity) and site specific (42,43). In 1985, Rubin and Lanyon observed bone adapatation to immobilisation and varied

strain rate and magnitude in a turkey ulna model (41). Interestingly, an application of a continuous load was as deleterious to bone as immobilisation or disuse (41). Mosley and Lanyon tested a variety of compressive loads (strain rate and magnitude) on rat ulna. They observed that high rate and magnitude strains presented in an unusual distribution provided the best osteogenic stimulus for periosteal expansion (44). In an immobilisation rat model, frequent bouts of high intensity activity (more than normal) are shown to assist in the restoration of bone to baseline values (45,46) and these activities must be continued to maintain bone health. Interestingly, more recent observations of daily strain history in a turkey ulna model suggests that a wide spectrum of strain is important (47) and not just high strains; in particular, there is a persistent contribution from low-magnitude strains such as the strain resulting from postural muscular activity.

2.5 Determinants of Bone Strength

> *"The mechanical properties of any structure are determined by two quite separate things, the mechanical properties of the material and the size and shape of the whole structure – its architecture."* *Currey 2001 (48)*

In this section, I review key concepts related to biomechanics and bone strength. In particular, I highlight the concepts of stress, strain, loading modes, structural and material properties and the determinants of bone strength. The section concludes with a description of bone adaptation with aging.

2.5.1 Basic Biomechanical Concepts

2.5.1.1 Stress and Strain

Stress and strain are integral components to the study of bone. Stress is defined as the response to imposed force. It is equal in magnitude to the applied force but opposite in direction and is measured in force per unit area. The unit of stress is called the Pascal and is equal to one Newton over one square meter (N/m^2) as discussed previously. Strains in the human body are in the microstrain range ($\mu\epsilon$) and are related to the mechanical properties of the material, the Young's modulus. Stress is the load applied to bone and different loading modes are compression, tension and torsion.

Figure 2.6 is a visual representation of these applied loads. The response of bone to loading will vary depending on the way the bone is loaded. Because bone is a composite material, mature lamellar bone responds to loads placed on it differently, depending on the direction of the load. This is known as anisotropy. Mature bone is strongest in compression (the orientation of osteons) and weakest in tension.

Compression causes the cylinder to shorten while tension causes lengthening of the object. Torsion is a combination of forces twisting it in equal but opposite directions. Interestingly, bending is a combination of tension and compression. In Figure 2.6 E, when the cylinder is bent, the area labeled (i) is compressed while the area labeled (ii) undergoes tension. The magnitude of stress is greatest at the ends and nears zero in the middle of the cross-section (or neutral axis; Figure 2.6E). Under normal physiologic conditions, long bones are loaded in compression and bending (30).

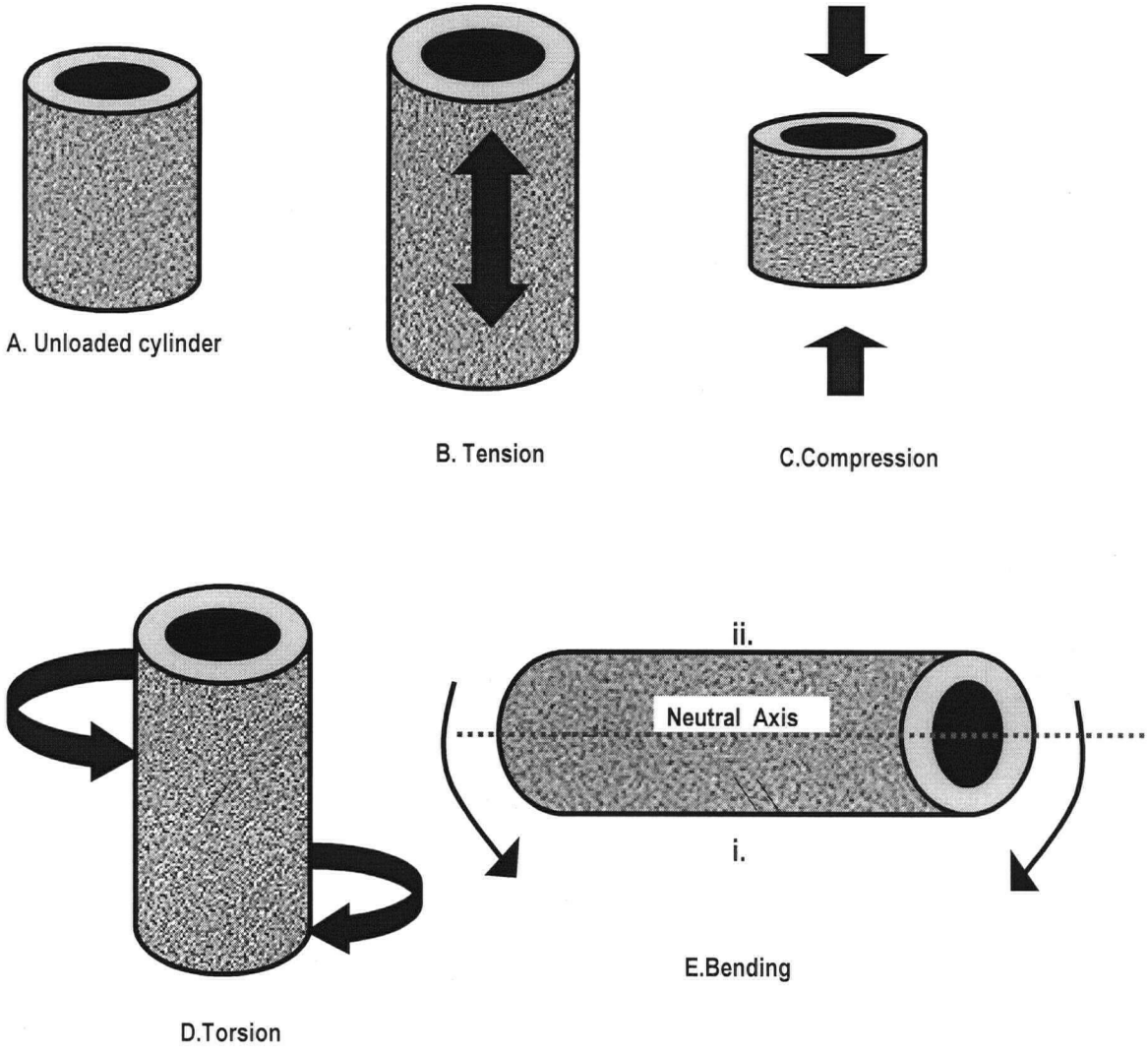


Figure 2-6. Types of loading forces acting on bones. Figure 2-6A is an unloaded cylinder; B represents a cylinder under tension; C compression; D torsional load and E is a cylinder under bending load.

2.5.2 *Bone Strength*

Although widely used, 'bone quality' is a nebulous term that does not describe the multiple components that influence bone health and predict fracture risk. The overall integrity of bone is determined by its structural and material properties while taking bone size and geometry into consideration. Applying principles and terminology from engineering has shifted focus in the medical literature from relying solely on DXA derived bone "density" as a measure of strength, to now investigating the relevant material constituents of bone, the distribution and bones' overall structure. Despite the importance of the mechanical behavior of bone, engineering principles alone cannot account for the altered biological responses that occur with aging and diminishing hormonal levels. These biological stimuli directly compete with mechanical stimulation to control bone adaptation (49).

Mechanically, bone strength is determined at the material (tissue) level and the whole bone level (structure). Bone strength is defined as the ability to withstand loads and is dependent on the i) structural material; ii) amount and distribution of the material in the cross-section and iii) amount of accumulated microdamage (30,50,51). Material properties include, tissue mineralization, collagen properties and accumulated microdamage and are reflected in the ultimate strength, stiffness and yield point of a test specimen. Whole bone strength depends on the amount of bone, geometric properties of bone including linear dimensions, cross-sectional area, cortical thickness and cross-sectional moment of inertia (CSMI). In order to determine overall strength or resistance to fracture, both material and structural characteristics play key roles (36,52). However, due to the nature of the rods and struts in trabecular bone, it is difficult to distinguish between its material and structural properties. Currey suggests that trabecular bone "should be considered in the middle of the spectrum" (between material and structural properties) (52).

Mechanically, bone strength is determined using either a whole specimen (e.g. an entire radius) or small sections removed from the whole bone. Mechanical testing results in four parameters used to quantify the strength of a bone: failure load, brittleness, work to failure and stiffness (53). Table 2-4 defines each of these parameters. I discuss the load-deformation curve (whole bone) in Section 2.5.2.1 under structural properties and I discuss the stress-strain curve (small bone section) under material properties in Section 2.5.2.2.

Table 2-4. Terminology and definitions used to describe the characteristics of bone (54,55).

Mechanical Parameter	Definition
Strength	Resistance to deformation. Ultimate strength is defined as the load at which bone fails and is measured in Newtons.
Hardness	Resistance to plastic deformation; resistance to abrasion and wearing.
Ductility	The ability to deform before failure.
Brittleness	The inability to deform before failure.
Toughness	The ability to absorb energy during plastic deformation; It is the area under the stress-strain or load-deformation curve.

2.5.2.1 Structural Properties

Structural properties generally refer to whole bone; the geometric distribution of material, and the overall size of the bone. The structural properties of bone are typically described by the load–deformation curve (Figure 2-7).There is a linear relation between the load applied and the deformation response. For example, in the early phase (elastic region), bone typically responds with non-permanent changes to its shape; returning to the original shape once the load has been removed. However, with continued loading, once the bone has reached the plastic region, any further changes that may occur (because of the load) will leave permanent deformation. The point at which the bone changes from the elastic to the plastic region is known as the yield point. If the load continues, it will reach the ultimate failure load whereby a fracture will result. As I discussed previously, the load-deformation curve can provide several important pieces of information; the stiffness of the material is represented by the slope of the curve (ductility, brittleness) and the energy to yield and energy to fail (toughness) are represented by the areas under the curve. The ultimate failure load is the strength of the bone.

Figure 2-8 depicts load-deformation curves from the cadaveric radii of two women. Specimen A is from a 78-year-old women and Specimen B is from a 68-year-old woman. Specimen A has an overall lower failure load (<3100 Newtons) while Specimen B required almost twice the load to cause failure. In these curves, the yield point is not obvious. The area under the curves represent the work done to cause failure (displacement; toughness); Specimen B has a higher work to failure. The slope of the curve represents the brittleness of the material. However, it is not possible to tell which specimen is more brittle because this graph does not account for the differences in size (cross-sectional area) between the two specimens.

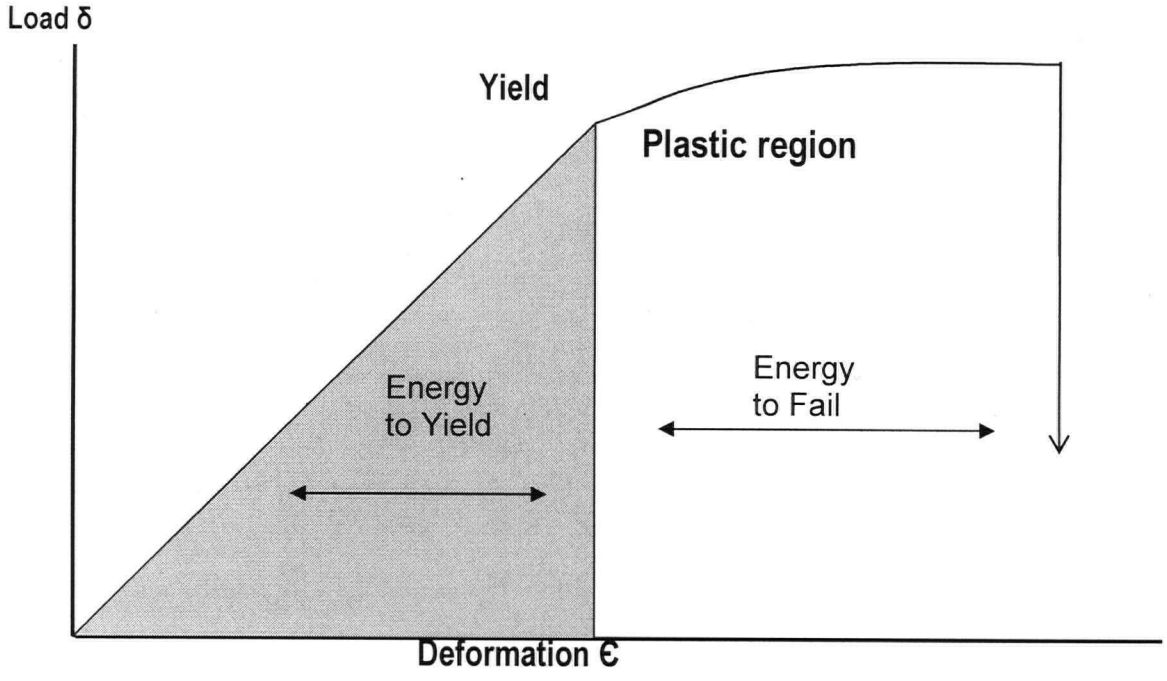


Figure 2-7. Schematic Load- Deformation Curve. Bone exhibits a linear relation between the applied load and the resultant deformation exhibited by the bone.

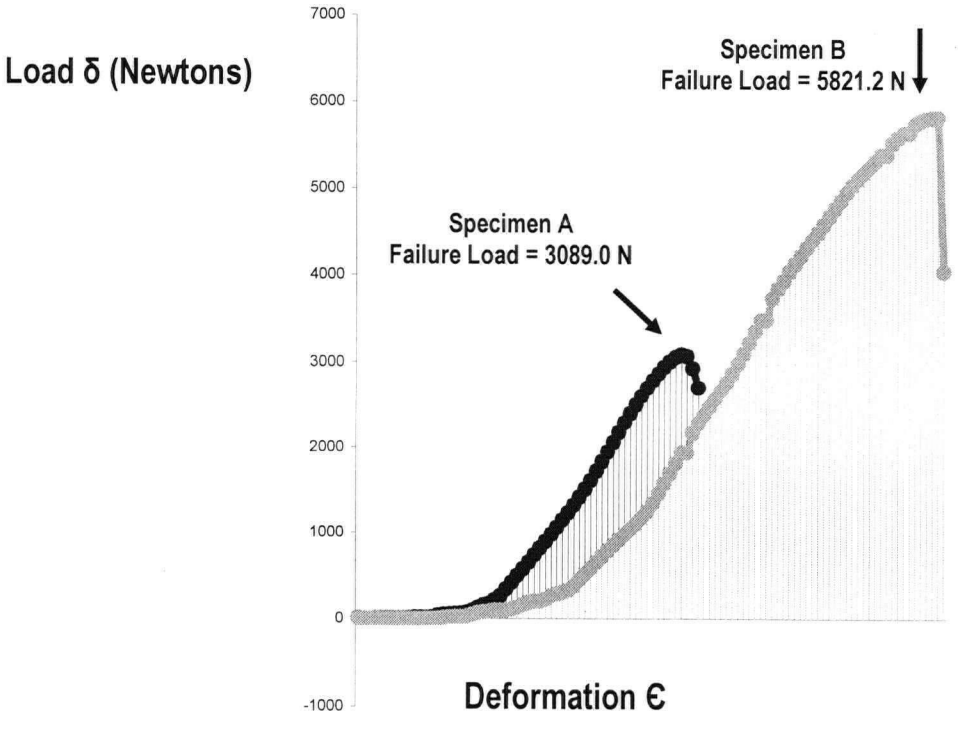


Figure 2-8. Load deformation curve for two test specimens. Both are the distal 30% of two radii tested under identical conditions (axial compression at 75 mm/sec).

2.5.2.2 *Material Properties*

> *"...structurally independent characteristics that influence the amount of stress required to cause failure"* *Beck (56)*

Factors that affect a material's stress-strain relation include the homogeneity of the material (or the consistency of the material contained within) direction of the load acting on the material; the rate of loading, and the viscoelasticity of the material (57).

Material properties reflect the intrinsic characteristics of the tissues that are independent of geometry. Ex vivo assessment of bone material properties is done by extracting and machining small sections of bone material and testing them under different loading configurations. The resultant curve is similar to the load-deformation but is known as the stress-strain curve (Figure 2-9). Young's modulus can be determined from the slope and is a measure of the material's resistance to loading.

Bone has viscoelastic properties. That is, bone has both elastic characteristics (able to return to its original shape after a load is applied) and viscous properties (material does not return to its original shape after deformation). Viscoelasticity is a time dependent property. Therefore ultimate failure load is affected by the load rate, hysteresis, creep and stress. A fast loading rate, such as 75-100 m/sec simulates a fall configuration but significantly increases the ultimate failure load and displacement (58). For example, if a bone was tested in axial compression at a fast rate (75 mm/sec) to stimulate a fall configuration, the bone's ultimate failure would be higher than if the rate of loading was slower (e.g. 5 mm/sec). The ultimate failure load would also be lower if a specimen was tested in 3-point bending because bone is strongest in (axial) compression (52).

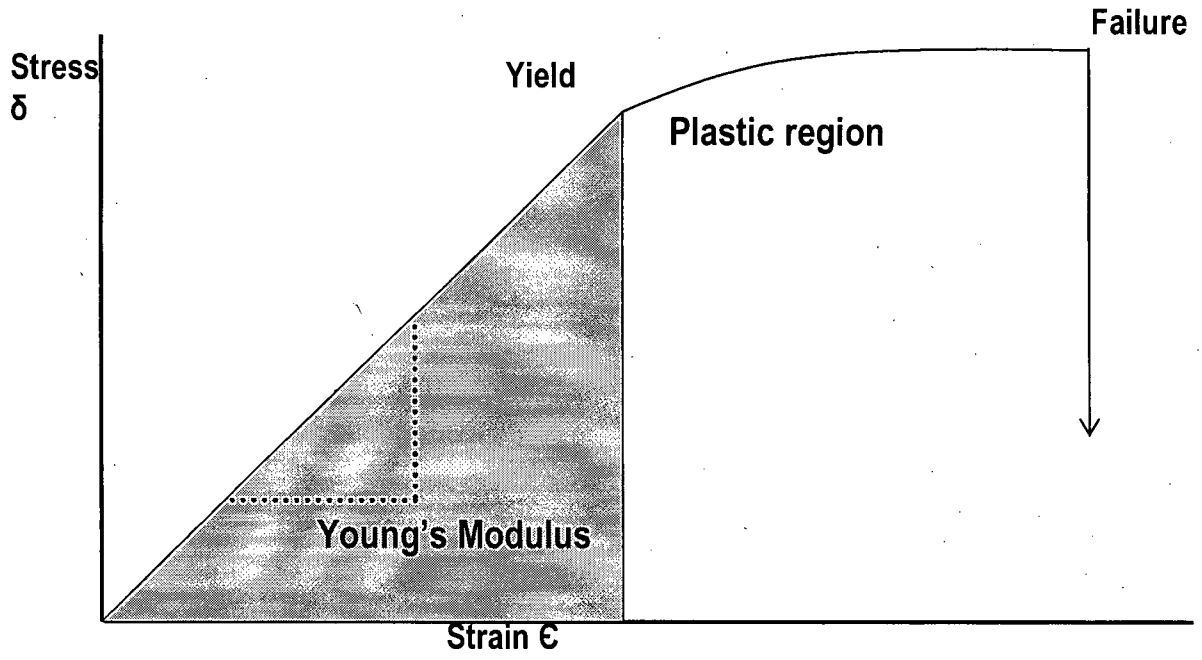


Figure 2-9. Stress-Strain Curve.

2.5.3 *Age-Related Changes in Bone Strength*

Changes occur with aging throughout all body systems; aerobic capacity decreases with a corresponding decline in the musculoskeletal system irrespective of activity level. Cross-sectional and prospective research has highlighted bone loss that occurs with aging and is similar to that experienced during disuse and spaceflight (23,59-61). However, we know relatively little about the structural mechanisms that underpin this loss.

At a cellular level, bone cells adapt to aging by decreasing in number and size. Osteocytes atrophy and there is an increase in the size of the hydroxyapatite crystal (62). The end result is a remodelling imbalance; an uncoupling of OB-OC and an incomplete filling of resorption cavities (62). At a material level, cortical bone becomes more porous and exhibits trabecularisation with a concurrent increase in anisotrophic properties. Haversian canals widen and BMD decreases with a corresponding increase in fracture risk. In trabecular material properties, there is a loss of mineral content and bone becomes less resistant to fracture. Bones become brittle with age and less able to absorb forces. There is also a decrease in ultimate stress (5%) and strain (9%) for each decade of life and porosity increases without a change in material content (63). In one observation of 47 right femora from men and women 20-102 years of age, porosity changes accounted for 76% in the reduction in bone strength. There was an observed loss of horizontal struts and a resultant propensity for individual trabecular "buckling", leading to decreased bone strength (64).

Bone mechanical properties also decline with age. Structural components of bone adapt to aging with thinning and trabecularisation of the cortical shell (17). Normally, the cortical shell of vertebrae in younger healthy adults is approximately 400-500 microns. With aging, it can decline to 120-150 microns or less. Cortical bone dominates the contribution to overall bone strength in older vertebrae. Mosekilde and Mosekilde (65) reported that the vertebral shell of young participant-donors contributes only 20-25% to bone strength, compared with a 70-80% contribution to load bearing capacity in the elderly.

Age-related changes affect both women and men but the pattern of change is different. Parfitt refers to a "rapid" and "slow" phase of bone loss that accompanies aging (32). In women, the loss of estrogen at the menopause initiates a rapid loss of mostly trabecular bone (radial metaphysis and vertebrae) accounting for 20-30%, but only a 5-10% loss of cortical bone (29). This loss eventually slows but continues throughout life. A slower loss of bone is observed in men and accounts for a 20-30% loss of cortical bone

over many years (29). Parfitt suggested that this early phase of rapid bone loss results from unrestrained OC resulting in trabecular perforation and loss of horizontal struts and subendosteal porosity (32). Conversely, the slow bone loss phase results from too few OB resulting in thinning of trabeculae and less bone formation (32). Bones adapt to diminished mineral density by increasing their total cross-sectional area with a loss of cortical bone (thin cortical shell). Men exhibit greater periosteal expansion and, because they had greater peak bone mass they tend to experience less age-related changes in bone strength compared with women. This highlights previous observations in men showing three times greater increase in cross-sectional area at the vertebrae and femoral neck compared with women with aging (66).

Conducting histomorphometric analyses of iliac specimens obtained from women and men participants, Aaron and coworkers also observed a different pattern of bone loss between genders (67). Men had decreased bone formation compared with women who exhibited increased bone resorption. Whole trabeculae were missing in the samples from women (67). Although men lose bone gradually over time they tend to experience fewer radial fractures (2% for men vs. 16% risk for women) and this may be related to higher peak bone mass, larger bones and fewer falls (68). Interestingly, although men do not undergo the same dramatic midlife hormonal imbalance, research suggests that their bone undergoes some adaptation with estrogen loss.

Despite the loss of bone mass attributable to the effects of aging, the skeleton tries to maintain bone strength. The cross-sectional moment of inertia (CSMI) provides an estimate of the resistance of a bone (or hollow cylinder) to fracture following acceleration in either bending or torsion (Figure 2-10). Note that CSMI is a geometric parameter and does not account for the material properties of bone. Bone that is displaced further from the central axis requires more force to cause a fracture. In other words, bone distributed farther from the centre or neutral axis (periosteal apposition) maintains bone strength more than if bone is laid down on the inner surface (endosteal apposition=thicker cortical shell). Figure 2-11 is an illustration of this principle. Deposition of bone at the periosteal surface over a long period of time has the potential to decrease risk of fracture (22), while maintaining a light skeletal frame. However, there are limits as to how far the bone can be displaced; a bone with a large cross-sectional area but thin cortical shell is subject to buckling failure.

A recent large population-based (n=696) study using pQCT (to describe volumetric adaptation) observed periosteal apposition with endocortical resorption with aging (61). Specifically, at the distal radius in women there was a 7% increase in total bone area compared with 16% increase in men. At the proximal

radius, there was 24% increase in total area in women compared with a 27% increase in men (61). Bone mineral density also decreased to a greater extent in women compared with men. This study had three main findings: 1) there was trabecular bone loss with aging (thinning of trabeculae, disruption of trabecular microstructure and loss of trabecular elements); 2) bone changes were consistent between the femoral neck and the distal radius but did not correspond with changes at tibial, weight-bearing sites and 3) the rate of endosteal resorption was greater than the rate of periosteal apposition (61).

$$CSMI = \pi \frac{(r_1^4 - r_2^4)}{4}$$

r_1= outer radius of a hollow tube

r_2= inner radius of a hollow tube

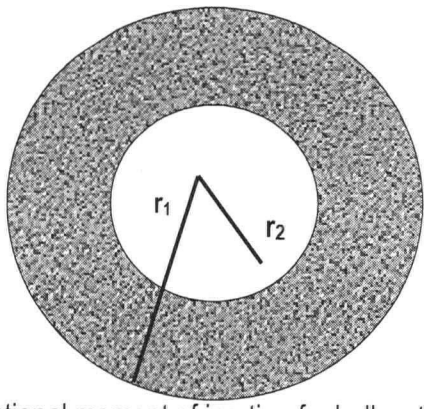
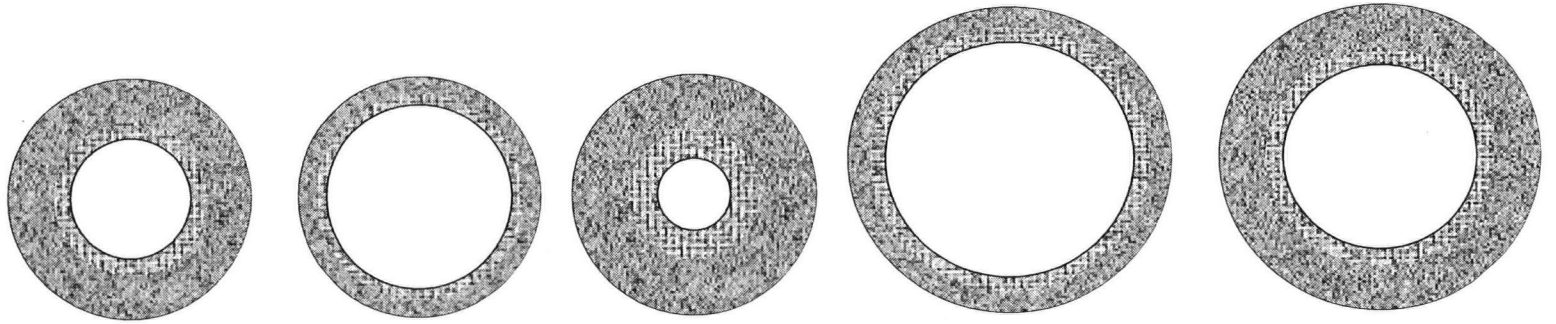


Figure 2-10. Diagram of the cross-sectional moment of inertia of a hollow tube.



A. Healthy Bone | **B.** Bone loss at endosteal surface | **C.** Bone gain at endosteal surface | **D.** Bone gain at periosteal surface | **E.** Bone gain at both surfaces

	A. Healthy Bone	B. Bone loss at endosteal surface	C. Bone gain at endosteal surface	D. Bone gain at periosteal surface	E. Bone gain at both surfaces
r^1(mm)	10	10	10	12	12
r^2 (mm)	4	7	2	9	7
Cortical thickness	6	3	8	3	5
CSMI (mm^4)	7649	5965	7843	11127	14392

Figure 2-11. Diagram of five different hollow cylinder cross-sections to demonstrate the change in cross-sectional moment of inertia (bone strength in bending) when more bone is added on the inner surface (endosteal apposition) vs. more bone added to the outer surface (periosteal apposition). **A.** represents normal healthy bone. **B.** represents bone loss from the inner surface (i.e. after inactivity or due to aging). This reduces the cortical thickness and over all bending strength. **C.** demonstrates the bending strength and cortical thickness if the bone responded to a stimulus by adding 2mm on the endosteal surface with a relative increase in bone strength. Addition of bone at the endosteal surface, in theory creates a heavier structure. Endosteal apposition also has a maximal limit otherwise the marrow space would be obliterated. **D.** If 2mm of bone is added to the periosteal surface, although the cortical shell (width) is reduced (compared with **C.**), the bending strength is still almost 1½ times greater than **C**. **E.** demonstrates that a combination of increased periosteal dimensions and a thicker cortex still provides the greatest bone strength.

2.5.4 *The Menopause: The Impact of Diminished Estrogen on Bone Strength*

In the first five years after the menopause, bone loss increases (69). This is attributable to diminishing amounts of estrogen. Estrogen plays an important role in bone remodeling. This is by maintaining the balance between bone resorption and bone formation. Estrogen receptors are found on bone cells. In particular, alpha and beta estrogen receptors (ERs) exist on the periosteal and endosteal surfaces in varying amounts (18). Estrogen receptors are thought to play an important role in identifying bone strain and therefore the reduction of ERs (as a result of the menopause) contributes to the disruption of bone remodeling (70).

Lower levels of estrogen can alter bone formation and overall remodeling homeostasis. For postmenopausal women, the loss of estrogen predominantly affects sites with less mechanical loading. This primarily affects trabecular bone, especially in the metaphyseal region where strain rates are low (71). Clinically, this translates into the steady increase in metaphyseal radial fractures observed in women after age 40 years (68). Frost hypothesized that biological events such as estrogen loss at the menopause alter the mechanostat (31,36). The presence of estrogen keeps the mechanostat threshold at a level compatible with maintenance of bone resorption-formation. However, decreased estrogen levels raise the remodeling threshold. Therefore, it takes greater strain to add bone (by way of mechanotransduction) and the consequences are an increased rate of bone turnover. In women therefore, reproductive biology must compete with mechanical loading (49). Noteworthy is the role of estrogen in men and the similar impact of a reduced number of ERs and osteopenia in males (72).

Finally, estrogen plays an important role in fracture healing. In an animal model, fracture healing was delayed when estrogen levels were lower in the early phase (3-16 days) of healing (73). Therefore, a post-menopausal woman with a distal radius fracture may experience delays in healing and bone remodeling because of lower estrogen levels.

2.6 In vivo Measurement of Bone Properties

The material and structural properties of bone have been well defined from animal and cadaveric investigations (39,74-76). The challenge for in vivo investigations lies in finding methods to define bone strength (resistance to fractures) without destroying tissue. Non-destructive imaging such as X-ray, dual energy X-ray absorptiometry (DXA), peripheral quantitative computed tomography (pQCT) and quantitative ultrasound (QUS) have been used to assess fracture risk. However, the overall risk of fracture is based on bone health (material and structural properties) and propensity to fall. The non-destructive determination of bone strength is an important part of preventative medicine and therapeutic intervention. In this section I outline non-invasive technologies used for assessing bone. In particular I highlight DXA and pQCT.

2.6.1 Overview of Densitometry Technologies: An Historical Perspective

Non-destructive measurement of bone can assess bone geometry and bone mineral density. These measures are able to predict (with limitations) who is at risk for future fractures. Determination of bone health provides a basis from which to diagnose bone health, commence appropriate treatment and monitor therapy. The evolution of non-destructive bone assessment has progressed from early techniques of cortical thickness measurement from standard Anterior Posterior (AP) radiographs (radiographic absorptiometry, RA) and using radionucleotides as an energy source, to measure the attenuation of radiation. Presently, there are many options available using derivatives of X-rays, ultrasound and magnetic resonance imaging. Table 2-5 provides an overview of the most commonly used techniques to assess bone.

RA was one of the earliest imaging techniques used to quantify bone mass. From AP X-rays of the metacarpals and phalanges calipers were used to measure cortical thickness. Although there were problems with precision initially, the most recent reliability studies report a Coefficient of Variation (CV) less than 5% (77). RA is still being used today although in limited situations (77).

Single (SPA) and dual photon absorptiometry (DPA) that used radionucleotides (Iodine I^{125} and Gandolinium) were developed in the 1960s to generate either one (single) or two (dual) photon sources in collimated beams that were projected through tissue. These techniques are based on attenuation of the

isotope energy beam as it passes through bone and soft tissue. A dense tissue such as calcified bone has many electrons. As nucleotides pass through tissues, some are absorbed (into areas of greater densities and electrons) and others pass through. The reduction in the signal (or isotopes) is called attenuation. Therefore, there is greater attenuation in bone (and fewer signals received by the detector after attenuation). Quantification of tissue densities is made by calibrating DPA and SPA to known densities (historically to ash weights and now to resin-based phantoms). These early techniques have known limitations including; high maintenance costs associated with replacement of the radioactive source; an extended scan acquisition time (over 60 minutes for a total body scan) and inaccuracies due to isotope decay and overlying soft tissue. Thus, the utility of DPA and SPA was only at peripheral sites (78-80).

Superceding photon absorptiometry (but based on the same principle of tissue attenuation) is single energy X-ray absorptiometry (SXA) which relies on a single X-ray energy source to provide a projectional area and dual X-ray absorptiometry (DXA) which uses two X-ray sources at two different attenuations. DXA and SXA work by recording the decrease or attenuation of the X-ray beam as it passes through tissues of different densities. The advantage of DXA is that there is no source decay, faster acquisition time and the separation of soft-tissue from mineralized tissue. The X-ray source technologies have many advantages but are limited because they cannot separate cortical from trabecular compartments; an important feature for quantifying bone strength. I will discuss DXA in more detail in Section 2.6.3.

Development of quantitative computed tomography (centrally and peripherally) has improved the understanding of bone properties and bone strength. Quantitative computed tomography (QCT) is an important tool that separates cortical from trabecular bone and will provide volumetric assessment of tissues. Although, technically there are many advantages to QCT, it utilizes a relatively high level of radiation and therefore is prohibitive in many situations. Peripheral QCT retains all the beneficial qualities of QCT, but the radiation dose to participants is minimized (because it only measures peripheral sites). More recently, microCT and magnetic resonance imaging (MRI) have been used to look specifically at trabecular bone microarchitecture. These technologies (while providing excellent detail) are still in the research stage for in vivo human application because of high radiation dose and long scan acquisitions times for microCT and cost/availability for MRI.

Finally, quantitative ultrasound is used experimentally and commercially to assess bone health. This technique does not involve radiation and therefore reduces patient risk. More recently, research has

tested the ability of QUS to measure bone material properties (81); a characteristic not available with the other absorptiometry technologies.

Table 2-5. Overview of the non-invasive assessment of bone parameters. (78-80)

Technology	Methodology and Scan Time	Precision	Accuracy	Radiation Exposure (millirem)	Outcome Parameters
Radiographic Absorptiometry **(RA)**	Radiographs are taken with aluminum wedges and cortical thickness measured using calipers	0.3-2.4% In vivo	4.8% (77)	5	aBMD hand (metacarpals and phalanges) Cortical thickness
Single Photon Absorptiometry **(SPA)**	Introduced in 1960s. Highly collimated photon beam from radionuclide (I^{125}) used to measure radiation attenuation. Superseded by SXA	1-3	3-8	1	BMC, aBMD at peripheral sites with minimal soft tissue
Single Energy X-ray Absorptiometry **(SXA)**	Highly collimated photon beam from single X-ray source used to measure radiation attenuation. Areal projectional measurements	1-3	3-8	1	BMC, aBMD at appendicular and axial sites. Affected by soft tissue.
Dual Photon Absorptiometry **(DPA)**	Used for areas with variable soft tissue composition such as axial skeleton, hip or whole body. Highly collimated photon beam from radionuclide ^{153}Gd used to measure radiation attenuation. Superseded by DXA in 1987	2-5	3-10	1-5	BMC, aBMD at appendicular and axial sites. Affected by soft tissue.
Dual Energy X-ray Absorptiometry **(DXA)**	Developed in 1970s. Highly collimated photon beam from two X-ray sources used to measure radiation attenuation. Uses beams of two distinct energy levels. Areal projectional measurements. WHO defined "Criterion standard"	1-2	3-9 5.2% radius (82)	1-5	BMC, aBMD at appendicular and axial sites. Affected by soft tissue.
Quantitative Computed Tomography **(QCT)**	Derivative of the larger CT machine developed by Hounsfield using a source of collimated beams and detectors that translate and rotate to acquire images. Computer reconstruction of images.	0.8-3% (83)	5-15	50	vBMD, BMC, Bone geometry, strength index Axial skeleton but high radiation dose Primarily used to measure trabecular vBMD in the spine
Peripheral Quantitative Computed Tomography **(pQCT)**	Peripheral version of QCT used to measure peripheral sites. Resolution of scan acquisition ranges from 100-600µms.	0.5-7.7 (84)	9-7-14.3% (85)	1-2 (86,87)	vBMD, BMC, Bone geometry, strength index Used predominantly at radius and tibia but has been use at the humerus (84) and rarely at the femoral neck (88)
MicroCT **(µCT)**	Research version of CT based on same principles. Resolution of scan acquisition less than 100µms (histological level).	0.64-1.29% (89)	2.5-6.1% (90)	Not available but higher than pQCT	vBMD, BMC, Bone geometry, strength index at radius in humans, animal and ex vivo studies Used to assess trabecular

					microarchitecture; mostly research and for use with finite element modeling. Scan times are long and radiation high for patient use.
Quantitative Ultrasound **(QUS)**	Two US transducers (transmitter and receiver)	3-4%		0	US transmission velocity (UTV); broadband US attenuation (BUA) usually assesses calcaneus. Units are meters/sec. If soft tissue is included is Speed of Sound (SOS). Limited ability to measure bone elastic properties (91,92)
Magnetic Resonance Imaging **(MRI)**	Based on the impact of magnet on electrons; primary work in soft tissue; only recently used for bone geometry	1.3-4.2% (93)	1.6-1.8% (94)	0	Magnetic coils of various sizes are used to quantify bone trabecular architecture. Not widely used clinically for bone measurement.

2.6.2 *Radiation Exposure*

Imaging technologies that employ radiation for absorptiometry techniques pose a risk to the participant/patient and the operator. Radiation exposure is a naturally occurring potential phenomenon by virtue of being outside and living in an industrialized environment. As such, The American Society of Physicists in Medicine has quantified radiation as "effective exposure" meaning the obtained dose is based on the area and amount of exposure. The International Commission on Radiological Protection developed a rating system based on the organ/tissue being ionized (95). The Effective Human Equivalent Dose (H_e) is measured in millirems (mrem) or microSieverts (μSv; 1mrem=10 μSv). A rem comes from roentgen – equivalent-man. Some biological tissues get a higher weighting; that is ionization would have a greater impact on the specific tissue type. The annual effective dose for natural background radiation is 300 mrem. Five rem is accumulated in the first 17 years of life and approximately 25 rem in 80 years (95). A dental X-ray is 10 mrems, a transcontinental return flight from Halifax to Vancouver is 6 mrems and a radius scan by DXA is < 1 mrem compared with 1-2 mrem by pQCT (86,87).

2.6.3 *Dual Energy X-ray Absorptiometry (DXA)*

Dual energy X-ray absorptiometry is considered by the World Health Organisation as the "gold or criterion standard" to diagnose osteoporosis. DXA is the most widely used assessment technique. It can measure the axial and appendicular skeleton at relatively low costs and minimal risks to the patient. However, DXA still only provides a two-dimensional (areal) view of three-dimensional objects. I restrict my discussion of DXA to bone parameters and will not discuss its capability to assess soft tissue.

2.6.3.1 Description of the technology

DXA has proven to be an important tool for advancing the field of bone health. It is based on the principle that two X-ray beams of two distinct energy levels are passed through the target tissue. X-rays have short-wave lengths within the electromagnetic spectrum. The X-rays produce small packets of energy or photons that pass through an object and if small enough, avoid collision with atoms of the scanned tissues. DXA experiences all tissue in its path as bone or non-bone (soft-tissue, fat, air). It records the decrease or attenuation of the X-ray beam as it passes through tissues of different densities. Bone has higher densities due to the hydroxyapatite mineral composition (X-rays only measure calcium and

phosphorus) and therefore has a higher attenuation coefficient (more X-ray beams are absorbed). Conversely, soft-tissue and fat have lower X-ray attenuations.

2.6.3.2 Measurement parameters

DXA is able to provide bone mineral content (BMC, g) and areal bone mineral density (aBMD g/cm^2) at both axial and appendicular sites. Figure 2-12 is a DXA report from a radial scan. This report is generated to provide clinically relevant information for the patient, physician and other health care providers. It outlines bone and soft tissue parameters and provides an estimation of bone health compared with healthy normal and age-matched norms. Areal BMD is reported as a T-score and Z-score (for aged-matched norms). I discuss the diagnosis of osteoporosis and T-scores in Section 2.11.1.

2.6.3.3 Radius and DXA

Some DXA instruments, including the Hologic 4500 DXA scanner, have a special arm trough and analysis program specifically for the radius. There are also portable peripheral DXA scanners specifically for the measurement of the forearm and lower leg. Figure 2-13 shows the patient set up in preparation for a DXA radial scan.

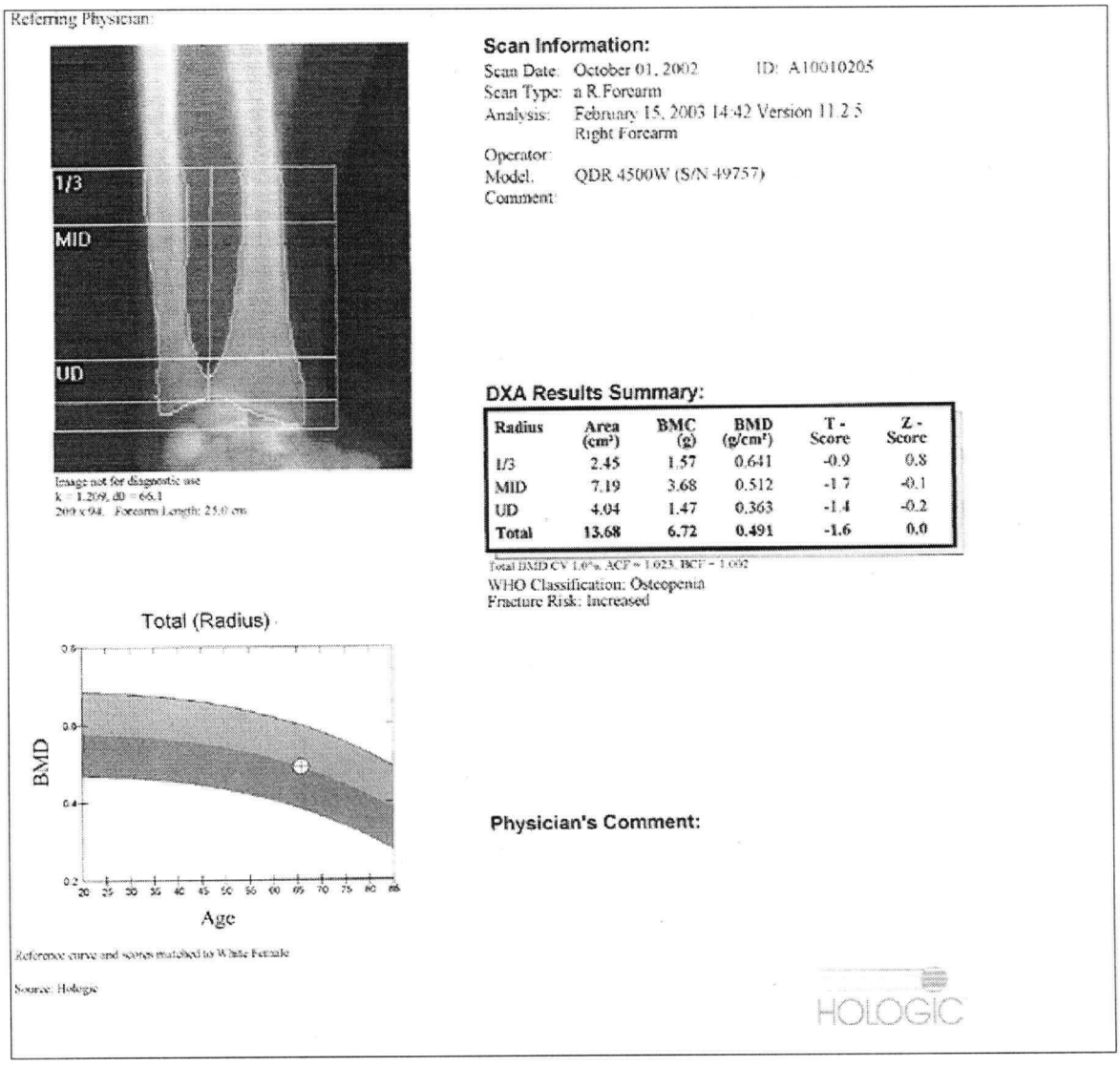


Figure 2-12. Sample DXA report from a radial scan.

Figure 2-13. Participant positioned in DXA forearm trough for scanning.

2.6.3.4 *Strengths and Limitations*

The advantages of DXA include its precision, relatively short scan time, and fracture risk prediction. However, due to DXA's inherent planar nature, the overall size of a scanned object will alter bone parameters (that is, a larger bone will appear to have greater bone density) and a person with large bones may have higher aBMD and a person with small bones may be inaccurately diagnosed with low aBMD (78). The fact that adjacent soft tissue influences DXA results is known (96). In theory this should not be an issue at the distal radius where there is only minimal soft tissue. DXA techniques cannot separate cortical from trabecular bone and cannot directly assess the structural changes in bone that underpin changes with immobilization-disuse (97). Lastly, with DXA it is not possible to adjust different acquisition and analysis parameters to optimize results for compromised bones.

2.6.4 *Peripheral Quantitative Computed Tomography (pQCT)*

In this section, I outline pQCT including a description of the technology, acquisition and analysis parameters and report its limitations.

2.6.4.1 *Description of technology: XCT 2000*

In 1979, Sir Godfrey Hounsfield won the Nobel Prize in Physiology-Medicine for inventing computed tomography imaging (CT) eight years earlier. In designing CT, Sir Godfrey hoped to overcome the three main limitations of conventional radiography: 1) difficulties of a two-dimensional technology to describe a three-dimensional object, 2) problems distinguishing between soft tissues, and 3) an inability to "quantify" density differences between tissues. CT is a technology that uses the attenuation from X-rays from multiple angles to reconstruct the image via computer-based algorithms (98,99).

X-ray attenuations are measured in Hounsfield Units (HU; named after the physicist) which quantify the relative density of material based on the calibration of a known phantom. Different tissues exhibit different HU. For example, bone has a reading of approximately 1000 HU, while fat is around -79 to -90 HU. Table 2-6 provides a summary of common densities in HU. The absorption is calculated by the following equation (98,99):

$$\text{Absorption} = \log \frac{\text{Intensity X-rays}}{\text{Detector reading}}$$

Table 2-6. Hounsfield Units for various substances. (99)

Substance	Density in Hounsfield Units (HU)
Air	-1000
Fat	-70 to -90
Water	0
Muscle Soft Tissue	+20 to +40
Bone	+1000

In 1976, Ruegsegger and coworkers developed a peripheral quantitative CT scanner. Although initially, the first pQCT systems used I^{125} as the source (100,101), it was quickly changed to X-ray. Currently, pQCT is a research tool only and its availability is limited in Canada. There is only one pQCT in Western Canada, and this exists in our laboratory.

There are four types of CT machines available and the main difference between them lies in the scanning methods or way the X-rays transmit. As with DXA, there is a source-detector coupling, but CT employs multiple detectors. The different scanners are classified as first generation, second generation etc. For the remainder of this section I discuss a second-generation pQCT scanner, the XCT 2000.

The XCT 2000 consists of an X-ray source that emits a fan beam at 12 detection channels that are one degree apart (Figure 2-14). Figure 2-15 provides an inside look at the pQCT gantry that houses the X-ray source and detectors. The beams work on a translate-rotate pattern. After the beams are collimated (transmitted in a narrow beam towards the detectors), attenuation levels are calculated and data are mathematically folded to recreate the image. Specifically, how the beam works is illustrated in Figure 2-16.

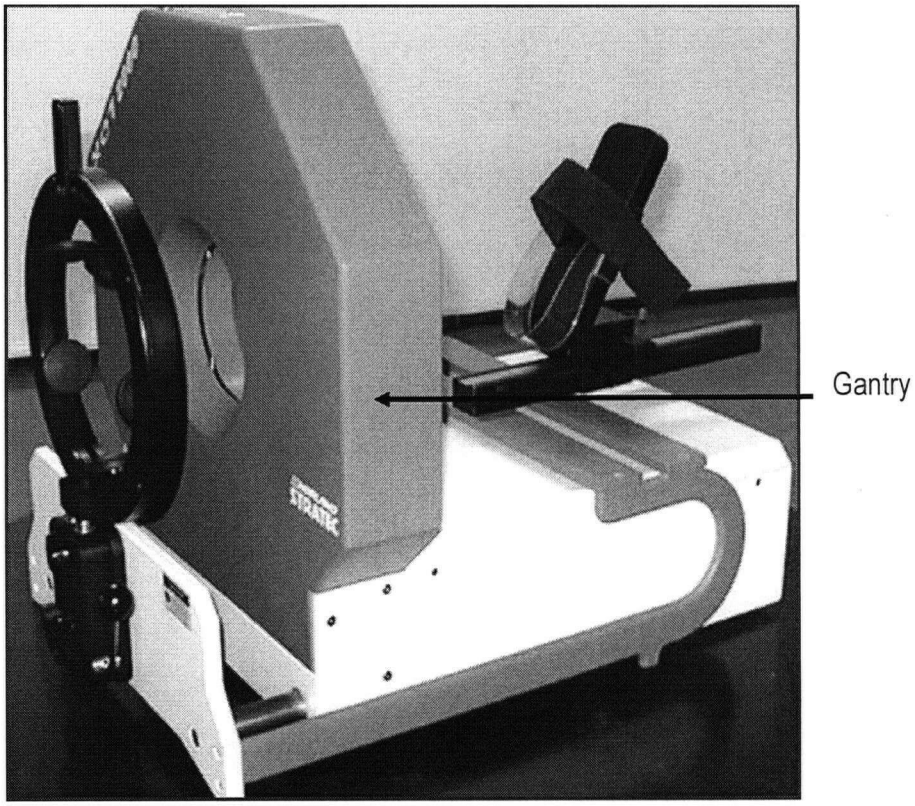


Figure 2-14. Peripheral quantitative computed tomography: Norland XCT 2000.

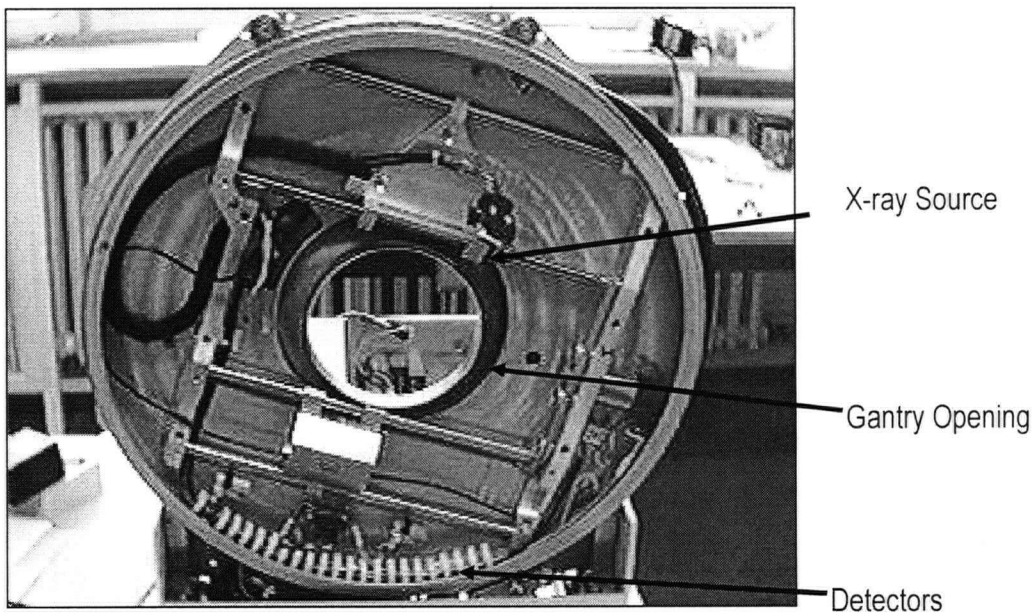


Figure 2-15. Inside the gantry of the XCT 2000 machine.

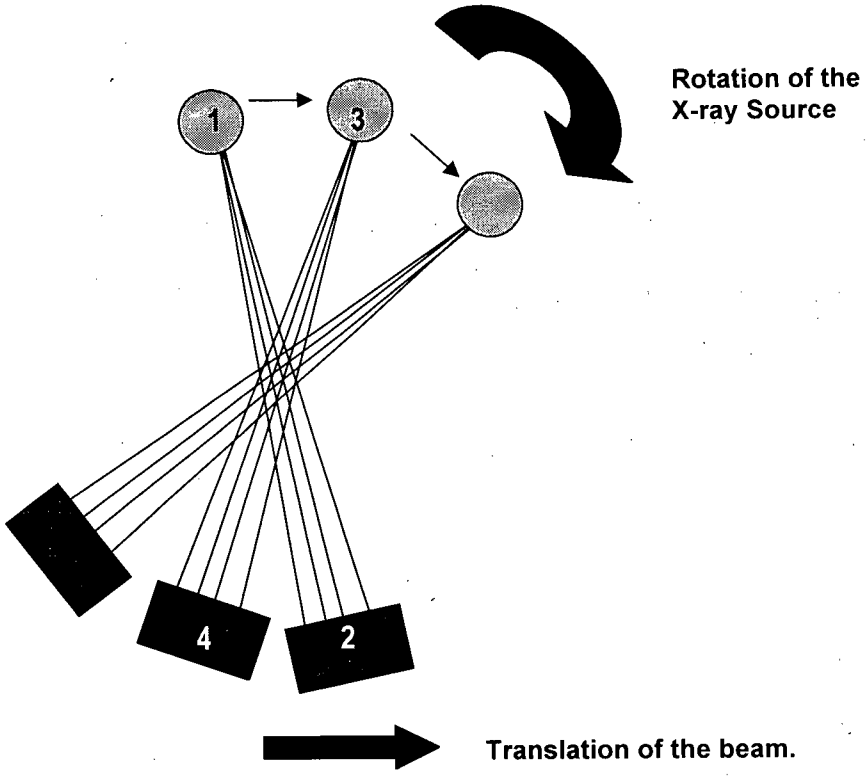


Figure 2-16. Diagram of second-generation pQCT scanning mechanism. The source (1) emits the beams in a narrow (collimated) pathway. Both the X-ray source and detectors translate across the object collecting 12 projections each a degree apart (2). Then the beam rotates 12 degrees to the next position (3) and so on. This motion continues until the gantry has rotated 180 degrees and 180 projections have been collected.

2.6.4.2 Measurement parameters

Peripheral QCT is able to distinguish cortical from trabecular bone based on tissue densities. The bone outcome parameters are volumetric BMD, BMC and geometric parameters such as total, trabecular and cortical area, cortical thickness, cross-sectional moment of inertia, section modulus and stress-strain index. From the geometric parameters obtained from pQCT, other bone strength indices are calculated such as Bone Strength Index (BSI). I discuss different bone strength parameters in Section 2.6.4.6. Peripheral QCT can also be manipulated to provide muscle cross-sectional area, although the algorithms are not developed for muscle (muscle is what is left after all the other tissues are subtracted).

2.6.4.3 Data Acquisition

There are two main manufacturers of peripheral CT machines; Scanco (Densican; Scanco Medical, Basserdorf, Switzerland) and Stratec Medizintechnik GmbH (Pforzheim, Germany). I will limit my discussion to the Norland XCT 2000, which is the latest generation of peripheral scanners that superceded the XCT 960.

Obtaining data from the pQCT requires a two-step process; data acquisition and data analysis. Unlike DXA, the pQCT operator has many choices. For example the operator can choose the bone area to be scanned, the size of the voxel (volumetric unit of digital imaging) or resolution used to acquire the data, the scan speed, and the size of the area or field of view. Few studies have examined the most accurate protocol to assess bone geometry by pQCT. For example, 1) for resolution, most researchers rely on the manufacturer recommended 400 or 500μm voxel size and for measurement sites on the radius, and 2) the most frequently reported sites are at the 4% (highly trabecular bone) and 30% (cortical bone) sites, while muscle cross-sectional area is acquired at the 66% site or the maximum muscle bulk (102).

2.6.4.3.1 Scan Resolution

CT imaging depends on digital image resolution. Specifically, the resolution is primarily dependent on the voxel or volumetric element. A voxel is the measurement unit that contains the attenuation coefficients (HU). A voxel is similar to a pixel or picture element but it contains the third dimension – slice thickness. Figure 2-17 is a picture of the 4% site of the distal radius. Superimposed on the image is a grid representing voxels. A voxel includes the width, height and slice thickness. If the voxel size is large (i.e. lower resolution 500μm) for scan acquisition, when the image is analysed it is subject to the partial volume effect (PVE).

A PVE occurs when there are tissues of different densities contained within the same voxel. The densities and their proportions are averaged and the overall density of the tissue in the voxel is lowered (103,104). Figure 2-18 represents four magnified voxels taken from a CT scan of bone at the bone-muscle interface. Potentially, if a voxel contains muscle and bone, the net result will be a decrease in the density value for that voxel. This has important implications for whether or not that voxel should be included as part of the analysis. For example, in Figure 2-18, if the outer threshold that defines bone as greater than 130 mg/cm^3, Voxels 1 and 2 will be excluded, even though Voxel 1 contains some bone (with porosity). In this way, it is hypothesized that there is an underestimation of bone in CT images.

In vivo, this means that the PVE can occur differently at the periosteal versus at the endosteal surface of bone. Figure 2-19 illustrates a cross-section of bone and muscle. At the periosteal surface there is an obvious boundary between bone and soft-tissue so that voxels incompletely filled with bone are less likely to be included in the analysis. However, at the endosteal surface, the distinction between lower density cortical bone, trabecular bone and marrow is not clear. The HU for these tissues are higher than for purely soft tissue and so within selected threshold limits, there is potential for these partially filled voxels to be included in the analysis. A thin cortical shell also increases the PVE (105-107). One solution to this is to use a smaller voxel size (100-300 μm) to improve the estimation of cortical area at the endosteal surface. The propensity for a surface-specific PVE is illustrated in Figure 2-20.

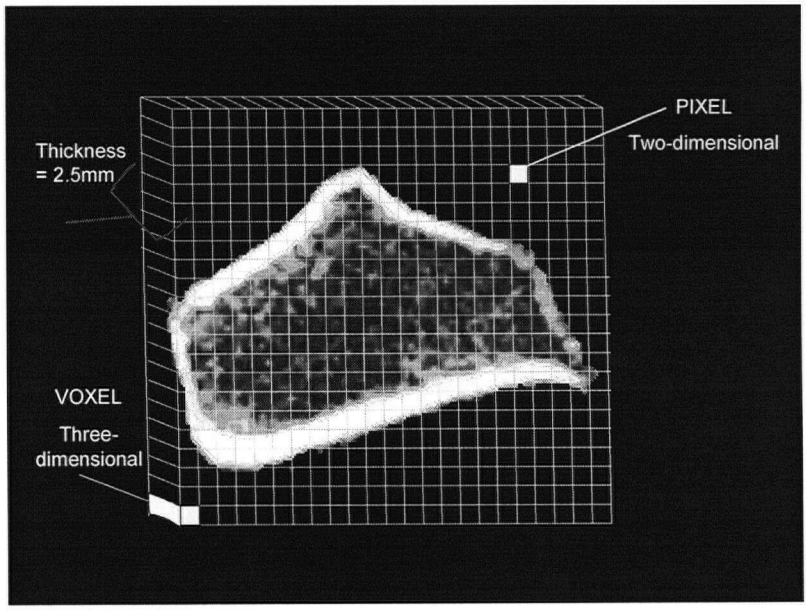
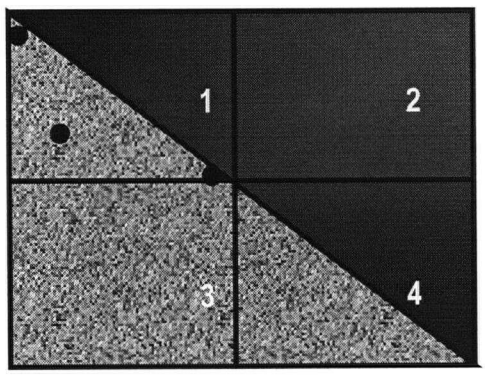


Figure 2-17. Illustration of the concept of voxel and pixel over a pQCT of the distal radius.



Voxel Number	Contents	Density (mg/cm^3)	Average Density (mg/cm^3)
1	MUSCLE + BONE	40 + 200	120
2	MUSCLE	40	40
3	BONE	200	200
4	MUSCLE + BONE	40 +250	145

Figure 2-18. Representation of four voxels taken from a scanned CT image. Table gives reference values for the contents of each voxel.

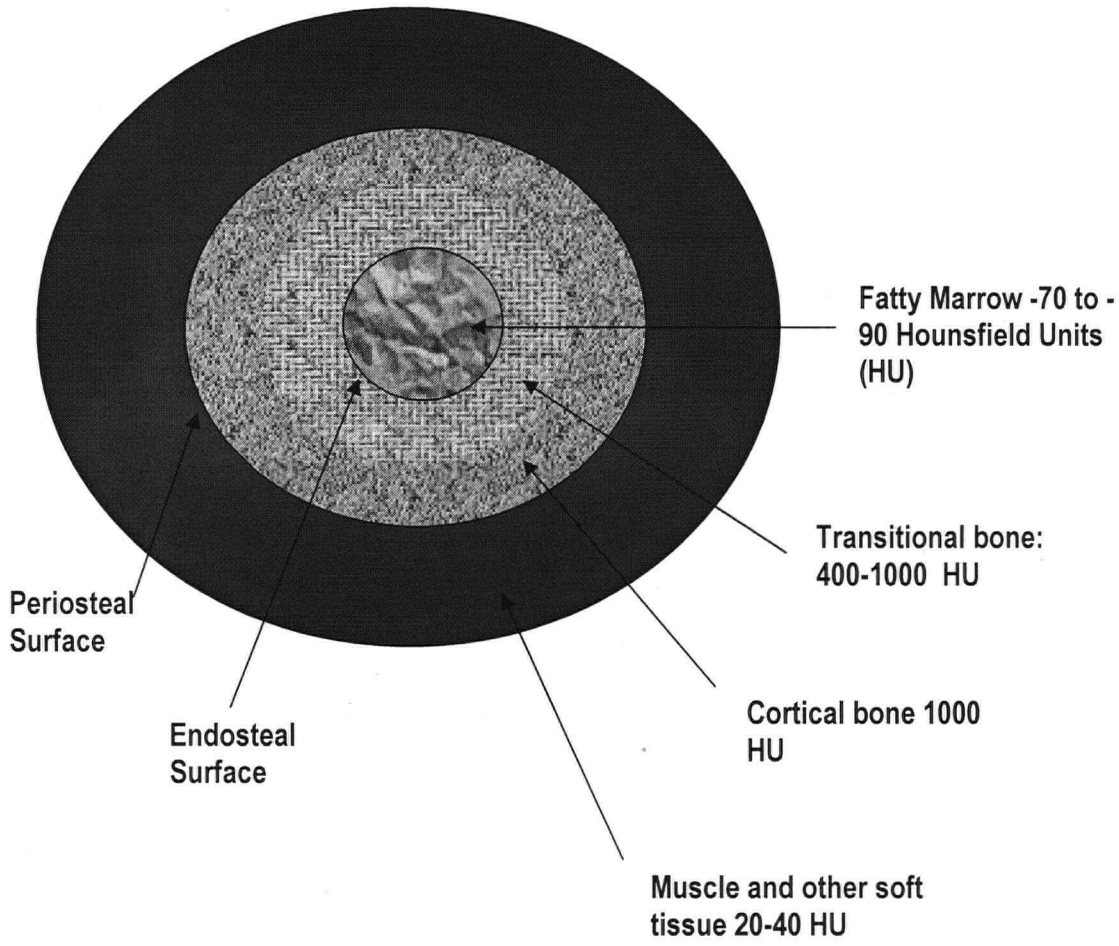


Figure 2-19. Illustration of muscle, bone and marrow interfaces. At the periosteal edge, the difference between soft tissue and bone is great. Therefore, voxels at the cortical edge will be totally excluded. However, at the endosteal interface, transitional zones of trabecular or demineralised bone may raise the average attenuation within the voxel so that the voxel is included in the analysis. This may account for an over or underestimationof cortical area depending on the thresholds used to analyse the scans.

2.6.4.4 *Analysis Software: Understanding Algorithms*

Two software analysis programs are currently available for the XCT machines; the manufacturer's program (XCT v.5.50) and Geanie Bonalyse 2.1. In this thesis, I discuss the XCT v. 5.50 software program.

First I outline the steps for analyzing a pQCT scan. Step 1: Defining the region of interest (ROI) after scan acquisition. Whatever is contained within the ROI will be included for analysis. Step 2: Once the ROI is defined, the analysis parameters must be determined. This includes setting the thresholds for separating trabecular from cortical and "subcortical" bone. One method is to determine the half-maximum height (HMH) threshold (108).

The HMH thresholding technique requires the operator to draw a line through the scanned image (Figure 2-21A). A profile of the tissue densities is calculated and displayed. The HMH threshold suggests that the density thresholds used to calculate the bone edge is half way between the minimum and maximum densities (Figure 2-21B). Figure 2- 22 illustrates the HMH threshold with a section of cortical bone.To my knowledge this procedure has not been validated with pQCT images.

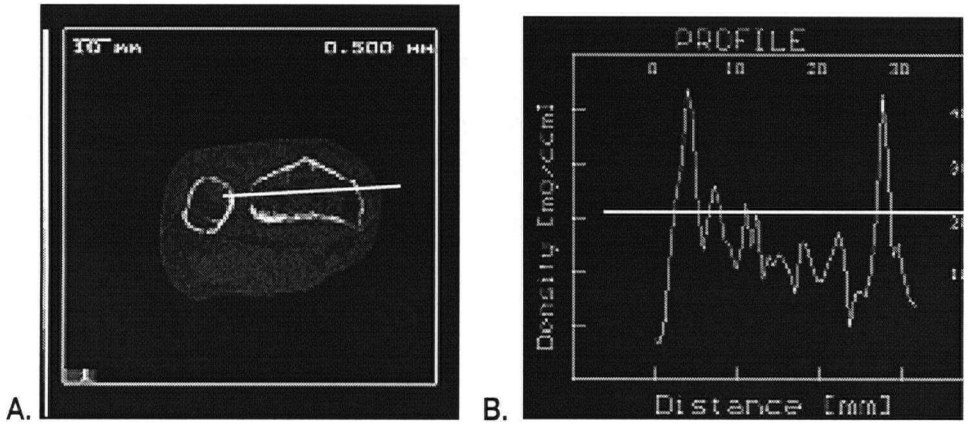


Figure 2-20. Scanned image of the distal radius with line representing profile.

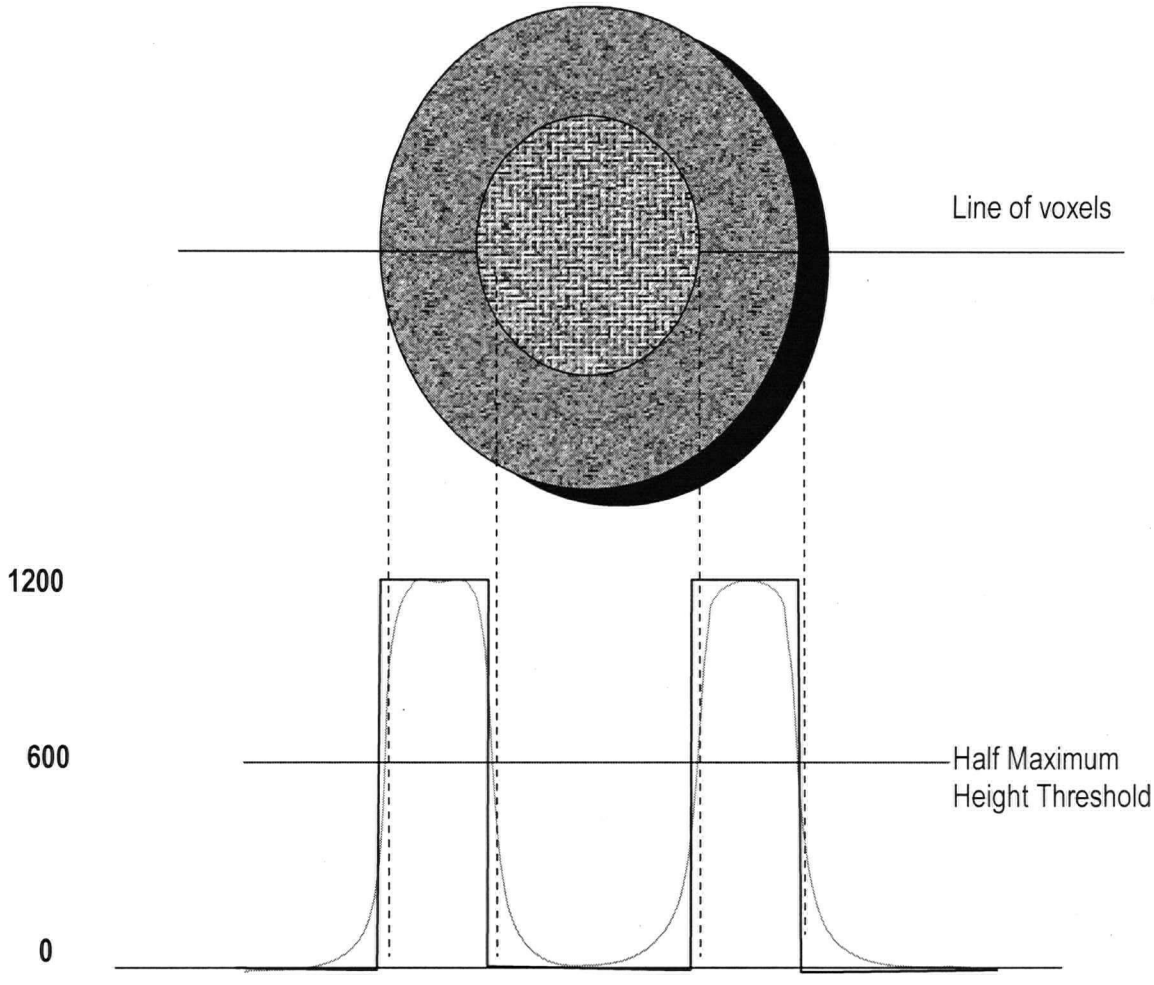


Figure 2-21. Illustration of the principle behind the half-maximum height threshold. The bone profile line through the bone gives a cross-section of the bone's density.

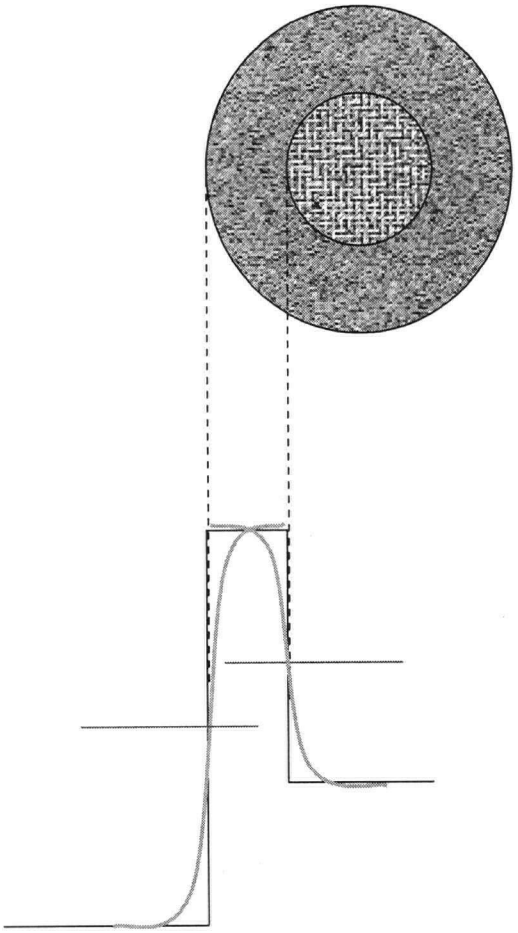


Figure 2-22. This figure illustrates the half-maximum height thresholds at the periosteal and endosteal surfaces of cortical bone.

Setting thresholds is still very subjective. The operator views the scan results to determine if an appropriate threshold is set. If the threshold is too low there will be popping points (Figure 2-23). Popping points means that the regions outside of the cortical edge are included in the analysis. If the threshold is set too high there will be streaking of the image (Figure 2-24). Results may also vary with the selection of a different analysis threshold. Although the total ROI remains unchanged, the ratio of cortical to trabecular bone within the ROI changes.

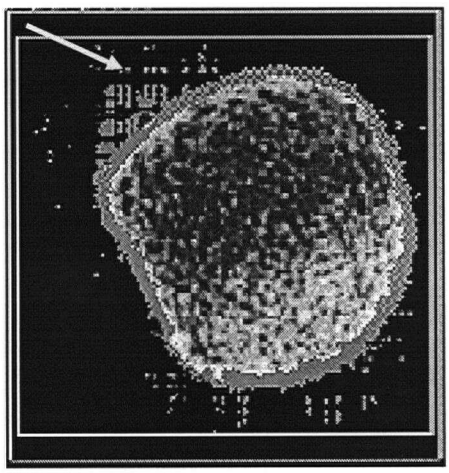


Figure 2-23. XCT results scan showing the appearance when the density threshold is set too low. Note the popping points on the outside of the cortical edge (indicated by the arrow).

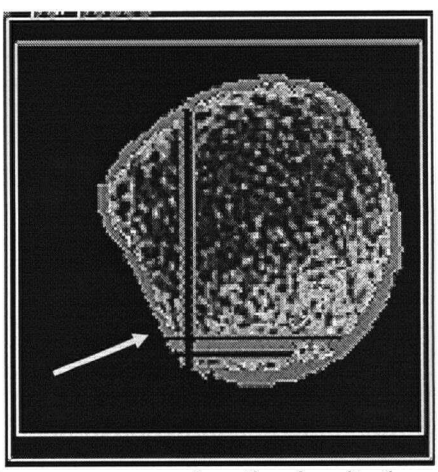


Figure 2-24. XCT scan showing the appearance when the density threshold is too high. Note the streaking inside the bone.

The XCT 2000 software provides the operator the choice of many combinations of analysis modes. CALCBD refers to the analysis of cancellous or trabecular bone and total bone; and CORTBD to the analysis of cortical bone. Table 2-7 provides an overview of the modes available with the XCT 2000.

Within CALCBD there are two parts: Contour Mode and Peel Mode. The software provides three Contour Mode and eight Peel Mode algorithms. Contour Mode (edge detection) provides information on total and cortical/subcortical bone parameters. Peel Mode separates trabecular bone from cortical-subcortical bone and CORTBD determines the cortical bone parameters. I discuss Contour Mode 3 and Peel Mode 2 for total and trabecular bone detection and CORTBD Modes 3 and 4 for the analysis of cortical bone.

Contour Mode 3. The algorithm searches lower density material within the ROI to find the bone edge and analyse the first voxel. It must then find a voxel of equivalent density directly adjacent to the first voxel otherwise it reports "integration =zero" and the scan fails. In Contour Mode 3, the operator can set the density threshold (based on the HMH and the visual display of analysis results as described above).
Peel Mode 2: This mode separates sub-cortical-cortical bone from trabecular bone using an operator-defined threshold starting at the endosteal surface.
CORTBD Mode 3 (automatic thresholds) or Mode 4 (user-defined thresholds): Defines cortical bone parameters.

Clearly, the most appropriate choice for analysis mode poses a challenge for the student or operator as the XCT manual does not provide a clear description of preferred analysis modes. This is especially true for the analysis of challenging populations such as those who have sustained a fracture or individuals with low bone mass.

Table 2-7. Summary of Stratec XCT Version 5.50 Analysis Algorithms

CALCBD		CORTBD
CONTOUR	**PEEL**	
Mode 1. *Threshold driven.* User defines threshold.	**Mode 1.** *Percentage Peel* from the periosteal surface.	**Mode 1.** *Threshold*
Mode 2. *Automatic detection.* User defines threshold. Algorithm finds bone edge with a minimum threshold of 169mg/cm^2.	**Mode 2.** *Threshold Defined Peel* from the endosteal surface.	**Mode 2.** *Threshold + Filter*
Mode 3. *Automatic detection + Min Threshold* Same as #2, but user defines the minimum threshold.	**Mode 3.** *Mode 2 and Percentage Peel* from the endosteal surface.	**Mode 3.** *Automatic Threshold* based on Contour Mode 2 Peel Mode 5.
	Mode 4. *Mode 2 and plus an additional Percentage Peel* from the endosteal surface.	**Mode 4.** *Threshold Based* on an inner and outer threshold and contour closing.
	Mode 5. *Automatic Peel*	
	Mode 6. *Mode 5 then a Percentage Peel* from the endosteal surface.	
	Mode 7. *Mode 5 plus an Additional Percentage Peel* from the endosteal surface.	
	Mode 20. *Mode 2 with a Percentage* entered instead of a threshold.	

2.6.4.5 *Strengths and Limitations of pQCT*

Peripheral QCT has an important role to play in the assessment of total and cortical bone parameters. It can determine the amount of volumetric bone mineral density and bone structure at a relatively low radiation risk to patients (because of short scan times and peripheral sites). Peripheral QCT can also provide an estimate of muscle cross-sectional area.

There are few limitations reported for pQCT despite the obvious challenge of selecting an appropriate analysis protocol. First, the most significant limitation is the pQCT's inability to clearly visualize trabecular bone. The lowest possible resolution available with pQCT is 100μm. The average trabecula is approximately 100μm, therefore, the scan cannot adequately capture true trabecular microarchitecture as PVE is an inherent problem. MRI and micro CT (resolutions < 100μm) provide the best technology currently available. Second, pQCT cannot assess sites such as the proximal femur which is important for fracture prediction. Although, there has been one study of femora of Japanese women, the XCT gantry is most often too small for large limbs (88). Third, only a few studies have reported the potential for underestimation of cortical bone by pQCT (109,110). Finally, there is only one published study (111) that compared analysis protocols.

2.6.4.6 *Measuring bone strength with pQCT*

Peripheral QCT provides a density-weighted bone parameter — Stress-Strain Index (SSI) — based on the volumetric cortical bone and the cross-sectional moment of inertia. Other bone strength indices (using the geometric parameters and density obtained by pQCT) are highlighted in Table 2-8.

Table 2-8. Summary of bone strength indices with descriptions.

Strength Index	Description	Bone Parameters
CSA Bone Strength Index (BSIcsa) (112)	Strength of bone in compression	product of cortical ToD and CoA
Compressive Bone Strength Index (cBSI) (113)	Reflects the strength of the bone in compression. g^2/mm^4	(the apparent density of the of the structural material) x Total CSA.
Cross-sectional Moment of Inertia (CSMI) (60)	In a bone cross-section, the distance of mass from the neutral axis of bending. The further the material from the axis of rotation, the greater the moment and the larger the resistance to deform or fail.	CSMI = $(\pi/4) \times (r_1^4 - r_2^4)$ r_1= outer radius of a hollow tube r_2= inner radius of a hollow tube
Section Modulus (Z) (60)	Geometric property: Estimate of the ability of the bone to withstand bending forces	CSMI / ½ periosteal diameter
Strength Index (114)	Bone mass and the structural appearance	Section Modulus x apparent vBMD.
Stress-Strain Index(SSI)	Resistance to bending or torsion	(CSMI/maximal distance of any voxel from the centre of gravity) x Cortical vBMD weighted
Torsional Bone Strength Index (tBSI) (113,115)	Reflects the torsional and bending rigidity of the long bone shaft.	Density-weighted polar section modulus mm^3.

2.7 Accuracy of pQCT with Compromised Bone

In this section, I review the relevant literature related to XCT 2000 and its accuracy. I define accuracy as the degree to which a measurement conforms to a standard or criterion.

2.7.1 Systematic Review of XCT 2000 and Measurement of Compromised Bone

I conducted a systematic review of the *accuracy* of the pQCT Norland/Stratec 2000/3000 peripheral quantitative computed tomography. I searched Medline, Embase and the Cochrane Database of Systematic Reviews to cover the period from 1966 to October 2003. The key words I included were Peripheral Quantitative Computed Tomography; radius; accuracy; bone density; reproducibility of results; sensitivity and specificity. I tried to include MeSH headings wherever possible. I applied my inclusion criteria to all titles and abstracts. I only included articles/abstracts written in English. I limited my results only to the Norland Stratec XCT pQCT. My inclusion criteria included "human cadaveric radius accuracy studies using pQCT", specifically: I sought information on: 1) radius cadaveric specimens from men or women over 50 years of age; and 2) accuracy studies of the pQCT.

I found only four (85,105,109,110) articles using my inclusion criteria (Table 2-9). I chose not to use a phantom as the testing specimen because human bone does not have uniform distribution of materials. A phantom for the pQCT is a resin-based cylinder that has embedded within uniform materials of known densities, and is used to complete the daily calibration of the pQCT.

When I examined the studies closely, none of the studies used the most recent pQCT system (XCT 2000) to assess for the accuracy of total area, density and/or mineral content. Of the four studies, two reported problems of underestimation of bone parameters using pQCT (85,109,116) and two papers (106,117) supported previous Computed Tomography (CT) literature (107) indicating systemic imaging problems when measuring cortical thickness less than 2mm. Phantom studies supported cortical bone underestimation (106). The only mineral content accuracy study (using ashing as the criterion) reported an error between 9.7 – 15.5% (85). Louis and coworkers used a relatively novel technique as the criterion standard (non-destructive neutron activation analysis and flame absorption spectrometry). They report an accuracy error of 7-10% for cortical BMC (109)

Table 2-9. Systematic Review of the Accuracy of the pQCT for the Cadaveric Human Radius.

First Author-Year	Cadaveric Preparation	N=	Model and Radius Sites	% CV	Acquisition	Analysis	Accuracy Outcomes
Augat 1998 (105)	Cadaveric frozen thawed 48hrs	14	XCT 960 4, 10%	NA	2.5mm slice 0.09 mm^2	Thresholds: 267-464; Peel 45%	Cortical thickness up to 40% underestimated if less than 4mm thick.
Louis 1996 (109)	Cadaveric Formalin	27 F_72yrs	XCT 960 Junction mid 1/3 and distal 1/3	0.2%	2.5mm slice	Cortical threshold 0.93 linear attenuation coefficient	Embedded in resin and used non-destructive neutron activation analysis. Accuracy for Cortical BMC =7-10%; for Trabecular BMC= 17-18%
Louis 1995 (110)	Cadaveric Formalin	30 F_72yrs	XCT 960 Junction mid 1/3	0.2%	2.5mm slice	Cortical threshold 0.93 linear attenuation coefficient	Used radiographs to assess cortical thickness as measured by pQCT. Machine specific algorithm based on Cortical Ring model r=0.94; based on "true" bone assessment r=0.88. True shape failures, but Cortical Ring Model underestimates results.
Takada 1996 (85)	Cadaveric frozen	12	XCT 960 4, 30%	1.15%	0.59mm 2.5 mm slice	Thresholds 112-377 Peel 55%	Compared single vs. Multiple slices at 4 and 30% sections cut and ashed. At 4% site 15.5% accuracy error correlations r=0.87 with ash weight. For multiple slices reduced to 9.7% accuracy error.

2.7.2 *Accuracy Testing Overview*

In this section, I outline techniques that are frequently used to assess the validity and predictive capability of imaging technologies.

2.7.2.1 Histomorphometry and pQCT

Histomorphometry is the technique used to quantify bone cells and tissue (118). There are two types of histomorphometry, static and dynamic. Static histomorphometry involves cell differentiation and areal determination. Measurements include lengths, area or cell counts. Dynamic histomorphometry involves using substances such as tetracycline to measure tissue growth. Static histomorphometry involves embedding bone in a resin then sanding the specimen down until it is very thin (<150 microns). The images are viewed under microscope at various magnifications. There is a distinct lack of literature comparing pQCT measures of total area and the criterion standard histomorphometry (109,116). Previous computed tomography literature highlighted the underestimation of cortical bone (107,119) and several authors have observed error with cortical thickness; especially with low acquisition resolution and bones with a thin cortical shell (106,107,110).

2.7.2.2 Ashing

Ashing is the accepted standard for the determination of bone mineral content and the early imaging technologies were calibrated with ashing (16,120). Bone consists of organic and inorganic components. When subjected to high heat, the organic material is burned and the remainder is inorganic mineral. This is the underlying premise behind ashing. It is a time-intensive process that involves multiple steps of drying specimens, reweighing samples and incinerating the sample in a muffle oven at high temperatures (>600^{0}C) until only mineral remains. The remaining ash weight is considered equivalent to mineral content. There is only one study for the radius that has used ashing to establish the accuracy of pQCT for mineral content, and they reported a 10-14% error (85) .

2.7.2.3 Biomechanical Testing and Predicting Failure Load

Biomechanical testing of the radius to determine failure load is usually done using 3 or 4 point bending and/or axial compression. The result is the load-deformation curve (for whole bone) or the stress-strain

curve for small sections of bone material. The results of testing (i.e. failure load) can be used to compare to bone imaging parameters to assess predictive capabilities.

Storage and preparation of specimens for mechanical testing are important aspects of mechanical testing. Previous literature suggests that storage and preparation of specimen samples can influence bone's mechanical properties. The literature suggests that long term (>100 days) freezing samples did not affect sample stiffness, nor did repeated cycles of thawing-freezing (5 cycles or less) have detrimental affects on bone mechanical properties (121-123). However, all specimens should be kept as moist as possible especially during the mechanical testing procedures. For optimum storage, bone is wrapped in saline-soaked gauze and placed in air-tight containers (124). Biomechanical testing is usually done with a servohydraulic system. Testing the distal radius in axial compression has challenges due to the slope of the articular surface at the radiocarpal joint. Several studies have embedded both ends of a cut specimen (i.e. only bone and no soft-tissue). Dental cement and polymethylmethacrylate (PMMA) are materials used to pot the specimen and prevent it from slipping during the application of force.

I conducted a systematic review of the ability of the pQCT Norland/Stratec 2000/3000 peripheral quantitative computed tomography to predict failure load. I searched Medline, Embase and the Cochrane Database of Systematic Reviews to cover the period from 1966 to October 2003. The key words I included were Peripheral Quantitative Computed Tomography; radius; fracture; bone density; failure load and prediction. I tried to include MeSH headings wherever possible. I applied my inclusion criteria to all titles and abstracts. I only included articles/abstracts written in English. I limited my results only to the Norland Stratec XCT pQCT. My inclusion criteria included "human cadaveric radius failure load studies using pQCT", specifically: I sought information on: 1) radius cadaveric specimens from men or women over 50 years of age; and 2) axial compression studies of the pQCT. I found nine relevant studies.

Previous pQCT literature highlights the value of cortical bone to predict the overall strength of the radius (125,126). There is limited research using pQCT to predict failure load at the distal radius, and the majority of the investigations have been from one group (127-132). Research has shown that even with intact specimens (entire limb including muscles and joints), pQCT outcomes have a high ability to predict failure load. In an axial loading configuration, BMC by SPA at the midshaft predicted 62% of the variance but when geometric parameters (total area and CSMI) were added, the variance, increased to up to 80% (133). Areal BMD by DXA predicts between 76-84% (130,134) of the failure load while pQCT (total and cortical content, area and density), can be up to 85% of the variance (130). Overall, total mineral content

of the radius played an important role in bone strength (132). The predictive ability of pQCT outcomes increases in axial compression testing with the addition of geometric parameters (130-132,134). I summarise the references for biomechanical testing of the radius and scanning with pQCT in Table 2-10.

Table 2-10. Literature Summary of pQCT Studies of Biomechanical Testing of Human Cadaveric Radii.

First Author-Year	Cadaveric Preparation	N=	Model and Radius Sites	Biomechanical Test Configuration	Outcomes: Correlations to pQCT
Augat 1996 (135)	Cadaveric formalin	20 13 F_7 M (85-77 yrs)	XCT 960 10, 30%	Axial Compression	r=0.91-0.93 with 4% trabecular vBMD and CoA 30% site.
Augat 1998 (105)	Cadaveric frozen thawed 36hrs	20 7F 13M (71,62 yrs)	XCT 960 4, 10, 15% DXA	Axial Compression 15º dorsal;10ºradial inclination; fixed both ends, 75mm/sec	2648±1,489N mean failure load 15% CoA and CoCNT 6%
Gordon 1998 (136)	Intact, defatted Shipped dry: corn oil	9 unknown	XCT 960 2 at distal sites	Axial Compression 3 cm/min	Range of failure load = 645.4-4726.0N r^2=0.57 ToD distal site
Hudelmaier 2004(134)	Cadaveric	74 formalin fixed left	XCT 2000 5, 33%	Fall simulation; 3.3mm/sec	1284±436N mean failure load DXA shaft BMC 0.76; ToCNT-pQCT r=0.83; QUS r=0.55.
Lochmüller 2002 (130)	Cadaveric	129 47 M 77yrs 82F_82yrs	XCT 2000 4, 20, 33%	Fall simulation; 3.3mm/sec	pQCT ToCNT r=0.75; DXA aBMD r = 0.84
Lochmüller 2003 (131)	Cadaveric Formalin Intact skin and tissues	126 46 M 76.4yrs 80F_82.2yr	XCT 2000 4, 20%	Fall simulation; 3.3mm/sec	pQCT ToCNT r=0.75; DXA aBMD r=0.84
Louis 1995 (110)	Cadaveric Formalin	33F_74yrs	XCT 960 Junction mid 1/3	Axial Compression 2cm cylindrical section 0.2mm/sec	CoA r=0.78; CTh r=0.74; CoCNT r=0.87 and failure load.
Muller 2003 (132)	Cadavers Frozen	38 18F,20M	XCT 960 4, 20%	Axial Compression 15ºangulation; both ends fixed;100mm/sec	SSI (4%) and CCNT r=0.82-0.85
Wu 2000 (137)	Cadaveric Frozen; thawed 15 hrs	13 63.9yrs	XCT-960 4,10,15%	Axial Compression; 75mm/sec	pQCT CoD r=(0.61-0.75); DXA aBMD r=(0.67-0.75);Ultrasound Speed of Sound r=(0.63-0.72)

2.8 Distal Radius Fractures

In this section, I outline literature relevant to the distal radius, focusing specifically on distal radius fractures.

2.8.1 Radius: Anatomy of Osteology and Muscle

The radius is the main long bone of the forearm and consists of a pyramid shaped distal end (metaphysis), long thin midshaft (diaphysis) and a smaller proximal end. It is located on the lateral side of the ulna at the distal and proximal radio-ulnar joints. The radial epiphysis appears at approximately 1 year of age and ossification occurs between 17-21 years of age in women and 20-26 years in men. Mean radial length is 24.6 cm in men and 22.0 cm in women; and the mean distal radial width is 3.6 cm in men and 3.2 cm in women (138). There are significant differences between the sexes; men have significantly larger bones (138). There have only been two extensive reports to highlight the distribution of cortical and trabecular bone along the length of the radius (16,114). In both of these investigations at the metaphysis, they reported a thin cortical shell with a large percentage of trabecular bone. In contrast, the diaphysis has very little trabecular bone, and is mostly cortical bone to provide strength against bending or excessive load.

The wrist joint has multiple axes of movement: flexion-extension, radial-ulnar deviation and pronation-supination all occurring at the distal radio-ulnar and radio-carpal joints. These provide mobility for hand function. The muscles of the forearm controlling movement, are divided into flexor-extensors and pronators-supinators (superficial and deep layers). The bulk of muscle in the forearm is approximately two-thirds proximal to the wrist joint. At the distal end, there is minimal soft tissue; mostly forearm muscle tendons and ligaments. Table 2-11 lists all forearm muscles and Figure 2-25 illustrates a view of the radius and its muscular attachments. Figures 2-26 and 2-27 highlight the soft-tissue differences between the distal end and the midshaft of the radius. Note, there are only three muscles that actually insert on to the radius and six that originate there. These are responsible for thumb abduction, finger flexion, elbow flexion and wrist pronation. I discuss muscle–bone interactions in Section 2.9.4.

There are two important implications of the relative lack of soft tissue at the distal end of the radius. From an imaging perspective, less soft tissue produces better results with technology such as DPA, SPA and

the like. Secondly, the lack of direct force over the radial metaphyseal area may contribute to the lower strain generated in this area (71).

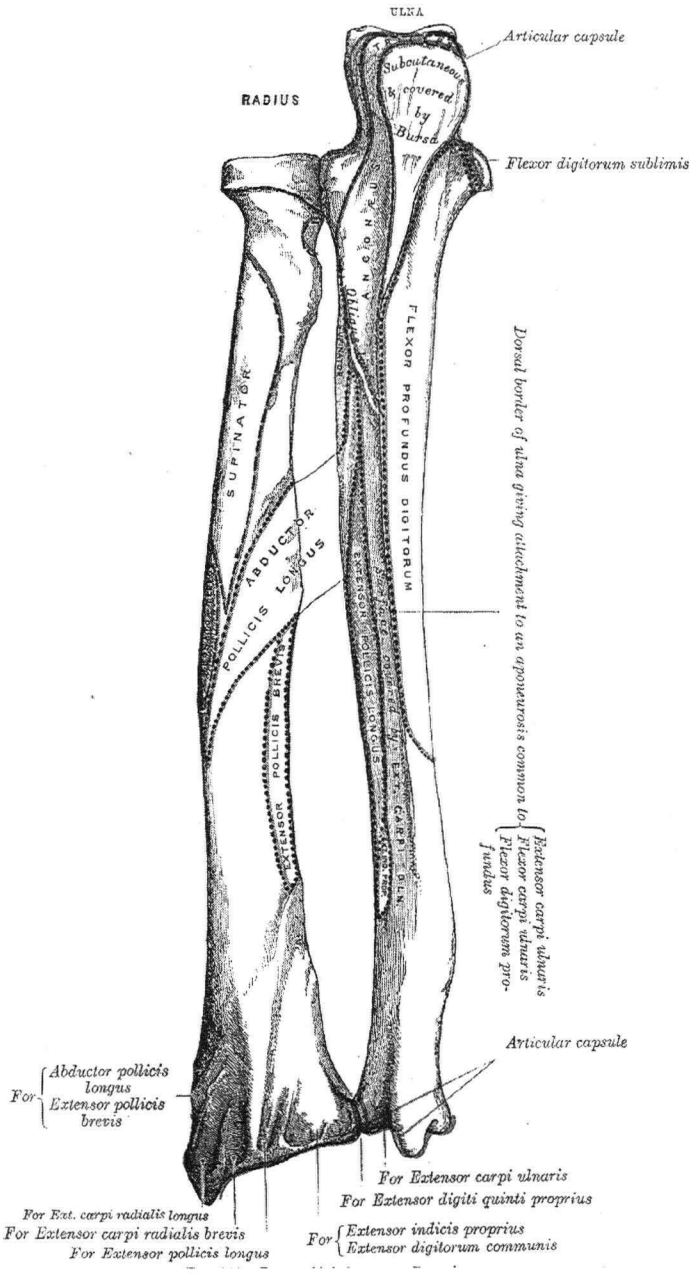


Figure 2-25. Osteology of the human radius with muscular origins and insertions.(139)

Table 2-11. Muscles of the Forearm.

Muscle	Origin	Insertion	Action
1. **Brachioradialis**	upper two-thirds of the lateral supracondylar ridge of the humerus	**lateral side of the base of the styloid process of the radius**	flexes the elbow, assists in pronation & supination
2. **Abductor pollicis longus**	**middle one-third of the posterior surface of the radius, interosseous membrane, mid-portion of posterolateral ulna**	radial side of the base of the first metacarpal	abducts the thumb at carpo-metacarpal joint
3. **Flexor digitorum superficialis**	**humeroulnar head: common flexor tendon; radial head: middle 1/3 of radius**	shafts of the middle phalanges of digits 2-5	flexes the metacarpo-phalangeal and proximal interphalangeal joints
4. **Flexor pollicis longus**	**anterior surface of radius and interosseous membrane**	base of the distal phalanx of the thumb	flexes the metacarpo-phalangeal and interphalangeal joints
5. **Pronator Quadratus**	medial side of the anterior surface of the distal one-fourth of the ulna	**anterior surface of the distal one-fourth of the radius**	pronates the forearm
6. **Pronator Teres**	common flexor tendon and (deep or ulnar head) from medial side of coronoid process of the ulna	**midpoint of the lateral side of the shaft of the radius**	pronates the forearm
7. **Extensor Carpi Ulnaris**			
8. **Extensor Digiti Minimi**			
9. **Extensor Digitorum**			
10. **Extensor Indicis**			
11. **Extensor Pollicis Longus**			
12. **Extensor Pollicis Brevis**			
13. **Supinator**			
14. **Flexor carpi radialis**			
15. **Flexor carpi ulnaris**			
16. **Flexor digitorum profundus**			
17. **Palmaris longus**			

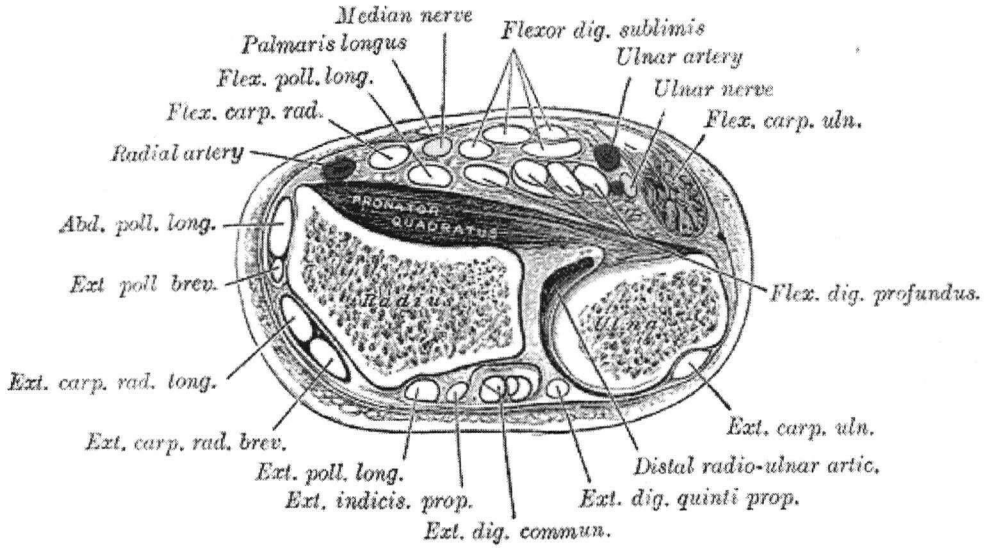


Figure 2-26. Diagram of distal forearm cross-section (139)

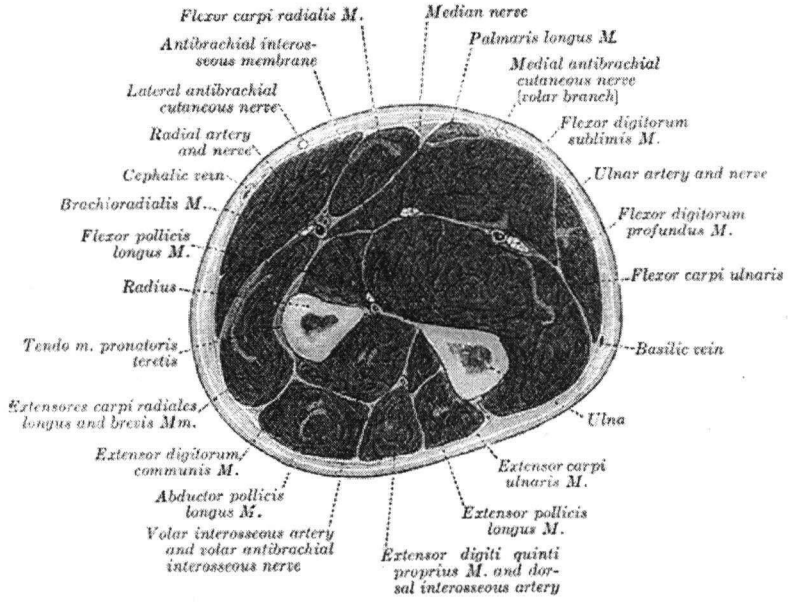


Figure 2-27. Forearm midshaft cross-section. (139)

2.8.2 *Epidemiology of Radial Fractures*

In the United States or United Kingdom, a white woman 50 years and older has a 16% lifetime risk of sustaining a radial fracture while the risk for white men is only 2% (9,140-144). This is the same risk as sustaining a hip fracture. Reports for lifetime risk for radial fractures from other countries range from 13.3% in Australia (145) up to 20.8% in Sweden (146). The risk for women is four times greater than it is for men (68). Distal radius fractures are the most common peripheral fractures seen in emergency departments (147). The estimated 27,690 distal radius fractures occurring annually cost Canada $19.4 million but costs associated with radial fractures have been difficult to quantify because so few patients are admitted to hospital (20%) (148).

A steady rise in the incidence of radial fractures commences at age 40 and plateaus or decreases around 65-70 years of age (149) except in Sweden, where the incidence continues to increase (146). The low incidence of radial fractures for men is relatively constant from 20-80 years of age, attributable to a reduction in fall events and higher aBMD (68). This increase in radial fractures between 40 and 65 years has been highlighted as an important predictor of osteoporosis and is potentially a signal for future fractures (149). There are theories as to why the incidence of radial fractures levels off after age 65. Most attribute it to an aging musculoskeletal system with reduced reaction time, thereby lessening the chance of putting out an arm to break a fall. Interestingly, as the risk for radial fractures plateaus, there is a concurrent increase in hip fractures (150) and this continues exponentially with age.

Jacobsen and coworkers have reported a seasonal variation of radial fractures in North America (151); more radial fractures occur in the icy winter months. Interestingly, the association between inclement weather and radial fractures is not as strong with older women (>65 years) compared with the younger group (35-64 years), indicating that older women are less likely to venture outside in bad weather. Further, others have suggested that factors other than poor weather contribute to increased fracture risk in the winter months. For example, lower levels of less sunlight (less natural vitamin D production) can lead to a decrease in bone mass (152).

Independent risk factors for a low trauma radial fracture include low aBMD at the distal radius, history of recurrent falls, overall good health and a previous fracture that occurred since age 50 (153). Poor cognitive status doubles the risk for a radial fracture in women age 75 years and older(153). Recently,

Kelsey and coworkers have extended their findings of distal radius risk factors to include that lower extremity problems are associated with a lower risk of radial fracture (154). The take home message is that healthy active women with low bone mass are more likely to fracture the distal radius. Table 2-12 provides a summary of risk factors for a radial fracture.

Table 2-12. Distal Radius Fracture Risk factors from the Study of Osteoporotic Fractures (n=9,704 women aged 65 years and older.

Author	Risk Factors
Kelsey et al. (154,155)	• ↓ aBMD radius • Number of falls in preceding year before fracture • Poor visual acuity • Frequent walking • Any lower extremity problems or impairments to mobility decrease risk
Vogt et al. 2002 Followed for 9.8 years (153)	• ↓ aBMD at axial and appendicular sites • history of recurrent falls • previous fracture since 50 years of age • poor cognitive status • diabetes mellitus • no current use of estrogen

2.8.3 Fracture Patterns and Common Treatment

The term "Colles fracture" is frequently used to describe any distal radius fracture, but the term is generic and offers little or no information as to the mechanism of injury or the specific details of pathology. The most commonly seen fracture pattern at the wrist is an extra-articular transverse fracture approximately 1.5 inches from the radio-carpal joint with a dorsally displaced radial end. It is caused by a fall on an outstretched hand. It is this pattern that was first described by Dr. Abraham Colles in 1814 although Pouteau first reported this common fracture pattern in 1783 (156). Initially, the orthopaedic classification system was based on the last name of the founder. However, there are many different types of intra and extra-articular fractures and the classification based on "Colles" or "Smith's" (volar or palmar displacement) soon became a problem. Consequently, there has been a number of classification systems developed; most notably by the Swiss orthopaedic group Arbeitsgemeinshaft fur Osteosynthesefragen (AO) and Frykmann (157). These two systems are based on the mechanism of injury and the extent of joint involvement and communition (158).

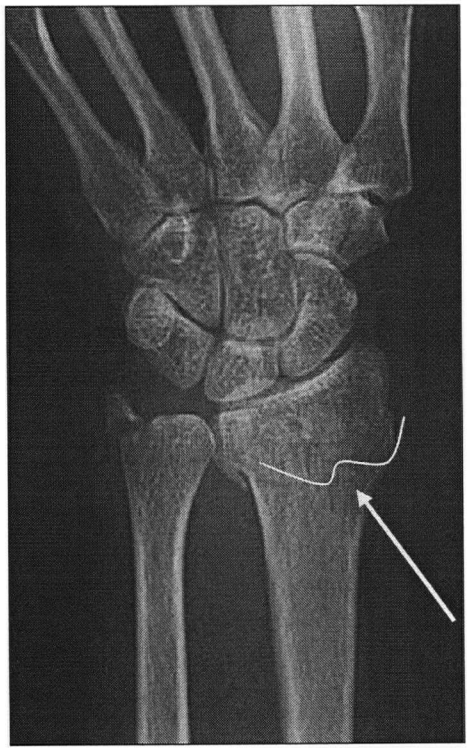


Figure 2-28. X-ray of a distal radius fracture. X-ray of the distal forearm of a 54-year-old woman who sustained a distal radius fracture. She sustained an AO A2.2 fracture. Note fracture line at the tip of the arrow.

There continues to be debate as to the most reliable method of fracture classification. Even the two most commonly used methods have been criticized for having poor reproducibility (158). Classification of fractures has been described according to several guidelines, such as location in the bone (diaphyseal, metaphyseal, articular), angle and number of fragments (transverse, oblique, spiral) and soft-tissue involvement (skin open or closed and severity of involvement) (159).

In 1967, Frykmann developed a system of classification with 8 different types (160) and although it is widely used, it is limited by not reflecting fracture displacement, degree of communition and any shortening of the radius that may occur (161). For example, a Colles fracture is Type I: extra-articular.

The Swiss AO developed a classification system in 1986 and revised it in 1990. This classification system is based on the severity of fracture and is divided into 3 groups: extra-articular, partial articular and complete articular. These 3 groups are then subdivided depending on the complexity of fracture and the difficulty of treatment (157). A typical Colles fracture is A2.2. Figure 2-28.

Regardless of classification, several key points of radiographic interested are reviewed by the radiologist and treating physician/orthopaedic surgeon to compare patient outcome to normative values. After a fracture, the goal of surgical intervention is to maintain joint congruency. X-rays ascertain the angular displacement of the fracture and the position of the radius relative to the position of the ulna. Patient measures are compared with norms to assess for risk of complications or functional limitations.

Typical management of a classic "Colles" fracture is usually conservative with closed reduction and cast immobilisation for up to six weeks (162,163) . The normal course of treatment is for fracture review at (2-3 week) to assess for fracture displacement. There is controversy as to placing the wrist in supination or pronation for cast immobilization. A systematic review of the treatment of distal radius fractures, has suggested that past trials have failed to show rigor in methodology (163) and therefore it is difficult to recommend any treatment as being superior given the current level of evidence. Usually the fractured radius is casted in wrist flexion and ulnar deviation (164).

2.8.4 *Mechanism of Distal Radius Fractures*

The most common mechanism of injury is a fall on an outstretched hand, and the landing position varies depending on position of the radio-carpal and distal radio-ulnar joints (Figure 2-29). In a controlled Finnish study, investigators reported that all (100%) of the 110 participants who sustained a radial fracture had fallen and the 34% of the participants reported an obliquely forward fall position (165). An interesting feature noted by Nevitt and coworkers (166) who investigated patient-recalled position of landing and fractures, reported a 2.2 relative risk (RR) of sustaining a radial fracture if the hand was positioned backwards compared with the hand landing in a forward position. This has been extended by other researchers who observed falls with hands in a backward position yields a higher chance of fracture(165). Interestingly, women who were taller or had stronger grip strength exhibited a higher risk for fracture and this supports previous population based studies of distal radius fractures (154,155).

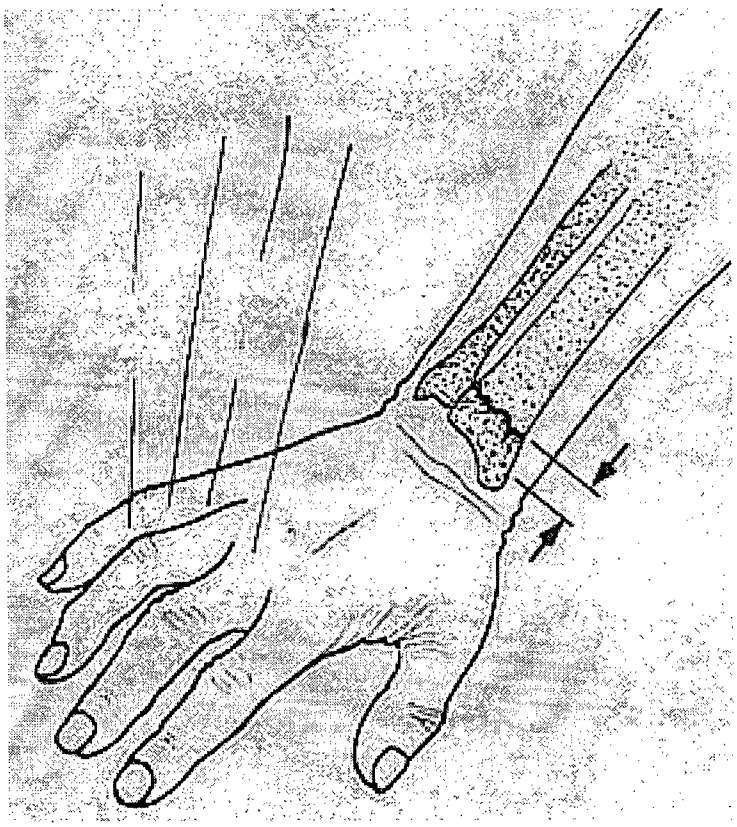


Figure 2-29. Illustration of the most common mechanism of radius fracture. (167)

2.8.4.1 *Buckling vs. Axial Compression and Bending*

When a bone is loaded, three factors determine whether it will fracture: 1) direction and magnitude of the load; 2) geometry and size of the bone; and 3) bone material properties (14). Bending, compression and torsion are all involved in a typical fracture. A radius fracture is the result of a compressive force. However, the transverse crack along the base of the distal end, suggests an element of bending. Most agree on the compressive component, but Neilson and coworkers suggest there is no bending involved, but rather a crushing action (117). A possible explanation in older bones (with thin cortical shells) that are subject to bending, is Euhler buckling and this was operationalised by Beck as the buckling ratio (56). With a long thin-walled tube that is subject to compression (when loaded) it tends to collapses or buckle, similar to a childhood greenstick fracture. The aging radius has the potential to buckle because of the large area and thin cortical shell (55). However, to date, this has not been reported in the literature.

2.8.5 *Fracture Healing*

There are three stages of fracture healing; inflammatory, reparative and remodeling. Following the initial fracture insult, there is an inflammatory response resulting in pain, swelling and redness. This phase lasts approximately 5 days and the hematoma hydrostatically splints the fracture site. During this time, there is a disruption of the blood supply and bone necrosis. From the end of the inflammatory stage to about 40 days, the reparative stage works to unite the fracture. The final stage commences around day 25 and consists of bone remodeling to return the bone to its pre-injury status (168,169).

Histologically, there is primary and secondary healing; primary healing involves healing of bone disruption by the cortex while secondary healing is the development of a fracture callus by the periosteum and other soft tissues (170). Fracture callus is woven bone (exhibiting isotropic characteristics) which is remodeled over several weeks into lamellar bone (170). The most important mechanism in fracture healing may be the response by the periosteum. It is fundamental to bone healing; enhanced by motion and inhibited by immobility or at its extreme, rigid fixation (171).

The pattern of fracture healing is slightly different in older, compromised bone. Animal studies suggest that the early phase (< 6 weeks) of fracture healing in an ovarietomized rat on a low-calcium diet, was delayed compared with a healthy control group (172) and by 12 weeks in the osteoporotic rats, vBMD and

tensile strength was significantly lower in the osteoporotic rats compared with the healthy control group (172).

2.8.6 Complications after a Distal Radius Fracture

Risk of long term complications following radial fractures include pain, deformity and functional impairment (173-175). The major complications include malunions resulting in arthoses, median nerve involvement (either from the fracture itself or iatrogenically from inappropriate casting), tendon ruptures, finger and radial stiffness and complex regional pain syndrome [CRPS; formerly known as reflex sympathetic dystrophy (RSD)]. In a large patient chart review following traumatic radial fractures (175), complications related to long-term arthoses and stiffness accounted for 22-31% of the cases, while other studies report a 50% reduction in grip strength at 6 months and 22% at 2 years (176).

Recent research suggest that radial fractures have more impact on overall function and independence (177) than was previously recognized. Specifically, at 1 year following a radial fracture, participants showed more dependence with household tasks such as shopping and preparing meals, and, for these tasks, the dependence for radial fractures was comparable to the decline observed with a hip fracture. Table 2-13 highlights common complications after a radial fracture.

Table 2-13. Complications after a Radius Fracture.

Complications After a Distal Radius Fracture
arthritis (175)
surgical complications (175)
decreased ROM (175)
functional limitations(177-179)
infection(175)
ligamentous instability (175,180,181)
malposition/malunions (175,182,183)
nerve entrapment (184)
complex regional pain syndrome (reflex sympathetic dystrophy) (185,186)
skin complications such as breakdown/deterioration (184)
tendon complications(175,184)
rare complications: compartment syndrome, vascular injuries (175,184)

2.8.7 Hand Dominance

In this section, I discuss the role of hand dominance as it relates to the discussion of bone and muscle parameters. The knowledge that differences exist highlights any observable differences in bone parameters that may be expected.

There exist three (3) handedness possibilities: right, left and ambidextrous (uses both hands). Handedness is considered a marker for cerebral hemispheric dominance for speech and language, but the handedness or hand dominance literature has been plagued with ambiguities and inconsistencies (187). The most commonly used method for assessing hand preference is self-report inventories. Between 10 and 25% of the population is left-handed with men reporting a higher incidence of left-handedness (188). Interestingly, humans are the only species to exhibit handedness and the etiology still remains unclear (189).

Grip strength and bone mineral density exhibit a relation to handedness. For right-handed individuals, research has shown a significantly stronger right dominant hand (10-12%), but this clear distinction was not present in left hand dominant participants (190,191). The fact that our environment is geared towards right-hand dominance may necessitate the need for equal strength on both sides for a left-handed individual. Bone mineral density as measured by pQCT has also shown to be affected by hand dominance, although again, these differences (3% higher) are observed in right hand dominant individuals only (190,192,193). Ultrasound showed no significant differences with dominance in the hand or distal radius (193). Lastly, it has been reported that a dominant-hand radial fracture impacts more on self-reported quality of life measures than a non-dominant fracture, yet, these fractures may also have a higher chance to return to pre-fracture status (194).

2.8.8 Measuring Outcomes after a Distal Radius Fracture

In this section I outline measurement tools relevant for the upper extremity. Specifically, to discern functional status after a radial fracture requires an objective measurement of relevant outcomes. Range of motion (ROM), grip strength, sensation, vascular supply and overall hand function are all-important elements to compare outcomes after a fracture. In the rest of this section, I focus on the objective measures of ROM, grip strength and the two mostly used outcome measures after a radial fracture: the Patient Rated Wrist Evaluation (PRWE) and the Disabilities of the Shoulder, Arm and Hand (DASH and Quick DASH). Overall, wrist instruments measure physical outcome to assess functional ability.

When using outcome measures certain criteria must be met to ensure accuracy and reliability of the measured variable (195). Therefore, a brief overview of these parameters is warranted to assess the quality of forearm-specific outcome measures. Reliability is the extent to which a measurement is consistent (195). In other words, if a measurement were repeated multiple times, how close would the results be. Types of reliability include test-retest and intra/inter rater reliability. Test-retest reliability refers to the observed variance in the outcome parameter when the same test is repeated multiple times; it reflects the stability of the test measurement. To establish that human (or rater) reliability is high, the same person (intra) repeats the measurements and a reliability coefficient is generated. In the same way, to test the repeatability between raters (inter-rater reliability) two different investigators complete the measurement and a reliability coefficient is generated. Reliability co-efficients include the Pearson Product Moment Correlation or Spearman Co-efficient (non-parametric). However, the intra-class correlation coefficient (ICC) is preferred because it provides both correlation and agreement (195). For machine reliability or precision, the current practice is the Coefficient of Variation expressed as a percentage (% CV), also called Coefficient of root mean square (C_{RMS}). This measures the amount of variation of the outcome parameter and is the (standard deviation /mean) X 100. The %CV expresses the standard deviation in relation to the mean and therefore it can account for differences in the magnitude of the mean between measurements of different values (195,196).

Validity is another important measurement criterion. Measurement validity is often divided into face, construct, content and criterion (195). These parameters are measured by testing an instrument to ensure that a measurement is free from error. Determination of an instrument's validity can be done in a variety of ways depending on the instrument being tested. Face validity is the premise that the measurement tool appears to test what is intended. Construct validity refers to the ability to measure an abstract concept or construct. It is often necessary to be specific and then operationalize these constructs; for example, strength can be defined as functional grip strength and this is operationally defined as static grip strength. Criterion validity refers to the agreement of the outcome measure to a criterion standard. For example, the accepted criterion standard for bone mineral content is ashing; therefore, aBMD would be compared with density weight by ashing. Content validity is the assessment to test if a measure has measured the topic adequately. Finally, an investigation should have internal and external validity. This means that the experimental results are a result of the investigation and not confounding or bias (internal validity) and that the results are generalisible outside of the investigation (external validity).

2.8.8.1 *Range of Motion*

A goniometer is used to measure the amount of motion (ROM) available at a joint but validation of this technique is scarce (197). Potential outcomes are passive (PROM), active (AROM) and torque (TROM) range of motion. Torque ROM requires a constant speed external force to move through the joint motion (198). The American Society of Hand Therapists (ASHT) recommendations for wrist ROM includes placing the goniometer on the medial (or ulnar border) of the wrist and lining up the axis of the goniometer with the radio-carpal joint (197). The normal motion for the radio-carpal joint flexion-extension is shown in Figure 2-29 (199); and normative and functional values for wrist ROM are listed in Table 2-14. Functional ROM is generally reported as approximately 70% of the normal range (200).

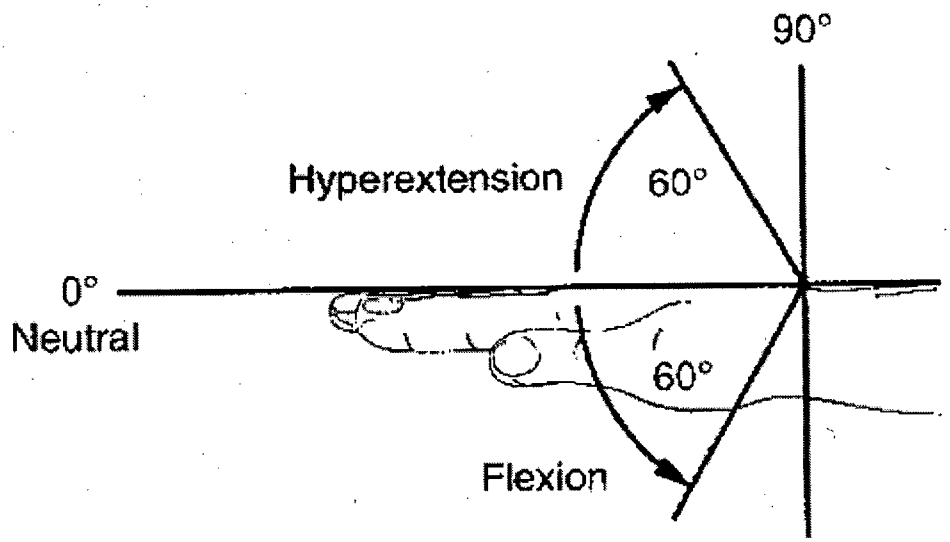


Figure 2-30. Measurement of radiocarpal range of motion (199)

Table 2-14. Normative and functional values for wrist range of motion.

	Normal Range (degrees)	Functional Range (degrees)
Flexion	80	40
Extension	70	40
Radial deviation	30	Combined total of 40
Ulnar Deviation	20	
Pronation	90	50
Supination	90	50

2.8.8.2 Dynamometry Grip Strength Measurements

The Jamar Handheld dynamometer (JAMAR Technologies, Horsham, PA) is the most common tool used to measure grip strength. The American Society for Surgery of the Hand (ASSH) recommends the second handle position be used, and the mean of 3 successive trials and percentages of previous or contra-lateral values (197). Recommended testing position for the Jamar is with the patient/participant sitting comfortably, elbow at 90^0, shoulder adducted and wrist/hand in neutral position (201) (Figure 2.30). Reliability and validity of the Jamar has been documented previously (202). Normative values for all age groups have been compiled and are reported for women and men 50 years of age and older (Table 2-15). Generally, men have a stronger grip strength compared with women and both decrease with age. Interestingly, previous research comparing grip strength by dynamometer and bone density is significantly correlated (r=0.87) (203), but these norms were obtained from healthier participants.

Table 2-15. Normal values for grip strength (in pounds). (202)

Age	Hand	Men (Mean ± SD)	Women (Mean ± SD)
50-54	Dominant	118 ± 24	71 ± 16
	Non-Dominant	106 ± 22	66 ± 15
55-59	Dominant	95 ± 20	64 ± 14
	Non-Dominant	88 ± 21	60 ± 13
60-64	Dominant	94 ± 14	56 ± 16
	Non-Dominant	86 ± 17	51 ± 14

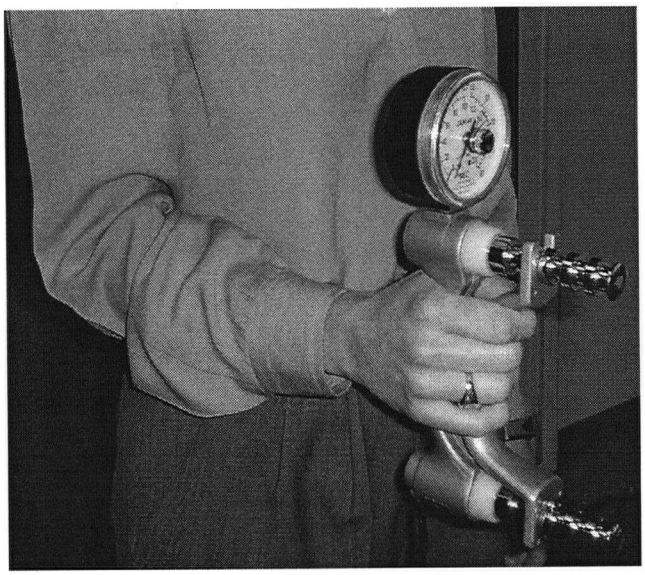


Figure 2-31. Jamar grip strength measurement.

2.8.8.3 *Wrist Outcome Measures*

There are two main outcome measures used for the wrist: Patient Rated Wrist Evaluation (PRWE) and the Disabilities of the Arm, Shoulder and Hand (DASH). PRWE is a valid and reliable measure of function of the wrist (204). It consists of two sections that measure functional limitations and pain levels. DASH is a valid and reliable measure of function of the upper extremity (205). The initial DASH tool consisted of 30 items, and is a self reported questionnaire designed to measure physical function and symptoms in patients with musculoskeletal disorders of the upper limb (206). The QuickDASH was developed in 2003 and is a shortened version of the original DASH with only 11 retained items. DASH normative value from the general population is 10.1 ± 14.68 (207). (I provide the accuracy and reliability of upper extremity outcome measures in Table 2-16.) Both the PRWE and the DASH were created in part by Canadian physical and occupational therapists.

Table 2-16. Accuracy and reliability of wrist-related outcome measures.

Outcome Parameter	Reliability	Accuracy
Range of Motion	ICC: 0.79-0.87 (208)	Difficult due to lack of criterion standard (209)
Jamar Grip Strength	Interrater ICC : 0.97 Test – retest ICC >0.80 (210) (201)	97% Accuracy (210)
Patient Rated Wrist Evaluation (PRWE)	Test – retest ICC= >0.90 (204)	Instrument able to detect differences overtime and correlated with alternative forms of assessing pain and disability (204)
Disabilities of the Arm Shoulder and Hand (DASH)	Test – retest ICC= >0.90 (206,211)	Construct Validity >0.70 (206) Moderate to high correlations with other markers of disabilities
Comparison of SF36, DASH and PRWE for responsiveness after a distal radial fracture; PRWE was the most responsive Standardized Response Mean (SRM) 2.27 for PRWE, DASH 2.01 and SF36 0.92). SRM: average change score (initial to follow-up) divide by the standard deviation of initial scores) (212).		

ICC=Intra-class Correlation Coefficient

2.9 Bone Response to Disuse

In this section, I outline details pertaining to fracture-immobilisation and stroke-disuse. As discussed previously, bone may respond to mechanical loads through mechanotransduction; the theory that there is a certain optimum range of bone microstrain for bone homeostasis. There is a set threshold above which bone is added (apposition) and below which bone is removed (resorption). Previous animal and human in vivo exercise studies have described the adaptation of bone to exercise (74,115,213-218). Specifically related to the upper extremity, Adami and coworkers observed a significant increase in cross-sectional area and density of the cortical compartment following an exercise regime focused on the radius (219). In contrast, the response to disuse or unloading of bone results in bone resorption. At microstrains below threshold, bone is removed.

At a cellular level, bone response to immobilisation has been likened to Parfitt's theory of a rapid and slow form of bone loss (32). As discussed in Section 2.5.3, the rapid phase results from unrestrained OC leading to deeper bone resorption, perforation and loss of whole trabecular and trabecularisation of cortical bone (32). The slowed rate of bone loss results in an overall thinning of trabeculae and cortical bone resulting from low numbers of OB or decreased OB function (220). In a rat model, bone loss is estimated to be from 30% increased bone resorption and 70% decreased bone formation (220).

Aging, spaceflight, immobilisation, bedrest and neurological deficits exhibit similar responses to bone unloading; decrease in mineral content and an increase in cross-sectional area to maintain bone strength. However, the response to disuse may be different in various situations depending on other competing elements of biology, such as diminished estrogen and Vitamin D. The loss or reduction of estrogen that occurs at the menopause can influence fracture healing and/or response to immobilisation. The mechanostat theory hypothesizes that estrogen lowers the με threshold and bone can be added at a lower threshold than if estrogen is absent or diminished (221). Animal studies have shown that 6 weeks of hind-limb non-fracture immobilisation in an osteopenic rat model, is associated with increased bone resorption and sustained decrease in bone formation (osteoblastic hypofunction) (220). Overall, estrogen and disuse leads to an uncoupling of the bone formation-resorption cycle, but the exact relation and mechanisms are still under investigation.

Decreased systemic calcium and vitamin D (with subsequent increase in parathyroid hormone) can also be competing consequences of immobilisation. Sato and coworkers have done numerous studies

investigating the rapid and sustained decrease in serum calcium levels after a stroke (222-227) but few studies have investigated bone biomarkers in response to upper extremity immobilisation. However, the limited literature (228,229) also highlights the rapid loss of calcium associated with disuse (but the magnitude of loss is lower in arm fractures compared with a stroke or bedrest). While mechanical loading influences bone formation-resorption, hormones such as estrogen control the rate of bone turnover; in combination there is a deleterious effect on bone health (230).

2.9.1 Fracture-immobilisation Model

I conducted an exhaustive search of the impact of fracture-immobilisation at the radius on human bone. I searched Medline, Embase and the Cochrane Database of Systematic Reviews to cover the period from 1966 to October 2003. The key words I included were radius; fracture; immobilisation; bone density; reproducibility. I tried to include MeSH headings wherever possible. I applied my inclusion criteria to all titles and abstracts. I only included articles/abstracts written in English. My inclusion criteria included "human radius fractures and immobilisation using imaging". Specifically, I sought information on the impact of distal radius fractures and immobilisation on bone health in men or women over 50 years of age.

I found eight studies that investigated compromised bone's response to fracture, immobilisation and remobilization (228,229,231-236). Westlin and Nilsson (235,236)were early key investigators who described bone tissue and geometric changes that occur in the distal radius after a fracture. Although these studies are fundamental to the understanding of an immobilisation model, they are also limited by the technologies developed and in use during the 1970s. Table 2-17 summarises the few studies that have investigated changes with disuse/immobilisation.

The response to fracture-immobilisation is generally a decrease in bone mineral density that reaches its nadir between 3-4 months and then increases but does not return to baseline (BMC comparing side-side differences) at 1 year (235). An interesting feature is the observed higher side-side differences observed with gamma absorptiometry compared with DXA. The early studies used SPA and observed a large difference between limbs (18%) in BMC (235,236). More recent investigations (228,229,232,234) have used DXA and observed either more modest differences or none at all. The early absorptiometry techniques required more operator intervention to assess bone parameters, compared with DXA where

essential algorithms are predetermined by factory set thresholds etc. and may account for some of the discrepancies.

There is a similar decrease in muscle strength. However, muscle recovers quicker and returns to baseline within three months in a younger population (234). Despite the documented differences associated with handedness, no studies have examined whether the fracture occurred in a dominant or non-dominant arm. To date, no studies have used pQCT to investigate response to immobilisation, therefore, previous research has not been able to describe true geometric changes or distinguish between trabecular and cortical compartments.

Table 2-17. Summary of studies investigating bone adaptation after radius immobilisation.

First Author and Year	Number of Participants	Age (years)	Imaging Technology	Sites	Results
1974, Westlin(236) Prospective	19	64± 8	Gamma Absorptiometry	Distal and midshaft	Midshaft BMC↓ 18% and ↓ 10% on non-fractured radius at 4 months. Muscle mass also ↓ and did not regain strength at 1 year. Cortical thickness did not change and suggestions of cortical porosity rather than cortical thinning. No restoration of bone mass at 1 year.
1975, Nilsson (235) Cross-sectional	74	62 ± 10	Gamma Absorptiometry	Distal and midshaft	Proximal site BMC ↓ 9%; distal site ↑ 20% on fractured side. Found greater loss of bone in peri and post menopausal women and older women suggesting less able to restore bone with time.
1991, Abbaszadegan (231) Prospective	31	66 (53-82)	Gamma Absorptiometry		↓15% in radial aBMD; no correlation with grip strength or ROM. Severity of initial trauma is of significance.
1995, Houde (232) Prospective	6 W 2M		DXA	Ultradistal and 8-24 mm from joint line	aBMD ↓ at all sites 3% at proximal site and 4% at Ultradistal. Areal BMD remained 5%↓ at all sites at 10 weeks; Contralateral limb ↑ at cast-off (8%) but no significant difference at 10 weeks.
1999, Ingle (228) Prospective	20	63 (47-79)	DXA; Ultrasound; Biochemical Markers	Ultradistal, Mid and Distal Third Radius	No significant changes at Mid and Distal Third. Ultradistal excluded because of callus. Bone loss greatest in the carpals using DXA and US; the ↑ biochemical markers occurred early.
2000, Ilich (233) Prospective Case Study	1	40	DXA	Ultradistal, Mid and Distal Third Radius	↓aBMD, BMC at all forearm sites (10-73%) ↓ at 10 weeks which remained at 1 year. ↓ at L3-L4 and Wards Triangle, although had no previous osteopenia. Had signs and symptoms of Complex Regional Pain Syndrome.
2001, Ingle (229) Cross-sectional	40	64 (42-81)	DXA; Ultrasound	Hand	↓ hand aBMD and finger Ultrasound. No difference between hands after 2 years.
2001, Macintyre (234) Prospective	9		DXA	Ultradistal, Mid and Distal Third Radius	↓ in BMC (recovered at 1 year), grip and ROM (recovered at 3 months). No differences in aBMD at distal third radius. Reflecting changes in gross morphometry

2.9.2 *Stroke-Disuse Model*

Every 10 minutes, someone in Canada sustains a stroke and there are over 300,000 Canadians living with the effects of stroke (237). A stroke is caused by a disruption in blood flow to the brain through either a blood clot or hemorrhage and can result in physical, perceptual and cognitive impairments. Annually in Canada, there are 50,000 incident strokes (237), and in the first year following a cerebrovascular accident (CVA) or stroke, 40% of individuals are likely to sustain a fall (238,239). Within two years post-stroke, one-third of survivors sustain a hip fracture and 24% sustain radial fractures (239). Although a number of factors contribute to this increased fracture risk (e.g., poor balance and number of falls), diminished bone health is an important factor in fragility fractures.

Recently, Frost (240) suggested several other models of physiological osteopenia in which there is a healthy mechanostat but muscle weakness. An example of this phenomenon occurs in individuals after a stroke where important skeletal changes have been reported that increase the risk for a serious fragility (low trauma) fracture. In the first year following a CVA or stroke, 40% of individuals are likely to sustain a fall (238,241) and for every two standard deviation decrease in femoral neck aBMD, there is a seven- fold increase in the risk of a hip fracture (226). Hip fractures are serious medical events that have high patient burden and significant economic consequences.

Most previous studies investigating bone health in this population, chose an earlier phase (within 6-12 months post stroke). As observed in the fracture-immobilisation studies, DXA results showed an initial rapid decrease in aBMD in the paretic limb compared with the non-paretic limb (242-246). The magnitude of the change in bone density in the paretic limb ranged from 5-12%, while a loss of 3-5% was reported in the non-paretic limb. The loss observed in the upper extremity is usually more pronounced in the lower extremity (247). Two investigations in the upper extremity report a negative correlation between BMC and time since stroke (248,249). Hamdy and coworkers (249) reported a significant reduction in total arm mineral content (BMC) and aBMD of the paretic side in a small group of men nine years post stroke. There have been few studies that have documented the long-term (greater than 12 months) impact of a stroke-disuse on bone health (248). To my knowledge, no one has reported bone adaptation using pQCT in a chronic stroke population. Table 2-18 summarises the literature related to upper extremity stroke-disuse and bone parameters.

Table 2-18. Studies of bone adaptation following stroke-disuse.

First Author and Year	#Participants	Age (years)	Stroke Duration	Imaging Technology	Sites	Results
1988 Prince Cross-sectional (248)	74	70	Chronic	Radiographic absorptiometry	Forearm	PA 1.3% trabecular and 1.5% total bone loss/ year BMC negatively correlated to duration of stroke and positively correlated to good functional outcome
1989 Iversen Cross-sectional (250)	15	62.5	Acute	DPA	Forearm	PA BMC ↓ 10.3%
1993 Hamdy Cross-sectional (247)	30	65	Acute Chronic	DPA	Upper limb	PA BMC ↓ 13%, aBMD ↓ 12% Correlated to time since stroke
1995 Hamdy Prospective (249)	11		Acute	DXA	Upper limbs	Significant ↓ BMC until 4th month when it stabilized at 10% side-side difference
1997 Tanaka Cross-sectional (251)	15	57.7 ± 10.9	Acute	DXA	Humerus Forearm Hand	BMC and aBMD ↓Compared with controls
1998 Sato Cross-sectional (225)	93	67 ± 7.0	Chronic	Computed X-ray densitometry	Second metacarpal	aBMD correlations with degree of paralysis
1999 Liu Prospective (252)	104	56.5	Acute	DXA	Humerus Forearm	↓ aBMD over time
1999 Ramnemark Prospective (253)	19	61-88	Acute	DXA	Total arm; humerus	PA Humerus -17% NPA ARM +6%
1999 Sato Cross-sectional (224)	129	70.2 ± 4.1	Chronic	Computed X-ray densitometry	NPA Second metacarpal	↓ aBMD compared with controls correlated to Barthel Index hypercalcemia
2001 Sato Prospective (226)	216	>65	Acute	Computed X-ray densitometry	Second metacarpal	aBMD ↓ and number of hip fractures ↑ 7X in Vit D deficient group

2.9.3 *Comparison of fracture-immobilisation vs. stroke-disuse models*

Many similarities exist between the fracture-immobilisation disuse model and the stroke-disuse models; for example, the rapid decrease in mineral content that stabilises between 3-6 months (249,254). However, a comparison of the geometric adaptation for stroke-disuse or fracture-immobilisation is difficult because no data are available. While bone density returns to pre-fracture levels 1-2 years following a wrist fracture, this pattern is not the observed norm in the stroke literature. Hamdy and coworkers found that maximal aBMD loss was at 3-4 months (249) while Prince and coworkers suggest that there is a side-side difference in bone density up to fifteen years after the incident stroke (248).

However, there are differences that need to be considered. First, metabolic changes occur after a stroke that affect calcium, vitamin D and parathyroid hormones levels (255). Hypercalcemia due to immobilisation is common after a stroke. If serum vitamin D levels are low, this can override the hypercalcemia to initiate parathyroid release and increase bone resorption. Second, for women, the mean age for a stroke event is in the early 70s while the mean age for a distal radius fracture is 50 years (68). Most women who suffer a stroke are post-menopausal and diminished estrogen impacts on bone mass (249). Finally, there are obvious muscle differences that exist between the groups; due to the paralysis associated with stroke-disuse, the fracture-immobilisation model has a better chance of full muscle return.

2.9.4 *Muscle and Bone Interactions*

The impact of muscle on bone formation is a relatively new area of musculoskeletal investigation that continues to grow. Bone responds to forces and the greatest force is generated by muscle (40). However, a key limitation in understanding how muscle strength influences bone parameters, has been the imaging technologies, in particular DXA's areal measurements. More recent literature used pQCT to measure bone structural properties and observed high correlations between grip strength or muscle cross-sectional area and bone strength index (SSI) in healthy populations (256-258); whereas Heinonen and coworkers reported a significant relation between MRI and tibial cortical and total muscle area (259). Finnish tennis studies report the adaptation of upper extremity bone with exercise in healthy participants (113,115). From animal studies, the importance of high intensity and rate of exercise after immobilisation were reported to restore and maintain BMC and aBMD (45). For in vivo investigation of older women following injury and exercise, only the impact of a wrist specific exercise (219) and the temporal relation of

diminished muscle strength prior to bone loss at the radius (234) has been reported. Thus, this remains an important area for future investigation.

2.10 Upper Extremity Bone Response to Interventions

In this section, I briefly outline the impact of exercise and other interventions on bone health, specifically at the radius.

2.10.1 Upper Extremity Specific Exercise Intervention and Bone Response

The human skeleton adapts rapidly to physical inactivity. Fluid shifts occur as a result of dynamic forces (260), and the greatest forces that act on bone are generated by muscle. Previous animal and non-stroke in vivo exercise studies have suggested that exercise can improve bone parameters (74,115,213-218). In tennis players, Kontulainen and co-workers found that exercise increased cortical area by periosteal apposition predominantly at the humerus (113). Specifically related to the wrist, Adami and coworkers tested a 6-month exercise intervention in 250 postmenopausal women, aged 52-72 years, and were able to show geometric changes at the distal radius (4% site) (219) . The intervention was an intensive 70 minute strengthening regime that maximized the brachioradialis muscle (inserts on the radial styloid process) (219). A significant increase in cross-sectional area and density of the cortical compartment was observed.

2.10.2 Pharmaceutical Interventions and Disuse-Immobilisation

Several investigations have assessed the benefit of bisphosphonates after a fracture (261-263). In a randomised controlled study (n=32) , participants were given either clondronate capsules (400mg) or placebo twice a day starting 48 hours after fracture for 8 weeks (261). Although participants experienced an increase in aBMD of the fracture callus using DXA, the pharmaceutical intervention did not reduce immobilisation osteopenia overall. Another investigation of the impact of alendronate on radial bone parameters using pQCT showed a 7% increase in total density at the ultradistal site with an increase in SSI (262). However, as discussed previously, SSI is dependent on cortical parameters and may be affected by the PVE; therefore the validity of this parameter at the 4% site remains to be determined.

2.10.3 Electrical Therapy

In persons with spinal cord injuries, functional electrical stimulation (FES) has been shown to impact on lower limb muscle strength and bone aBMD as measured by DXA (264). A 24 week intervention was used with 14 persons with spinal cord injury. Investigators observed a significant increase in aBMD at the distal femur and proximal tibia. Muscle stimulation, either passive FES or electromyogram (EMG)-triggered neuromuscular stimulation has been evaluated on arm and hand functions following a stroke (265). However, there have been no reports of bone adaptation in response to the electrical stimulation. For those individuals, who have paralysis, FES may be ideal for secondary prevention of bone loss.

2.10.4 Vibration

The use of vibration has been investigated as a therapeutic intervention to maintain or increase bone mass (266). Rubin and coworkers reported a 34% increase in trabecular bone density in a vibration sheep model (267). In the study, sheep were placed on a low-frequency vibration platform for 20 minutes a day. After one year, the sheep given the intervention increased trabecular bone density at the proximal femur. Studies have been extended to include menopausal women and children with disabilities (268,269), but to my knowledge this has not been tested in a radial model. For populations who have muscle paralysis (stroke, spinal cord injury), vibration may be an ideal intervention but the clinical utility for bone remains to be established.

2.11 Contribution of the Radius to Bone Health Research

The distal radius is an ideal model: i) to estimate the determinants of bone strength; ii) to quantify the influence of immobilisation; and iii) to study secondary prevention of osteoporosis. The radius provides easy access for imaging technology and, due to the peripheral location, ionizing radiation is lower than when scanning the axial skeleton. In this section, I will highlight the attributes of the radius that makes it an important contributor to bone health.

2.11.1 Osteoporotic Bone Definition

> *"Such bones are weak with narrow shafts, thin cortices, and sparse trabeculae and could not withstand normal loading without high risk of damage."*
> *Lanyon and Skerry 2001(70)*

Compromised bone is defined by a decrease in bone mineral mass with subsequent reduction in the cortical shell which leaves structures with a reduced strength and increased susceptibility to fracture. As defined by the National Institutes of Health (NIH) in 2000, osteoporosis is a musculoskeletal condition of compromised bone strength such that there is micro-architectural deterioration and fractures occur with minimal trauma (falling from a standing height or less) (270). Conceptually, osteoporotic bone has a normal mineral-to-collagen ratio but is decreased overall, leading to enhanced bone fragility and an increased fracture risk. Fractures occur in osteoporosis when the load applied to the bone exceeds its biological strength. Osteoporosis is distinguished from osteomalacia in which there is a deficiency of mineral-to-collagen ratio (less mineral-to-collagen). For the duration of this thesis, I define compromised bone as exhibiting bone mass deterioration with increased porosity and lower-than-average bone strength predisposing to fractures.

There are two main types of osteoporosis: primary and secondary. Primary osteoporosis is composed of three types; Type 1 is postmenopausal osteoporosis and is characterised by a disproportionate loss of trabecular bone with a resultant high proportion of fractures affecting sites rich in trabecular bone (distal radius, femoral neck and vertebrae). Type 2 osteoporosis or age-associated osteoporosis affects all skeletal sites resulting in an overall loss of bone. Type 3 is idiopathic osteoporosis and it affects pre-menopausal women and young to middle aged men. Secondary osteoporosis can be caused by an identifiable agent such as glucocorticoids or by a disease state such as hyperthyroidism.

Operationally, osteoporosis is defined diagnostically by the World Health Organisation (WHO) using dual energy X-ray absorptiometry (DXA) scores. Normal bone is defined as aBMD greater than one (1) standard deviation (SD) below peak young adult normative values. Osteopenia is defined as greater than or equal to one SD but less than 2.5 SDs below peak young adult normative values. Osteoporosis is defined as aBMD greater than 2.5 SD from normative vales. Areal BMD greater than 2.5 SD combined with a fragility fracture is called Severe Osteoporosis. Bone density is determined by peak bone mass and rate of bone loss. This definition is dependent on DXA and although it has many advantages, (most notably its ease of application, low patient radiation dose and availability) it is still only a two-dimensional view of bone.

Osteoporosis is a serious condition affecting over 1.4 million Canadians including 25% of women and 12% of men aged > 50 years and Canadian health care costs for osteoporosis exceed $1.3 billion annually (2,271). Over 44 million Americans over the age of 50 years have osteoporosis and in 1995 it cost over US $13.8 billion (272). Prevention and containment of osteoporosis is of paramount importance, and fortunately, there is treatment available to limit the impact of the disease.

2.11.2 Osteoporosis and the Impact of Radius Fractures

The three most common fractures associated with osteoporosis occur at the hip, the spine and the wrist. These fractures are painful, disabling and can cause death (1). Figure 2-31 is from a large population-based prospective study (273) and highlights the pattern of radial fractures. An interesting phenomenon is the gradual increase in radial fractures commencing at 40 years of age perhaps suggesting that something more than the menopausal state is contributing to fracture risk.

Although, there is no doubt as to the magnitude of burden associated with hip fractures, radial fractures are generally regarded as a mere nuisance. However, distal radial fractures are the most common peripheral fractures seen in emergency departments (147). The mean direct cost/distal radius fracture in people over 50 years of age was approximately US $800 - $1000 (79,274,275), not accounting for the burden on the individual or community. Previous research has observed that function often fails to return to pre-injury status (177) and this has long-term implications for muscle strength and consequently bone health (177). In a large population-based, cross-sectional investigation of the late effects of osteoporotic fractures on function, a previous radial fracture had a significant impact on activities of daily living. Specifically, participants reported difficulties with climbing [odds ratio (OR) 1.8] and descending stairs (OR

2.5), shopping (OR 3.3) and preparing meals (OR 10.2). Previous researchers have reported that more than 75% of women with a fragility radial fracture are diagnosed by DXA with either osteoporosis or osteopenia (276). This indicates a systematic level of bone fragility and justifies its name as a "true osteoporotic fracture" and warranting investigation (9,140-144).

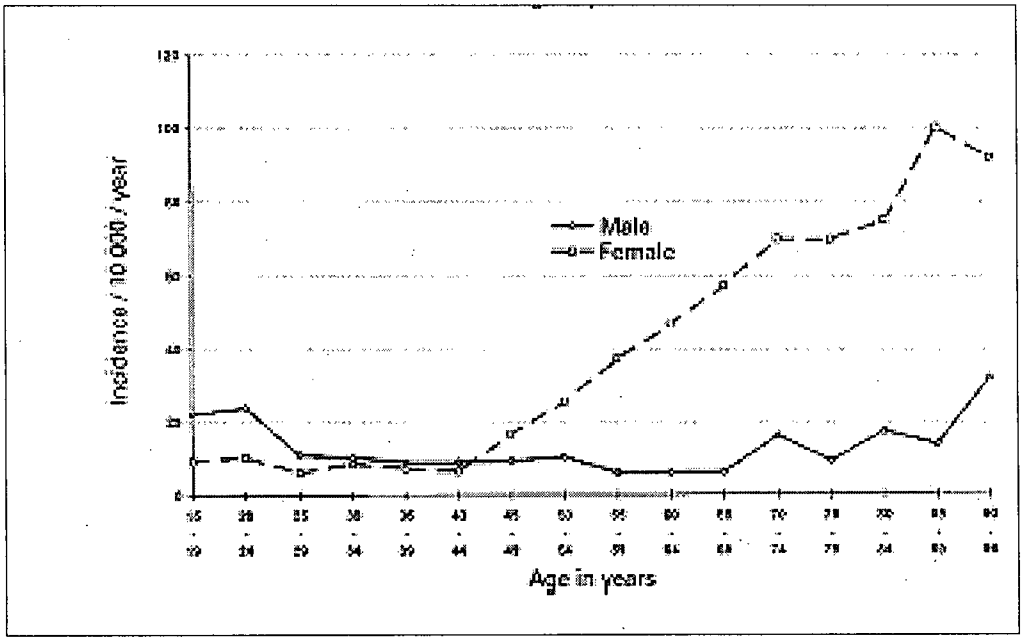


Figure 2-32. Incidence of annual distal radius fractures per 10, 000 by age and gender (N=15, 000). (273)

2.11.3 Radius Fracture as a Risk Factor for Osteoporosis

In 1982, researchers at the Mayo Clinic reported that history of a previous fracture was associated with a 50% increased risk of subsequent hip fracture (9). Eight subsequent publications (3,6-8,277-280) provided evidence that this was an under-estimation of the risk. Radial fractures often signal the presence of osteoporosis and may be harbingers of the more serious hip fracture (9). In an extensive meta-analysis (January 1966 to September 1999), Klotzbuercher and coworkers summarised the risk for future fracture given a prior fragility fracture (6). Table 2-19 summarises the results from peri-post menopausal women. Interestingly, Honkanen and coworkers (5) from Finland, in a retrospective population-based questionnaire study (n=12,162 women) observed that early pre-menopausal radial fractures (ages 20-34 years) doubled the risk of a post-menopausal fragility fracture.

Some controversy remains as to whether women who sustain a wrist fracture have lower radial aBMD. Several investigations have observed that the non-fractured radial aBMD is lower compared with aged-matched normals (143,281,282) while a more recent evaluation (using pQCT and DXA) have observed that a fragility radial fracture is not strongly associated with low aBMD at the radius (283).

Table 2-19. Summary of fracture relative risk estimates by site following a prior fragility fracture. (6)

	Hip	Radius	Spine
Hip	2.3	n/a	2.5
Radius	1.9	3.3	1.7
Spine	2.3	1.4	4.4

n/a=not available

2.11.3.1 Radial Fractures and Osteoporosis Investigation

National guidelines in Canada emphasize that low trauma fractures should not merely be treated orthopaedically (1) but should prompt a primary care provider workup to assess osteoporosis risk and manage appropriately. Despite this ideal opportunity for secondary prevention of osteoporosis, numerous publications have highlighted the continual low investigation (~20%) rates after a sentinel fracture (10) . Even fewer patients received adequate therapy, highlighting the 'knowledge-care gap'. In a review of the largest series of radial fractures to date, only 23% of "at risk" patients were treated for osteoporosis (284). Feldstein and coworkers (285) reported from a retrospective review of a large hospital database that only 9.8% of the women and 2.9% of the men were screened for osteoporosis. Yet, Cummings (286) suggested that screening for these "sentinel fractures" could reduce hip fractures by 9%.

There is, however, little evidence that this opportunity to prevent osteoporosis is used clinically to investigate after a fragility fracture. A retrospective chart review that sampled hospital-based fracture clinics, found that more than 80% of people over 50 years of age who had sustained a low trauma fracture [and thus, by definition, had osteoporosis (1)] were not told they had osteoporosis (10). Even fewer received adequate therapy. Recent publications (287,288) have highlighted the gap between 'guideline care' and actual clinical practice. Table 2-20 summarises the literature (from 1966-2003) highlighting the gap in care for osteoporosis following a fragility fracture. The heading labeled "Investigated" refers to any osteoporosis relevant investigation offered to the patient. The heading labeled "Diagnosed" is a subset of Investigated and reports the outcome of the investigations.

This summary of the literature highlights two important points. First, overall there is an under-investigation rate of osteoporosis in a high-risk group. Prior to 1998 there were no published reports assessing physician osteoporosis assessment practice yet the importance of fragility radial fractures and osteoporosis was noted in the literature as early as the 1970s (144). In the literature, the highest investigation rate was from South Australia with 32% of patients; however, these data included both radial

and hip fractures (289). Second, there were few patients who received treatment for osteoporosis (medications or lifestyle modifications offered). Overall, there is a gap in care that may be ameliorated with a simple intervention. As of 2002, there were no published data on interventions designed to change physician practice patterns.

The importance of fragility radial fractures raises an important question: Can we use bone density measures from the radius as a surrogate for the risk of fracture at the hip? This has been investigated using mechanical testing of the femur failure load in ex vivo investigations (131) and compared to aBMD of a non-fractured and/or non-dominant radius. The results suggest that the radius does predict femoral fracture but aBMD of the femur is a better predictor (290). The International Society of Clinical Densitometry (ISCD) has also recommended that a radial DXA scan be used to determine t-scores if femoral neck aBMD is unavailable/ not appropriate (291). In other words, radius aBMD (Distal Third aBMD) can have limited predictive ability for the femoral neck. Nonetheless, the simple fact of sustaining a fragility fracture should be enough to prompt investigation of osteoporosis through blood work and/or DXA at the femoral neck. In a recent investigation, Schousboe and coworkers found that radial fractures were an independent risk factor for incident vertebral but not for hip fractures (292). The authors still recommended that individuals who sustain a fragility radial fracture should undergo aBMD assessment to ascertain hip fracture risk.

To summarise, radial aBMD may have utility in predicting a future radial fracture or possibly even vertebral fractures. Assessing the radius at the time of fragility fracture for osteoporosis diagnosis has limited clinical utility; primarily because of the changes that both limbs undergo after a fracture (with the risk of a false positive). Secondly, if a fracture has already occurred and the goal is to ascertain risk for hip fracture then, femoral neck DXA would be more appropriate.

Table 2-20. Literature Summary of Secondary Prevention of Osteoporosis using a Radial Fracture (1966-2003).

First Author-Year	Study Design	N=	Participants	Fractures	Investigated	Diagnosed	Treatment
1998, Torgersen (293)	Retrospective chart review	300	Women >50 years From a General Practice Research Database	Radius, hip or spine	n/a	n/a	Use of "Bone Drugs" the year before, during and after fracture. No significant ↑ in prescriptions
2000, Hajcsar (10)	Retrospective chart review	228	Women and men who attended community hospital-based fracture clinics	Radius, humerus, hip or spine	22% Bone densitometry	18.5%	32.4% calcium advice 7.4% bisphosphonates
2001, Castel (294)	Retrospective chart review	183	Women and men >50 years attended Emergency room	Radius, humerus or hip	n/a	1%	30% any treatment
2001, Smith (289)	Retrospective chart review and follow-up questionnaire	218	Women and men, mean age 69.9 years (41-82)	Radius (127) or hip (91)	32% Bone densitometry	56.5%	39% any treatment
2001, Khan (140)	Follow-up questionnaire at 1 year since fracture.	112	Women and men who attended a tertiary care facility.	Radius	21%	n/a	38% bisphosphonates or HRT
2002,Charalambous (295)	Retrospective chart review	50	Women >50 years seen in fracture clinic	Radius	none	none	none
2003, Simonelli (296)	Retrospective chart review with telephone follow-up at 1 year	227	Women >59 years seen at hospital	Radius, hip or spine	10% Bone densitometry	26%	26% medications recommended
2003, Feldstein (285)	Electronic database from HMO	289	Women and men >50 years with a fragility fracture and received health care treatment from HMO	Radius	9.8% women and 2.9% men had Bone densitometry	n/a	34.9 % women and 2.9% men received medications
2003, Andrale (284)	Electronic database from HMO	1620	Women and men >50 years with a fragility fracture and received health care treatment from HMO	Radius	n/a	n/a	12% received medications
2003, Myers(297)	Retrospective chart review and follow-up questionnaire at 1-2 years	111	Women and men	Radius	9% in hospital and 37% at follow-up Bone densitometry	n/a	15% in hospital and 27% at follow-up for any treatment

N/A=not available

2.11.3.2 *Role of the Health Care Team in the Secondary Prevention of Osteoporosis*

Research supports a radial fragility fracture as a catalyst to initiate investigation for osteoporosis. However, who should co-ordinate this role, and what is the best way to initiate care has received little attention in the literature. Two recent publications discuss physician barriers to osteoporosis assessment following a fragility fracture: a survey (298) and a qualitative focus group investigation (288). The both primary care providers (PCP) and orthopaedic surgeons stressed the importance of the PCP as the ideal team member to manage osteoporosis. The PCP is a natural choice to manage osteoporosis because she/he is likely to maintain a long-term relationship with patients and co-ordinate/manage issues related to osteoporosis medication prescription, diet, and exercise or lifestyle modifications.

In the present health care system with physician shortages and long waiting lists, it may be difficult for a PCP to manage the many issues related to the fragility fracture in a short visit. Other health care team members, such as physiotherapists, could assist in "case finding" for secondary prevention of osteoporosis. The benefits of secondary prevention of osteoporosis are multiple. By recognizing the risk for osteoporosis early, interventions (education on calcium, vitamin D, diet and exercise) can be implemented. This area has received little prior attention.

3 Rationale, Objectives, Hypotheses and Contribution

In this chapter, I outline specific details for each of my six studies, including the study rationale, main objectives, hypotheses and conclude with the contribution that each study makes to the overall thesis.

3.1 **Part 1A: Optimizing Results from pQCT: Reliability of operator-dependent pQCT parameters in cadavers and humans with low-bone mass.** Described in Chapter 4

3.1.1 Rationale

Peripheral quantitative computed tomography (pQCT) is a safe and precise technique to differentiate cortical from trabecular bone and assess both bone geometry and volumetric density. Currently, pQCT data acquisition and analysis protocols are seldom reported and there are no universal standards. Smaller voxel size (and slower scan speed) enhances scan resolution but increases scan time, radiation exposure and the likelihood of movement. On the Norland Stratec XCT 2000 and 3000 instruments, the recommended resolution voxel size is 400 µm or 500 µm. However, in a severely compromised skeleton where cortices are thin, lower resolution scans may lead to an inability to analyse (analysis failures).

3.1.2 Objective

The purpose of this methodological investigation was to investigate pQCT outputs when several technical aspects of the scan were altered. Specifically, I report the variability that resulted from 1) changing resolution, 2) changing the scout view reference line; and 3) failure of scan analysis when investigating very low bone mass. These results have practical implications for pQCT scanning in clinical populations.

3.1.3 Hypotheses

There will be no significant differences in operator dependent parameters that affect bone outcome parameters. More specifically, i) there will be no significant difference when measuring from a distal reference line compared with the manufacture recommended mid-line; ii) scan data acquired from multiple acquisition resolutions will not vary; and iii) scan failure rate will not be influenced by the scan acquisition resolution.

3.1.4 Contribution

This pQCT technical study lays the groundwork for establishing acquisition and analysis protocols for low-bone mass. I use the results of this study to acquire appropriate in vivo and ex vivo images and to analyse low bone mass pQCT scans. Importantly, this study highlights previously unpublished limitations of pQCT.

3.2 Part 1B: Accurately Predicting Failure Load at the 30% Site of the Aged Distal Radius.

Described in Chapter 5

3.2.1 Rationale

Dual energy X-ray absorptiometry (DXA) is the criterion standard for the clinical assessment of bone mass. The advantages of DXA include its precision, relatively short scan time and fracture risk prediction. However, due to its inherent planar nature, DXA can neither distinguish cortical from trabecular bone nor can it detect structural changes that may occur with growth, aging, disease, or intervention (e.g., pharmaceutical agents, exercise). Peripheral quantitative computed tomography (pQCT) permits researchers to investigate bone's geometric properties, while separating cortical and trabecular bone compartments. Despite these potential benefits of pQCT, few studies have reported on the accuracy of the most commonly used pQCT: Norland Stratec XCT 2000/3000 (Stratec Medizintechnic GmbH, Pforzheim, Germany).

3.2.2 Objective

My objectives of this multiple component study were to: 1) validate pQCT - generated parameters with ash weight of a section from the 30% site of the distal radius; 2) validate pQCT total area with histomorphometry of the 30% site of the distal radius; and 3) use pQCT bone parameters to predict failure load in low mass radii using axial compression. I used the information obtained from this study to understand pQCT imaging with low bone mass and to assist in the development of pQCT acquisition protocols. This study also assisted in determining the relative contribution of different bone components to overall bone strength.

3.2.3 Hypotheses

1) Peripheral QCT measurement of cortical bone will not be dependent on acquisition resolution. 2) Total and cortical material content will both contribute to failure load in axial compression at the distal radius.

3.2.4 *Contribution*

To my knowledge, this is the first study to investigate resolution-dependent accuracy with the XCT 2000 pQCT. This investigation makes a significant contribution to my thesis and to the field of densitometry of low bone mass and highlights previously unpublished limitations of pQCT. I used the information gained from this study to develop protocols for my clinical studies.

3.3 **Part 2A: Bone Adaptation after a Radial Fracture: A pQCT Study.** Described in Chapter 6

3.3.1 *Rationale*

With disuse-immobilisation, long bones respond to diminished loading stimuli in a variety of ways. The peripheral skeleton may respond to disuse by decreasing its mass (content/density) or by changing its geometric properties. The specific geometric adaptation of bone to decreased mechanical loading is not well defined but may include: a change in overall cross-sectional area, a decrease in the width of the cortical shell, and/or a change in the mineral content of the bone. Alone or together, these changes can influence the overall strength of bone. Peripheral quantitative computed tomography is a relatively new technology that can measure in vivo volumetric structural and volumetric content of bone. It can also separate cortical and trabecular bone and can quantify structural changes that may occur in the peripheral skeleton with growth, aging, disease, or intervention (e.g., pharmaceutical agents, exercise). Radial fractures provide an ideal model to study the impact of bone immobilisation.

3.3.2 *Objective*

My primary objective of this investigation was to describe bone mass and geometric changes that occur at the distal radius. Outcomes include pQCT and DXA total and cortical area, content and density as well as functional outcomes. Specifically, my aim was to compare side-side differences in bone after fracture, immobilization and remobilization using a cross-sectional design.

3.3.3 *Hypotheses*

Peripheral QCT will reveal significant radial side-side differences in structure following fracture and immobilization compared with the non-fractured radius. The bone strength at the midshaft (proximal to the

fracture) will be decreased on the previously fractured limb compared with the non-fractured limb. The fractured radius will maintain overall bone strength (as measured by the stress-strain index) at the 30% site but total area will be significantly increased on the previously fractured limb. The bone parameters from a non-dominant radial fracture will not be significantly different than the bone parameters from a dominant fracture.

3.3.4 Contribution

This study uses a radial fracture to highlight bone geometric and material content changes that can occur over time after a radial fracture to develop hypotheses for future testing. I used the imaging knowledge gained from my accuracy study to strengthen my investigation. The information from this study can assist therapists to investigate the role of hand dominance or bone outcomes after fracture. Exercise protocols that target immobilisation bone response can potentially maximize bone strength after a fracture.

3.4 **Part 2B: Bone Structural Adaptation to Chronic Disuse following Stroke**. Described in Chapter 7.

3.4.1 Rationale

In the first year following a cerebrovascular accident (CVA) or stroke, 40% of individuals are likely to sustain a fall and within two years post-stroke, one third of survivors sustain a hip fracture and 24% sustain a radial fracture (239,299,300). Although a number of factors contribute to this increased fracture risk (e.g., poor balance and number of falls), diminished bone health is also important in fragility fractures. Few studies have documented the long-term (greater than 12 months) impact of stroke-disuse on bone health.

3.4.2 Objective

Using pQCT, the objectives of this study were to compare side-side differences in bone material and geometric properties (ultimately affecting bone strength) for participants who were 1 and 10 years post cerebrovascular accident. More specifically, I i) describe side-side differences in radial bone mineral content density, total area and bone strength; ii) compare bone outcomes to physical measures of muscle strength; and iii) compare results of bone response to my immobilisation model to understand the similarities and differences between stroke-disuse and fracture-immobilisation.

3.4.3 Hypotheses

Peripheral QCT will reveal significant radial geometric changes on the paretic upper extremity compared with the contra-lateral upper extremity. Specifically the paretic upper extremity will have decreased mineral content but increased total area. A decrease in bone strength at the midshaft will be present on the paretic upper extremity.

3.4.4 Contribution

This study uses the radius to provide observations of bone response to stroke-disuse. I use the results to compare with the radial fracture-immobilisation study and highlight the similarities and differences between immobilisation and disuse. This study also highlights the long-term impact of stroke-disuse on bone parameters.

3.5 Part 3A: Upper Extremity Fragility Fracture Initiates Osteoporosis Investigation: A Controlled Trial. Described in Chapter 8

3.5.1 Rationale

Osteoporosis is a condition of generalized skeletal fragility such that fractures occur with minimal trauma. The three most common fractures associated with osteoporosis occur at the radius, vertebrae and the hip. In 1982, researchers at the Mayo Clinic reported that history of a previous minimal trauma or fragility fracture was associated with a 1.3 relative risk (RR) of subsequent hip fracture (9). This underscores why national guidelines for Canada emphasise that minimal trauma fractures should not merely be treated orthopaedically but should prompt a primary care physician workup to assess osteoporosis risk and provide appropriate management. However, numerous studies have shown that using a fragility fracture to initiate secondary prevention of osteoporosis is underutilized. Despite how common and important a problem, there have been few controlled studies testing interventions to address this gap in care.

3.5.2 Objective

The primary objective of this study was to test a 4-part intervention aimed to increase osteoporosis investigation rate following a fragility fracture.

3.5.3 *Hypotheses*

1)There will be a suboptimal [operationally defined as <70% (10)] rate of diagnosis of osteoporosis in patients with an upper extremity fragility fracture who receive usual care. 2) In patients age >50 years, the rate of osteoporosis investigation following fracture will be significantly greater in the intervention group (that receives patient and physician alerts) than in the usual care group.

3.5.4 *Contribution*

This study represents the health services research component of my dissertation and highlights the novel contribution that the radius can make to understanding relevant bone health issues. This study also highlights a key role that rehabilitation therapists (hand, physical and occupational) can play in the early identification of people at risk for osteoporosis.

3.6 **Part 3B: Barriers to Investigating Osteoporosis after a Fragility Fracture: A Survey of BC Physicians.** Described in Chapter 9

3.6.1 *Rationale*

Although a minimal trauma fracture provides an excellent opportunity for secondary prevention of further osteoporotic fractures, studies in Ontario and Alberta both found low rates of intervention following these sentinel events. A recent study found that more than 80% of people over 50 years of age who sustained a minimal trauma fracture were not told they had osteoporosis (10). Even fewer received adequate therapy, highlighting the gap between 'guideline care' and actual clinical practice. The present study investigated physician knowledge and self-reported behaviour in urban and rural communities of British Columbia using a questionnaire to ascertain: (i) osteoporosis practice patterns for at-risk patients and, (ii) perceived barriers to osteoporosis intervention.

3.6.2 *Objective*

To measure physician-reported i) practice patterns for osteoporosis assessment for at risk patients and 2) perceived barriers to investigating osteoporosis after a fragility radial fracture.

3.6.3 *Hypothesis*

Physicians will report that time constraints are barriers to early identification of osteoporosis after a fragility radial fracture.

3.6.4 *Contribution*

This study extends my controlled trial (reported in Chapter 8) by recording physician-reported osteoporosis practice patterns. This study also aims to provide a scientific foundation for innovative ways to improve bone health care delivery.

4 Optimizing pQCT Results. Reliability of operator-dependent pQCT parameters in cadavers and humans with low-bone mass.[1]

In this chapter, I outline the results of my preliminary pQCT methodological work. When I commenced my investigations in 2001, there were few studies validating the most common pQCT, (Norland-Stratec XCT 2000) in evaluating low bone mass. In the early stages of my investigations, I noticed numerous image scan failures in older female participants, particularly at the distal trabecular site of the radius. Upon investigation, I observed no standards for pQCT analysis and few studies reporting the limitations of pQCT.

4.1 Introduction

Peripheral quantitative computed tomography permits researchers to investigate bone geometric properties and provide the relative contribution of cortical and trabecular bone in humans. Although there have been a number of accuracy and precision studies of pQCT in animals (301,302) and in humans (85,105,109), there are few data on the accuracy and precision of the most commonly used pQCT in practice today: Norland Stratec XCT 2000/3000 (Stratec Medizintechnic GmbH, Pforzheim, Germany)(111,130-132). Most precision studies have used a constant analysis and acquisition protocol, whereas a number of steps in the Norland Stratec pQCT scan acquisition are operator-dependent. These include: (i) resolution/voxel size, (ii) locating the anatomical reference line, (iii) participant positioning, and (iv) the approach to account for scar failure. At the beginning of this study, I could find no studies describing which acquisition or analysis protocols were most reliable. Furthermore, precision studies should ideally be undertaken in the type of bone that will be investigated in future studies. There have been very few reports of pQCT reliability in populations with bone compromised by disuse or osteoporosis. These patients may provide the greatest challenges to those seeking high-quality reproducible scans.

Therefore, the purpose of this methodological investigation was to investigate pQCT outputs when several technical aspects of the scan were altered. Specifically, I report the variability that resulted from changing resolution and changing the scout view reference line. Further, I quantify failure of scan analysis

[1] A version of this chapter has been published as a manuscript. MC Ashe, T Liu-Ambrose, KM Khan, HA McKay. Reliability of Peripheral Quantitative Computed Tomography: Cadaveric and Clinically Relevant Studies. *Journal of Clinical Densitometry.* IN PRESS

at different resolution when scanning very low bone mass. These results have implications for pQCT scanning in clinical populations.

4.2 Methods

I undertook cadaveric and human studies to examine the effect of changing modifiable parameters of the Norland/Stratec XCT 2000 pQCT (Stratec Medizintechnic GmbH, Pforzheim, Germany). All studies were approved by the University of British Columbia Clinical Research Ethics Board.

4.2.1 Ex Vivo Studies

In this section, I review the cadaver studies I undertook with the pQCT.

4.2.1.1 Four (4) % Site Scan Resolution

I submersed ten right radial specimens from female cadavers (mean age = 79 ± 6 years) in saline (sodium chloride 0.9%) and scanned at the 4% site (4% of the radial length proximal to the distal endplate of the radius). Each specimen was scanned 4 times in total using 4 different resolutions: 200µm, 300µm, 400µm, 500 µm voxel size. I was not able to measure my specimens according to the manufacturer recommended arm length because I did not have intact forearm specimens; therefore, I measured from the most distal end of the medial side of the radius (corresponding to the groove for the ulna at the distal radio-ulnar joint) to the proximal end of the head of the radius. I set the reference line for data acquisition at the distal endplate of the radius. I analysed the data with Norland/Stratec XCT v. 5.50 software. I set analysis protocols at CALCBD Contour Mode 3, Peel Mode 2 (4% 130-400mg/cm^3) CORTBD Mode 3 (automatic). At the 4% site, regions of interest (ROI). I defined images with both the default rectangular ROI and automatic custom ROI. I compared Total Area (ToA (mm^2), Total Content (ToCNT mg) and Total Density (ToD mg/cm^3) among the 4 different resolutions.

4.2.1.2 Four (4) % Scan Failure Study

For the Scan Failure Study, I used the same cadaveric specimens used in the spatial resolution study above to record scan failures (defined as the program output reading "integration equal to zero" and yielding no database results). This occurred when the program was unable to define a cortical edge.

4.2.2 *In Vivo Studies*

In this section, I outline the study comparing two acquisition reference lines that I undertook in female volunteers.

4.2.2.2 Thirty % Reference Line Position

I assessed the midshaft radius in 6 participants with 2 different reference lines. For each specimen, I scanned a single 2.5 mm slice of the left forearm at the 30% site five times using the most distal medial end of the radio-carpal joint line and 5 times using the manufacturer recommended mid-position of the distal end of the radio-carpal joint line. I completed the five scans without repositioning between scans. I analysed data with Norland/Stratec XCT V. 5.50 software. Analysis protocols were –CALCBD: Contour Mode 3, Peel Mode 2, and CORTBD Mode 4 (30% 710 g/cm^3).

4.3 Statistical Analysis

I analysed data using SPSS (Windows Version 12.0) software. For the ex vivo voxel size/resolution studies I determined the difference between total density at different spatial resolutions with a repeated measures one-way analysis of variance (ANOVA). When significant differences were observed, I performed a Bonferroni post-hoc test and adjusted the significance level according to the number of comparisons. I calculated ex vivo scan failure rate as the number of scans (the XCT program) that read "Integration equal to zero" over the total number of scans acquired. I tested differences among the four different voxel sizes using a chi-square statistic. For the reference line studies, I calculated the root mean square coefficient of variance (C_{RMS}) for each individual within each condition of pQCT assessment (i.e., distal vs. mid reference line) and then I calculated the C_{RMS} for each pQCT parameter. I compared the C_{RMS} between the two conditions of assessment by one-way analysis of variance (ANOVA). I set theType I error at $P<0.05$ for all statistical tests unless otherwise noted.

4.4 Results

4.4.1 Ex Vivo Studies

4.4.1.1 Four % Site Scan Resolution

I found significant differences in total area, content and density at the 4% site using four different acquisition resolutions. (Figures 4-1, 4-2, and 4-3). I was only able to compare bone parameters using

seven specimens due to the high number of scan failures at lower resolutions. Overall, the better the resolution the larger the value of the parameter (Figures 4-4, 4-5, 4-6). I performed Bonferroni post-hoc testing using six possible comparisons and I increased the significance level to $p<0.008$. I noted significant differences for ToD for 200 µm-400 µm and 200 µm-500 µm (Table 4-1).

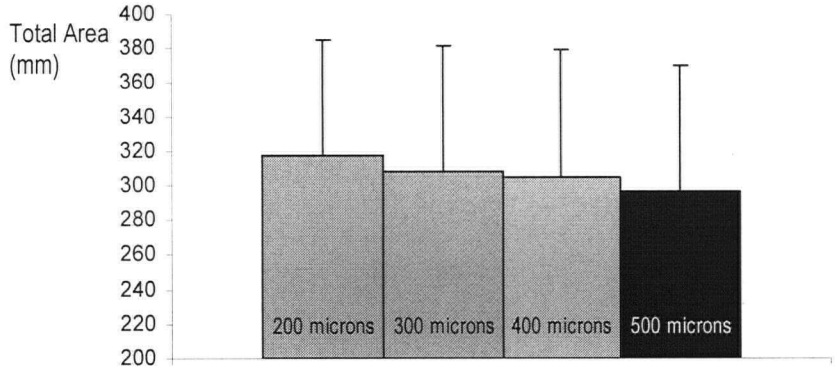


Figure 4-1. Total area (mm) of cadaveric radius 4% site scanned at 4 different resolutions.

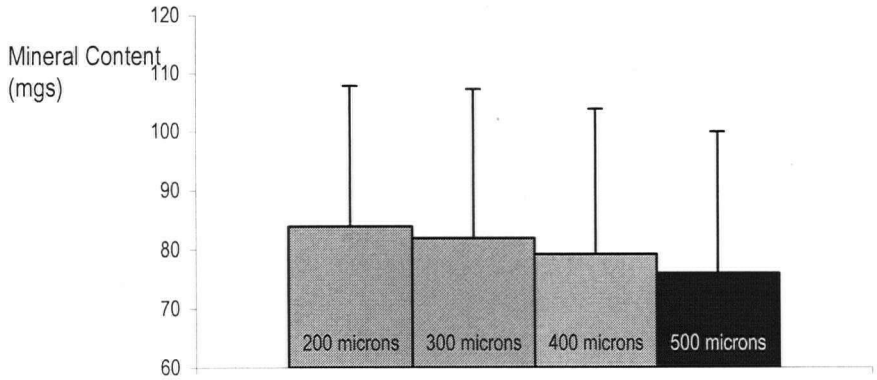


Figure 4-2. Total mineral content (mg) of radius cadaveric 4% site scanned at 4 different resolutions.

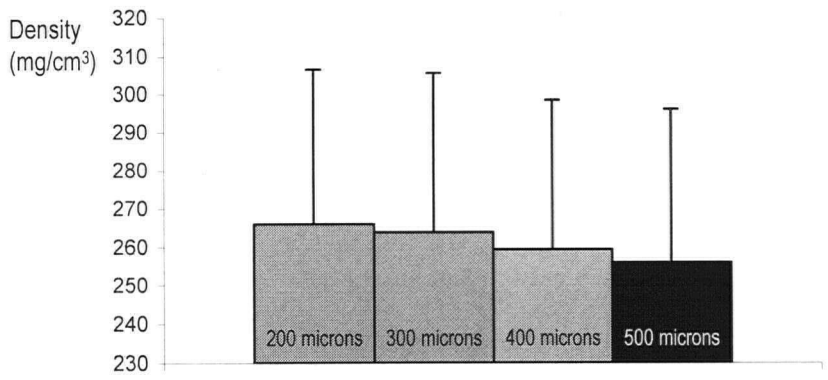


Figure 4-3. Total Density (mg/cm^3) of radius cadaveric 4% site scanned at 4 different resolutions.

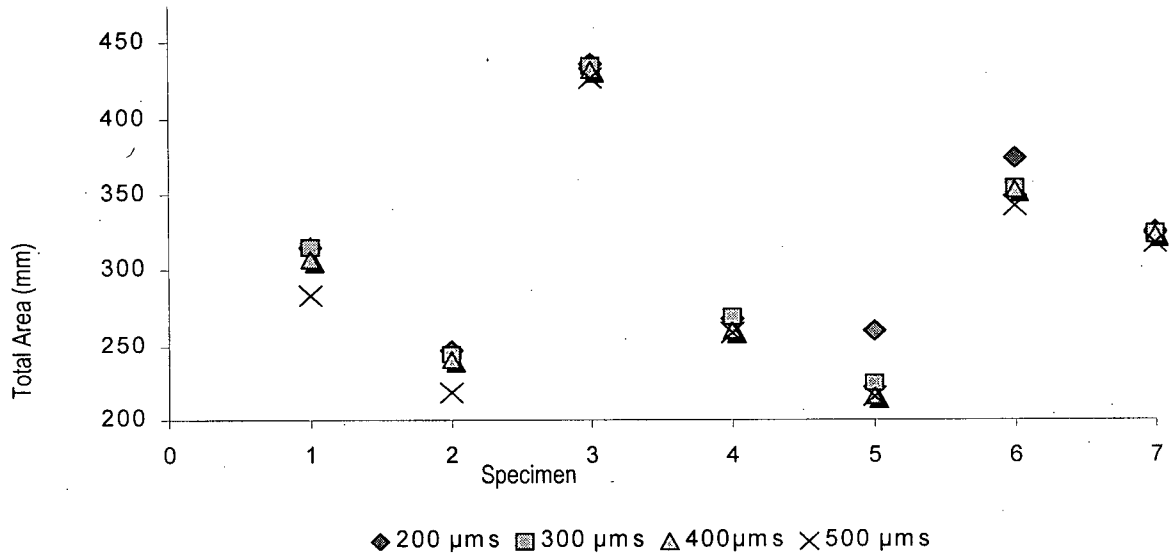


Figure 4-4. Total area (mm) of cadaveric radius 4% site scanned at 4 different resolutions. Raw data for each of the seven specimens.

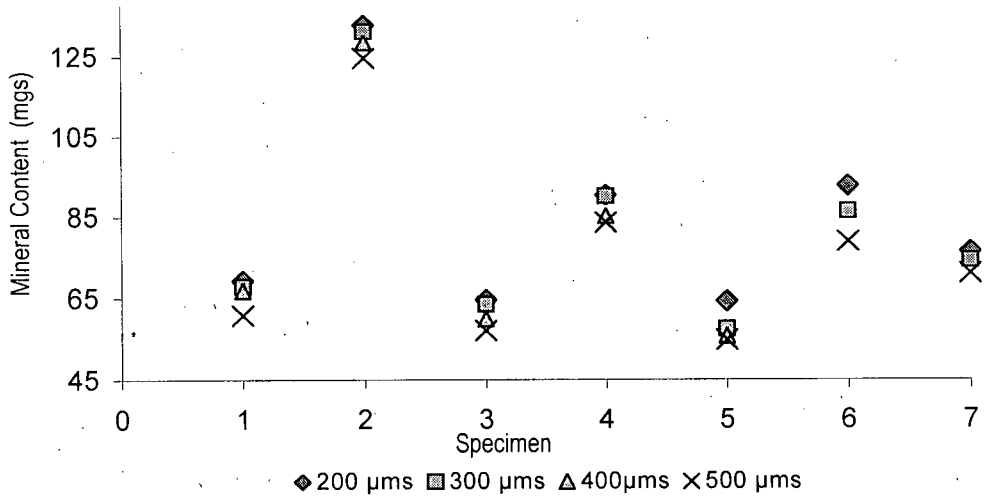


Figure 4-5. Total mineral content (mg) of radius cadaveric 4% site scanned at 4 different resolutions. Raw data for each of the seven specimens.

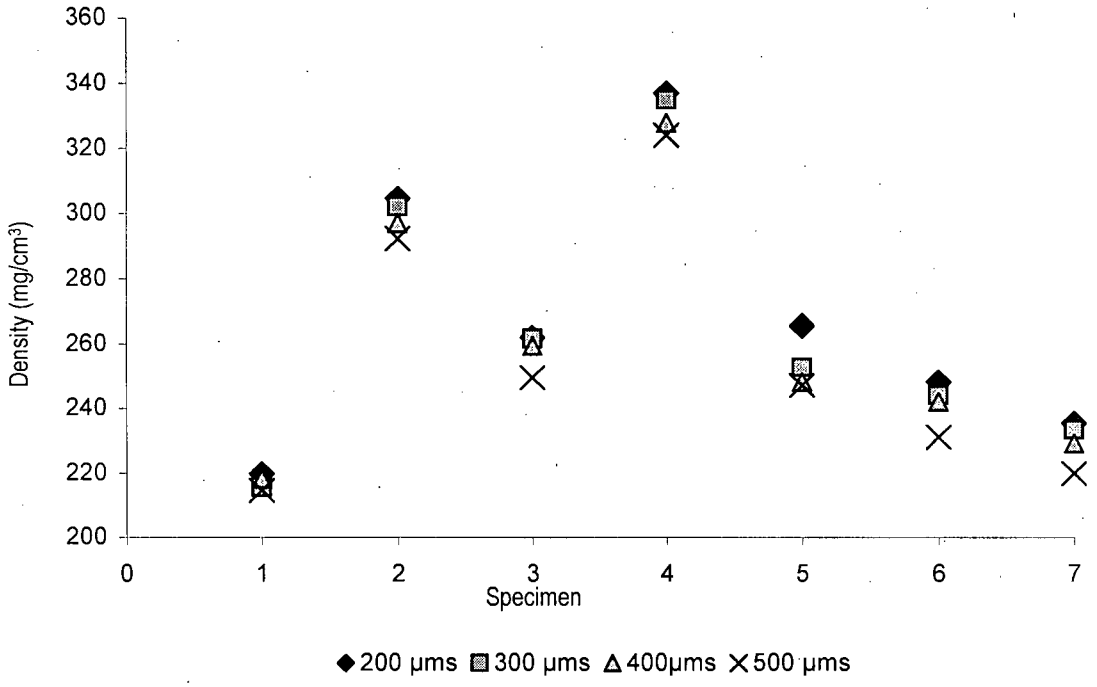


Figure 4-6. Total Density (mg/cm^3) of radius cadaveric 4% site scanned at 4 different resolutions. Raw data for each of the seven specimens.

Table 4-1. p-values for Bonferroni post-hoc analysis between resolutions using Total Density (ToD).

Resolution Comparisons ToD (mg/mm^3)	Post-hoc Test p-value
200 µm and 400 µm	0.006
200 µm and 500 µm	0.007

4.4.1.2 *Four % Scan Failure Study*

I found scan failure rate increased significantly with lower resolutions (Table 4-2).

Table 4-2. 4% Scan failures by resolution. There were 30 possible scans at each resolution (10 specimens with 3 slices each at the 4% site)

	200 µm	300 µm	400 µm	500 µm
4% Radius Site	**0**	**7**	**12**	**17**

*Chi-Square p≤ 0.001

4.4.2 In Vivo Studies

4.4.2.1 Reference Line Position Analysis

There was no significant difference in reference line position between the mid and end-point reference line protocols. Data are shown in Table 4-3.

Table 4-3. Mean % CV for radius: Endpoint vs. Midpoint reference line.

	pQCT Variable	% CV Midpoint	% CV Endpoint
30%	Total Bone Density	6.05	5.81
30%	Total Bone Area	10.79	10.81

4.5 Discussion

These novel data draw attention to methodological factors that may influence the results obtained when using pQCT, and to my knowledge, this is the first study to assess spatial resolution extensively. My study provides relevant data on which researchers can base decisions about pQCT scan acquisition and analysis. I addressed practical issues– outcome variability because of spatial resolution, scan failure rate and scout scan reference line.

Image quality is dependent on spatial resolution (voxel size) and the present study showed that increasing voxel size is associated with a systematic reduction of reported results. This is likely to be due to the partial volume effect (PVE)— the loss of accurate data when tissues of different densities are present in a single voxel. Other researchers have noted that pQCT can underestimate bone parameters (107,301) and I would speculate that the partial volume effect would cause this under-estimation in my data. Interestingly, the Stratec XCT manual (page 28), notes [due to the partial volume effect] "the larger the resolution element, the smaller the cortical area" (303). Using the Stratec XCT v. 5.50, the operator can select a voxel size ranging from 100 µm to 590 µm for scan acquisition. In clinical practice, 200µm resolution is generally not used because of the amount of radiation exposure and the longer scan time increasing the risk of movement artifacts. Instead, most studies report using a 500 µm voxel size. To my knowledge, Eser and colleagues (304) were the first to report results from pQCT obtained from individuals following a spinal cord injury, and they discuss the need to use a 300µm voxel size (rather than the 'standard' 500 µm) because of the "thin cortical shell" of the distal femur in this non-load bearing population. My data extend the results of primate studies (305) that reported lower total bone density in scans acquired using 400 µm compared with 300 µm voxels.

Although my present results do not provide evidence for using a higher resolution (as I did not test the accuracy of using different voxel sizes), I propose that accuracy studies are necessary to ascertain the optimum resolution without a significant increase in ionization to the participants/patients. I also recognise that image acquisition involves more than simply adjusting the size of the voxel— parameters such as the number of block projections and field of view are important but were not addressed in the present study.

I report scan analysis 'failure' across four resolutions. Few previous studies have drawn attention to this phenomenon. Occasionally, authors report that the 'pQCT software' was "unable to distinguish trabecular

and cortical bone at the 4% site" (132) or that there was a "need to develop improved edge detection algorithms for the multilayer pQCT device when measurements of thin cortices are made" (117). I report a significant failure rate dependent on spatial resolution, despite using different thresholds and analyses to address this problem. These analyses failed because the pQCT analysis software was unable to detect the outer contour of bone. I speculate that some of these failures may have been avoided if data had been acquired with better resolution (i.e., smaller voxel size), but these modifications would have resulted in longer scan times and increased likelihood of movement artifacts.

In addition to the technical aspects of pQCT acquisition and analysis I addressed, there are other methodological challenges for the pQCT researcher and technician. First, because the location of the 'anatomical reference line' defines the measurement region of interest, it should be a universal reproducible landmark. The 'pQCT manufacturers' protocol suggests the "middle" of the epiphyseal plate but I believe that the 'middle' is likely to rely on visual estimation. I used the distal medial edge of the radius as a more reproducible landmark. Although my reference comparison study did not yield significant differences, I have over four years of experience using the pQCT; novice operators may not achieve similar consistency. Regardless of the reference line chosen, it is essential for researchers to report which bony landmark is used.

4.5.1 Practical Implications and Recommendations

First, based on the findings related to scan failure rate and resolution-dependent outcome variability (given the significant differences obtained for total density), I recommend the need for accuracy studies to ascertain valid results for low bone mass. As results will vary depending on the acquisition and analysis parameters, I recommend that all studies report detailed parameters, to ensure valid comparisons to other research. In addition, only scans analyzed using identical protocols can be used to calculate sample means and any customised analyses must be excluded from these calculations. Secondly, based on my experience with higher scan failure rate with lower resolution, I recommend the need for accuracy studies to validate the XCT 2000 for area and density.

Inconsistent participant positioning and limb or body movement during scan acquisition are sources of measurement error (84). Takada and coworkers reported that participant positioning had a dramatic impact on pQCT precision (total bone density and area) at the 4% site of the radius (85). Accurate positioning is not always straightforward. For my study of persons with stroke, a specialised arm trough

was built so that the whole arm could rest during the data acquisition. This provided a standardized arm position and minimized movement. Current pQCT limb-stabilizing devices need to be improved to ensure more consistent positioning within and between participants. Furthermore, these devices should be modified to ensure optimal participant comfort as this might ultimately reduce movement artifacts.

4.6 Limitations

I discuss several limitations with this investigation. First, I did not have intact cadaver specimens (e.g. no surrounding soft tissue) and therefore there may be limitations because of the contrast perceived by the imaging. To correct this, I scanned the specimens in saline, which has a density value close to muscle. Secondly, precision and accuracy are necessary to provide reliable and valid results. In the present study, I did not evaluate the precision of pQCT at the 4 different spatial resolutions. Several previous authors showed that the short-term in vitro C_{RMS} for these measures was low (0.2%). However, Sievanen and coworkers noted higher C_{RMS} for the in vivo radius scans at the 4% site (7.6% for 4% trabecular area and 2.2% for trabecular density) using a low resolution (500 µm voxel) (84). The authors discussed positioning and arm movements as possible sources of error. Although I would have anticipated better C_{RMS} with smaller resolution, I recommend further research to clarify this question.

4.7 Summary and Future Directions

Peripheral QCT has potential to greatly advance bone health research but appropriate acquisition and analysis requires consideration of data reported here and elsewhere (111). I found voxel size influenced total area and density, and that scan 'failure' can affect cadavers with low bone mass. Certain technical adjustments can minimize the number of scan 'failures' but this phenomenon cannot be eliminated. As outcome parameters vary significantly by changing either acquisition or analysis modes, bodies such as the International Society for Clinical Densitometry (ISCD) should strive to develop universal standards as has been the case for the field of histomorphometry (118). In any case, universal reporting of acquisition and analysis parameters is essential. In summary, this study provided important technical information for the pQCT in the cases of low bone mass.

5 Improving the Accuracy of pQCT for Evaluating the Aged Human Radius[2]

In this section, I present the results of my accuracy study testing pQCT against histomorphometry and ashing. I also investigated the predictive capabilities of pQCT bone outcomes against failure load.

5.1 Introduction

Quantifying the determinants of bone strength is essential to understanding if or how bone will fail under load. Areal BMD as measured by DXA provides an estimate of bone strength and has many benefits (low level of radiation exposure; accurate and precise; accessible, capacity to measure axial and appendicular skeleton). Although DXA provides a reasonable population-based prediction of fracture risk, considerable scope for improved capacity to predict which bones will fracture remains (306). Importantly, DXA provides only a two-dimensional view of bone and is therefore unable to evaluate true density or describe bone geometric properties. Although previous studies have shown high correlations between DXA areal BMD and failure load (133,307), this information is not sensitive enough to ascertain which bone parameter (or its relative contribution) is responsible for failure.

Predicting failure in the appendicular skeleton requires knowledge of material and geometric properties in both the trabecular and cortical compartments of a long bone. There is, however, not one valid imaging technology that evaluates in vivo, bone's material properties (mineral integrity, micro cracking and porosity) and structural properties. Therefore, characterizing the relative contributions of different bone compartments (i.e., trabecular, cortical) to bone strength has been limited by available technology. Peripheral QCT can assess bone structure and estimate bone strength in the peripheral skeleton. It is a relatively safe technique that differentiates cortical from trabecular bone and assesses bone geometry and volumetric density. Previous studies investigated the capacity of pQCT outcomes to predict failure load (112,130,134,135,137,308-311). To my knowledge the accuracy of these pQCT parameters was not assessed first. Further, few pQCT studies have examined whether the osteoporotic distal radius in older women can be accurately represented (85,105,109-111,125). In a compromised osteoporotic skeleton, when cortices are thin, low resolution scan acquisition may not permit the technician to detect the outer bone edge, which may, in turn, result in an inaccurate analysis (107).

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[2] A version of this chapter has been submitted as a manuscript. MC Ashe, KM Khan, P Guy, D Liu, HA McKay. Improving the Accuracy of pQCT for Evaluating the Aged Human Radius. *Osteoporosis International* submitted.

Peripheral QCT image acquisition is based on a number of factors; number of blocks, field of view, scan speed and voxel size (resolution). Binkley and Specker have previously evaluated the precision and accuracy of these parameters using a fabricated lucite cylinder phantom (106). To my knowledge, however, the impact of scan resolution on scan accuracy has not been investigated in older human osteoporotic bones. A thin cortical shell may lead to inaccurate CT scan outcomes (107) due, in part, to the size of the structure being measured. Thus, it is important to ascertain the appropriate resolution for the dimension of the bone compartment of interest. The voxel or volumetric element is the three dimensional unit that encompasses the two-dimensional pixel (image element) and slice thickness to determine scan resolution. For example, a typical trabecula has an average thickness of 100 μm. Therefore, a voxel size of 200 μm provides insufficient detail to highlight individual trabeculae. More importantly, there will be more than one type of tissue in a voxel (especially at the bone and soft-tissue boundary of the periosteal and endosteal surfaces) leading to the partial volume effect (PVE) (312). Augat and coworkers reported a 40% underestimation of cortical bone density at the distal radius with a 1 mm cortical shell (105).

Therefore, the purpose of this 3-component study was to: (1) evaluate the ability of the Norland/Stratec XCT 2000 pQCT to accurately characterize low density bone as compared with the criterion standards of ashing and histomorphometry, (2) determine failure load at the distal radius in axial compression and, (3) identify the most robust, biologically appropriate combination of pQCT bone outcomes to predict failure load. Recently, Veitch and co-workers (111) tested the accuracy of different software analyses using 4 young tibial cadaveric specimens and ashing. My study extends these findings by evaluating a clinically relevant "at risk" population by measuring more specimens, testing against two criterion standards and by acquiring the data at multiple resolutions for comparison.

5.2 Methods

I obtained ten pairs (n=20) of radial specimens from female cadavers from Vancouver General Hospital and Health Science Donation Service and scanned them with the Norland/Stratec pQCT XCT 2000. All specimens were fresh frozen at -20^{0}C and thawed initially for scanning (122). After scanning with pQCT and DXA, I used the 10 Left specimens for histomorphometry and biomechanical testing. I used the 10 Right specimens for the ashing experiments. All studies were approved by the University of British Columbia Clinical Research Ethics Board.

5.2.1 Peripheral QCT Data Acquisition and Analysis

5.2.1.1 Scan Acquisition

I cleaned each specimen (n=20) of all soft tissue and measured radial length from the medial border of the distal radius (medial border of lunate fossa) to the proximal end of the head of the radius. I radiographed all specimens using standard techniques and examined the radiographs for previous injuries or pathologies.

For pQCT measurement, I attached each specimen securely to a rigid plastic platform with a plastic tie (Figure 5-1A) and submersed this structure in normal saline (sodium chloride 0.9%) within a sealed plastic cylinder (Figure 5-1B). The saline provided a contrast medium with a density similar to soft tissue. I then placed the cylinder that housed the specimen inside a larger tube secured within the Stratec XCT 2000 gantry. The specimen cylinder was not moved until all scans were completed. I controlled for bone position by measuring the angle of the bone within the scanning cylinder. The specimens were positioned to replicate the standard pQCT position for the radius (radial pronation).

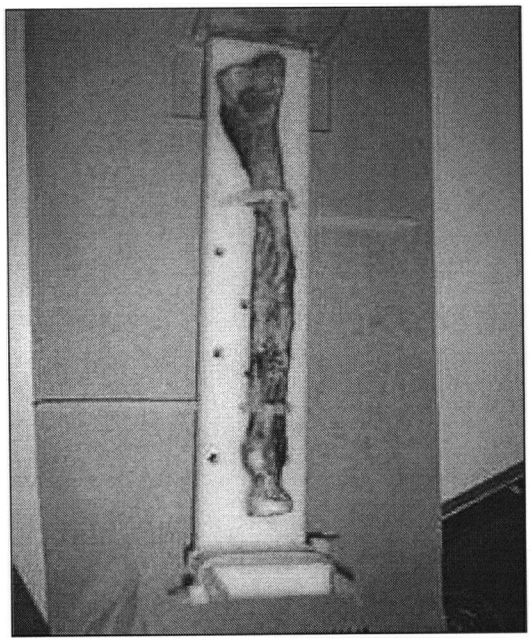
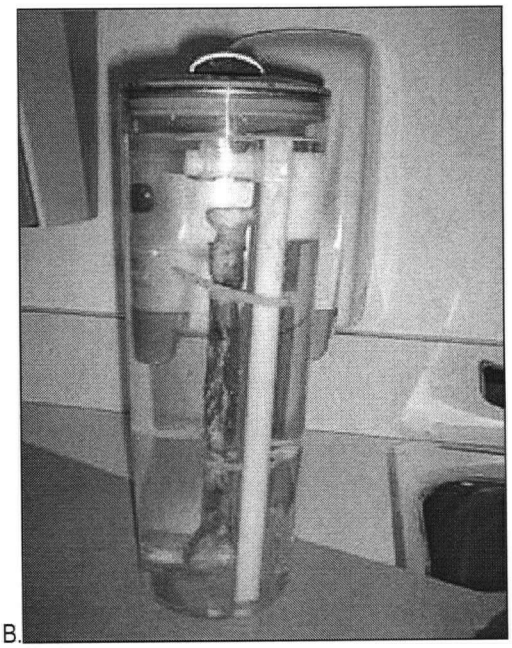
A.  B. 

Figure 5-1. Positioning of cadaveric specimen for pQCT scanning. A) The specimen was secured with plastic ties and B) submersed in normal saline in a plastic housing.

I first acquired 3 contiguous 2.5 mm slices at the 4, 6, 8, 10, and 30% sites (Figure 5-1) using a voxel size of 200 µm. I then repeated that protocol using voxel sizes of 300 µm, 400 µm and 500 µm. To ensure a quality scan the scan speed was 10, 15, 20 and 25 mm/s for the 200, 300, 400 and 500 µm voxel sizes, respectively. Only one projection block was used. At the radial 4% site, scan times (including scout scan) varied from 15 minutes at 200 µm voxel to 7 minutes for the 500 µm voxel size. Each specimen was marked at the 30% site with an insoluble marker. During scanning, I ensured that the red light from the pQCT scanner was over the 30% site marked. I returned specimens to the freezer immediately after scan acquisition.

5.2.1.2. Scan Image Analysis

I used the Norland/Stratec XCT 550 software for scan analyses. I determined the image thresholding using the technique known as half-maximum height (HMH) threshold (108). For each pQCT scan, I used the XCT-2000 "Profile" function and drew two perpendicular lines (Figure 5-2). The bone density thresholds for the two lines were averaged to obtain the mean HMH. I calculated the HMH for the periosteal and endosteal surfaces.

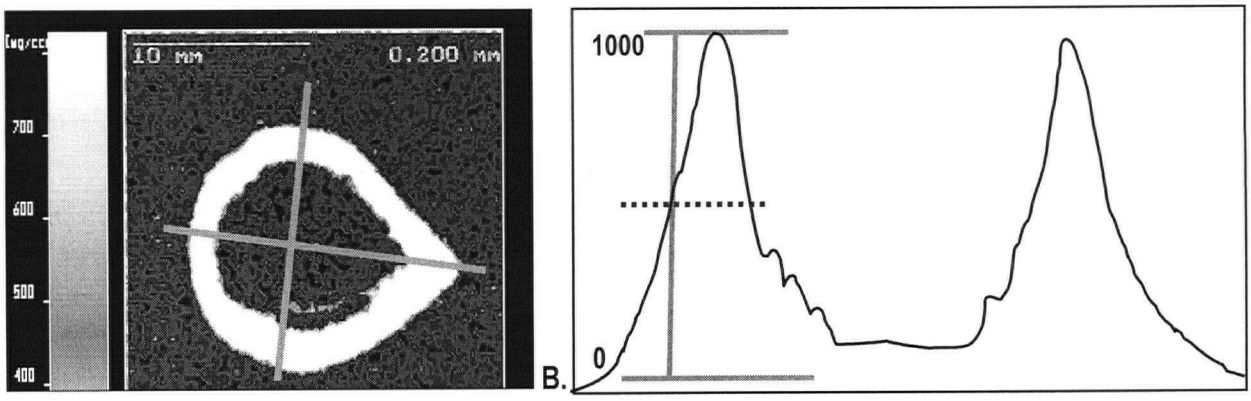


Figure 5-2. A. Scan of the 30% radius taken with a 200 µm resolution and the two lines that I used to calculate the half maximum height (HMH) threshold for each specimen at the subregions of interest. **Figure B.** represents a typical profile for midshaft cortical bone. This specimen was submersed in saline which has a Hounsfield Unit (HU) of zero. The HMH threshold is determined by determining the lowest and the highest value within the ROI cross-section and dividing to obtain half the value. This is one way to determine thresholds for scan analysis. For in vivo scans, the HMH threshold is more complex due to the muscle soft-tissue boundary at the periosteal surface, and depending on the age and health of the participant, there could be a gradual decrease in density values from the periosteal to the endosteal surface.

At all sites I used XCT v.550 software and CALCB Contour (edge-detection) Mode 3 and Peel Mode 2 and CORTBD Mode 4 (separate trabecular from cortical bone). I report the thresholds at each site as 4% (130-400 mg/mm^3); 6% (200-400 mg/mm^3); 8% (200-400 mg/mm^3 and 10% (300-600 mg/mm^3). For edge detection at the 30% site I analysed all scans with multiple thresholds (300, 400, 540, 600 and 710 mg/cm^3). The 600 mg/cm^3 threshold was based on the recommended HMH threshold (108). Table 5.1 outlines the thresholds used to analyse the scans taken at the 30% site. I also used the Concentric Peel function to observe the distribution of bone density from the centre of the specimen outwards to the cortical edge. The XCT Concentric Peel function is the average density of tissue of concentrically peeled rings commencing centrally and progressing to the periosteal surface, to provide an overview of the total bone area.

At the 4%, 6% and 8% sites I measured total density (ToD, mg/mm^3), total content (ToCnt mg), total bone area (ToA, mm^2), trabecular content (TrabCNT mg), trabecular density (TrabD mg/mm^3) and trabecular area (TrabA, mm^2). At the 10% and 30% sites I measured ToD, ToA, ToCNT, cortical density (CoD, mg/mm^3), cortical bone area (CoA, mm^2), cortical content (CoCNT mg), cortical thickness (CTh, mm) and Stress-Strain Index (SSI mm^3). I defined total/cortical density/area as the density/area of all material contained within the ROI at or above the set threshold.

Table 5-1. XCT 550 scan image analysis parameters at different bone sites on the radius.

Site	Edge Detection Threshold	Trabecular- Cort/sub-cortical Separation Threshold
30%	710	300, 540, 600, 710
30%	540	300, 540, 600, 710
30%	400	300, 540, 600, 710
30%	300	300, 540, 600, 710

5.2.2 DXA Data Acquisition and Analysis

While the specimens were still contained within the plastic housing, I scanned them with dual energy X-ray absorptiometry (DXA) Hologic 4500 (Waltham, MA). I positioned all specimens in a clinically relevant pronated position. I analysed all scans using the standard forearm protocol (Hologic User's Guide(313)). I report results as aBMD (g/cm^2) and bone mineral content (BMC;g) at the Ultradistal and the Distal Third site of the radius.

5.2.3 Ashing

I used ashing at the 30% site of the right radius in 10 specimens as the criterion standard to determine bone total content and density. Prior to scanning, I marked the 30% site and removed the 7.5 mm slice after scanning (corresponding to three 2.5 mm contiguous slices). Each 7.5 mm section was then soaked in water for approximately 10 hours. All soft tissue and visible marrow was removed. Each specimen was air dried and weighed. Each reading was recorded to the nearest 0.0001g on a Mettler AE 166 (Delta Range,Toledo Ltd., The Netherlands) analytical balance. Each specimen was weighed and placed onto a dessicator to remove moisture. New porcelain crucibles and lids (that were used to contain the specimens for ashing) were purchased and placed in a Thermolyne (Sybron Corporation, USA) muffle furnace for 24 hours at 650^{0}C in preparation for ashing. This was done to remove any residual organic material. Each specimen was oven dried at 100^{0}C for 24 hours until it maintained a stable weight. Stable weight is defined as no change in mass at two different time points. All specimens were then placed within individual pre-weighed crucibles. Specimens were placed in the muffle oven for 22 hours at 650^{0}C. Following cooling in the muffle oven (4 hours), specimens were then placed on the dessicators with lids intact. Crucibles and ashed bone were weighed again. Ash weight was determined from (ash weight and crucible) minus (crucible weight). Ashing outcomes were compared with (1) pQCT-derived total content

(ToCNT, mg) for the three slices at the 30% site.

5.2.4 Histomorphometry

I utilized histomorphometry at the 30% site of the left radius in 10 specimens as the criterion standard to determine bone structural outcomes. I marked the 30% site prior to scanning. Following the scan, each 2.5 mm section was excised and soaked in water for approximately 10 hours. All soft tissue and visible marrow was removed. Each specimen was then placed in a plastic container and coated with Epo-thin epoxy resin (Buehler, Lake Bluff, IL) . All specimens were placed in a vacuum for 1 hour to remove any visible air bubbles. Following removal from the vacuum, all specimens were left to air dry overnight. Once hardened, each specimen was cut with an Exakt diamond band saw (Exakt, Apparatebau, Norderstedt, Germany) and mounted on a plastic slide. The slice was reduced to 150 microns using 800-grain paper and finished with 1200-grain paper using an Exakt grinder (Exakt, Apparatebau, Norderstedt, Germany). I photographed 20-25 images of each specimen using a Nikon Optishot microscope camera (Nikon, Tokyo, Japan) at 32x magnification. All images were reconstructed using Adobe Photoshop v. 8 (Adobe, Seattle WA), and analysed for ToA, CoA and CTh using Image Pro Plus software (version 5.1 San Diego, CA). ToA was obtained by outlining the entire histomorphometric radial specimen (Figure 5-3). Cortical area was obtained by using the Image Pro automatic function to outline marrow space and any observable holes/porosity within the specimen > 20 microns in width were included. That is, cortical area was defined as total area minus marrow spaces and porosity (Figure 5-3). For cortical thickness estimation, 8 lines of cortical width were drawn on the histomorphometry slice and the thickness in mm was recorded (Figure 5-4). All areal and length determinations were measured three times and the mean was used for analysis. The percent Coefficient of Variation (%CV) for cortical area was 0.02% and for cortical thickness was 2.4%.

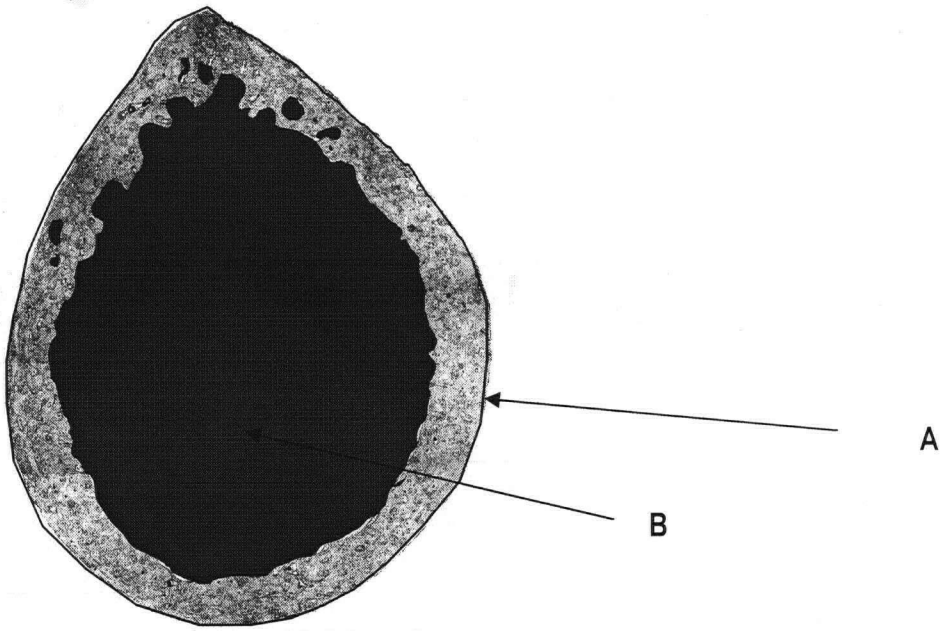


Figure 5-3. Histomorphometric image at 32 times magnification, taken from the 30% of the radius outlining the calculation of total and cortical areas. Total area was defined as the contents contained within the outer black line labelled A. The shaded blue areas labelled B. represents marrow and porosity whose total was subtracted from the ToA to obtain cortical area.

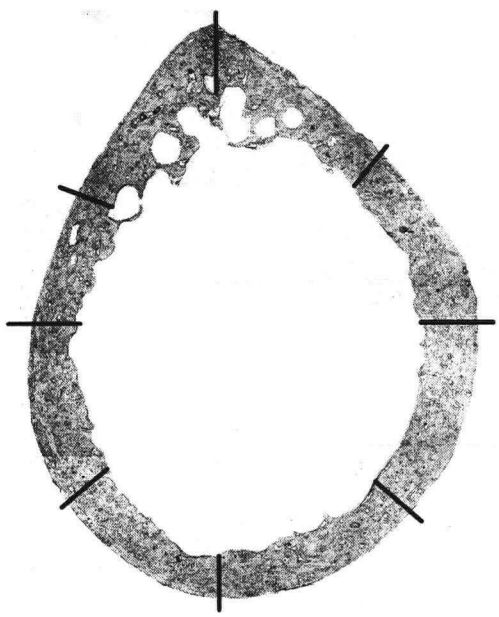


Figure 5-4. Histomorphometric image at 32 times magnification, taken from the 30% of the radius outlining the eight places where the cortical thickness was measured using Image Pro. The eight sites were measured three times and the mean width at each site was calculated. Cortical width was calculated as the mean of all eight sites.

5.2.5 *Biomechanical Testing*

I cut 10 left radial cadaveric specimens with an Exakt diamond band saw (Exakt, Apparatebau, Norderstedt,Germany) at approximately 30% from the distal end of the radius. The specimens had been previously scanned at multiple resolutions at the 30% site. I wrapped all specimens in saline soaked gauze and returned them to the freezer. I prepared each specimen by embedding the cut midshaft in dental cement. The distal end of the radius was embedded ~ 1 cm in polymethylmethacrylate (PMMA) and the specimen was mounted at 10^0 as described by Muller and coworkers (132). Each specimen was loaded at 75 mm/sec using an Instron (Instron Corporation, Canton, MA) materials testing machine to reproduce a clinically relevant distal radius fracture pattern. Each of the 10 specimens were loaded to failure and I recorded displacement and ultimate failure load.

5.3 Statistical Analysis

I report descriptive results for the donors as mean +/- standard deviations (SD) (Table 5-2).

5.3.1 *Criterion standard Assessment: Ashing and Histomorphometry.*

The accuracy of pQCT derived ToCNT and ToA at the 30% site was determined by comparing the results from four different resolutions to the ashing or histomorphometry criterion standard. For ToA, CoA and CTh, I measured each specimen three times and reported the mean. For all resolutions, I reported 1) mean absolute difference and 2) mean % difference between pQCT derived ToA and histomorphometry [(histomorphometry-pQCT ToA)/histomorphometry*100], and between pQCT derived ToCnt and ashing [(ashing-pQCT ToCnt)/ashing*100]. I used simple linear regression to determine the association between criterion standard values and pQCT and DXA derived outcomes. Finally, I determined the percent Standard Error of the Estimate (SEE) between variables and the criterion standard (% SEE was calculated as the distribution of residuals mean of the dependent variable). The SEE is the distribution of residuals around the regression line and is the average error of prediction (195).

5.3.2 *Biomechanical Testing*

The association between failure load [Newtons (N)] ToD, CoD, ToA, CoA and polar Stress-Strain Index

(SSI) from pQCT at multiple sites was determined using all resolutions. I used simple linear regression to establish the associations of selected variables (ToCnt, ToD, ToA, TrabCnt, TrabD, TrabA, CCnt, CoD, CoA, CTh) at the 4, 6, 8, 10 and 30% sites and SSI-Polar at the 10% and 30% sites with failure load. I used linear regression (enter) to identify the primary predictors of bone strength (failure load in Newtons was the dependent variable) using two variables (mineral density/content and structural parameter). Type I error was set at $p<0.05$ for all statistical tests. I used SPSS version 12 (SPSS, Chicago, IL).

5.4 Results

The data were normally distributed and adhered to all assumptions for parametric statistics. I describe the specimens in Table 5-2. Specimen donors were all women aged 73 years and older. On average, donors were at the high end of normal for the body mass index (BMI). On average, the radii in this investigation were comparable to previous reports of mean radial length of 22.0 cm for women (138). In Figure 5-5, I illustrate the difference in pQCT scan images between acquisition resolutions. Figure 5-5B taken at 500 µm has blurring noticeable at both periosteal and endosteal edges.

Table 5-2. Description of 10 radial specimens from female cadavers.

	Mean ± sd	Minimum	Maximum
Age (years)	77.8 ± 5.8	73.0	88.0
Height (cm)	143.1 ± 54.3	147.0	170.0
Weight (kg)	64.1 ± 14.0	48.0	93.0
BMI	24.4 ± 4.0	20.3	33.0
Length of Radius (cm)	21.5 ± 1.5	19	23.2

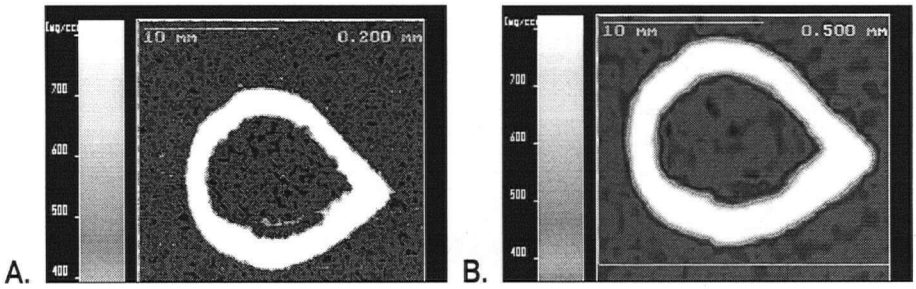


Figure 5-5. A and B. Images from pQCT scans at the 30% site of the distal radius taken from the same specimen but acquired at two different voxel sizes (200 µm -Figure A and 500 µm- Figure B). Note the blurring of the edges in Figure B.

5.4.1 Criterion Standard Assessment: Ashing and Histomorphometry

My specimens had very thin cortices at the 30% site (midshaft); mean thickness 1.93 ± 0.5 mm (range from 1.15 to 2.66 mm). I provide a visual display of the densities contained within the ROI using a Concentric Peel application. Figures 5-6 and 5-7 represent how densities varied across the specimen cross-section.

Overall, I found that a lower resolution improved the accuracy of ToA, CoA and ToD. For ToA and ToD, the lower the analysis threshold, the smaller the error compared with the criterion standard. I found that pQCT underestimated ToA and ToD. Figure 5-8 represents the results of ashing as the criterion standard against pQCT derived ToCNT using two protocols. This graph highlights the consistent underestimation of pQCT derived parameters across specimens.

In Table 5-3, I present differences in ToA between histomorphometry criterion standard and the pQCT derived bone parameters at the 30% site at four different density thresholds using a 300 µm voxel resolution. I report differences between histomorphometry/ashing and the pQCT derived bone parameters at the 30% site using four different acquisition resolutions and two different analysis thresholds in Table 5-4. I provide a graph of ash weight and BMC using two different resolutions and two different analysis thresholds (Figure 5-8).

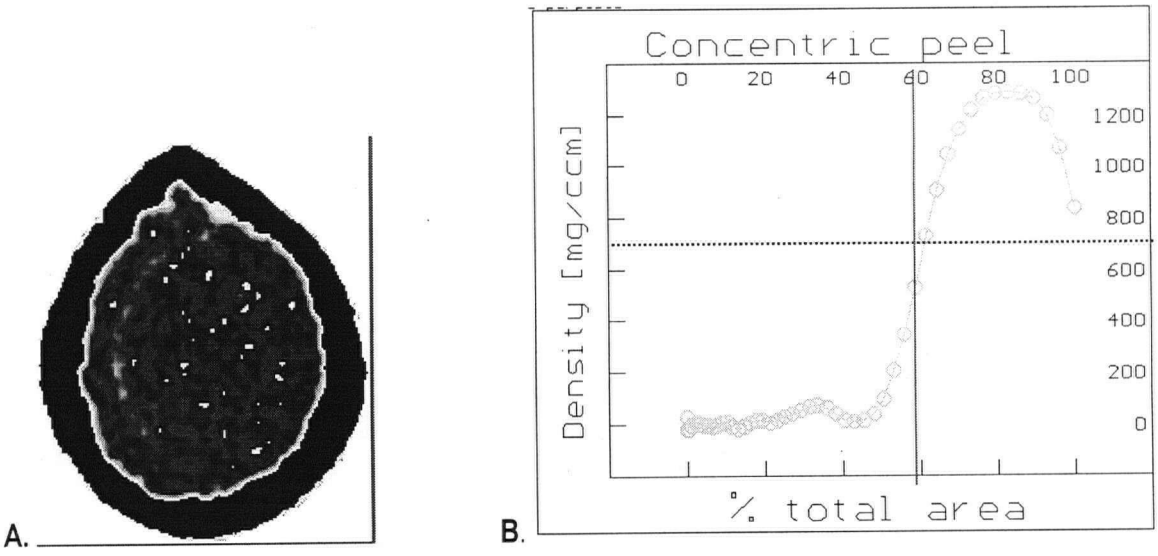


Figure 5-6. A pQCT image taken from the 30% site of a female cadaver. Mean cortical thickness was 1.15 mm. Figure A shows the pQCT scan; the black region is the cortical shell. Figure B illustrates the distribution of average tissue density determined from concentric rings starting from the centre of the region of interest specimen. In this investigation, I defined cortical bone as tissue densities > 700 mg/cm^3. Only 40% of this specimen had tissue densities greater than 700 mg/cm^3.

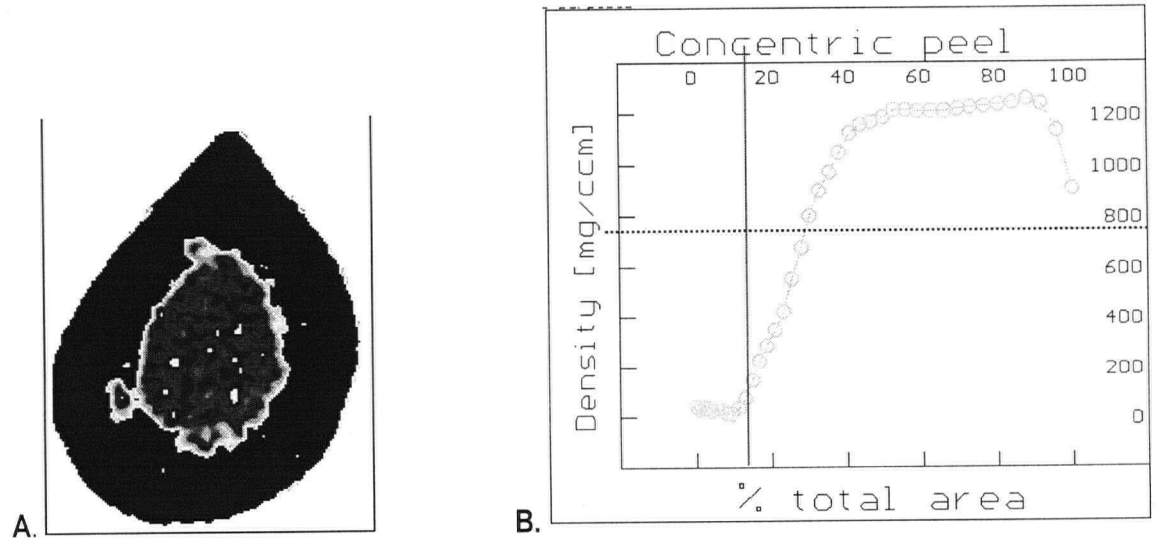


Figure 5-7. A pQCT image taken from the 30% site of a female cadaver. This bone had a mean cortical thickness of 2.66 mm. Figure A is the pQCT scan; the black region is the cortical shell. Figure B is the distribution of average tissue density determined from concentric rings starting from the centre of the region of interest specimen. In this investigation, I defined cortical bone as tissue densities > 700 mg/cm^3. In contrast to Figure 5-6, the average densities from this specimen are higher. Almost 75% of the specimen had a tissue density greater than 700 mg/cm^3.

Table 5-3. Differences between histomorphometry criterion standard at pQCT derived outcome parameters at the 30% across four different density thresholds. I report percent and absolute differences.

Edge Detection Density Thresholds	Total Area	Mean Absolute Difference from Criterion	Mean Percent Difference from Criterion
300 mg/cm3	91.3 ± 17.1	5.2 ± 2.2	5.3
400 mg/cm3	89.3 ± 17.0	7.2 ± 2.1	7.5
540 mg/cm3	86.9 ± 17.0	9.6 ± 2.2	10.1
710 mg/cm3	82.5 ± 16.2	13.9 ± 2.6	14.6

Table 5-4. Differences between ashing and histomorphometry criterion standards for pQCT-derived outcome parameters at the 30% site, presented as mean absolute and percent differences ± standard deviations. Simple linear regression and % Standard Error of the Estimate (SEE) are also provided.

	Analysis Threshold	Bone Parameter	Mean Absolute Difference from Criterion	Mean Percent Difference from Criterion	R^2	% Standard Error of the Estimate
HISTOMORPHOMETRY Total Area Criterion Content	300 mg/cm³	ToA 200 µm	3.1 ± 1.9 mm	3.2	0.99	1.8
		ToA 300 µm	5.2 ± 2.2	5.3	0.98	2.2
		ToA 400 µm	7.6 ± 2.1	7.9	0.99	1.8
		ToA 500 µm	9.5 ± 2.4	9.9	0.98	2.2
	710 mg/cm³	ToA 200 µm	9.4 ± 2.4	9.8	0.99	1.9
		ToA 300 µm	13.9 ± 2.6	14.6	0.99	2.0
		ToA 400 µm	19.2 ± 3.2	25.3	0.98	2.4
		ToA 500 µm	24.1 ± 4.5	33.7	0.97	2.9
ASHING Mineral Content Criterion Standard	300 mg/cm³	ToCNT 200 µm	35.1 ± 29.2 mg	5.8	0.96	5.3
		ToCNT 300 µm	50.5 ± 29.3	8.7	0.96	5.3
		ToCNT 400 µm	63.5 ± 29.3	11.1	0.95	5.3
		ToCNT 500 µm	82.8 ± 29.7	14.7	0.95	5.3
	710 mg/cm³	ToCNT 200 µm	102.2 ± 34.4	18.3	0.95	5.7
		ToCNT 300 µm	143.7 ± 33.7	25.9	0.93	7.0
		ToCNT 400 µm	189.2 ± 31.4	34.1	0.96	5.0
		ToCNT 500 µm	245.4 ± 46.3	44.6	0.87	8.6

(ToA=total area; ToCNT = total mineral content) Mean % difference=[(criterion standard-pQCT output)/ criterion standard *100]

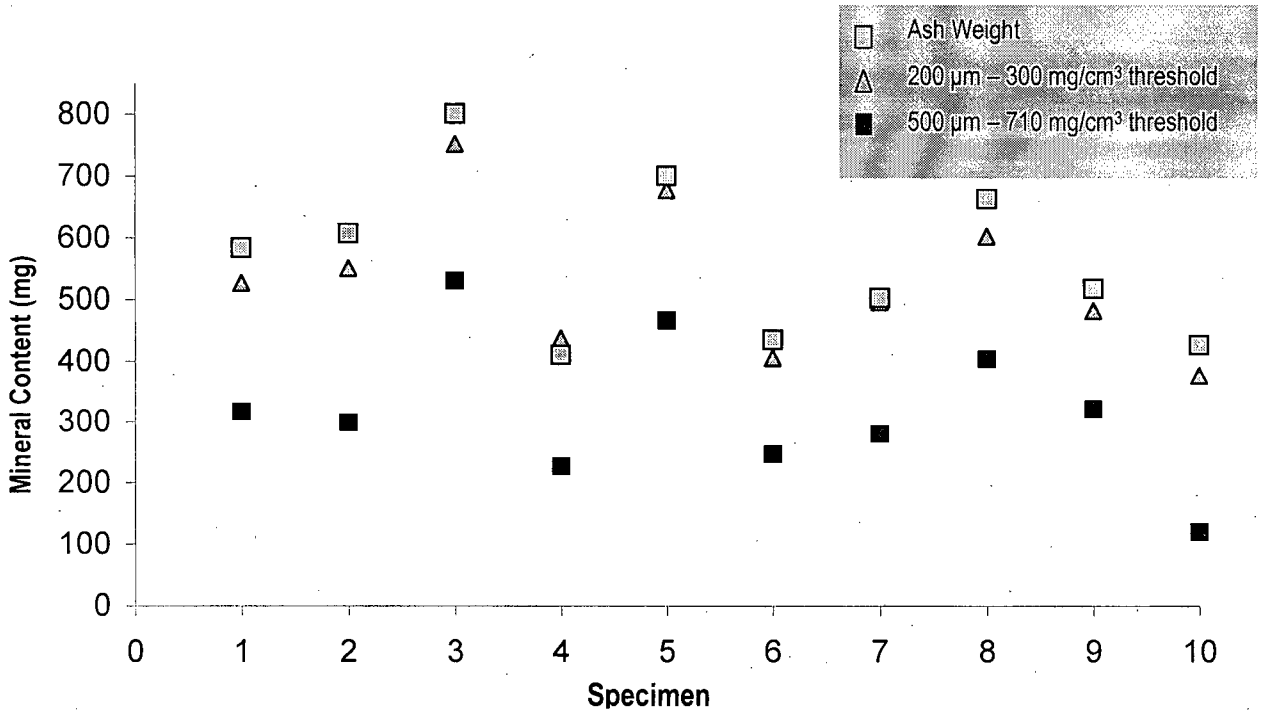
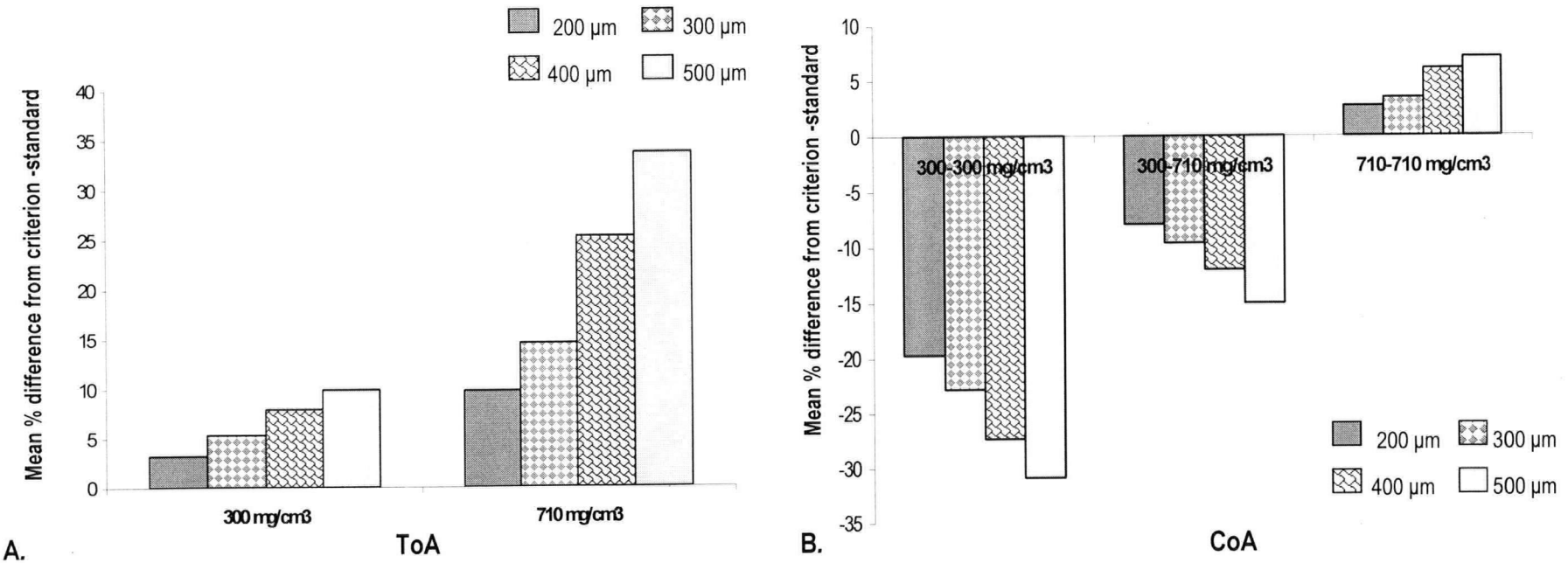


Figure 5-8. Graph of ash weight versus pQCT-derived bone mineral content (BMC) at two different acquisition resolutions and different analysis thresholds.

For CoA, I observed that the higher the resolution, the closer to the criterion-standard; however, I also observed that the higher the threshold the more accurate the results. Overall, pQCT overestimated CoA if the outer threshold was low; however if the threshold was high at both surfaces, then CoA was underestimated only slightly. Figure 5-9 represents the differences in ToA observed using two different cortical edge thresholds (710, 300 mg/cm^3) and CoA using three different settings (300-300 mg/cm^3; 300-710 mg/cm^3 and 710-710 mg/cm^3) across four different resolutions (200, 300, 400, 500 µm).



Mean % difference=[(criterion standard-pQCT output)/ criterion standard *100]

Figure 5-9. Figure A represents the mean percent difference from histomorphometry derived ToA and pQCT derived ToA. This graph represents the difference across four resolutions and two different thresholds. Figure B represents the mean percent difference between histomorphometry derived CoA and pQCT derived CoA. Note the underestimation of ToA with a higher threshold and CoA with a high edge-detection threshold and separation threshold; but overestimation of CoA with lower edge-detection threshold.

5.4.2 Biomechanical Testing

The mean failure load in compression was 2852.5 ± 1605.4 Newtons. After normalization to body weight, the mean force generated to break the radius was 5.0 ± 2.5 times the donor's body weight.

5.4.2.1 *Strength Prediction: Geometric Parameters*

Overall, ToCNT and CoCNT were strong predictors of failure load, explaining up to 87% of the variance. In Table 5-5, I provide r^2 values from simple linear regression for DXA and pQCT outcome variables (a 300 µm resolution and 300 mg/cm^3 edge detection analysis threshold) against failure load (Newtons). I found strong associations with ToCNT at all sites and CoCNT at the 30% site of the distal radius (r^2 = 0.753-0.871 $p<0.001$; 0.672 $p<0.01$). I found the pQCT generated SSI-Polar had significant associations with failure load (r^2 = 0.690,0.716; $p<0.01$) depending on the site (10% vs. 30%). There was a significant association for DXA (distal third) aBMD (0.749; $p<0.001$). pQCT vBMD at the 4 and 30% also yielded significant associations with failure load (r^2 = 0.637,0.616; $p<0.01$). There were no significant associations between DXA parameters (area, BMC or aBMD) at the ultradistal radius and failure load. When geometric parameters were entered into the equation (CTh, CoA, ToA) there was only a 1% or less increase in variance (r^2 = 0.872-0.883 $p<0.001$).

Table 5-5. Relation between DXA outcomes (BMC, aBMD, vBMD); pQCT outcomes and failure load at 5 radial sites (4,6,8,10,30%). (N=10) At the 30% site a 300 µm resolution was used; ToA was analysed at 300 mg/cm^3 and CoA was analysed using 710-710 mg/cm^3 thresholds.

Bone Mineral Content	r^2 Value	SSI-Polar	r^2 Value	Bone Mineral Density	r^2 Value	Combined Parameters-	r^2 Value
CoCNT 30%	0.871***	**SSI-P 10%**	0.690**	**DXA-33%-aBMD**	0.749***	**ToCNT 4% + Cortical Thickness 30%**	0.883***
ToCNT 4%	0.811***	**SSI-P 30%**	0.716**	**Total vBMD 4%**	0.637**	**CoCNT 30% + CoA 30%**	0.883***
ToCNT 6%	0.762***			**Total vBMD 30%**	0.616**	**CoCNT 30% + ToA 4%**	0.872***
ToCNT 10%	0.759***			**CoD 30%**	0.444*		
ToCNT 30%	0.739***			**Total vBMD 6%**	0.431*		
ToCNT 8%	0.754***						
CoCNT 10%	0.672**						

ToCnt = total content; ToD= total density; CoCNT= cortical content; CoA= cortical area. DXA= dual energy X-ray absorptiometry; vBMD= volumetric bone mineral density. SSI-P= Stress-Strain Index-polar *** Correlation is significant at the 0.001 level (2-tailed). ** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed)

5.5 Discussion

I highlight three key findings from this novel investigation: 1) lower resolution of pQCT scans can underestimate total bone area and total bone mineral content but over or underestimate cortical area at the 30% site of the radius when the thresholds are adjusted; 2) bone mineral content at multiple sites of the distal radius plays a significant role in predicting failure load of the distal radius, and 3) bone content and structural parameters (from pQCT) have an enhanced ability over DXA to predict failure at the distal radius.

5.5.1 Accuracy of pQCT: Low Resolution Scans Affect Total Area, Content and Cortical Area.

The present study extends previous work by showing that low resolution scans (400, 500 μm) underestimated bone area and mineral content at the 30% site of the radius. That is, the lower the resolution the smaller the area and mineral content (305) as a result of the partial volume effect (PVE) (111). PVE can occur when more than one tissue composed of different densities is present in a single voxel (314), and is most pronounced at the periosteal interface between soft tissue and bone, transitional, cortical-trabecular bone regions and at the endosteum. The end result is a combined average of the densities of each tissue within the measured voxel which consequently lowers the overall density. This may cause the voxel to be excluded from the analysis if it does not reach the defined density threshold for bone. Hwang and Wehrli (104) reported partial volume blurring when the voxel size exceeded the area of the scanned structure. In the present study, I observed blurring of images (Figure 5-5) at lower resolutions (400, 500 μm) which corresponded with my observed decrease in bone parameter values as voxel size increased.

I observed an interesting phenomenon at both the periosteal and endosteal surfaces. I noted that there was an underestimation of ToA by pQCT by resolution and density threshold, yet there was an observed variation by pQCT for cortical area. An overestimation has been reported in previous studies (107,110,301), but these studies did not evaluate the impact of varying both threshold and resolution. There may be a greater impact of the PVE at the endosteal surface compared with the periosteal surface, due to proximity to the surrounding soft tissues. At the periosteal surface, the tissue density difference between bone and muscle was much greater than the tissue densities at the endosteal surface. As measurements approach the marrow cavity, there is a potential for highly porous bone, trabecularisation of cortical bone and trabecular bone to be present. These tissues have densities higher than muscle-soft

tissue making the distinction between compartments more difficult. Therefore, voxels that are partially filled with different bony tissues will be included in the analysis. This may result in an overestimation of cortical area. However, this was corrected when the cortical analysis was performed with a high threshold for both edge detection and separation.

Although PVEs have been reported at the 4% site of the distal radius, I observed that lower resolution scans were also inaccurate at the highly cortical 30% site, due to the thin cortical shell in these aged specimens. This phenomenon became progressively more pronounced as voxel size increased. Note that even at the highly cortical 30% site, the mean cortical thickness was only 1.9 mm. Although these values have not previously been reported, there are important clinical implications given that Augat and coworkers suggested the voxel:image size ratio should be no less than 7:1 (105). Thus, a minimum resolution of 300 μm is recommended to acquire images. As the width of the cortical shell decreased nearer the distal end of the radius (ranging from 1.0 to 1.6 mm), it is unlikely that pQCT would be able to accurately assess cortical bone at the 4% site. Measurement accuracy at the commonly reported 4% site warrants further investigation.

I also found that the percent difference between the histomorphometry criterion standard and ToA was lower on average when we used analysis thresholds that were lower than those recommended by the pQCT manufacturer. My study has extended previous research in this field by investigating bone parameters by pQCT in cadaveric specimens with low bone mass. Thus, this investigation is relevant to clinical populations of women with osteoporosis. Although I am not suggesting specific thresholds be routinely used for assessing the distal radius in older women, there may be a need to customize threshold values for specific populations and individual skeletal sites. My study design does not allow me to propose these thresholds but my findings certainly underscore the need for consistent reporting of all measurement parameters until accurate evidenced-based thresholding protocols are developed.

5.5.2 Fracture Prediction: Contribution of Geometric Properties

The mean failure load was 2852.5 ± 1605.4 Newtons which is consistent with previous research for this load configuration and age of the specimens (132). The higher mean failure load I observed is likely explained by the fast loading speed (75 mm/sec) (58). A lower loading rate, as utilized in previous studies, can yield lower ultimate failure because bone is a rate-dependent material (58).

Total bone mineral content at the 4, 6, 8, 10 and 30% and CoCNT at the 30% sites were the most robust predictors of radial bone failure. My findings extend previous research by Muller and coworkers (132) by showing the predictive ability of ToCNT and are consistent with the fact that larger bones require higher forces to cause a fracture. Previous studies have investigated only the 4% distal site and/or a highly cortical site (20 or 30%). Although ToCNT significantly predicted failure at all measurement sites, the strongest relations were noted at the 4 and 30% sites. Previous investigations at the 30% site have suggested that the cortical shell contributes significantly to the overall strength of bone (315). Although I cannot conclude this from my present results, cortical content at the 30% site was a significant predictor of failure load explaining more of the variance than BMD by DXA. DXA is considered the criterion for fracture prediction in population based studies.

One of my primary objectives was to establish parameters to predict failure utilizing biologically relevant variables from pQCT. Previous research has clearly shown that aBMD is a strong predictor of failure/fracture (131), but DXA-derived outcomes only provide a global description of bone and cannot delineate the relative contribution of specific structural parameters or bone compartments (trabecular or cortical) to failure. Although, a combination of bone outcomes from pQCT accounted for up to 88% of the variance in bone strength, CoCNT alone was a strong predictor of bone strength in axial compression.

5.6 Limitations

I note several limitations to this study. First, my specimens were from older female radii. Thus, my results cannot be extended to men or younger participants. Second, I did not use intact forearms and acknowledge the limitations of only using the radius and a single load configuration. Thus, testing did not reflect the damping forces provided by muscle and soft tissue. Third, I was not able to use the protocol recommended by the pQCT manufacturer to determine arm length because I did not have intact forearm specimens. Therefore, I measured length from the most distal end of the medial side of the radius (corresponding to the groove for the ulna at the distal radio-ulnar joint) to the proximal end of the head of the radius. Using this method, the 4% site I measured could be slightly more distal to the 4% site measured in vivo. Lastly, I used the Norland Stratec XCT 2000 with the scan slice set at 2.3 ± .2 mm. As slice thickness may impact on resolution results, using a smaller slice thickness must also be evaluated. Future studies that include more specimens would allow predictive equations that use more independent variables. This would allow me to fully understand the relevant contribution of bone geometry, mass and structure to bone strength.

5.7 Summary and Future Directions

I report that at a standard 400-500 µm resolution total bone area and density is underestimated but cortical area is varied, depending on the edge detection threshold at the 30% site. Further, bone structure as assessed by pQCT can improve failure prediction and provide details regarding specific parameters that contribute to bone failure.

6 Bone Adaptation after a Radial Fracture: A pQCT Study[3]

In this chapter, I present the results from a cross-sectional study that I undertook investigating bone adaptation following fracture and cast immobilisation. Although understanding the impact of disuse on bone is important, it is an area relatively void of current investigations for the upper extremity. At the time that I commenced this study, there were no published studies using pQCT to investigate bone adaptation to a radial fracture. The importance of this topic is two-fold. First at a local level, understanding how bone adapts assists in generating hypotheses on the most effective treatment options and secondly, the radius is an ideal model to understand long bone adaptation to immobilisation.

6.1 Introduction

Distal radial fractures are the most commonly seen fracture in the hospital emergency department (147). In women, there is a steady rise in the incidence of radial fractures commencing at age 40 and plateauing around 65-70 years of age (68,149,316). Previous research suggests this increased risk of radial fracture around the menopause is attributable to a decrease in bone strength as a result of declining estrogen (32) and the increase in fall incidents (316). Common treatment for low-trauma radial fracture includes closed reduction followed by cast-immobilisation for up to 6 weeks (163). Whether or not this period of immobilisation irreversibly increases local bone fragility and thus, further compounds a patient's future susceptibility to fragility fractures has received little research attention (228,229,235,236,254,317).

Long bones adapt to diminished loading (e.g., disuse, immobilization) by decreasing mass (content/density) or by changing geometric properties (61). For example, after a radial fracture, there is a characteristic early loss of areal bone mineral density (aBMD), as measured by dual-energy X-ray absorptiometry (DXA) that reaches its nadir at or around 3-4 months post-injury (236). After this time, bone appears to adapt to the reduced loading. The specific adaptation in bone geometry to decreased mechanical loading is not well defined but may include: a change in total cross-sectional area, a decrease in the width of the cortex and/or a change in BMD. Each of these changes can influence the overall strength of bone. Few studies have investigated which of these phenomena occur after radial fractures in older women, where aged bone is affected by immobilisation and subsequent remobilization.

[3] A version of this chapter has been submitted as a manuscript. MC Ashe, KM Khan, Davis JC, P Guy, HA McKay. Bone Adaptation after a Distal Radius Fracture: A pQCT Study. *Calcified Tissue International.* submitted.

Westlin and Nilsson (235,236,254,317,318) used single photon absorptiometry (SPA) to describe bone mineral content (BMC) changes at the distal radius post fracture. These studies reported an 18% side-side difference in BMC but were limited by the inability of SPA to distinguish cortical from trabecular bone and provide true volumetric measures. More recent studies of fracture-immobilisation used DXA (232,234). As was the case with SPA, the planar DXA techniques also cannot distinguish cortical from trabecular bone and cannot directly assess bone structural adaptation to disuse. Thus, no investigators have reported volumetric changes and cortical adaptation of the radius subsequent to a fracture.

Peripheral QCT is a relatively new technology that can measure, in vivo, bone geometry and structure and the volumetric mineral content of bone. Peripheral QCT can also distinguish cortical from trabecular bone and can quantify structural changes that occur in the peripheral skeleton with growth, aging, disease, or interventions (e.g., pharmaceutical agents, exercise). Peripheral QCT also calculates a bone strength index that reflects the combined strength of trabecular and cortical bone to resist stress in bending or torsion.

The influence of hand dominance on bone parameters should be considered when determining bone response to immobilisation. There are three handedness possibilities (right, left or ambidextrous) and between 10 and 25% of the population is left-handed (188). Bone mineral density as measured by pQCT and DXA is about 3% higher (192) in right hand dominant individuals but about equal in the left-hand dominant (193). Importantly, previous immobilisation research has not reported hand dominance when assessing bone adaptation to immobilisation (228,229,235,236,317) .

Therefore, the aim of this cross-sectional investigation was to extend previous studies of radial fractures and immobilisation by using both pQCT and DXA to describe bone mass, geometry and strength at the distal radius in older women who were between 6 months and 12 years post distal radius fracture. Specifically, our primary objectives were to compare: 1) side-side differences in volumetric bone mineral density (vBMD), bone structural properties (ultimately affecting bone strength) at the radius; and 2) grip strength and functional outcome with bone strength (Bone Strength Index (BSI) and Stress-Strain Index; SSI). Our secondary objectives were to compare changes in areal bone mineral density (aBMD) and assess change in bone outcomes and grip strength over time.

6.2 Methods

6.2.1 Experimental Participants

I recruited women aged 50 years of age and older who had previously attended a hospital-based fracture clinic. This study was conducted at the University of British Columbia (UBC) Bone Health Research Laboratory and approved by the University of British Columbia and the Vancouver Hospital and Health Science Centre Clinical Research Ethics Boards. All participants signed a written informed consent.

6.2.1.1 Inclusion criteria

Participants were i) community dwelling; ii) had sustained a low-trauma distal radius fracture [defined as falling from a standing height or less (1)] within the past 12 years; iii) able to speak and write in English and iv) 50 years of age or older. Distal radius fractures were treated by closed reduction and cast immobilisation for approximately 6 weeks.

6.2.1.2 Exclusion criteria

Participants were excluded if the fracture required treatment using open reduction and internal fixation.

6.2.2 Measurements

I measured each participant once using the following procedures and tools; anthropometry, pQCT, DXA, Patient Rated Wrist Evaluation (PRWE), Disabilities of the Arm, Shoulder and Hand (DASH), active range of motion at the radio-carpal joint and grip strength dynamometry. These are described in more detail below.

6.2.2.1 Anthropometry

I undertook standard measurement of height to the nearest millimeter with a customized wall-mounted stadiometer (Seca Model # 242, Hanover, MD). I used the mean of two measures for analysis. I assessed body weight with an electronic scale to the nearest 0.1kg and used the mean of two measures for analysis. Arm length was measured using a steel tape from the ulnar styloid tip to the olecranon process, and the protocol recommended by the pQCT manufacturer (Stratec).

6.2.2.2 *Peripheral QCT Data Acquisition*

I used the Norland Stratec XCT 2000 (Stratec Medizintechnik GmbH Pforzheim, Germany) for all scans. All participants were seated comfortably in a chair next to the pQCT gantry. After obtaining a scout view and positioning the anatomical reference line at the distal medial edge of the radius, I scanned one 2.5 mm slice at the 4% (predominantly trabecular bone) and 30% (predominantly cortical bone) site of the distal radius. Figure 6-1 is an x-ray of a radial fracture from a 54-year-old woman that highlights the two measurement sites. Resolution/voxel size was set at 500 µm and scan speed was 25 mm/sec and one block. Laboratory precision (reported as coefficient of variation; % CV) for our laboratory was 1.39 for Cortical Density (CoD) and 3.76 for Cortical Area (CoA) at the 30% site.

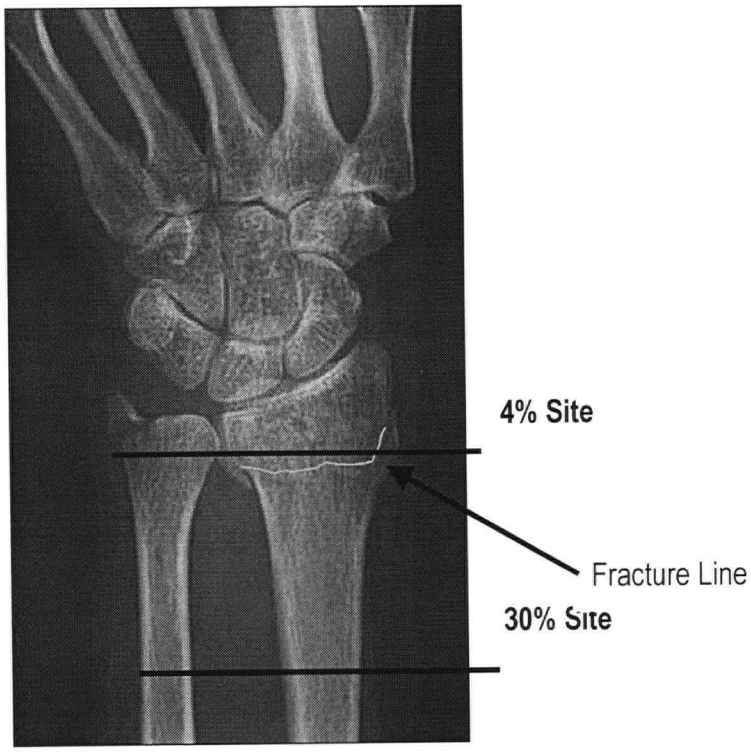


Figure 6-1. X-ray of the distal forearm of a 54 year old woman who sustained a radial fracture, highlighting the fracture site (outlined and indicated by the arrow) relative to the two pQCT measurements sites; 4% and 30% from the distal medial edge of the radius. The 4% site is primarily trabecular bone and 30% site is predominantly cortical bone.

6.2.2.3 *Peripheral QCT Data Analysis*

All scans were analysed with XCT v. 5.50 software. The algorithms used in this software are divided into two modes. The first mode is used to analyse total and trabecular bone, and the second cortical bone. I used CALCBD (Contour Mode 3, Peel Mode 2) to assess total and trabecular bone and CORTBD Mode 4 to assess cortical bone (Figure 6-2A). I used the half-max height (HMH) threshold to determine density thresholds. Using HMH, density levels were determined by drawing a line through the bone profile. This line represents the tissue density from one side of the radius to the other (Figure 6-2B). At the boundary of a structure imaged by computed tomography (CT) there is a gradual change in CT numbers from the level of the soft tissue to mineralized tissue. Previous research reports that the interface between the two tissues lies half way between the two CT numbers and is calculated as the mean of the two heights (108). In practice, this profile is used to estimate an appropriate threshold for cortical edge detection. Thus, I assessed the HMH from each scan to estimate this threshold (319).

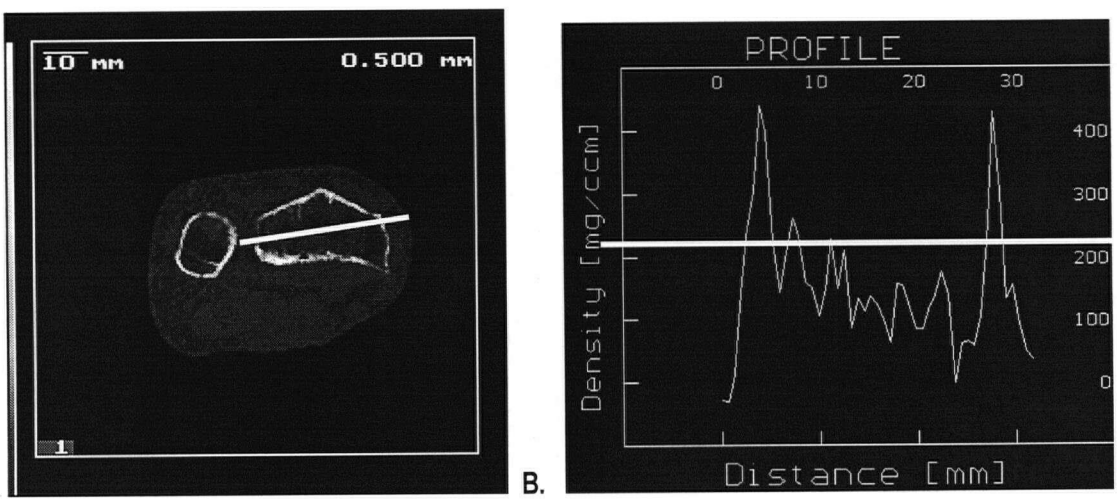


Figure 6-2. Analysis density thresholds using the half-maximum height threshold (HMH) at the 4% site. Figure A is the 4% site of the distal radius in a 74-year-old woman. The image was scanned at 500 microns and shows a transverse slice through the distal forearm including muscle, fat, radius and ulna. The cortical shell is visible but there is little trabecular bone present. Figure B.The profile line at the scan site. This represents the tissue density from one side of the radius to the other. Analysis density threshold is determined as half the maximum height threshold from the scan profile.

Density thresholds for all scans were therefore set at 130-400 mg/cm^3 at the 4% radius and 300-710 mg/cm^3 at the 30% site. I drew the regions of interest (ROI) using the XCT v. 5.50 custom drawing feature whereby the software automatically detects the outer bone edge and defines the ROI for analysis. The primary outcomes from the radial pQCT measurements were side-side differences in total area (ToA, mm^2) and total density (ToD, mg/mm^3) at the 4% and 30% sites and Cortical area (CoA, mm^2), Cortical density (CoD, mg/mm^3), cortical thickness (CTh, mm), cortical mineral content (CoCNT, mg) at the 30% site. I used polar Stress Strain Index (SSI, mm^3) and a Bone Strength Index based on cortical cross-sectional area (BSI_{CSA}) at the 30% site to estimate bone strength. BSI_{CSA} is the product of cortical ToD and CoA (112). I do not report cortical parameters at the 4% site because the thin cortex can cause an underestimation of bone values at this site (107).

6.2.2.4 DXA Measurements

I assessed aBMD (g/cm^2) and bone mineral content (BMC; g) in both forearms using DXA (Hologic 4500W; software version 11.2, Waltham, MA, USA). Regions of interest at the radius were ultradistal (UD) and distal one-third (D1/3) sites. Images were acquired using standard DXA forearm positioning as per the manufacturer's instructions. The same laboratory technician analyzed all scans. Precision (reported as coefficient of variation; CV %;) in our lab for these measurements was 3.2% for aBMD at the Distal Third site. The primary outcomes from the DXA measurements include bilateral forearm aBMD (g/cm^2) and BMC (g) at the Distal Third and Ultradistal bone sites.

6.2.2.5 Functional and Outcome Measurements

I assessed range of motion (ROM) and grip strength for all participants in both arms. The Non-Fractured forearm was considered the control. For ROM I used standard goniometry techniques recommended by the American Society of Hand Therapists (ASHT) (197). Three measures (degrees) were obtained and the mean and standard deviation is presented. I assessed grip strength (pounds) using a Jamar Hand Dynamometer (JLW Instruments, Chicago, IL). Three measures were obtained for grip strength and the mean and standard deviation is presented.

Participants completed the Patient Rated Wrist Evaluation (PRWE) and the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaires specifically designed for the upper extremity. PRWE is a valid and reliable measure of function of the radius (204). It consists of two sections that measure functional

limitations and pain levels. The DASH consists of 30 items and is a self report questionnaire designed to measure physical function and symptoms in any or multiple musculoskeletal disorders of the upper limb (206). It has an Intraclass Correlation Coefficient (ICC) of 0.96, and has been tested for construct validity (r=0.70) (320). All participants completed the valid and reliable Canadian Multi-centre Osteoporosis Study (CaMOS) (321) questionnaire to ascertain baseline descriptive characteristics.

6.2.3 Sample Size -Statistical Power

Power calculations were based on bone mineral content (BMC) at the distal radius midshaft from a cross-sectional investigation of bone response to fracture and immobilisation (236). Based on an anticipated 9% decrease in BMC on the fractured side of the distal radius, 34 participants using both arms were needed for 80% power to detect effectiveness at a Type 1 error of $p<0.05$.

6.3 Statistical Analysis

I report characteristics of the participants as means ± standard deviation. In our initial analysis, I grouped all participants regardless of whether or not the fracture occurred in the dominant hand. For our secondary analysis, I grouped participants based on hand dominance and fracture location. I compared descriptive characteristics obtained from the participants who had suffered either a dominant hand or non-dominant hand radial fracture using independent t-tests for continuous variables and chi-square statistics for dichotomous variables. I used paired t-tests for parametric data and paired Wilcoxon Signed Rank tests for non-parametric data to compare side-side differences in bone, grip strength and functional outcomes. I report the absolute and percent difference for each comparison. I assessed the relations between SSI, grip strength, ROM and functional measures (PRWE, DASH) using partial correlations controlling for fracture dominance and time since fracture. I assessed time since fracture and bone parameters using Spearman Rank Correlation coefficients. I used SPSS version 12 (SPSS, Chicago, IL). A priori power calculation was performed using G* Power version 2.0 (.G*Power, Kiel, Germany). I set the Type I error at $p<0.05$ for all statistical tests.

6.4 Results

6.4.1 Descriptive Information

Thirty-four women were enrolled in this study. I excluded three participants who had bilateral fractures. Thirty-one women, whose ages ranged from 51-86 years, were included in the analyses. Overall, the women who volunteered to participate were generally healthy with low levels of disability reported in the upper extremity (DASH 12.9 ± 15.6). There were 27 right hand dominant and 4 left hand dominant women who reported 16 non-dominant hand radial fractures and 15 dominant hand radial fractures. The mean time since fracture was 4 years. Sixty-five percent of participants were diagnosed with osteoporosis; 29% were taking calcium-vitamin D and 55% were taking a bisphosphonate at the time of assessment. On average, participants reported one other fragility fracture in addition to the radial fracture. Participants were overweight (BMI = 28.5 ± 5.6) and only two participants reported a fall in the previous month. When participants were separated by non-dominant hand or dominant hand radial fracture, there were no significant differences between groups except right/left fracture side ratio and calcium use. Table 6-1 is a summary of descriptive characteristics for the entire cohort of participants and the dominant and non-dominant hand radial fracture sub-groups.

6.4.2 Bone and Grip Strength Outcomes

For all participants, the fractured limb had significantly larger ToA ($p<0.05$) with more ToCNT ($p<0.01$) at the 4% site compared with the Non-Fractured arm. At the 30% site in the previously fractured arm, I observed lower ToCNT and ToD ($p<0.05$) with significantly lower CoCNT ($p<0.01$) and thinner cortical shell ($p<0.05$) which contributed to the significantly lower bone strength ($p<0.05$). DXA provided similar results; BMC and aBMD values were higher at the ultradistal site ($p<0.001$) and lower ($p<0.05$) at the distal third site. Similarly, grip strength and wrist flexion were 15-16 % lower on the previously fractured side (Table 6-2)

When participants were analysed based on whether the dominant (n=15) or non-dominant (n=16) radius was fractured, different results emerged. For those who fractured the non-dominant limb there was a significant side-side difference in all pQCT outcomes (except CoD) at the 30% site. For those who fractured the dominant limb, there was a significant difference only for ToCNT at the 4% site (Table 6-3)

Table 6-1. Descriptive characteristics of the entire cohort, and by subgroups defined by whether their radial fracture occurred on the side of the dominant hand or non-dominant hand.

	Entire Cohort Mean ± sd	Dominant Radius Fracture	Non-Dominant Radius Fracture
N=	31	15	16
Age (years)	72.4 ± 9.7	68.8 ± 11.2	75.1 ± 6.8
Height (cm)	155.1 ± 11.9	155.1 ± 11.9	154.6 ± 12.7
Weight (kg)	65.2 ± 10.5	68.2 ± 12.6	61.8 ± 7.2
BMI	28.5 ± 5.6	29.0 ± 6.3	28.0 ± 5.2
Time Since Fracture (years)	4.0 ± 3.5	2.8 ± 2.8	5.4 ± 3.8
Fracture Side Ratio (Right/Left)	13/18	12/3	1/15***
Diagnosed with Osteoporosis	20/31 (65%)	10/15 (66%)	10/16 (62.5%)
Reported Falls in past month	2/31 (6%)	1/15 (6.7%)	1/16(6%)
Co-existing diseases/participant	2	2	2
Previous fractures/participant	1	1	2
Prescribed medications/participant	4	3	4
Currently taking Bisphosphonates	17/31 (55%)	7/15 (46.7%)	10/16 (47.3%)
Taking Calcium and Vitamin D	9/31 (29%)	7/15 (46.7%)	2/16 (12.5%)*
Taking Calcium or Bisphosphonates	20/31(65%)	10/15 (66%)	10/16 (62.5%)
PRWE∞	14.4 ± 21.0	12.6 ± 20.5	18.1 ± 22.1
DASH∞	12.9 ± 15.6	13.6 ± 18.5	12.1 ± 12.7

PRWE: Patient Rated Wrist Evaluation; DASH; Disabilities of the Shoulder, Arm and Hand. *** significant at $p < 0.001$; * significant at $p < 0.05$;

Table 6-2. Cross-sectional bone area, content and density by pQCT, density and content at the Distal Third Radius by DXA and functional measures for the Entire Cohort.

	Outcome Parameters	Fracture arm	Non-Fractured arm	Absolute Difference (Non-Fractured - fractured)	Mean Percent Difference (%) [(Non-Fractured - fractured)/Non-Fractured] x 100
Peripheral QCT Outcomes	**4% Total Bone (N=21)**				
	ToA (mm^2)	340.8 ± 74.3	316.6 ± 54.2	-24.2 ± 48.3	-8%*
	ToD (mg/cm^3)	261.9 ± 58.5	238.7 ± 52.7	-23.1 ± 64.7	-13%*
	ToCNT (mg)	87.5 ± 19.6	73.9 ± 12.7	-13.6 ± 17.4	-20%**
	30% Total Bone (N=27)				
	ToA (mm^2)	87.7 ± 12.8	89.7 ± 15.1	1.8 ± 6.4	1.5%
	ToD (mg/cm^3)	698.0± 144.0	725.6 ± 150.4	26.6 ± 55.1	3.5%*
	ToCNT(mg)	60.8 ± 13.3	64.0 ± 11.1	2.9 ± 6.3	4.9%*
	SSI (mm^3)	175.8 ± 39.0	185.8 ± 43.0	9.6 ± 19.8	4.6%**
	BSI_{csa}	70378.7 ± 2620.4	74453.5 ± 2117.5	4047.7 ± 7272.2	5.6%**
	30% Cortical Bone (N=27)				
	CoA (mm^2)	75.8 ± 11.3	80.8 ± 9.6	4.8 ± 8.0	6.1%**
	CoD (mg/cm^3)	925.1 ± 62.5	914.8 ± 90.8	-9.8 ± 58.0	-1.1%
	CoCNT(mg)	70.5 ± 13.6	73.9 ± 11.4	3.3 ± 6.1	4.9%**
	CTh (mm)	3.5 ± 0.9	3.9 ± 0.9	0.31 ± 0.6	7.5%*
DXA	**Radius- Ultradistal (N=31)**				
	aBMD (g/cm^2)	0.350 ± 0.1	0.308 ± 0.1	-0.04 ± 0.1	-16%***
	BMC (g)	1.45 ± 0.3	1.21 ± 0.3	-0.25 ± 0.3	-29%***
	Radius- Distal Third (N=31)				
	aBMD (g/cm^2)	0.497 ± 0.1	0.514 ± 0.1	0.015 ± 0.1	3%
	BMC (g)	1.27 ± 0.2	1.35 ± 0.3	0.08 ± 0.2	6%*
Strength ROM	Grip Strength (lbs)	30.5 ± 13.3	35.8 ± 11.3	5.3 ± 8.8	15% **
	Wrist Flexion (degrees)	57.8 ± 12.4	70.4 ± 13.4	12.6 ± 13.0	16% ***
	Wrist Extension(degrees)	54.7 ± 13.8	57.6 ± 11.4	2.9 ± 8.9	5%

ToCNT= total content; ToA = total area; ToD= total density; Trab CNT=trabecular content; TrabA = trabecular area; TrabD= trabecular density; CoCNT= cortical content; CoA= cortical area; CoD= cortical density; CoThk= cortical thickness; SSI = stress strain index.* significant at p< 0.05; ** significant at p< 0.01, *** significant at p< 0.001

Table 6-3. Cross-sectional bone area, content and density by pQCT, density and content at the Distal Third Radius by DXA and functional measures; non-dominant vs. dominant side fracture

	Outcome Variables	Dominant Fractured (N=15) Fractured arm (A)	Dominant Fractured (N=15) Non-Fractured arm (B)	Non-Dominant Fractured (N=16) Fractured arm (C)	Non-Dominant Fractured (N=16) Non-Fractured arm (D)	Dominant Fractured (N=15) Mean % Difference (B-A)/B*100	Non-Dominant Fractured (N=16) Mean % Difference (D-C)/D*100
pQCT Outcomes	**4% Total Bone**						
	ToA (mm^2)	334.1 ± 86.0	308.1 ± 61.4	350.0 ± 58.7	328.1 ± 43.5	-8%	-7%
	ToD (mg/cm^3)	281.8 ± 64.2	254.4 ± 51.2	234.3 ± 37.7	217.2 ± 49.6	-13%	-14%
	ToCNT (mg)	91.8 ± 21.4	76.5 ± 11.7	81.6 ± 16.4	70.4 ± 13.9	-20%**	-19%
	30% Total Bone						
	ToA (mm^2)	87.8 ± 13.9	85.3 ± 15.8	87.9 ± 12.4	93.76 ± 13.7	-3%	6%***
	ToD (mg/cm^3)	780.7 ± 150.1	798.4 ± 160.0	621.2 ± 86.3	657.92 ± 106.6	2%	5%*
	ToCNT(mg)	67.7 ± 12.8	66.6 ± 10.6	54.5 ± 10.6	61.33 ± 11.4	-1%	11%***
	SSI (mm^3)	179.7 ± 44.0	181.9 ± 40.6	172.3 ± 35.0	189.42 ± 46.2	1%	8%**
	BSI_{csa}	75978.7±13483.3	75280.5±12213.0	65178.8±11937.0	73685.57±10154.9	<1%	12%***
	30% Cortical Bone						
	CoA (mm^2)	80.7 ± 9.9	81.2 ± 10.4	71.3 ± 10.9	80.41 ± 9.2	<1%	11%***
	CoD (mg/cm^3)	952.4 ± 75.5	952.7 ± 98.9	899.8 ± 33.7	879.74 ± 68.7	<1%	-3%**
	CoCNT(mg)	77.1 ± 13.2	77.1 ± 10.9	64.3 ± 11.2	70.97 ± 11.5	<1%	9%***
	CTh (mm)	4.0 ± 0.8	4.2 ± 0.9	3.1 ± 0.7	3.6 ± 0.8	2%	12%*
DXA	**Radius- Ultradistal**						
	aBMD (g/cm^2)	0.372 ± 0.08	0.330 ± 0.06	0.329 ± 0.0	0.289 ± 0.1	-14%**	-17%*
	BMC (g)	1.58 ± 0.23	1.31± 0.33	1.32 ± 0.3	1.11 ± 0.3	-28%**	-31%**
	Radius- Distal Third						
	aBMD (g/cm^2)	0.540 ± 0.1	0.530 ± 0.1	0.458 ± 0.1	0.490 ± 0.1	<1%	6%*
	BMC (g)	1.4 ± 0.2	1.4 ± 0.3	1.2 ± 0.2	1.3 ± 0.2	2%	10%*
Strength	Grip Strength (lbs)	34.2 ±13.5	39.5 ± 11.7	26.8 ± 12.4	32.1 ± 9.9	14%*	17%*
ROM	Wrist Flexion (degrees)	59.1 ± 9.6	72.3 ± 9.8	56.5 ± 14.8	68.5 ± 16.1	17%**	16%**
	Wrist Extension(degrees)	53.9 ±15.9	57.7 ± 13.6	55.5 ± 11.9	57.5 ± 9.5	6%	3%

ToCNT= total content; ToA = total area; ToD= total density; Trab CNT=trabecular content; TrabA = trabecular area; TrabD= trabecular density; CoCNT= cortical content; CoA= cortical area; CoD= cortical density; CoThk= cortical thickness; SSI = stress strain index.* significant at p< 0.05; ** significant at p< 0.01, *** significant at p< 0.001

6.4.3 Relation between bone parameters and functional outcomes

For the entire group (n=31) I found no significant relations between fracture side grip strength (weaker side) and bone parameters using partial correlations. I found significant associations between non-fractured side grip strength and pQCT [30% ToCNT, CoCNT, BSI_{csa} (r=0.405-0.478; p<0.05)] and DXA (BMC ultradistal; r=0.399; p<0.05) using partial correlations controlling for time since fracture for the entire group. Table 6.4.

Table 6-4. Grip strength vs. bone variables on the non-fractured side using partial correlations (controlling for time since fracture) N=31.

Bone Variables	Partial Correlation	Significance level (p-value)
30% CoCNT	0.478	0.02
30% ToCNT	0.469	0.02
BSI_{csa}	0.405	0.05
BMC Ultradistal	0.399	0.05

6.5 Discussion

At the 4% site of the radius, I observed significant differences in total area, content and density between the fractured and non-fractured arm. At the 30% site, I observed less cortical and total bone content, area and density in the fracture arm. Overall, I report less bone strength on the previously fractured side compared with the non-fractured side and the magnitude of difference was dependent on hand dominance. To my knowledge, this is the first study to use pQCT to compare side-side differences in bone structure following a radial fracture.

My pQCT study extends previous research (235,236,254) by showing a greater ToA in the previously fractured arm at the distal 4% site. This could occur for several reasons: 1) arm dominance can influence bone size; 2) a displaced fracture around the 4% site could potentially increase total cross-sectional area; and 3) previous research has indicated that bone responds to demineralization by increasing cross-sectional area through periosteal apposition (23). In the present study, I observed an overall decrease in cortical bone at the 30% site in the fractured arm including a significantly thinner cortical shell. Periosteal apposition (and increased ToA) in response to diminished mineralisation is thought to maintain bone strength. Although my study design does not permit me to draw this specific conclusion, our findings are consistent with such a phenomenon.

6.5.1 Dominant vs. Non-Dominant Fracture: Impact on Bone Outcomes

In the present cross-sectional report, I found that those who sustained a radial fracture on the non-dominant side had significantly greater side-side difference in all bone variables at the midshaft between limbs as measured by both DXA and pQCT. These differences were present even after accounting for the reported 3% difference between dominant and non-dominant limb at the distal radius aBMD using DXA (192) and a 5.5% difference at the pQCT distal site (190). One explanation for this phenomenon could lie in the necessity to use a fractured dominant arm more during and after recovery compared with a fractured non-dominant arm. Previous reports suggest that a dominant arm fracture has more initial impact on daily function, but there is also a better chance for recovery (194). Secondly, two studies that highlight the role of hand dominance in functional recovery after a radial fracture (194,322) suggest that muscle strength in the non-dominant fractured arm remains significantly weaker at 1 year post-fracture. However, despite the importance of hand dominance in fracture recovery, to my knowledge this variable has not been considered in bone studies of fracture-immobilisation. A clinical implication from my finding

that a non-dominant arm, when fractured is weaker and has less bone strength compared with the non-fractured sides is that these fractures may benefit from targeted rehabilitation focused on improving bone strength.

6.5.2 Bone Strength vs. Grip Strength and Functional Measures

I observed significant associations between bone parameters and non-fractured arm grip strength. This extends previous studies that reported an association between grip strength and bone strength parameters as measured by pQCT (203,256). Interestingly, my study does not show a significant association between these outcomes and grip strength on the previously fractured side (weak side). There are several possible explanations. First, our participants were older and the mean grip strength was less than 40lbs, which is well below normative values (dominant arm 56±16 lbs and non-dominant arm 51± 14 lbs) reported for women between 60-64 years of age (210). Secondly, my grip strength and functional results are similar to a recent investigation that compared aBMD by DXA to grip strength and upper extremity muscle strength (323). In this study, there was a positive association (low magnitude) between dominant arm grip strength and muscle strength and aBMD. However, this association was not significant for the non-dominant side (or weaker side) or those with osteoporosis. Although, other research showed high correlations between grip strength and bone strength (BSI) (r=0.87), this study assessed the dominant arm of healthy participants (girls, boys, women and men) age 3-62 years of age (102). Thus, it is not surprising that results from our cohort of older individuals with weak grip strength and previous fractures were different.

Other considerations for this population besides muscle disuse impact on bone resorption. Menopause results in diminished estrogen levels that ultimately impacts bone mass (60). In addition, overall physical activity level and bisphosphonate use may affect the outcome of our findings. In a population with a history of fragility fracture, grip strength alone may be insufficient to predict bone strength. Using muscle cross-sectional area and/or muscle strength of the complete upper extremity may be preferable as these muscle measures are known to contribute to skeletal integrity. It is plausible that the combination of muscle-bone disuse, as well as metabolic and hormonal changes, influenced the bone loss I observed after a radial fracture. Regardless, my observations advance many clinically important hypotheses that require further investigation.

6.6 Limitations

I note several study limitations. First, the cross-sectional nature of the study limits conclusions about the temporal nature of any 'bone loss' that may have occurred and the relatively low participant numbers in the individual groups (dominant fracture; non-dominant fracture) limits the use of multiple regression modeling to examine predictors of bone strength over time. In the present study, I only assessed grip strength based on limited previous literature. A more robust investigation would include a composite muscle strength score and pQCT generated muscle cross-sectional (CSA). Future investigations using pQCT in this population would benefit from a higher resolution and an additional image taken at the 66% site for muscle analysis.

6.7 Summary and Future Directions

In summary, in this novel study of post-fracture bone health, I report significant side-side differences in volumetric bone density, content, cortical thickness and strength at the radius as measured by pQCT and the magnitude of difference was larger when the non-dominant side was fractured. To my knowledge, this side-side difference post-fracture has not previously been reported. Grip strength was lower on the previously fractured side and was significantly correlated with pQCT bone strength parameters on the non-fractured side. Distal radial fractures are the most common fractures seen in emergency departments (147) and are common in older women with impaired bone health. This cross-sectional study suggests the need for prospective research to investigate the muscle-bone interaction, describe longitudinal bone changes in response to unloading following a radial fracture, and to test the possible contribution of rehabilitation to strengthening bones.

7 Bone Structural Adaptation to Chronic Disuse following Stroke: A pQCT study[4]

In this section, I present the results of my cross-sectional study investigating bone response to stroke-disuse. Although there have been investigations of bone adaptation, there are no published reports using pQCT and reporting structural changes.

7.1 Introduction

In the first year following a cerebrovascular accident (CVA) or stroke, 40% of individuals are likely to sustain a fall (238,239) and within two years post-stroke, one-third of survivors sustain a hip fracture and 24% sustain a radial fracture (239,300). Although a number of factors contribute to this increased fracture risk (e.g., poor balance and number of falls), diminished bone health is also important in fragility fractures. Therefore, a focus of rehabilitation should consider secondary prevention strategies to reduce potential complications such as low bone mass and fragility fractures.

Previous investigations of bone health in survivors of stroke reported an initial rapid decrease in areal bone mineral density (aBMD) in the paretic limb compared with the non-paretic limb in the early phase (within 6-12 months): and the magnitude of the loss in bone density ranged from 5-12%, and 3-5% in the paretic, and non-paretic limb respectively (242-245,324). After the acute phase, cross-sectional observations suggested that bone mass, following disuse or with aging, adjusted to an overall decrease in physical activity, or more plausible, there are structural adaptations that occurred to maintain bone strength (20,59). That is, when bone mass decreases in response to disuse, aging or spaceflight, an increase in bone area maintains the overall strength of the bone by increasing the cross-sectional moment of inertia (20,325). A biological defense mechanism for bone adaptation to become theoretically more resistant to fracture.

Following a stroke, there are observed musculoskeletal changes that highlight a model of physiological osteopenia that exists in bone when there is muscle weakness (240). The relation between muscle and bone is an emerging field. In the late 1980's, Frost and coworkers proposed the Utah paradigm and the concept that mechanical loads determine bone strength and muscle generates the greatest load on bone (35). However, a key limitation in understanding how muscle strength impacts on bone parameters has

[4] A version of this chapter has been submitted as a manuscript. MC Ashe, P Fehling, JJ Eng, KM Khan, HA McKay. Bone Structural Adaptation to Chronic Disuse following Stroke: Implications for Rehabilitation. *Journal of Musculoskeletal and Neuronal Interactions*. submitted.

been the imaging technologies. Peripheral QCT provides a measure of the amount of volumetric bone mineral density (vBMD) and defines bone's structural properties at a low risk to participants. Peripheral QCT also generates a bone strength index that reflects the combined strength of trabecular and cortical bone to resist bending or torsion. To my knowledge, no previous study has used pQCT to measure bone changes or the muscle-bone strength relation in a chronic stroke sample.

Therefore, the aims of this study were 1) to compare side-side differences in vBMD, bone structural properties (ultimately affecting bone strength) at the radius; and 2) to compare physical measures of muscle strength to pQCT generated bone strength (Stress-Strain Index; SSI) in a sample that was between 1 and 10 years post stroke. Specifically, I hypothesized that the paretic side would have reduced side-side differences in total, trabecular and cortical area, density and mineral content; and cortical thickness compared with the non-paretic side. Secondly, I hypothesized that these bone parameters would relate to physical measures of muscle strength and motor impairment. Understanding the mechanisms of bone loss can provide the foundations upon which to develop rehabilitation strategies to improve bone health and reduce the risk of fragility fractures.

7.2 Methods

7.2.1 Experimental Participants

I recruited men and women who were part of a large prospective study investigating post-stroke balance (326) to participate in this study. This study was approved by the University of British Columbia Clinical Research Ethics Board. All participants signed a written informed consent.

7.2.1.1 Inclusion-Exclusion Criteria

Eligible participants were i) community dwelling; ii) aged 50 years or older; iii) able to walk, with or without an assistive device, for a minimum of 10 meters, and iv) had sustained a single stroke that had occurred at least one year previously. Participants were excluded if they: i) were not medically stable; ii) had neurological conditions not related to stroke (e.g. Parkinson's disease) or severe musculoskeletal conditions (e.g. recent joint replacement surgery, amputation) and iii) scored less than 22 on Folstein's Mini-Mental State Exam (327). Each participant's physician confirmed the presence of stroke and the inclusion/exclusion criteria. For pQCT measurements, participants were excluded if there was any metal fixation in the radius or any obvious tremor or spasticity that would prevent or affect positioning within the gantry.

7.2.2 *Measurements*

7.2.2.1 Anthropometry

I undertook standard measurement of height to the nearest millimeter with a customized wall-mounted stadiometer (Seca Model # 242, Hanover, MD). The mean of two measures was used for analysis. I assessed body weight with an electronic scale to the nearest 0.1kg and used the mean of two measures for analysis. Arm length was measured using the manufacturer recommended ulnar styloid tip to olecranon process.

7.2.2.2 Functional Ability and Impairment

The functional ability of participants was assessed with the American Heart Association (AHA) Stroke Functional Classification. This five-level scale provides a classification score of residual impairment and disability from stroke in the areas of basic (BADL) and instrumental activities of daily living (IADL). Level one indicates independence in both BADL and IADL and level five indicates complete dependence.

Each participant was assessed with the upper extremity score of the Fugl-Meyer Scale to evaluate physical recovery from a stroke. This scale is based on the work of Brunnstrom (328), and rates movement, coordination, and reflex action about the shoulder, elbow, forearm, wrist, hand. The maximum motor performance for the upper extremity is 66 points.

7.2.2.3 Composite Muscle Strength Score

Upper extremity strength using a Jamar Hand Dynamometer (JLW Instruments, Chicago, IL) was assessed. A composite muscle strength score (measured in kilograms) was derived from a combined mean of three trials of shoulder flexion, extension and abduction, elbow and wrist flexion and extension. I calculated a percent side-side difference. I considered a >10% difference between arms, more than normal side-side age-matched upper extremity strength differences (189) . Therefore, this "sub-group" is defined as participants having a composite muscle strength score > 10% different between limbs.

7.2.3 *Peripheral QCT Scan Acquisition*

I measured both forearms of each participant using peripheral quantitative computed tomography (pQCT; Stratec Medizintecnik XCT 2000; software version 550; Pforzheim, Germany). All participants were seated comfortably in a chair adjacent to the pQCT gantry. I obtained a scout view and positioned the anatomical reference line at the distal medial edge of the radius. I used this reference to obtain a single

2.5 mm slice at the 4% and 30% site of the distal radius. Voxel size was 500μm and scan speed was 25 mm/sec to minimize the potential for fatigue or movement/tremor.

7.2.3.1 Peripheral QCT Data Analysis

Two investigators reviewed and accepted scans by consensus. All scans were analysed with XCT v. 5.50 software. The algorithms of this software are divided into two modes that correspond to the analyses of 1) total/trabecular and 2) cortical bone. That is, total/trabecular bone was assessed using CALCBD (Contour Mode 3, Peel Mode 2) and cortical bone was assessed using CORTBD Mode 4. I used density thresholds 130-400 mg/cm^3 at the 4% radius and 169 mg/cm^3 at the 30% site. This means the outer edge of the bone at the distal sites was detected using 130 mg/cm^3 and then it separated trabecular from subcortical bone using a threshold of 400 mg/cm^3. Cortical bone at the 30% site was defined as densities greater than 710 mg/cm^3. I drew the regions of interest (ROI) using the XCT v. 5.50 custom feature whereby the operator sets the cursor in centre of the bone image and initiates the threshold-based outlining process.

The software automatically detects the outer bone edge and defines the ROI for analysis. The primary outcomes from the radial pQCT measurements were side-side differences in: total area (mm^2) at 4% and 30% sites; Cortical area (mm^2) at the 30% site; Total density (4 and 30% site); and Cortical density (30% radius) vBMD (mg/cm^3); Total mineral and cortical mineral content (mg); and cortical thickness (mm). I used polar Stress Strain Index - Polar (SSI; mm^3) at the 30% site to estimate bone strength. I do not report cortical parameters at the distal sites because of the thin cortical shell and the known CT limitations that cortical bone should be 2.0-2.5 mm minimum thickness to avoid the partial volume effect that causes an underestimation of bone parameters (107).

7.2.4 Sample Size-Statistical Power

Power calculation for the primary hypotheses of bone mineral density differences at the ultradistal radius was based on predictions of differences between the two limbs (paretic vs. non-paretic). Based on an anticipated 17% decrease in BMC in the distal radius at 12 months post-stroke, 25 participants using both arms were needed for 80% power to detect effectiveness at a Type 1 error of $p<0.05$ (253).

7.3 Statistical Analysis

I report characteristics of the participants as means ± standard deviation, except the AHA Stroke Classification, which is presented as the median. Within each group separately (main and sub-groups) I used paired t-tests to compare side-side differences in bone outcomes. I reported the percent difference. I assessed the relations between SSI, composite muscle strength scores and the impairment measure (Fugl-Meyer) using partial correlations (controlling for paretic side and time since stroke). I used SPSS version 12 (SPSS, Chicago, IL). A priori and post-hoc power calculations were assessed using G* Power. I set theType I error at $P<0.05$ for all statistical tests.

7.4 Results

Twenty-five participants were examined for bone, muscle strength parameters and Fugl-Meyer score of impairment. Table 7-1 provides descriptive characteristics for the entire cohort and the sub-group of participants who had a >10% side-side composite muscle strength difference.

Table 7-1. Descriptive Characteristics of Entire Stroke Cohort (N=25) and Subgroup who had a > 10% Side-Side Composite Muscle Strength Score Difference.

	Entire Cohort N=25	Sub-Group N=15
Gender (Women: Men)	6:20	4:11
Age (years)	65.1 ± 6.7	66.6 ± 5.8
Height (cm)	169.6 ± 9.3	168.6 ± 9.9
Mass (kg)	79.7 ± 15.8	81.5 ± 14.5
Time since stroke (months)	44.1 ± 21.5	46.8 ± 22.6
Fugl-Meyer Score (Upper Extremity)	53.5 ± 14.8	64.5 ± 16.1
AHA Stroke Classification*	2	2

*Median reported

7.4.1 Peripheral QCT Analysis

In this section, I detail the results from the entire cohort and then from the sub-group who had greater than 10% side-side difference between limbs for muscle strength.

7.4.1.1 Entire Cohort

I found a significant difference between the paretic limb and the non-paretic limb at the 4% and 30% site of the distal radius (Table 7-2). I found the paretic limbs had 6% less total density at the 30% site compared with the non-paretic limbs. At this site I also found less cortical bone density, content and cortical thickness in the paretic limbs. At the 4% site, I found a 15% reduction in total density on the paretic side. In addition to the loss of total bone (4 and 30%) and cortical bone (30% site) on the paretic side compared with the non-paretic side, there was a trend towards increased total area at the distal site.

7.4.1.2 Sub-Group

In Table 7-3, I report the pQCT results from those participants who presented with greater than 10% side-side difference in composite muscle strength score. Overall, I found the paretic limbs had 7% less total density and content at the 30% site compared with the non-paretic limbs. At the 4% site, I found 15% less total density and 11% less total mineral content compared with the paretic side. Figures 7-3 is a visual representation of the 4% sites of the radius comparing the paretic to the non-paretic limbs of a 68-year-old woman who had sustained a stroke 4 years previously.

Table 7-2. Entire Stroke Cohort: Bone Area, Strength and vBMD by pQCT at the Radius 4% and 30% Radial Sites.

Bone Site	Paretic Limb	Non-paretic Limb	p Value	% Difference
30% Total Bone (N=26)				
Total area (gm^2)	128.8 ± 27.6	130.3 ± 29.1	0.35	1
Total density (gm/cm^3)	820.2 ± 137.2	874.3 ± 107.2	0.02	6
Total content (gm)	108.2 ± 32.5	113.2 ± 28.2	0.07	4
Stress strain index (mm^3)	301.6 ± 103.7	316.4 ± 89.0	0.07	5
30% Cortical Bone				
Cortical area (gm^2)	91.5 ± 25.4	96.4 ± 21.0	0.04	5
Cortical density (gm/cm^3)	1137.9 ± 44.03	1159.0 ± 26.1	0.01	2
Cortical content (gm)	104.8 ± 30.8	112.0 ± 25.2	0.02	6
Cortical thickness (mm)	3.7 ± 1.1	4.2 ± 1.1	0.01	12
4% Total Bone (N=20)				
Total Area (gm^2)	404.4 ± 76.3	379.9 ± 90.3	0.21	6
Total Density (gm/cm^3)	303.3 ± 96.3	357.6 ± 73.2	0.01	15
Total Content (gm)	131.7 ± 34.2	125.3 ± 36.5	0.06	5

Table 7-3. Sub-group: bone area, strength and vBMD by pQCT at the radius 4% and 30% sites from participants who exhibited a greater than 10% difference in muscle composite score. Results are reported as mean ± SD, p-values and percent difference.

Bone Site	Paretic Limb	Non-paretic Limb	p Value	Percent Difference
30% Total Bone (N=15)				
Total Area (gm^2)	126.5 ± 33.2	125.6 ± 32.9	0.52	-1
Total Density (gm/cm^3)	823.2 ± 166.4	887.3 ± 108.8	0.08	7
Total Content (gm)	105.4 ± 38.2	113.2 ± 33.3	0.05	7
Stress-Strain Index (mm^3)	288.0 ± 119.2	315.2 ± 106.5	0.01	9
30% Cortical Bone				
Cortical Area (gm^2)	91.3 ± 30.3	98.1 ± 23.8	0.07	7
Cortical Density (gm/cm^3)	1033.3 ± 53.5	1155.7 ± 29.0	0.05	2
Cortical Content (gm)	104.5 ± 36.9	113.7 ± 28.5	0.05	8
Cortical Thickness (mm)	3.8 ± 1.3	4.4 ± 1.1	0.06	13
4% Total Bone (N=13)				
Total Area (gm^2)	404.4 ± 79.4	387.4 ± 89.4	0.42	4
Total Density (gm/cm^3)	312.8 ± 93.2	367.6 ± 66.7	0.006	-15
Total Content (gms)	126.2 ± 39.0	141.2 ± 35.6	0.000	11

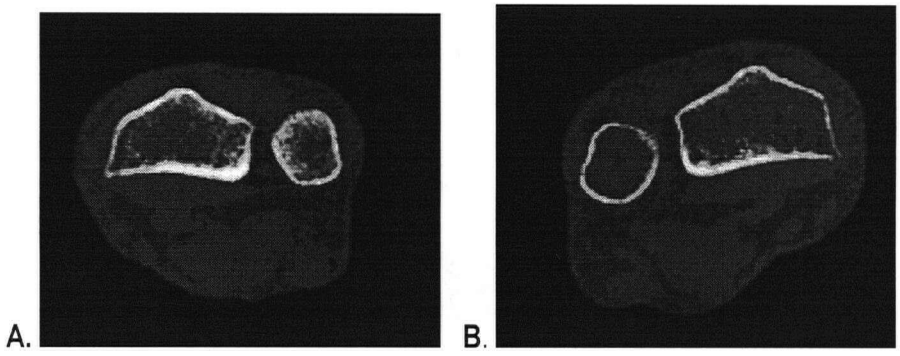


Figure 7-1 Examples of paretic and non-paretic radius and ulna at the 4% site highlighting differences between bone parameters. Figure A represents the 4% site of the non-paretic distal radius in a 68-year-old woman who sustained a stroke 4 years previously. Figure B represents the radius from the same participant on the paretic side. Note the differences in the amount of bone inside the cortical shell between the paretic and non-paretic limbs, particularly evident on the ulna in Figure B.

7.4.2 *Muscle-Bone Relations*

In both the entire cohort and the sub-group [participants who had a greater than 10% difference in composite muscle strength score (paretic < non-paretic)], I found significant relations between SSI, composite muscle strength score and motor impairment (Table 7-4). Specifically, there were highly significant correlations between paretic SSI and paretic muscle score (r=0.86-0.90), paretic SSI and Fugel-Meyer Score (r=.68-0.77) and non-paretic SSI and muscle score (r=0.77-0.82).

Table 7-4. Partial correlations between SSI, composite muscle strength score and impairment for the entire cohort (N=26) and sub-group; controlling for time-since-stroke and paretic-side (N=15).

Comparison	Entire Cohort (N=25)	Significance	Sub-Group (N=15)	Significance
Paretic SSI – Muscle Score	0.86	0.00	0.90	0.00
Paretic SSI- Fugel Meyer Score	0.68	0.01	0.77	0.01
Non-Paretic SSI- Muscle Score	0.77	0.00	0.82	0.00

7.5 Discussion

In this study, I report a significant reduction in bone strength on the paretic side compared with non-paretic side at the 30% site of the radius and significant correlations between bone strength indices and physical measurements of muscle strength and motor impairment. This work extends previous work using DXA areal assessment that showed a lower bone mineral density on the paretic side (248,329) by reporting specific bone compartment adaptation in response to disuse. This is the first study to use pQCT to examine the amount of volumetric tissue mineralization, bone structural dimensions and bone strength parameters in persons with long-term stroke and upper extremity disuse.

An important factor to consider when evaluating bone loss is the length of time since stroke. In the current study the average length of time since stroke was 44 months while in past bone density studies it was 12 months or less (242-245,330). Prospective studies of the acute phase of stroke-disuse showed a rapid decline in bone on the paretic side (331). That is followed by another phase where the bone mass of the paretic limb makes an adjustment to an overall decrease in physical activity, or more plausible, there are structural adaptations that occur to maintain bone strength. When bone mass decreases in response to disuse, aging or spaceflight, an increase in bone area maintains the overall strength of the bone by increasing the cross-sectional moment of inertia (20,325).

Cortical bone has two different surfaces: endosteum and periosteum. The endosteum is in contact with the inner surface of bone marrow and is metabolically active and involved in bone remodeling. On the outside of bone is the periosteum, thought to be responsible for the periosteal apposition observed with aging and disuse. Previous research has indicated that bone responds to demineralization by increasing in cross-sectional area (periosteal apposition) (23), with a concurrent decrease in cortical thickness. DXA, a planar measurement is unable to assess structural adaptations (97) and explains why structure has not been reported previously. I found the paretic side had a smaller cortical thickness at the midshaft, and although not significant, I observed that the paretic limb was larger at the distal 4% site than the non-paretic limb. This phenomenon leads to greater maintenance of bone strength than if demineralization occurred at a constant bone size. My study design does not permit me to draw this conclusion, but my findings are consistent with such a phenomenon.

Another novel feature of this study is the significant correlations between SSI and physical measures of muscle strength and impairment. These data support the muscle-bone interaction — mechanical loads determine bone strength and muscle generates the greatest load on bone (35). Further, it highlights a potential role for rehabilitation to maintain muscle and bone strength after a stroke.

7.5.1 Implications for Rehabilitation

7.5.1.1 Radius as a Model

The distal radius is an excellent model to examine the role of muscle disuse and bone in stroke. Distal radius fractures are the most common fractures seen in emergency departments (147) and generally precede a more serious hip fracture by up to 15 years (3). Contributing to the distal radius and the femoral neck fracture risk is the amount of trabecular bone and cortical shell, both of which have been shown to change with aging (29) leaving a loss of trabecular horizontal struts (or support networks) and a reduced cortical shell. The radius is an ideal model for research because geometric parameters can easily be measured using pQCT, a feature not available for the femoral neck. By using this non-invasive technology, radial changes that result from exercise or functional electrical stimulation (FES) can be observed and compared with physical measures of bone strength.

7.5.1.2 Exercise

The human skeleton adapts rapidly to physical inactivity. Previous research suggests that bone remodeling (that is, the process where old bone is removed and new bone is added) is initiated by a process known as mechanotransduction (33,34). Bone cells known as osteocytes are embedded in bone matrix and can transmit signals generated by fluid shifts within bone channels known as canuliculi. These shifts occur as a result of dynamic forces (260). Previous animal and non-stroke in vivo exercise studies have suggested that exercise can alter bone parameters (74,115,213-218). Specifically related to the upper extremity, Adami and coworkers tested a 6-month exercise intervention in 250 postmenopausal women, aged 52-72 years, and were able to show geometric changes at the distal radius (4% site). The intervention used an intensive 70-minute strengthening regime that maximized the brachioradialis muscle (inserts on the radial styloid process) (219), and observed a significant increase in cross-sectional area and density of the cortical compartment. Finally, preliminary findings (332) have suggested that exercise interventions of balance and weight-bearing training can maintain bone density at the hip and reduce fall risk in a chronic stroke sample.

Results suggest there is potential for strength training to improve the strength of both the paretic and the non-paretic limbs (264) and maintain hip aBMD. In light of the potential for exercise to maintain or even improve bone health, clinical trials are necessary to investigate the potential benefits of site-specific muscle strengthening as part of rehabilitation on bone health and fall reduction as part of a fracture prevention plan following stroke.

7.5.1.3 Functional Electrical Stimulation (FES)

In persons with a spinal cord injury, FES has been shown to influence lower limb muscle strength and bone aBMD as measured by DXA (264). In a 24-week five times a week intervention of 1 hour dureation, 14 persons with spinal cord injury, there was a significant increase in aBMD at the distal femur and proximal tibia. Muscle stimulation, either passive FES or electromyogram (EMG)-triggered neuromuscular stimulation, has been evaluated on arm and hand functions following a stroke (265). However there have not been any reports of bone adaptation in response to electrical stimulation for the upper extremity. For those individuals who have no motor return, FES may be ideal for prevention of bone loss. Peripheral QCT and the distal radius would be ideal to assess the impact of interventions on bone health and potentially to assist in the development of exercise protocols.

7.6 Limitations

I note several study limitations. First, I used a relatively low resolution (500 μm voxel) for image acquisition of the pQCT with a fast scan speed acquisition (25 mm/sec). Low resolution predisposes to the presence of a partial volume effect that occurs when there is heterogeneous material contained within the same imaging voxel (or volumetric element). This was done intentionally to limit the time that each participant was in the scanner and to reduce movement artifacts. A second limitation is the lack of statistical significance of a greater cross-sectional area on the paretic limb. As this is the first report study using pQCT in a stroke population, I set my sample size calculation based on density. A post-hoc calculation at the 4% site using an effect size of 0.5, alpha at 0.5 and a power of 0.80 suggested that 51 participants would be required (comparing both limbs N=102) to ascertain differences in ToA. Another limitation that affected the generalisibility of my findings is that my participants were reasonably healthy and exhibited only moderate levels of dysfunction. The American Heart Association Stroke Functional Classification median score of 2 indicates some level of dysfunction (i.e. the participants were functioning at a relatively high level but were still dependent

for some activities of daily living). Even though my participants were diverse, I intentionally designed the study to make a within-participant comparison (paretic side to non-paretic side). The cross-sectional nature of the study limits conclusions about the temporal nature of any 'bone loss' that may have occurred and the relatively low participant numbers in the sub-group limited the use of multiple regression modeling to examine predictors of bone strength over time.

There are other considerations following a stroke besides muscle disuse that can influence bone resorption. First, metabolic changes occur that affect calcium, vitamin D and parathyroid hormones levels (224,225,227). Hypercalcemia due to immobilisation is common after a stroke. If serum vitamin D levels are low, this can override the hypercalcemia to initiate parathyroid release and increase bone resorption. Secondly, for women, the mean age for a stroke event is in the early 70s (255) and post-menopause can diminish estrogen levels that ultimately impacts on bone mass (60). It is plausible that the combination of muscle-bone disuse, metabolic and hormonal influences influence the bone loss observed after a stroke. Ascertaining the mechanism(s) can assist in the development of preventative strategies.

7.7 Summary and Future Directions

In summary, in this novel study, I report significant side-side differences (paretic<non-paretic) in volumetric bone density, content, cortical thickness and strength at the radius as measured by pQCT. Muscle strength was significantly correlated with pQCT bone strength parameters. The changes I observed were similar to the cross-sectional radial fracture group. The distal radius is an excellent model to investigate stroke-disuse muscle-bone interventions with the ultimate goal of preventing fragility fractures. This cross-sectional study suggests the need for prospective research to investigate the muscle bone interaction, describe longitudinal bone changes in response to unloading following a stroke, and test the possible contribution that rehabilitation can make to strengthen bone and reduce the risk of fragility fractures.

8 Upper Extremity Fragility Fracture Initiates Osteoporosis Investigation: A Controlled Trial [5]

Probably the only clinically applicable index of bone quality at present is a patient's history of a fragility fracture.
Canadian Osteoporosis Clinical Practice Guidelines (1)

In this chapter, I report the results of a controlled trial that I completed in 2002-2003 at the Orthopaedic Fracture Clinic of the Vancouver Hospital and Health Science Centre. The aim of this study was to increase the rate of osteoporosis investigation in an "at risk" sample of participants who had sustained a fragility radial or humeral fracture. At the time of initiating this research, there had been no published interventions that aimed to improve secondary prevention of further osteoporotic fractures after a low or moderate trauma index fracture.

8.1 Introduction

In 1982, researchers at the Mayo Clinic reported that history of a previous minimal trauma or fragility fracture was associated with a relative risk (RR) of subsequent hip fracture of 1.3 (9) and this likely an underestimated the risk (3,4,6). In response, national guidelines in both the US and Canada emphasized that fragility fractures should not merely be treated orthopaedically (1) but should prompt a primary health care provider to assess osteoporosis risk and then manage the patient appropriately. Despite low-trauma fractures providing an ideal opportunity for secondary prevention of further osteoporotic fractures, numerous publications have continually highlighted the low investigation (~20%) rates after a sentinel fracture (10) . Even fewer patients received adequate therapy, highlighting the 'knowledge-care gap'. In a review of the largest series of radial fractures to date, only 23% of "at risk " patients were treated for osteoporosis within 1 year of fracture (284). Also, Feldstein and coworkers (285) reported from a retrospective review of a large database that only 9.8% of the women and 2.9% of the men were screened for osteoporosis. Yet, Cummings 1998 (286) suggested that screening for these "sentinel fractures" could reduce hip fractures by 9%.

[5] A version of this chapter has been published both as a manuscript and as a letter to the editor. MC Ashe, KM Khan, P Guy, P Janssen, HA McKay. WristWatch : Distal Radial Fractures as a Marker for Osteoporosis Intervention. *Journal of Hand Therapy* July-September 2004. MC Ashe, HA McKay, P Guy, P Janssen, KM Khan. Improving Osteoporosis Management in "At Risk" Fracture Clinic Patients (Letter). *Journal of the American Geriatrics Society* April 2005 IN PRESS.

Despite the enormous clinical burden of osteoporosis, few controlled studies have tested interventions to promote investigation and management of osteoporosis after a fragility fracture. Thus, I compared a novel 4-part intervention with usual care in patients with upper extremity fractures. My primary outcome was the number of patients investigated for osteoporosis and the secondary outcomes included the number of "osteoporosis best practices" that each participant was offered.

8.2 Methods

This study was a prospective controlled trial that evaluated the effectiveness of a 4-part intervention designed to increase the osteoporosis investigation and osteoporosis best practice treatment as recommended by the Canadian Consensus on Osteoporosis guidelines (1). This study was approved by the University of British Columbia and Vancouver General Hospital and Health Science Centre Clinical Research Ethics Board. All participants signed a written informed consent.

8.2.1 Participants and Setting

I identified men and women over 50 years of age who had sustained a minimal trauma (defined as falling from a standing height or less) radial or humeral fracture and had attended a hospital-based fracture clinic in Vancouver, British Columbia, Canada.

Vancouver, Canada, has a population of 2 million people (333) with 195 licensed physicians per 100,000 people in the province of British Columbia (334). Canada has a universal health care insurance policy, and the cost for DXA following a minimal trauma fracture is covered for residents (335). In addition, the government covers 75% of the cost of standard osteoporosis therapies including,etidronate, but not 2nd generation aminobisphosphonates such as alendronate or risedronate, for individuals over 65 years of age (336).

8.2.1.1 Exclusion Criteria

Potential participants were excluded if: i) she/he was already diagnosed with and/or were being treated for osteoporosis prior to having their index fracture; ii) could not speak English or iii) were not living independently within the community.

8.2.2 *Experimental Protocol*

Participants were enrolled at fracture clinics from July 2002-October 2003. I enrolled participants as she/he waited for the fracture clinic appointment. As all fracture clinic participants waited in a small common area, there was a potential to overhear conversations or converse amongst eligible participants; a potential contamination of treatment groups. Therefore, I used an alternating "month on" and "month off" design for enrollment (337). In this design, participants were allocated to the control group ('usual care') for one month, after which new participants were enrolled into the intervention group for the following month. Over the course of 15 months, there were a total of 8 one-month periods during which new participants were enrolled in the control group and 7 one-month periods where new participants were enrolled into the intervention group. I outline the flow of participants through the investigation. Figure 8-1.

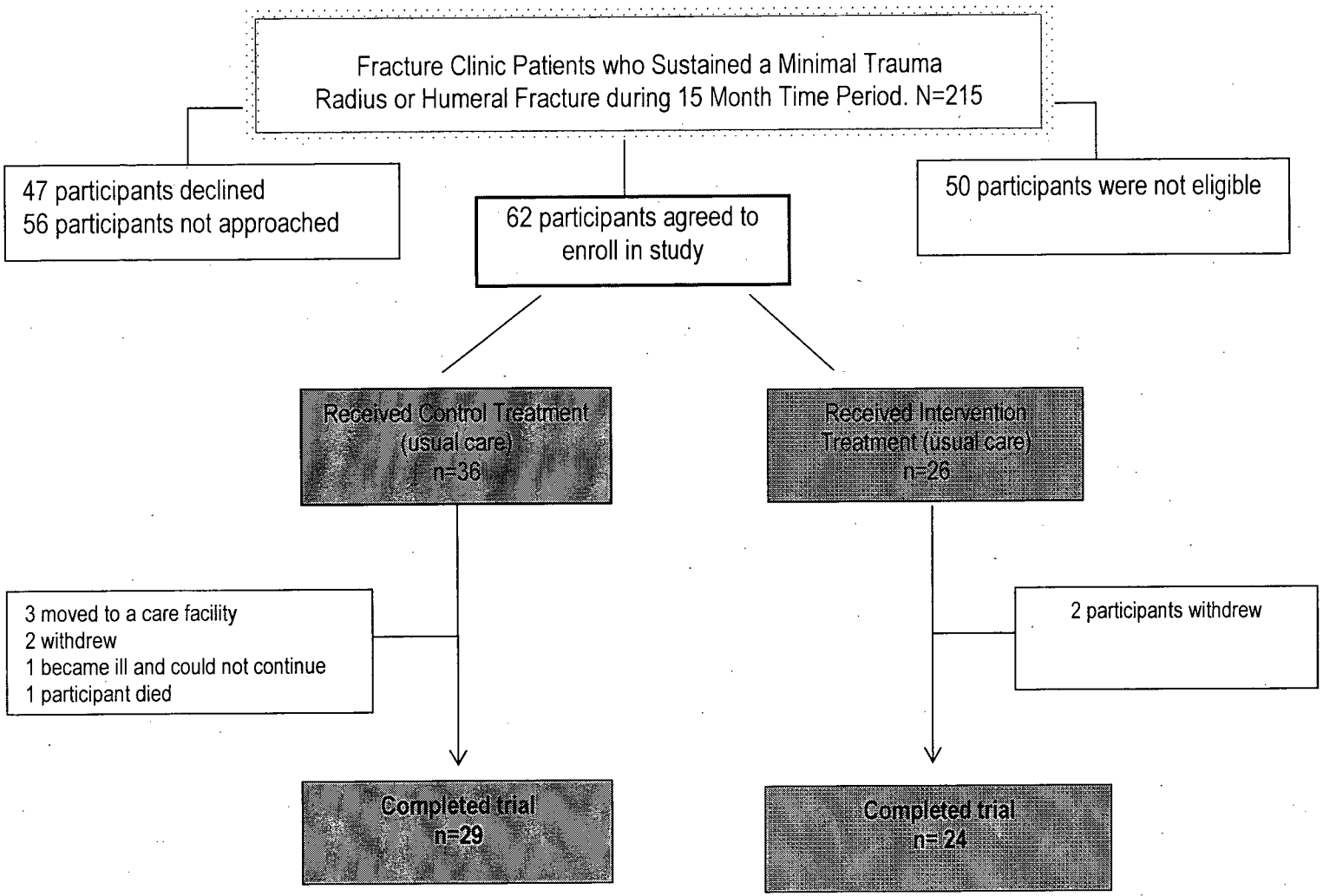


Figure 8-1. Participant flow through the controlled trial.

Baseline data were collected for all participants using the Canadian Multicentre Osteoporosis Study (CaMOS) (321) questionnaire and the DASH (Disabilities of the Arm Shoulder and Hand) (206,212). The CaMOS is a researcher-administered questionnaire that records participant lifestyle and health related characteristics such as number of co-existing diseases, number of falls, and family history of fractures. The DASH measures function, symptoms and quality of life issues pertinent to the upper extremity using a scale from 0-100 with higher scores suggesting more disability. Both tools have been assessed for validity and reliability (206,212,321).

8.2.2.1 Intervention

The intervention consisted of: (i) an information sheet given to the participants explaining that she/he had suffered a minimal trauma fracture (defined as falling from a standing height or less) diagnostic of osteoporosis, (ii) a request for the participant to take a letter from the orthopaedic surgeon who was managing the fracture to the PCP alerting her/him to the recent minimal trauma fracture (this was more than is currently provided under "usual care"); (iii) a faxed letter to the PCP referring the participant back for assessment and management of osteoporosis; and (iv) a follow-up telephone call at 4-6 weeks to remind the participant to visit her/his Primary Care Physician (PCP) to be assessed for bone health status.

Control group patients received "usual care" — defined as treatment for the fracture by the hospital staff and routine notification to the PCP of the fracture and any follow-up plans. Fracture clinic health care team members (e.g., nurses) were aware of the study but were not aware of participant group assignment. The control group was told that the study was investigating radial and arm fracture outcomes. Table 8-1 illustrates the comparison between the intervention and control group protocols.

Both groups were telephoned at 6 months post-fracture by a researcher blinded to group allocation. She administered the Diagnosis Management Questionnaire (DMQ) (Figure 8-2). I developed this questionnaire specifically to ascertain the osteoporosis investigation rate and osteoporosis "best practices" as recommended by the 2002 Osteoporosis Consensus (1).

At 6 months post-fracture and following administration of the DMQ, participants in the control group and their PCP received the intervention. All control participants were informed of the risks of osteoporosis and

a recommendation was made to return to the PCP for follow-up. Secondly, the primary care physician was faxed the Intervention letter outlining the risk of osteoporosis.

Table 8-1. Overview of fracture care and osteoporosis intervention for each group.

A. Intervention	B. Control
1. Usual care for fracture	1. Usual care for fracture
2. Letter to patient indicating risk of osteoporosis	
3. Letter from Orthopaedic Surgeon to PCP alerting to risk. Patient to take to PCP	
4. Faxed Letter for PCP alerting to risk	
5. Reminder telephone call at 4-6 weeks	

Figure 8-2. Diagnosis and Management Questionnaire

Diagnosis and Management Questionnaire
(Researcher-administered)

1. In the past six (6) months, has your doctor investigated you for osteoporosis?
   Yes No

2. In the past six (6) months, has your doctor told you that you have osteoporosis?
   Yes No

3. Please tell me what health services you were offered in the past six (6) months:

- ☐ DXA
- ☐ Blood tests
- ☐ Ultrasound
- ☐ Specialist referral (orthopaedic/internal medicine/rheumatology/other)
- ☐ Advice regarding calcium and Vitamin D
- ☐ Medications (hormone therapy/selective estrogen receptor modulators/bisphosphonates/calcitonin)
- ☐ Exercise prescription

8.2.2.1.1 Primary Outcome

The primary outcome was the participant's self-report of physician investigation or diagnosis of osteoporosis as indicated on the Diagnosis Management Questionnaire (DMQ) (Figure 8-2).

8.2.2.1.2 Secondary Outcome

Participants were asked which components of 'standard of care' were offered during the six-month Intervention as defined by the 2002 osteoporosis consensus guidelines (1). Participants answered "yes" or "no" to each item. The checklist included investigation (DXA, blood tests (secondary causes of osteoporosis), diagnostic ultrasound, specialist referral (orthopaedic, internal medicine, rheumatology, etc.), advice regarding calcium and vitamin D, discussion of suitable medications (e.g., hormone therapy, selective estrogen receptor modulators, bisphosphonates, calcitonin, etc.) and exercise prescription. A research assistant, not involved in the recruitment/enrollment process, administered the DMQ.

8.2.3 Sample Size-Statistical Power

Power calculations were based on estimated rate of investigation (20-30%) of osteoporosis after a fracture (18). Based on an anticipated improvement in investigation rate within the intervention group to 60%, 27 participants in each group were needed for 80% power to detect effectiveness at a Type 1 error of $p<0.05$.

8.3 Statistical Analysis

I used an intention to treat (ITT) analysis. I reported the characteristics of the participants as means ± standard deviations, except level of education for which I reported the frequency or mode. Independent t-tests or a chi-square statistic were used to compare differences between groups depending on whether the data were continuous or binary. I present the number of practices offered as a percentage. I presented relative risks (RR and 95% confidence intervals) for the intervention between groups and the number needed to treat (NNT and 95% confidence intervals). I set the Type I error at $P<0.05$ for all statistical tests.

8.4 Results

8.4.1 Descriptive Characteristics

Sixty-two participants were enrolled in this study (36 control and 26 intervention) Table 8-2. The mean age in the intervention group was 65.5 ± 12.2 years and for the control 69.6 ± 10.9 years. There were almost 4 times as many women enrolled in the study compared with men, consistent with the pattern of upper extremity fragility fracture presentation. Although there were no significant differences between groups, except the control group had a greater number of radial fractures.

Table 8-2. Description of the Intervention and Control Groups

	Intervention	Control
n=	26	36
Age (years)	65.5 ± 12.2	69.6 ± 10.9
Women	23	26
Men	3	10
Height (m)	1.7 ±0.1	1.7 ± 0.1
Weight (kgs)	73.8 ±16.6	72.9 ± 16.2
BMI	25.9 ± 5.5	26.0 ± 4.7
Radial Fracture	14	28*
Humeral Fracture	12	8
DASH at Baseline	37.9 ± 18.2	40.2 ± 25.3
DASH at 6 months	21.5 ± 18.7	19.2 ± 20.5
Previous Fractures	1 ± 1	1 ± 1
Number of Medications	2 ± 2	2 ± 2
Number of Comorbidities	1 ± 1	2 ± 2
Number of Falls/past Week	0	0
Number of Falls/past Month	3/26	0
Level of Education (mode)	Grades 9-13 (33%) University (20%)	University (44%) Grades 9-13 (6%)

BMI=Body Mass Index; * $p<0.05$

8.4.2 Primary Outcome

In the intervention group, two of 26 participants withdrew from the study due to inability to complete the follow-up. Nineteen of the 26 participants were investigated for osteoporosis (73%). In the control group, seven participants were unavailable for follow-up: two withdrew because they would not be available for follow-up, three were moved to a care facility, one became ill and was unable to complete the study and one participant died. Seven of the control participants (19%) were investigated for osteoporosis by the

PCP as reported by the participant. Investigation for osteoporosis was significantly higher in the Intervention group ($p<0.001$). The relative risk was 3.8 (95%CI 1.9-7.6) (Table 8-3). The number needed to treat (NNT) with the intervention to increase investigation by one participant was 2 (95%CI 1-3).

Table 8-3. Investigation and Diagnosis Rates for the Intervention and Control Groups

	Investigated for Osteoporosis	Diagnosed with Osteoporosis
Intervention n=26	19 (73%)*	5/19 (26%)
Control n= 36	7 (19%)*	2/7 (28%)

*Chi Square significant at $p<0.001$

8.4.3 Secondary Outcomes

Overall, thirty-seven best practices were offered to participants in the intervention group and 17 to those in the control group. Sixteen partipants in the Intervention group reported being offered bone densitometry whereas only 4 participants in the control group reported this offering ($p<0.001$). (Figure 8.3) I separated the best practices into assessment and treatment. The intervention group was offered significantly more assessments (as recalled by participants) as compared with the control group. Only 7/26 (27%) intervention participants recalled being offered calcium and vitamin D compared with 6/36 (16%) in the control group (Figures 8.4, 8.5).

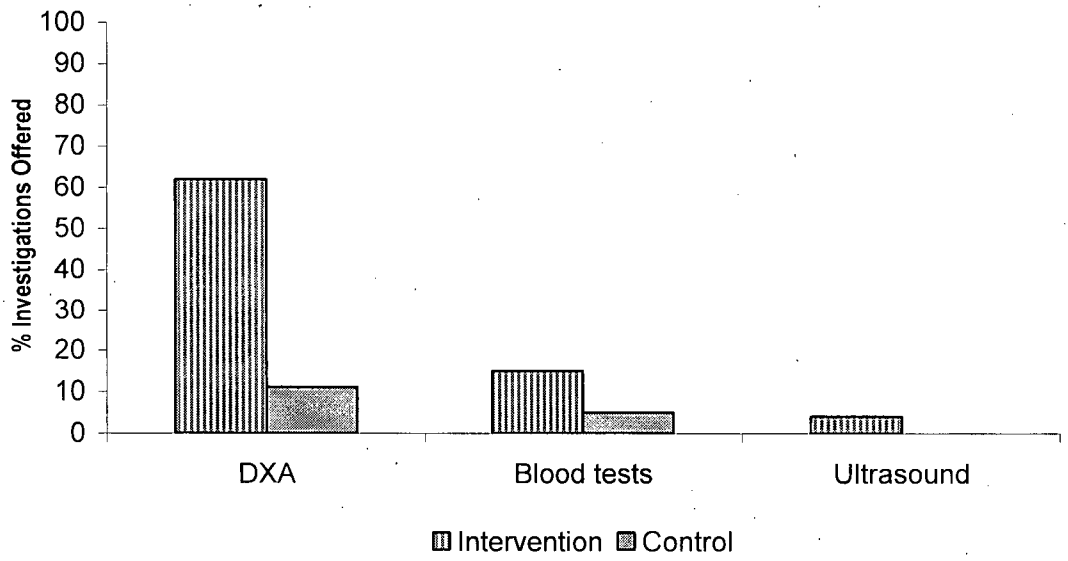


Figure 8-3. Percentage of 'Best Practice' Investigations Offered to Participants by Group

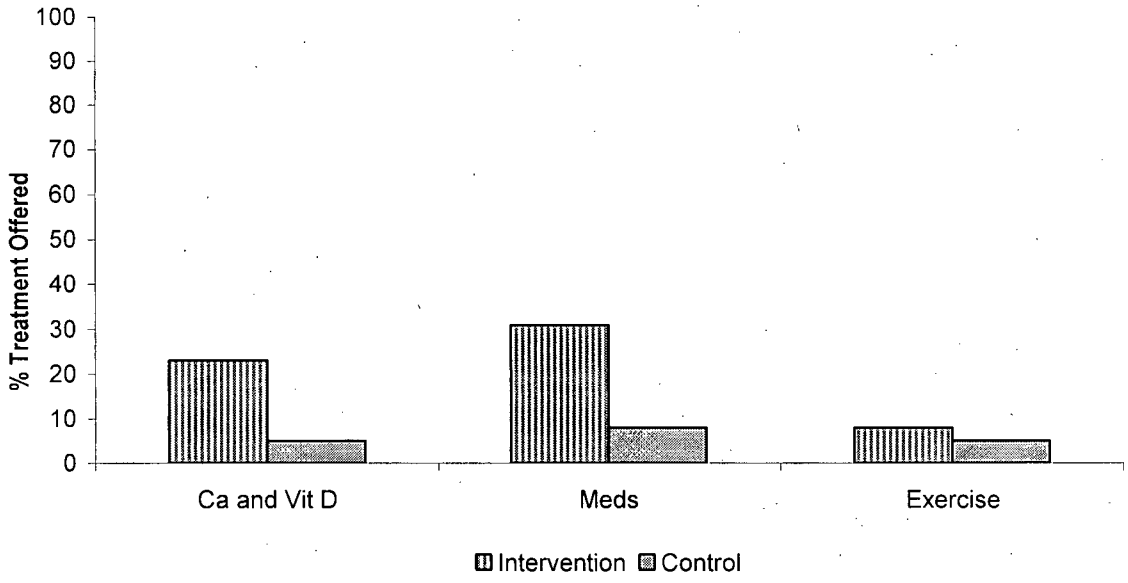


Figure 8-4. 'Best Practice' Treatment Offered to Participants by Group.

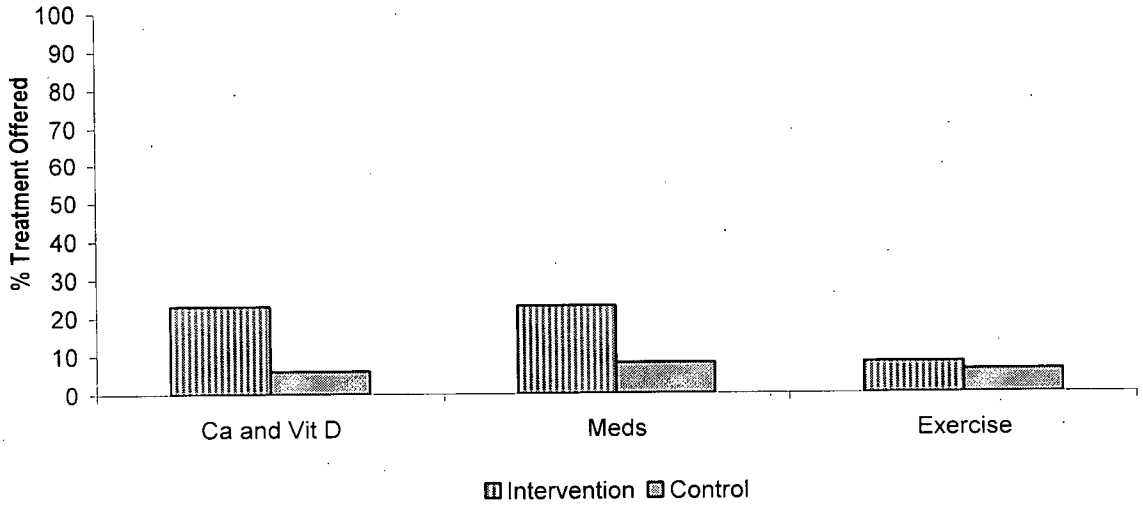


Figure 8-5. Percentage of Best Practices Offered by Physicians to Participants Investigated.

8.5 Discussion

Nearly four times as many participants in the intervention group were investigated for osteoporosis after a fragility fracture. This highlights the effectiveness of this multiple-component quality improvement intervention of a patient education and physican alerting system, and offers a foundation for the development of an evidence-based clinical care pathway.

My intervention contained innovative components. First, I designed my study using a multifactorial intervention because of previous research suggesting that a comprehensive intervention targeting change in practice patterns yields better results than targeting physician behaviour alone (338). Secondly, numerous publications in the pharmacy literature support practice feedback reports and academic detailing (338-340) and peer-influence to affect practice change; therefore, I used a letter directly from local osteoporosis experts addressed to the primary care physician to highlight the need for osteoporosis assessment.

This investigation was very 'applied' and thus, it is important to discuss how the findings could be translated into clinical physican practice. First, standing orders contained within the orthopaedic surgeon's follow-up note to the PCP would ensure that patients and PCPs instigate optimum osteoporosis care.

Alternatively, a health care worker could liaise between patients at risk and the health care service providers to initiate the care pathway (fracture liaison service).

There are several reasons to support the use of standing orders to promote osteoporosis investigation. In a large hospital setting with weekly fracture clinics with orthopaedic surgeons, a statement outlining risk of osteoporosis and need for investigation could be part of the orthopaedic follow-up letter. However previous investigations of surgeon-initiated orders for osteoporosis assessment and treatment found poor results due to poor surgeon compliance with the protocol (341). An alternative plan would be to initiate standing orders at the level of the radiology department; it could initiate an automatic DXA referral for individuals with a major osteoporosis risk factor (fragility fracture) and another minor risk factor (age and family history etc.). Regardless of whether DXA is initiated, simple instructions on calcium/vit D usage and exercise prescription is essential after a fragility fracture.

Service delivery via a "Fracture Liaison Service" also warrants consideration. In this model, a designated team member performs case-finding and initiates appropriate investigation. In a recent Ontario trial, a hospital-based nurse co-ordinated osteoporosis case-finding and initiated appropriate investigations/ treatments. The salary for nurse-practioner in Canada in 2005 can range between Canadian $43, 000 to $68, 000 (342). Despite the obvious benefit of a dedicated case-finding position, this may still be cost prohibitive in most community based hospitals, but warrants an economic evaluation.

Despite the higher reported rate of investigation in the intervention group, the rate of prescription of consensus-based osteoporosis treatments was not significantly higher compared with the control group. This extends previous work (343) reporting the same pattern of practice. In particular, there was no difference between calcium, vitamin D and exercise between groups. This highlights several important issues. First, it is possible that this intervention successfully highlighted the need for investigation, however, the intervention did not go far enough to encourage/recommend simple treatment options such as calcium, vitamin D and exercise to improve balance and overall strength. Secondly, as the primary outcome was based on patient recall, it is possible that physicians did suggest these options but it was not specific enough to be interpreted as a treatment option by the patient.

Although my study showed that PCPs will investigate at-risk patients for osteoporosis when prompted by the orthopaedic surgeon, future studies could investigate the use of clinical pathways that utilise the expertise of other health professionals (e.g., physical therapist, nurse) at either the fracture clinic or

emergency department level and systematically initiate PCP follow-up regarding osteoporosis. Secondary prevention is an important avenue for other health care providers such as physiotherapists to be more holistic in the treatment of a fragility fracture. A clinical pathway (for after a peripheral fragility fracture) should be developed whereby physiotherapists routinely prescribe exercise for strengthening, strategies for fall reduction and recommend calcium and vitamin D usage. Finally, the physiotherapist should encourage patients to return to the PCP for osteoporosis assessment and management.

My control group data suggest that health professionals' awareness of the risk of osteoporosis associated with minimal trauma fracture does not guarantee appropriate investigation for all patients. Thus, involving patients in their own management (as in my intervention) may improve followup and diagnosis rates. However, my study was not designed to test the efficacy of individual components. Strategies such as prominently-placed handouts in emergency, radiology and physiotherapy departments may remind at-risk patients to request assessment by the family physican, but the effect of such single interventions remains to be tested.

8.6 Limitations

This study has several limitations. At the time that I commenced this controlled trial, I considered random asiignment but decided on a month-on month-off assignment for several reasons. Primarily I wanted to minimize the potential for contamination between participants waiting together for appointments in a small room. The fracture clinic environment has little space available to speak confidentially to prospective participants. Secondly, the length of the initially randomisation process would have disrupted the delivery of medical services during the fracture clinic visit. However, I tried to maintain internal validity by using a before and after design with contemporaneous controls.

Secondly, the primary outcome depended on patient recall, which is subject to bias and may underestimate or overestimate levels of investigation or treatment. Due to anxiety associated with a fracture, it is conceivable that patients could have forgetten they had received osteoporosis-related material or had an intervention offered. However, DXA is a reliable and accurate outcome that patients are unlikely to forget; significantly more intervention participants had DXA testing. Secondly, an outcome of this study was the diagnosis of osteoporosis. Using this strict definition, some participants who may have been diagnosed with osteopenia were not included as 'diagnosed with osteoporosis'.

My intervention had multiple components (alerting both the physician and the participant). Thus, it is not possible to say which element of the intervention, if any, was 'most' effective. Lastly, this study did not provide any insight into physician-related barriers to investigation. Interestingly, in a recent qualitative study involving physician focus groups (288), family doctors expressed their desire that "the public be made more aware so patients can come in and prompt the physician and then the physician can react". The physicans who took part in those focus groups believed that because they were busy, osteoporosis investigation was often overlooked because of its non-urgent nature. However, the physicians also believed that if prompted, they would investigate for osteoporosis (288).

8.7 Summary and Future Directions

In this study, I tested a simple intervention aimed to improve investigation rates in an at-risk population. I am a licenced physiotherapist and certified hand therapist, and I see that secondary prevention measures are not routinely used to reduce the risk of disease. An upper extremity fracture is a sentinel event in the course of osteoporosis and it can be used to effectively initiate investigation. I showed in this controlled study that an education/alerting system can increase osteoporosis investigation three-fold. Although it is important to discern the most efficacious component of this health delivery (patient vs primary health provider), it may be advantageous to compare my combined model against its individual components. This may help to ascertain which part of the intervention is more effective – educating the patient or alerting the physician, or both. Also, each of these goals could be achieved in a variety of ways, so future studies could test various ways of delivering either patient, or physician, information. I conclude that there is an urgent need for more research that addressess the 'gap in care' between osteoporosis management guidelines and current medical practice.

9 Barriers to Investigating Osteoporosis after a Fragility Fracture: A Survey of BC Physicians[6]

In this chapter, I report the results of a questionnaire sent in 2002 to primary care providers (PCP) and orthopaedic surgeons in two locations of British Columbia. As chapter 9 is closely related to the investigation reported in Chapter 8, I provide a short introduction here to avoid redundancy with the introduction of the previous chapter.

9.1 Introduction

Osteoporosis costs the Canadian health care system in excess of $1.3 billion annually (2). The crucial fact that underpins the rationale for this Chapter 9 study is that although minimal trauma fractures are excellent predictors of future fractures (3,6,7), my recent research described in chapter 8, and the work of others (10) shows that the rate of intervention following these sentinel events remains low.

Therefore, this study investigated physician osteoporosis knowledge as measured by response to brief clinical questions to ascertain their self-reported practice patterns for patients at-risk of osteoporosis and to highlight barriers to osteoporosis intervention. My primary aim was to provide new knowledge as to why investigation rates following a fragility fracture were on average less than 20%. I specifically chose to investigate physicians who practiced outside Vancouver and its associated 'Lower Mainland' because I was conducting a controlled trial in Vancouver (Chapter 8) contemporaneously and I did not want to cross-contaminate the physicians in both studies. At the time of this questionnaire, there had been very few reports of physician osteoporosis practice patterns following a fragility fracture (288,298).

9.2 Methods

9.2.1 Participants

A 2-page 5-question survey was mailed to PCPs and orthopaedic surgeons (OS) in Prince George and Victoria, British Columbia. In total 517 (501 PCP and 16 OS) questionnaires were mailed. Names were obtained from the 2002 British Columbia College of Physicians and Surgeons Directory. Participants were sent the questionnaire if her/his name was listed as either Family Practice or Orthopaedic Surgeon. This study was approved by the University of British Columbia Behavioral Research Ethics Board.

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[6] A version of this chapter has been published as a manuscript. MC Ashe, KM Khan, P Guy, P Janssen, HA McKay. Fragility fracture and Osteoporosis Investigation. *British Columbia Medical Journal* Vol45, No.10;506-509.

9.2.2 *Questionnaires*

I printed questionnaires to the OS on different coloured paper to distinguish between participant specialties without compromising anonymity. A cover letter accompanied each survey with instructions. A self-addressed returned envelope was included and respondents were given the option to fax the questionnaire back. Although responses were anonymous, respondents were asked specific identifying questions such as gender, type of practice, etc. Age was not requested in this survey. All responses were included for analysis if received within 30 days of having been sent out. The survey was approved by the University of British Columbia Ethics Review Committee.

9.3 Statistical Analysis

All questionnaires were analysed for frequency of responses and reported as the number of responses received and percentage where appropriate.

9.4 Results

Five hundred and seventeen (517) questionnaires were mailed. Twenty responses were returned because the physician had moved and two responses were returned by practitioners who excluded themselves, as they were no longer practicing family medicine. In total 141 surveys were received. Table 9-1 details the response rate. Table 9-2 summarises the top 3 responses to each question with the corresponding response rate.

Table 9-1. Physician's Questionnaire Response Rate.

Questionnaire Response History		
Surveys Sent	**517**	501 PCPs (162 F, 333 M, 22 Not disclosed) 16 Orthopaedic Surgeons (16 M, 0F)
Returned Surveys	**20**	Reason: Address change, No forwarding address
Excluded Surveys	**2**	Self excluded because no longer working in family practice.
Total Surveys	**495**	479 PCPs 16 Orthopaedic Surgeons
Surveys Received	**141**	103 PCPs (34 F, 64 M, 5 Not disclosed) 6 Orthopaedic Surgeons (6 M)
Overall Response Rate	**29%**	28% PCPs (21% F, 17% M) 40% Orthopaedic Surgeons (100% M)

Table 9-2. Physician responses from questionnaire concerning barriers to investigation after a wrist fragility fracture.

Question	Top 3 responses	Response rate
1. Who do you believe should address osteoporosis management in patients over 50 years of age with a minimal trauma fracture (e.g. fall from a standing height or less)?	Overall 76% of all respondents reported that the PCP is the best practitioner to manage osteoporosis related issues; compared with 0% for the Orthopaedic Surgeon and 24% for a shared responsibility of PCP and OS	
2. Of the following, who would you investigate for osteoporosis after a low-impact fracture?	> 60 years of age	134 (95)
	Obvious secondary cause of osteoporosis	124 (88)
	Women	123 (87)
3. What would prevent you from using dual energy X-ray absorptiometry (DXA) to investigate a patient older than 50 years of age with a minimal trauma fracture?	Nothing	91 (65)
	Can treat without DXA result	29 (21)
	Do not have access to DXA	13 (9)
4. What do you believe are barriers to investigating a patient for osteoporosis after a minimal trauma fracture?	Nothing	91 (65)
	Medical Services Plan not paying for DXA	33 (23)
	Other	9 (6)*
5. What do you see as an effective way of increasing the diagnosis and management of osteoporosis in a population at risk for the disease?	Wider coverage by Medical Services Plan for drugs which have been proven effective	98 (70)
	Routine referral for DXA > 50 yrs with a low-impact fracture	93 (66)
	Wider Medical Services Plan reimbursement of DXA	71 (50)

* Other reasons: unwillingness of (patient) to use treatment; patient transportation issues; responsibility of primary care physician (orthopaedic surgeon);do not always think about it (2x); lack of follow-up.

9.5 Discussion

This questionnaire highlighted that the BC physicians who responded to this survey were knowledgeable about osteoporosis management and reported no barriers to appropriate patient care following a fragility fracture. In both an urban and a rural area of British Columbia, both PCP and OS consistently indicated that primary care physicians should be the appropriate providers of osteoporosis management. These findings extend results from eastern Canada and the US (288,298).

The purpose of this BC-based survey was to understand possible physician barriers to osteoporosis investigation following low or moderate trauma fractures. My findings are of interest because on the one hand, physicians do not investigate routinely for osteoporosis after a fragility fracture (10), yet, 65% of respondents reported either "nothing" was stopping them from investigating for osteoporosis or that there were "no barriers" to investigation. This dramatically highlights the difference between 'opinion' and 'action', or, to put it another way, 'theory (knowledge)' and 'practice (behaviour)'. Combining my findings with those in the literature, it would appear that the lack of secondary prevention of osteoporosis represents a gap in *service delivery or practice behaviours rather than physician knowledge*.

A successful intervention could involve specific physician and patient reminders. Although the PCP could be the co-ordinator of the investigation, many other health care providers could assist in the case-finding pathway. In the present survey, physicians advocated routine referral for DXA scan for secondary prevention of osteoporosis. Attainment of good health is a multi-dimensional issue and a team approach is necessary to assist in the identification of potential risk and initiate effective management strategies. Data suggest that effective programs normally include the involvement of the physician, the patient and other health care members (344).

My study seems to demand that I offer potential solutions to the current 'gap in care' that might be tested in future research. One avenue is to consider novel health care pathways that would lead to osteoporosis investigation. For example, referrals for densitometry could be generated on admission to the emergency department as part of hospital care plans (in centers where DXA is available) and results could be sent directly to the PCP for follow-up. Concurrently, patients with fragility fractures could routinely be prescribed calcium, vitamin D and appropriate exercises. Although this scenario could be occurring in clinical practice, data from my controlled trial suggest that this is not the case at present (345). As educating patients is a vital component to health care management, research should test whether

strategically locating pamphlets in radiology offices, emergency departments and physicians' offices would alert patients and prompt them to ask the PCP for a bone health assessment.

It is plausible that other health care professionals, such as physical therapists and occupational therapists (who see many potential patients routinely for therapy following a fragility fracture), could successfully provide education on exercise, bone health and refer the patient back to the PCP for osteoporosis-specific management, i.e. a dedicated appointment to deal solely with the non-urgent problem of osteoporosis. In a recent study (297), investigators observed that, like physicians, physiotherapists were concerned only with treating the orthopaedic fracture and did not address bone health, balance and fall-related issues.

9.6 Limitations

This questionnaire provided some important information on physician reported barriers to secondary prevention of osteoporosis. The response ratecould have been increased by identifying respondents who did not return the questionnaire and following up. In the interest of maintaining anonymity, I did not number/identify the respondents, but this could increase the response rate in a future investigation. Secondly, physicians in general, tend to have lower response rates to questionnaires [mean response rate of 54% compared with 68% for a non-physican sample (346)], and there is speculation, that physicians are more likely to respond to a questionnaire if she/he feels knowledgeable about the topic area (347).

The possibility remains that the sample of respondents studied do not adequately reflect the entire physician population. It is theoretically possible that the respondents who suggested that there were no barriers to investigating osteoporosis after a fragility fracture may be those very physicians who *do* investigate appropriately. But my results (345) from a large urban centre, show that this would only account for less than 20%. On a positive note, the response rate was the same as that achieved by Simonelli and coworkers (28%)(298) and overall the raw number of responses (141) is the highest of the studies published to date. Nevertheless, it is prudent for me to limit the conclusions that I can draw from the study.

9.7 Summary and Future Direction

This questionnaire highlighted that BC physicians who responded to this survey were knowledgeable about osteoporosis management and saw no barriers to appropriate patient care. I believe this survey raises some important issues. The PCP is a key member of the health care team and should be the co-ordinator of osteoporosis-bone health management. However, as I found with my controlled investigation (Chapter 8), additive strategies such as patient and physician reminders following a minimal trauma fracture may be more effective in initiating assessment/management. Other health care team members (e.g., physiotherapists, pharmacists) and the patient need more education on bone health to encourage appropriate management. A positive step in health care delivery is to support the PCP in their role as central co-ordinator by i) recommending orthopaedic surgeons strongly encourage "at–risk" patients in fracture clinics to follow-up with the family doctor *specifically* about osteoporosis; 2) educating physiotherapists to routinely recommend calcium and vitamin D after a fracture, assess for balance and strength problems and to encourage the patient to return to the PCP for follow-up *specifically* about osteoporosis; and 3) test other initiatives such as educating patients with information located in strategic areas such as emergency and radiology departments, pharmacies and private therapy clinics. Overall, I believe there needs to be a shift in thinking from "why aren't physicians investigating for osteoporosis ?" to "how can we collectively contribute to improve bone health in our communities ?".

10 Summary, Knowledge Translation and Future Directions

10.1 Overview

In this three-part thesis, I undertook cadaveric and human studies of a novel bone imaging technology – pQCT-- and I completed an intervention trial that aimed to contribute toward improving management of osteoporosis. Specifically, I investigated the variability of pQCT using 4 different acquisition resolutions (200, 300, 400 and 500μm) to test total mineral content and total area. Then, based on the observed variability, I conducted an extensive validation study of pQCT measures in aged cadaver bones. In the cross-sectional studies of this thesis, I examined radial bone adaptation using both a fracture-immobilisation and a stroke-disuse model. In particular, I compared bone strength, muscle strength and functional measures. In a controlled trial, I examined the impact of a simple intervention aimed to increase investigation rates of osteoporosis after a radial or humeral fracture. To complement this, I conducted a survey of physicians to ascertain barriers to osteoporosis investigation after a fragility fracture. In this chapter, I draw conclusions, suggest future directions for each area of study, and highlight the clinical implication of my work.

10.2 Optimizing pQCT Results. Reliability of operator-dependent pQCT parameters in cadavers and humans with low-bone mass.

In Chapter 4, I reported the variability associated with changing pQCT acquisition parameters. This methodological investigation highlights the need for universal pQCT reporting protocols — something that needs be addressed by an international standards committee to ensure studies are comparable. Examples of similar agreements are those used for bone histomorphometry nomenclature (118) and the CONSORT statement for randomized trials (348).

The variable results of the reliability study using different acquisition parameters raised the question, 'Which result is correct?', and hence, motivated me to undertake the accuracy study. Peripheral QCT provides novel insight into aspects of cortical bone but, as with any new technology, research to discover its limitations is as important as research using its proven capabilities. My study provided a great deal of novel data about pQCT which then can underpin future studies in our laboratory, as well as in other centres.

I believe that there is an urgent need for further evaluation of pQCT software, hardware, and attempts to make the technology available at more proximal, clinically-relevant sites such as at the hip. There are at

present only 2 main types of pQCT analysis software, and not surprisingly at this early stage of this instrument's life, neither is ideal. Software limitations include some user-'unfriendliness' and concerns about accuracy of trabecular bone measurement. I see collaboration between software engineers, mechanical engineers, imaging physicists, and bone biologists as having great potential to develop 'state-of-the' art pQCT software. With respect to hardware, future research will refine pQCT instrumentation. During a brief traineeship with software engineer Tom Beck at Johns Hopkins University, I learned that there are plans to develop a pQCT device that will provide superior resolution by 'sampling' at numerous sites around a bone and interpolating data from algorithms to 'complete' the image *(personal communication Tom J. Beck, Baltimore, Maryland)*. Further along this field, but outside the scope of my dissertation, is the bone imaging technique of micro computerized tomography (micro-CT). This provides more detailed information about trabecular bone than is otherwise possible, but at present is limited to use in small blocks of excised bone. There are emerging instruments that have this capacity for humans, in vivo.

In addition to this research in technology, I see a great opportunity to use pQCT in other populations at high risk of fracture; patients who have used corticosteroids for significant periods, older men (which would complement my studies in women) and those who have sustained a spinal cord injury (which would complement my studies in stroke). As always, studies in clinical populations provide unique human data in the form of a 'natural experiment'. Such studies commonly lead to hypotheses being generated about underlying mechanisms, and these hypotheses are often best tested in an appropriate animal model. I believe that a combination of human and animal model studies could greatly advance the understanding of the important, but rather under-researched physiology of the muscle-bone interaction.

10.3 Improving the Accuracy of pQCT for Evaluating the Aged Human Radius.

In chapter 5, I reported the results of an extensive validation study of pQCT in aged cadaver bone. Imaging technology is advancing rapidly and this provides new information about in vivo bone structure, but the challenge remains to develop the best possible operating protocols. At first glance it would appear that this is even more important for pQCT technology than with DXA, as the latter does not permit acquisition and analysis parameters to be manipulated. In particular, DXA acquisition parameters cannot be adapted for testing very low bone mass (e.g., older osteoporotic women) and yet this is the very group that requires accurate assessment. 'Low resolution' software exists to analyse DXA scans but I have found little rigorous testing of the accuracy of this software and data on which to base the decision on when to use it. My data showed that low resolution (400μm-500μm) acquisition resulted in pQCT

underestimating total bone area and content. This had important implications for my present investigations—I have been analysing the scans with lower bone thresholds at the cortical edge (periosteal surface) but a higher threshold at the endosteal surface, as per my histomorphometry observation in my accuracy study. Further, I have commenced a prospective investigation of bone response to fracture-immobilisation in older participants, and with their inherently lower mass bone, I have commenced using 300μm resolution to acquire data.

As I completed an extensive investigation of the largely cortical 30% site, I believe that more research is needed to validate pQCT measurements made at the highly trabecular 4% site. My data suggest that whether or not pQCT is a suitable instrument for providing accurate data regarding trabecular bone remains questionable.

I also highlight the need for accuracy studies of muscle cross-sectional area as measured by pQCT. That pQCT is able to measure muscle cross-sectional area is a boon for certain types of investigations of the bone-muscle interaction but the technology for this purpose is in its infancy. To obtain muscle measures, a pQCT scan is taken at the greatest limb circumference (or muscle bulk —approximately 66% site of tibia or radius). The criterion standard for this measurement is MR imaging which does not provide bone mineral data. Peripheral QCT may provide a very useful combination of muscle and bone data but to my knowledge, there have been no studies of the relative accuracy of pQCT against MR imaging for muscle measures. If pQCT proved accurate for muscle, it would be an ideal tool with which to investigate the impact of exercise-based treatments on bone health.

10.4 Bone Adaptation after a Distal Radius Fracture: A pQCT Study.

This cross-sectional study provided novel data particularly relevant to therapy. As a physiotherapist and Certified Hand Therapist, I was intrigued by the magnitude of difference between the bone outcomes after fractures of the non-dominant side and the dominant side. My results lead me to propose a future study to examine the time course of the (presumed) bone loss after fracture depending on hand dominance. Such a study would be greatly enhanced by having longitudinal measures of important hormones of bone metabolism (including PTH, vitamin D, calcitonin, estrogen, testosterone, IGF-I) with the aim of gaining insights into the mechanisms regulating this bone loss. A limitation of such a study would be that there may be many local factors acting (as well as paracrine or autocrine effects), and these would not be detected by serum assays. In addition, future investigations should focus not only on attempting to

understand the pattern of loss but to also focus on the necessary solution for patient health — interventions designed to minimize the deleterious effect of the fracture.

10.5 Bone Structural Adaptation to Chronic Disuse following Stroke: A pQCT Study.

In chapter 7, I highlighted bone structural adaptation to inactivity imposed by a stroke and thus, broadened my examination of bone adaptation to neurological disuse. Taken together, chapters 6 and 7 suggest important possible roles for physiotherapists in the development of bone health in populations at high risk of future fracture. In my post-doctoral studies I will extend this field of research to investigate the effectiveness of community-based exercise in people with chronic stroke. I will measure bone parameters to see what change (if any) occurs with intervention. It is noteworthy that while hip fractures cause patients to have a 20% risk of dying within the first 3 months, people who have had a stroke are up to 7 times more likely to sustain a hip fracture. This likely occurs because of poor bone health and an increased propensity to fall. My future studies will investigate treatments to reduce fall events and improve bone density and structure in this high-risk population.

10.6 Upper Extremity Fragility Fracture Initiates Osteoporosis Investigation: A Controlled Trial.

Effective health care delivery is an important part of evidence based medicine. My controlled trial showed that a simple reminder about the risk of osteoporosis when a fracture had occurred caused a four-fold increase in the rate of osteoporosis investigation. I recognize the potential bias and limitations associated with patient self-reporting as the primary outcome measure and I suggest future investigations involve cross-referencing patient recall with chart data obtained from family physicians, or administrative data where appropriate (i.e., prescription taken up) via the British Columbia Linked Health Database and British Columbia PharmaNet. This would provide independent confirmation of resource allocation and of prescription uptake.

In future investigations, I believe it would now be unethical to include a usual care group (control group) given the overwhelming evidence supporting the relation between upper limb fragility fracture and osteoporosis. Rather, I recommend future investigations focus on the best possible mechanism to influence change in physician practice patterns, improve patient knowledge of osteoporosis and commence initiatives that utilize the expertise of other health professionals in the area of secondary prevention. I see value in studies that test the effectiveness of the intervention I used for upper limb fractures as applied to other at-risk populations such as those who have sustained a hip fracture, stroke or spinal cord injury. I have been involved in a chart review of 100 patients who sustained a hip fracture

and were admitted to Vancouver Hospital and Health Science Centre (VHHSC). The results showed that less than 1% of patients were investigated for osteoporosis, when clearly bone health is an issue that needs to be addressed (349). A randomised controlled trial "HipWatch" has commenced at VHHSC to test a protocol similar to WristWatch on the impact of osteoporosis investigation and treatment rates. Ideally, interventions such as the one I demonstrated to be effective, need to be incorporated into policy so that appropriate patient care does not rely completely on individual health practitioner recall of appropriate management.

10.7 Barriers to Investigation after a Fragility Fracture.

Primary care physicians are an integral part to osteoporosis identification and management. The results from my survey reported in Chapter 9, however, highlight the urgent need to develop effective care pathways to assist physicians. There are many opportunities for novel care pathways to involve other health care professionals and I have highlighted these. An extension of this study would include qualitative research with patients, primary care physicians and allied health professionals to better understand participants' experience of the process of post-fracture management. Better understanding of patient knowledge of osteoporosis may help us understand what factors influence whether she/he would seek investigation after fragility fracture, and focus group sessions with practitioners such as physicians, physiotherapists and nurses would assist in the development of feasible care pathways.

10.8 The Role of the Upper Extremity in Osteoporosis

The upper extremity (in particular the distal radius) provides a valuable window for detection and clinical management of osteoporosis. My dissertation showed that after a fragility fracture, a targeted prevention intervention can greatly increase the rate of investigation for osteoporosis and thus, provide an impetus toward reduction of future fractures. I also demonstrated that the radius is a suitable model to study bone after a period of inactivity. Future studies could use this model longitudinally and also use it to investigate the effect of exercise or pharmaceutical interventions on long bones. As a clinician-scientist, my primary objective was to investigate osteoporosis and develop clinical pathways for reduction in disease burden. To do this effectively, and to better understand the pathophysiology of the condition that I seek to ameliorate, I broadened my knowledge base by completing cadaveric and laboratory studies as well as undertaking detailed testing of a novel bone measuring instrument, the pQCT.

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Appendix 1 : Study Letters

Letter to Patient
Letter to Primary Care Physician

VANCOUVER GENERAL HOSPITAL
A Site of Vancouver Hospital & Health Sciences Centre

WRISTWATCH

K. Khan (Principal Investigator) - Department of Family Medicine, UBC
M. Ashe- Department of Family Medicine, UBC
K. Kruse - BC Women's and Children's Hospital
K. Hughes, S. Wong, - Richmond Hospital
P O'Brien, J Wade - Vancouver Hospital and Health Science Centre

You have been given this letter because you have had a wrist fracture. Osteoporosis may be a factor in your fracture and you need to be assessed.

We would like you to return to your family doctor for review. Please take the referral letter that is contained in this package to your family doctor within the next two or three weeks to discuss osteoporosis assessment and management.

Your wrist fracture will continue to be managed by your Orthopaedic Surgeon in the Clinic at Vancouver Hospital.

Sincerely,

_____

MD, FRCSC

Consulting Orthopaedic Surgeon

855 West 12th Avenue Vancouver, British Columbia, Canada V5Z 1M9 **Tel: (604) 875-4111** Fax: (604) 875-4035

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WRISTWATCH

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K. Hughes, S. Wong, - Richmond Hospital
P O'Brien, J Wade - Vancouver Hospital and Health Science Centre

Your patient recently had a wrist fracture and is involved in a study evaluating the medium term management of such fractures. A wrist facture as a result of a low trauma fall is considered a diagnostic criterion for osteoporosis. We are following these patients to see if they are in fact diagnosed with osteoporosis and how they are managed.

The purpose of this letter is to alert you to the possibility that your patient may have osteoporosis. The current guidelines from a panel of doctors at the Osteoporosis Program at BC Women's Hospital and Health Centre would suggest that patients might benefit from a DXA scan to assess BMD at the hip and lumbar spine.

We feel that osteoporosis is a condition that is well managed by family physicians. The orthopedic surgeon involved in the care of your patient is collaborating in this study and **has referred the patient back to you for osteoporosis assessment and management.**

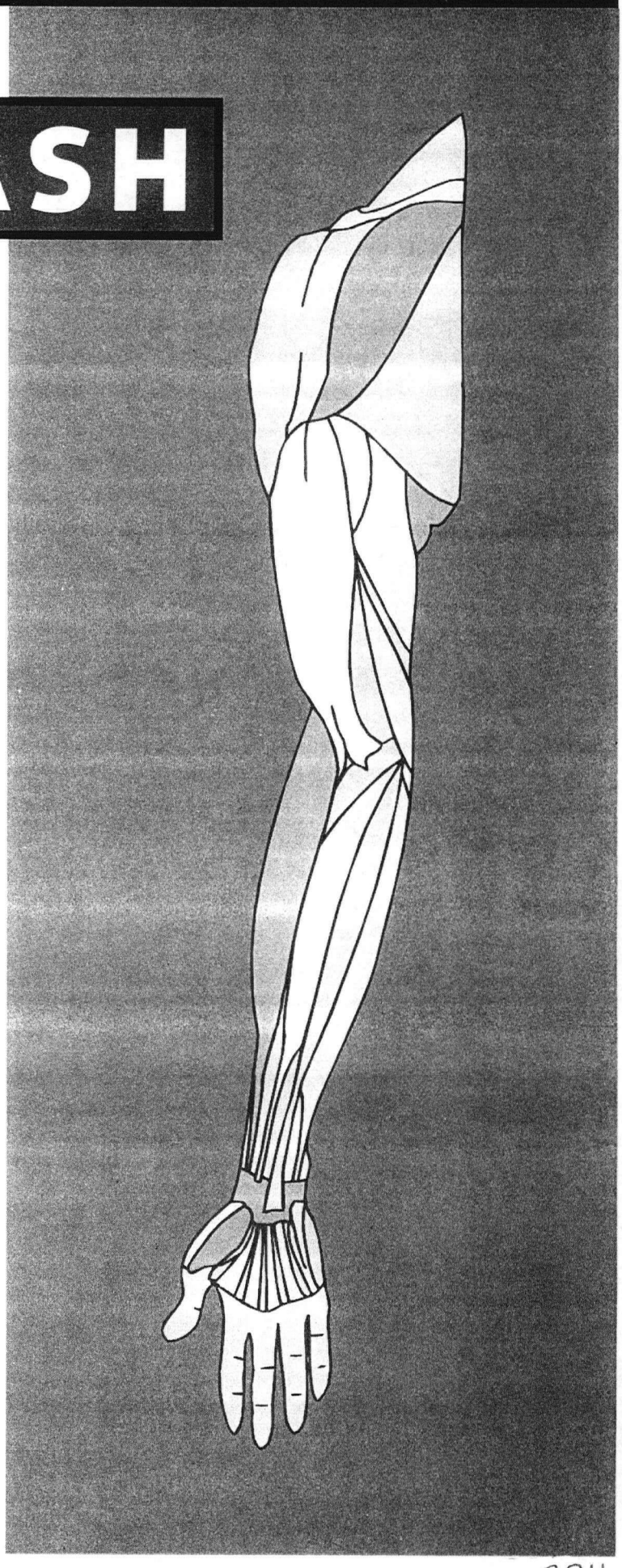
Sincerely,

Dr. Karen Kruse
Dr. Karim Khan
Osteoporosis Program
British Columbia Women's & Children's Hospital

Appendix 2 : Outcome Measures

Disabilities of the Arm Shoulder and Hand (DASH)
Patient Rated Wrist Evaluation (PRWE)
Modified CaMOS

THE DASH



INSTRUCTIONS

This questionnaire asks about your symptoms as well as your ability to perform certain activities.

Please answer *every question*, based on your condition in the last week, by circling the appropriate number.

If you did not have the opportunity to perform an activity in the past week, please make your *best estimate* on which response would be the most accurate.

It doesn't matter which hand or arm you use to perform the activity; please answer based on your ability regardless of how you perform the task.

DASH

Disabilities of the Arm, Shoulder and Hand

Acknowledgements

Developers of the DASH Outcome Measure: Peter Amadio, MD (Mayo Clinic, Rochester, MN), Dorcas Beaton, BScOT, MSc (Institute for Work & Health/St. Michael's Hospital, Toronto, ON), Claire Bombardier, MD (Institute for Work & Health/Wellesley Hospital, Toronto, ON), Donald Cole, MD, MSc (Institute for Work & Health, Toronto, ON), Aileen Davis, BScPT, MSc (Mount Sinai Hospital, Toronto, ON), Gillian Hawker, MD, MSc (Women's College Hospital, Toronto, ON), Pam Hudak, BScPT, MSc (Institute for Work & Health/The Toronto Hospital [Western Division], Toronto, ON), Jeffrey Katz, MD, MS (Robert Brigham Multipurpose Arthritis & Musculoskeletal Disease Center, Boston, MA), Matti Makela, MD, PhD (Helsinki, Finland), Robert Marx, MD (Institute for Work & Health, Toronto, ON), Laura Punnett, SCD (University of Massachusetts at Lowell, MA), James Wright, MD, MPH (Hospital for Sick Children, Toronto, ON).

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DASH Outcome Measure

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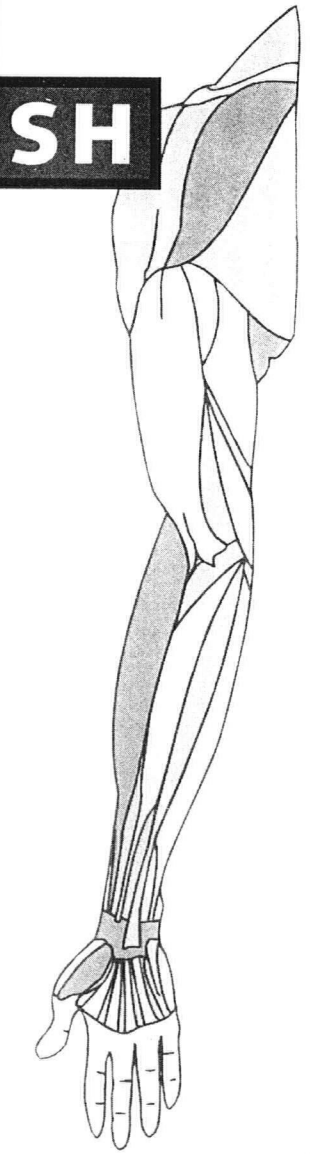
A A COMSS S

MODEMS™
Musculoskeletal Outcomes Data Evaluation and Management System

Disabilities of the Arm, Shoulder and Hand

DASH



DASH Outcome Measure

... measuring upper extremity disability and symptoms.

DISABILITIES OF THE ARM, SHOULDER AND HAND

Please rate your ability to do the following activities in the last week by circling the number below the appropriate response.

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. Open a tight or new jar.	1	2	3	4	5
2. Write.	1	2	3	4	5
3. Turn a key.	1	2	3	4	5
4. Prepare a meal.	1	2	3	4	5
5. Push open a heavy door.	1	2	3	4	5
6. Place an object on a shelf above your head.	1	2	3	4	5
7. Do heavy household chores (e.g., wash walls, wash floors).	1	2	3	4	5
8. Garden or do yard work.	1	2	3	4	5
9. Make a bed.	1	2	3	4	5
10. Carry a shopping bag or briefcase.	1	2	3	4	5
11. Carry a heavy object (over 10 lbs).	1	2	3	4	5
12. Change a lightbulb overhead.	1	2	3	4	5
13. Wash or blow dry your hair.	1	2	3	4	5
14. Wash your back.	1	2	3	4	5
15. Put on a pullover sweater.	1	2	3	4	5
16. Use a knife to cut food.	1	2	3	4	5
17. Recreational activities which require little effort (e.g., cardplaying, knitting, etc.).	1	2	3	4	5
18. Recreational activities in which you take some force or impact through your arm, shoulder or hand (e.g., golf, hammering, tennis, etc.).	1	2	3	4	5
19. Recreational activities in which you move your arm freely (e.g., playing frisbee, badminton, etc.).	1	2	3	4	5
20. Manage transportation needs (getting from one place to another).	1	2	3	4	5
21. Sexual activities.	1	2	3	4	5

DISABILITIES OF THE ARM, SHOULDER AND HAND

	NOT AT ALL	SLIGHTLY	MODERATELY	QUITE A BIT	EXTREMELY
22. During the past week, *to what extent* has your arm, shoulder or hand problem interfered with your normal social activities with family, friends, neighbours or groups? *(circle number)*	1	2	3	4	5

	NOT LIMITED AT ALL	SLIGHTLY LIMITED	MODERATELY LIMITED	VERY LIMITED	UNABLE
23. During the past week, were you limited in your work or other regular daily activities as a result of your arm, shoulder or hand problem? *(circle number)*	1	2	3	4	5

Please rate the severity of the following symptoms in the last week. *(circle number)*

	NONE	MILD	MODERATE	SEVERE	EXTREME
24. Arm, shoulder or hand pain.	1	2	3	4	5
25. Arm, shoulder or hand pain when you performed any specific activity.	1	2	3	4	5
26. Tingling (pins and needles) in your arm, shoulder or hand.	1	2	3	4	5
27. Weakness in your arm, shoulder or hand.	1	2	3	4	5
28. Stiffness in your arm, shoulder or hand.	1	2	3	4	5

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	SO MUCH DIFFICULTY THAT I CAN'T SLEEP
29. During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder or hand? *(circle number)*	1	2	3	4	5

	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
30. I feel less capable, less confident or less useful because of my arm, shoulder or hand problem. *(circle number)*	1	2	3	4	5

DISABILITIES OF THE ARM, SHOULDER AND HAND

SPORTS/PERFORMING ARTS MODULE (OPTIONAL)

The following questions relate to the impact of your arm, shoulder or hand problem on playing *your musical instrument or sport or both*. If you play more than one sport or instrument (or play both), please answer with respect to that activity which is most important to you.

Please indicate the sport or instrument which is most important to you: _____

☐ I do not play a sport or an instrument. (You may skip this section.)

Please circle the number that best describes your physical ability in the past week. Did you have any difficulty:

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. using your usual technique for playing your instrument or sport?	1	2	3	4	5
2. playing your musical instrument or sport because of arm, shoulder or hand pain?	1	2	3	4	5
3. playing your musical instrument or sport as well as you would like?	1	2	3	4	5
4. spending your usual amount of time practising or playing your instrument or sport?	1	2	3	4	5

WORK MODULE (OPTIONAL)

The following questions ask about the impact of your arm, shoulder or hand problem on your ability to work (including homemaking if that is your main work role).

Please indicate what your job/work is: _____

☐ I do not work. (You may skip this section.)

Please circle the number that best describes your physical ability in the past week. Did you have any difficulty:

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. using your usual technique for your work?	1	2	3	4	5
2. doing your usual work because of arm, shoulder or hand pain?	1	2	3	4	5
3. doing your work as well as you would like?	1	2	3	4	5
4. spending your usual amount of time doing your work?	1	2	3	4	5

INSTITUTE FOR WORK & HEALTH
INSTITUT DE RECHERCHE SUR LE TRAVAIL ET LA SANTÉ

THE AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS INC. Ορθόν Παιδίον MCMXXXIII

A A COMSS

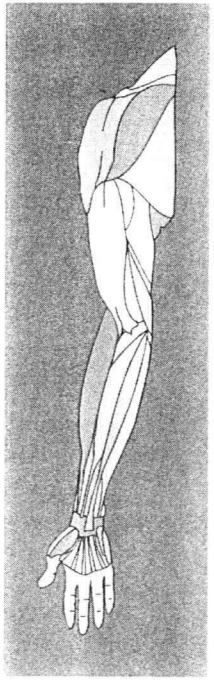
MODEMS™
Musculoskeletal Outcomes Data Evaluation and Management System

228

DASH

Disabilities of the Arm, Shoulder and Hand

DESCRIPTION OF THE DASH



The DASH questionnaire has been developed to measure disability and symptoms related to upper extremity musculoskeletal disorders. The 30-item questionnaire includes 21 physical function items; 6 symptom items and 3 social/role function items. There are also two optional 4-item modules: one intended for athletes and performing artists, and the other for working populations.

The DASH does not cover all aspects of health, and it is recommended that it be supplemented by a generic questionnaire such as the SF-36, the SF-12, or the Sickness Impact Profile.

The DASH is self-completed, allowing for follow-up by mail, and minimizing observer bias in outcome assessment.

This instrument was designed to be sensitive to disability from disorders affecting any part of the upper limb, thus eliminating the need for separate questionnaires for shoulder, wrist or elbow problems.

DEVELOPMENT OF THE DASH

There are 3 stages to questionnaire development; the first 2 stages, described below, have already been completed. The 3 stages are:

Stage 1: Item Generation
Stage 2: Item Reduction
Stage 3: Reliability and Validity Testing

Stage 1: Items from 13 existing outcomes scales applicable to a variety of upper extremity disorders were combined to produce a pool of 821 items.

Stage 2: Items which were redundant or obviously unrelated to the upper extremity were removed. Later, items which did not reflect disability or symptoms were also removed. The result: 177 unique items relevant to the upper extremity. These were rated by 15 content experts concerning the importance of inclusion of each item in an upper extremity measure. The resulting 70 items were formatted into a questionnaire which was field tested on over 400 patients in Canada, the U.S. and Australia. Further clinical judgement and statistical analysis of the data collected from field testing produced the final 30-item questionnaire.

Stage 3: Preliminary validity and reliability testing is currently in progress.

TESTING OF VALIDITY AND RELIABILITY

It is anticipated that the DASH will be useful in describing individuals with upper limb disorders, estimating the prognosis of these individuals and evaluating clinical change. Formal studies to evaluate the test-retest reliability, validity, and sensitivity to clinical change are being carried out by the developers.

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DASH PUBLICATIONS

Marx R. A comparison of clinimetric and psychometric techniques for item reduction in the development of an upper extremity disability measure. MSc Thesis, Clinical Epidemiology, University of Toronto Press, 1996.

Hudak P, Amadio PC, Bombardier C and the Upper Extremity Collaborative Group. Development of an upper extremity outcome measure: The DASH (Disabilities of the Arm, Shoulder and Hand). American Journal of Industrial Medicine 1996;29:602-608.

Upper Extremity Collaborative Group. Development of an upper extremity outcome measure: The DASH (Disabilities of the Arm, Shoulder and Hand). Arthritis and Rheumatism 1996;39(9):S112.

Upper Extremity Collaborative Group. Measuring disability and symptoms of the upper limb: A validation study of the DASH Questionnaire. Arthritis and Rheumatism 1996;39(9):S112.

Davis A, Beaton D, Hudak P and the Upper Extremity Collaborative Group. Measuring disability of the upper extremity: A rationale supporting the use of a regional outcome measure. Institute for Work & Health Working Paper, 1997.

Name _____ Date_____

PATIENT RATED WRIST EVALUATION

*The questions below will help us understand the amount of difficulty you have had with your wrist in the past week. You will be describing your **average** wrist symptoms **over the past week** on a scale from 0 to 10. Please provide an answer for **ALL** questions. If you did not perform an activity, please **ESTIMATE** the pain or difficulty you would expect. If you have **never** performed the activity, you may leave it blank.*

1. PAIN

Rate the average amount of pain in your wrist over the past week by circling the number that best describes your pain on a scale from 0 to 10. A zero (0) means that you did not have any pain, and a ten (10) means that you had the worst pain you have ever experienced or that you could not do the activity because of pain.

Sample scale: 0 1 2 3 4 5 6 7 8 9 10

No Pain Worst Ever

RATE YOUR PAIN:

At rest	0 1 2 3 4 5 6 7 8 9 10
When doing a task with a repeated wrist movement	0 1 2 3 4 5 6 7 8 9 10
When lifting a heavy object	0 1 2 3 4 5 6 7 8 9 10
When it is at its worst	0 1 2 3 4 5 6 7 8 9 10
How often do you have pain?	0 1 2 3 4 5 6 7 8 9 10

Never Always

2. FUNCTION

A. Specific Activities

*Rate the **amount of difficulty** you experienced performing each of the items listed below, over the past week, by circling the number that best describes your difficulty on a scale of 0 to 10. A **zero (0)** means you did not experience any difficulty, and a **ten (10)** means it was so difficult you were unable to do it at all.*

Sample scale 0 1 2 3 4 5 6 7 8 9 10

No Difficulty Unable to Do

Turn a door knob using my affected hand	0 1 2 3 4 5 6 7 8 9 10
Cut meat using a knife in my affected hand	0 1 2 3 4 5 6 7 8 9 10
Fasten buttons on my shirt	0 1 2 3 4 5 6 7 8 9 10
Use my affected hand to push up fro a chair	0 1 2 3 4 5 6 7 8 9 10
Carry a 10-lb object in my affected hand	0 1 2 3 4 5 6 7 8 9 10
Use bathroom tissue with my affected hand	0 1 2 3 4 5 6 7 8 9 10

B. Usual Activities

*Rate the **amount of difficulty** you experienced performing your **usual** activities in each of the areas listed below, over the past week, by circling the number that best describes your difficulty on a scale of 0 to 10. By "usual activities" we mean the activities that you performed **before** you started having a problem with your wrist. A **zero (0)** means you did not experience any difficulty, and a **ten (10)** means it was so difficult you were unable to do any of your usual activities.*

1. Personal care activities (dressing, washing)	0 1 2 3 4 5 6 7 8 9 10
2. Household work (cleaning, maintenance)	0 1 2 3 4 5 6 7 8 9 10
3. Work (your job or everyday work)	0 1 2 3 4 5 6 7 8 9 10
4. Recreational activities	0 1 2 3 4 5 6 7 8 9 10

Comment / interpretations:

MODIFIED CaMOS QUESTIONNAIRE

To begin the questionnaire I would like to ask you general questions about yourself.

A. SOCIO-DEMOGRAPHIC INFORMATION

1 Date of Birth: _____/ _____/ _____ (Present age _____)
Day Month Year

2 In what country were you born?

3 How many years of school have you finished? (Mark the highest grade completed)

- ☐ less than grade 9
- ☐ grades 9-13, without certificate or diploma
- ☐ high school certificate or diploma
- ☐ trades or professional certificate or diploma (CEGEP in Quebec)
- ☐ some university certificate or diploma
- ☐ university degree

4 What is your current employment status?

- ☐ Employed full time
- ☐ Homemaker (full time)
- ☐ Employed
- ☐ Disability
- ☐ Retired if so, how old were you? _____ years
- ☐ Other (specify _____)

5 Do you live alone? ☐ Yes ☐ No

If no, do you live with another adult?
☐ Yes ☐ No

6 Do you have a particular doctor or clinic that you would call your regular doctor or clinic? ☐ Yes ☐ No
If yes - Name of regular doctor or clinic _____

Now we'll review your past health.

B. MEDICAL HISTORY

1 Has a doctor ever told you that you have any of the following conditions?

	DIAGNOSIS			TREATMENT			
	Yes	No	DK	Yes	No	DK	N/A
Osteoporosis							
Rheumatoid arthritis							
Osteoarthritis							
Thyroid disease:							
1 = Hyperthyroidism							
2 = Hypothyroidism							
Liver disease							
Scoliosis							
Hypertension							
Heart attack							
Stroke							
TIA (Transient Ischemic attack)							
Neuromuscular Disease							
1 = Parkinson's Disease							
2 = Multiple Sclerosis							
3 = Other							
Diabetes: Age____							
1 = Insulin Dependent							
2 = Non Insulin Dependent							
Peripheral neuropathy (numbness)							

2 Which of the following surgeries have you had in the past? How old were you?

	Yes	No	Details
Joint replacement			
Other orthopaedic			
Other (list)			

3 Have you fallen in the past week? ☐ Yes ☐ No
if yes, how many times? ____

4 Have you fallen in the past month? ☐ Yes ☐ No
if yes, how many times? ____

Now I will ask you about any medicines you may have taken.

C. DRUGS AND MEDICATIONS

1 Current medications and or self administered supplements taken on a regular basis.

Medications: From contents of medicine cabinet		
NAME	DOSE	FREQUENCY

2 Fall-related medication check list

Category	Medication Name	Prescription Details
Neuroleptics (eg. chlorpromazine)		
Antidepressants (eg. amitryptiline)		
Sedative / hypnotics (eg. benzodiazepenes)		
Cardiovascular drugs • Diuretics • Digoxin • Type 1 anti-arrhythmic agents		

D. FRACTURES

1 Have you ever fractured any bones? ☐ Yes ☐ No If no, go to E1

Complete the table below

(Refer to picture of body skeleton (if necessary)

Use the following trauma codes to indicate how it happened.

1 = severe trauma

2 = minimal trauma

3 = other disease

(See below for definitions)

			BONE SITE										OTHER			
Incident(s)	Trauma Code	Age(years)	BACK		RIBS		PELVIS		FOREARM WRIST		HIP		Bone Site		Bone Site	
			#	X	#	X	#	X	#	X	#	X	#	X	#	X

# = fracture
X = x-ray

1. Severe trauma = falling from greater than standing height, motor vehicle accident, skiing accident, or hit by moving object.

2. Minimal trauma = falling from a standing height or broke bone without injury or fall.

5 Do you or did you ever take estrogen for menopause or for any other reason?

☐ Yes, currently
☐ Yes, but not now
☐ Total number of months taken

☐ No
if no, go to E6

6 Do you or did you ever take Provera®, for menopause or for any other reason?

☐ Yes, currently
☐ Yes, but not now
☐ Total number of months taken

☐ No
•if no, go to 5.7

Now I will ask about your family history.

F. FAMILY HISTORY

1 How many brothers and/or sisters do/did you have? (not adopted)

_____ siblings ☐ do not know

2 I would like to ask about the following family members and their medical history

Diagnosis	Parents			Siblings				Children			
	Yes	No	DK	Yes	No	DK	NA	Yes	No	DK	NA
Fracture											
Osteoporosis											
Fall-related injury											

In this section I will ask you about diet, exercise programs and eating habits.

G. PHYSICAL CHARACTERISTICS

1 What was your greatest adult height? _____ feet _____ inches -or- _____ cm

☐ do not know

In this section I would like to ask you questions that will help us understand how women's hormones relate to bone structure. We ask everyone these questions.

E. REPRODUCTIVE HISTORY (FEMALES)

1 Before menopause, have you ever gone 3 months or more without a menstrual period?

☐ Yes ☐ No
if no, go to E2

What was the longest single period of time without a menstrual flow? _____ months

If you count all the periods you have missed throughout your Menstruating years, how many months would that be? _____ months
(this question asks for the cumulative time)

2 At what age did your menstrual periods stop. _____ age

3 Have you had your uterus removed (hysterectomy)?

☐ Yes ☐ No
if yes, at what age? _____ years

4 Have you ever had one or both ovaries removed:

☐ Yes, one ovary removed at what age? _____
☐ Yes, both ovaries removed at what age? _____
(if ovaries were removed on separate occasions, write the age at which the second ovary was removed)
☐ Yes, do not know how many at what age? _____
☐ No

Now the questions I will ask will relate to the use of tobacco

H. TOBACCO

1 Have you ever used any of the following tobacco products daily for at least 6 months?

Cigarettes	☐ yes	☐ no	
Pipes	☐ yes	☐ no	
Cigars	☐ yes	☐ no	
Chewing tobacco	☐ yes	☐ no	If NO to all: go to 9.3

2 Complete the following table for each product used

	Age Started	Currently Smoking	Age Stopped	Amount Per Day	Temporarily Stopped (Years)
Cigarettes					
Pipe					
Cigar					
Chewing tobacco					