



DEVCOM DAC-TR-2024-039
May 2024

Quantitative Imaging Analysis to Understand Variation in Skeletal Injury

by Randee L. Hunter, Zachary A. Haverfield, Michael T. Wassick, David R. Barnes, Kate E. Sandora, Kathryn L. Loftis, and Amanda M. Agnew

DISCLAIMER

The findings in this report are not to be construed as an official Department of the Army position unless so specified by other official documentation.

WARNING

Information and data contained in this document are based on the input available at the time of preparation.

TRADE NAMES

The use of trade names in this report does not constitute an official endorsement or approval of the use of such commercial hardware or software. The report may not be cited for purposes of advertisement.



DEVCOM DAC-TR-2024-039
May 2024

Quantitative Imaging Analysis to Understand Variation in Skeletal Injury

by Randee L. Hunter, Zachary A. Haverfield, and Amanda M. Agnew
Injury Biomechanics Research Center, Ohio State University

Michael T. Wassick
Altus Engineering

David R. Barnes
SURVICE Engineering

Kate E. Sandora and Kathryn L. Loftis
DEVCOM Analysis Center

REPORT DOCUMENTATION PAGE

1. REPORT DATE		2. REPORT TYPE		3. DATES COVERED					
May 2024		Technical Report		<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%;">START DATE</td> <td style="width: 50%;">END DATE</td> </tr> <tr> <td>23 March 2020</td> <td>22 March 2024</td> </tr> </table>		START DATE	END DATE	23 March 2020	22 March 2024
START DATE	END DATE								
23 March 2020	22 March 2024								
4. TITLE AND SUBTITLE									
Quantitative Imaging Analysis to Understand Variation in Skeletal Injury									
5a. CONTRACT NUMBER		5b. GRANT NUMBER		5c. PROGRAM ELEMENT NUMBER					
5d. PROJECT NUMBER		5e. TASK NUMBER		5f. WORK UNIT NUMBER					
6. AUTHOR(S)									
Randee L. Hunter, Zachary A. Haverfield, Michael T. Wassick, David R. Barnes, Kate E. Sandora, Kathryn L. Loftis, and Amanda M. Agnew									
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)				8. PERFORMING ORGANIZATION REPORT NUMBER					
Director DEVCOM Analysis Center 6896 Mauchly Street Aberdeen Proving Ground, MD 21005				DEVCOM DAC-TR-2024-039					
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)			10. SPONSOR/MONITOR'S ACRONYM(S)		11. SPONSOR/MONITOR'S REPORT NUMBER(S)				
12. DISTRIBUTION/AVAILABILITY STATEMENT									
DISTRIBUTION STATEMENT A. Approved for public release: distribution unlimited.									
13. SUPPLEMENTARY NOTES									
ORCID IDs: Randee L. Hunter, 0000-0002-3079-1320; Zachary A. Haverfield, 0000-0001-8700-4925; Amanda M. Agnew, 0000-0001-8733-4078.									
14. ABSTRACT									
It is critical to understand the biological components of the skeletal system and contextualize population variation to apply postmortem human subject (PMHS) experimental data towards developing injury risk functions. This report's objective was to quantify bone mineral density (BMD) from CT scans to develop a multi-anatomical site normative population of volumetric BMD (vBMD). Both phantom-based and phantomless methods were established and validated for PMHS CT scans of 200 males aged 24 to 102 years. Regions of interest included the lumbar spine, femoral neck, humerus, radius, tibia, and calcaneus. Extensive variation in vBMD was characterized across the body. A normative vBMD population was created for each skeletal site to investigate scaling injury risk curve data applied to Warrior Injury Assessment Manikin (WIAMan) subjects. Z-scores calculated from the normative population were compared with dual X-ray absorptiometry (DXA) values to determine if the technologies would provide commensurate injury risk assessments. Results demonstrated a mismatch despite site-specific analyses. This suggests bone quality should be quantified using highly standardized methods applied to the region of interest for injury and are not similar between DXA and CT. Consequently, developing biofidelic anthropomorphic test devices and scaling injury risk curves from experimental data should employ more comprehensive and discriminative measures of skeletal fracture risk.									
15. SUBJECT TERMS									
bone mineral density, Warrior Injury Assessment Manikin, WIAMan, injury risk, skeletal fracture, quantitative CT									
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT		18. NUMBER OF PAGES				
a. REPORT	b. ABSTRACT	c. THIS PAGE	UU		55				
UNCLASSIFIED	UNCLASSIFIED	UNCLASSIFIED							
19a. NAME OF RESPONSIBLE PERSON				19b. PHONE NUMBER (Include area code)					
Kathryn Loftis				(410) 306-0344					

STANDARD FORM 298 (REV. 5/2020)

Prescribed by ANSI Std. Z39.18

(U) Table of Contents

List of Figures	iv
List of Tables	vi
Executive Summary	vii
1. INTRODUCTION	1
2. MATERIAL AND METHODS	2
2.1 OSU Male PMHS Normative Population Demographics.....	2
2.2 Skeletal Locations for Quantitative CT Analysis	3
2.3 QCT vBMD Method Development and Standardization.....	4
2.3.1 Phantom-based Method Development.....	4
2.3.2 Phantomless Method Development	10
2.4 Internal Reference Tissue Phantomless Method	11
2.5 Regression Equation Phantomless Method	13
2.6 Statistical Analyses	15
3. RESULTS AND DISCUSSION	17
3.1 Normative Male vBMD Population	17
3.2 Comparison Between Methods for Measuring Bone Mineral Density (DXA vs. QCT)	22
3.3 WIAMan Male PMHS vBMD Data Collection	34
4. CONCLUSIONS	37
5. REFERENCES	38
Appendix – Quantitative Computed Tomography Volumetric Bone Mineral Density Descriptive Statistics.....	41
List of Acronyms	44

List of Figures

Figure 1.	Variation in HU values (y-axis) for each phantom rod. X-axis represents the location/slice number along the length of the scan.	7
Figure 2.	Phantom rod identification (ROI within blue circles) determined by mean X and Y coordinates, circular shape, and proximity to each other using customized MATLAB code.....	9
Figure 3.	Example of minimal differences in calibration curves constructed from the automated MATLAB code compared to manual process.....	9
Figure 4.	Exemplar site-specific calibration curve used to calculate vBMD. R^2 values near 0.999 (as represented) indicate good linearity within this range of density values when compared to the INTABLE phantoms.	10
Figure 5.	Lumbar (L2–L4) total QCT vBMD z-score (OSU) compared to L2–L4 DXA t-score derived from NHANES reference population	24
Figure 6.	Femoral neck QCT vBMD z-score (OSU) compared to femoral neck DXA t-score derived from NHANES reference population	25
Figure 7.	Distal radius QCT vBMD z-score (OSU) compared to distal radius DXA t-score derived from NHANES reference population.....	26
Figure 8.	30% radius QCT vBMD z-score (OSU) compared to 33% radius DXA t-score derived from NHANES reference population.....	27
Figure 9.	The distributions of the L2–L4 total vBMD z-score and L2–L4 DXA calculated z-score for the normative population appear to be more similar than the comparison with the t-score (Figure 5).....	28
Figure 10.	Femoral neck vBMD z-score compared to femoral neck DXA calculated z-score derived for the normative population	29
Figure 11.	Distal radius vBMD z-score compared to distal radius DXA z-score calculated from normative population	30
Figure 12.	30% radius vBMD z-score compared to 33% radius DXA z-score calculated from normative population	31
Figure 13.	Bone quality assessment relative to the normative population of a 66-year-old (red), 58-year-old (blue), and 87-year-old (yellow) for L2–L4. Dotted lines are DXA z-scores specific to OSU sample. Solid lines are OSU QCT z-scores.....	32
Figure 14.	Bone quality assessment relative to normative population of a 66-year-old (red), 75-year-old (blue), and 26-year-old (yellow) for femoral neck. Dotted lines are DXA z-scores specific to OSU sample. Solid lines are OSU QCT z-scores.....	32
Figure 15.	Bone quality assessment relative to normative population of a 102-year-old (red), 54-year-old (blue), and 35-year-old (yellow) for the distal radius. Dotted lines are DXA z-scores specific to OSU sample. Solid lines are OSU QCT z-scores.....	33
Figure 16.	Bone quality assessment relative to normative population of a 35-year-old (red), 54-year-old (blue), and 62-year-old (yellow) for the distal diaphysis of the radius. Dotted lines are DXA z-scores specific to OSU sample. Solid lines are OSU QCT z-scores.....	33

List of Figures

Figure 17.	WIAMan vBMD z-score distribution (red) compared to OSU normative population z-score distribution (gray) for L2–L4 total vBMD values	35
Figure 18.	WIAMan vBMD z-score distribution (red) compared to OSU normative population z-score distribution (gray) for right femoral neck total values.....	35
Figure 19.	WIAMan vBMD z-score distribution (red) compared to OSU normative population z-score distribution (gray) for left femoral neck total values.....	36
Figure 20.	WIAMan vBMD z-score distribution (red) compared to OSU normative population z-score distribution (gray) for averaged calcaneus total values.....	36

List of Tables

Table 1.	PMHS male normative population demographics	2
Table 2.	PMHS male normative population demographics by age decade.....	2
Table 3.	Elements, locations within the bone measured relative to the distal end, and tissue type analyzed for vBMD	3
Table 4.	Threshold values by tissue type for all VOIs	5
Table 5.	Demographics for PMHS clinical CT scans chosen to investigate variance in phantom rod HU values along the length of the body	5
Table 6.	Intra-scan variation (CV) per PMHS with respect to BMI	6
Table 7.	Variation in vBMD equivalent densities (mg/cm ³) reported across studies	11
Table 8.	vBMD equivalent densities (mean ± SD) from OSU PMHS sample (n = 50)	12
Table 9.	Accuracy of internal reference material PL vBMD compared to PB vBMD for n = 10	12
Table 10.	PL regression equations from method development sample (n = 50 PMHS)	13
Table 11.	Accuracy of regression PL vBMD compared to PB vBMD for n = 30 method validation sample	14
Table 12.	Paired t-test comparisons between right and left vBMD values per site and tissue type (SDs reported in Table A-1)	17
Table 13.	Lumbar spine level comparison for vBMD per tissue site	18
Table 14.	Descriptive statistics for normative vBMD population by site and tissue type (all bilateral values were averaged except left and right femoral neck totals)	18
Table 15.	Trabecular vBMD ANOVA (with post hoc Tukey tests) results	19
Table 16.	Total vBMD ANOVA (with post hoc Tukey tests) results.....	20
Table 17.	Cortical vBMD ANOVA (with post hoc Tukey tests) results	21
Table 18.	Pearson correlations between skeletal sites per tissue type	22
Table 19.	NHANES DXA t-score compared to OSU calculated DXA z-score (Pearson correlations).....	23
Table 20.	NHANES DXA t-score compared to OSU QCT vBMD z-score (Pearson correlations and linear regressions)	23
Table 21.	OSU DXA z-scores compared to QCT z-scores for the normative population	28
Table A-1.	QCT vBMD descriptive statistics per site used for calculation of vBMD z-scores of the normative population	42

Executive Summary

Improving Soldier survivability, particularly during evolving warfare strategies and/or in new geographical regions of conflict, requires researchers to utilize surrogates to evaluate the efficacy of new safety technologies. Anthropomorphic test devices (ATDs) are used to predict the risk of injury but must be biofidelic or representative of the human biological response to real-world traumatic events. In order to predict skeletal injury using ATDs, it is necessary to develop a biological metric that allows for scaling injury risk curves from experimental data to the Soldier population. The objective of this collaborative research between Ohio State University (OSU) and the U.S. Army Combat Capabilities Development Command (DEVCOM) Analysis Center (DAC), formerly the DEVCOM Army Research Laboratory (ARL), was to understand the important contributors to skeletal response and injury due to high-rate traumatic loading by developing a rigorous method for quantifying volumetric bone mineral density (vBMD) from CT scans. These data were used to establish a large, male postmortem human subject (PMHS) vBMD normative population of multiple skeletal sites which can be applied to scaling injury risk curves and improving technologies to prevent fracture and ensure Soldier survivability.

The Injury Biomechanics Research Center (IBRC) at OSU houses an extensive repository of PMHS whole-body CT scans. A sample size of 200 male PMHS ranging in age from 20 to 102 years was chosen for retrospective vBMD analysis. In order to create a normative population of vBMD from multiple anatomical sites, it was necessary to capture a wide range of variation in bone that may be associated with age or body size. Variation in vBMD is driven by a combination of systemic and environmental influences including habitual mechanical loading. Recent work has demonstrated the importance of assessing vBMD at the anatomical location of interest for injury. Thus, this work included nine skeletal elements representing the axial and appendicular skeletons, regions of interest that capture vBMD from each bone compartment (e.g., cortical and trabecular) in addition to a combined (total) measurement, and multiple sites within each element to reflect intra-element variation.

Initial steps required establishing a rigorous methodology for quantifying vBMD from CT scans particularly due to the lack of attention to skeletal elements other than the spine and hip in published work. The IBRC developed a standardized and validated phantom-based method to transform Hounsfield units (HU) to vBMD using an INTable phantom of known density rods. 175 CT scans included phantom rods in all anatomical regions of interest while 25 were scanned without a phantom and required the development of a comparable phantomless methodology. Substantial variation in phantom rod HU across the body within a single CT suggested the need for site-specific calibration curves to

mitigate any error from X-ray attenuation. Thus, using a customized and validated MATLAB code, site-specific calibration curves were created for each anatomical volume of interest.

Two phantomless methodologies were tested using the phantom-based subjects to evaluate accuracy. Published literature uses both an “internal reference tissue” method where the density of tissues such as muscle and aortic blood as well as air in the scan are assumed, as well as a regression-based approach that incorporates characteristics of the CT acquisition parameters, subject (age, height, weight), and bone (HU values). This work found that the regression-based phantomless methods were more accurate with respect to phantom-based vBMD values and were subsequently utilized to calculate vBMD from the remaining 25 CTs without an INTable phantom.

A normative vBMD population was created for all anatomical sites and bone types. Significant variation in vBMD across the body was found suggesting one measure of vBMD may not be representative of the entire skeleton. Despite the tendency to use global measurements of bone quality, these results suggest this approach may be suboptimal for informing injury risk in PMHS and analyzing specific anatomical sites of interest would prove more valuable.

Additional comparisons between typically employed methodologies for bone quality assessment (dual X-ray absorptiometry [DXA] and CT) were conducted to determine if PMHS were categorized similarly with respect to the normative population. DXA t-scores created using a national sex- and race-specific reference population were collected from the PMHS included in this study. Results from these comparisons demonstrate a discordance between technologies in their assessment of bone quality (i.e., they are not representing the same components of bone). This suggests that PMHS inclusion/exclusion criteria for experimental injury biomechanics testing, explanations of injury outcomes or severity, and scaling injury risk curves should be done with caution using DXA, and would be better served by using the 3D CT vBMD.

IBRC’s standardized phantom-based or phantomless methods were used to collect vBMD from all available Warrior Injury Assessment Manikin (WIAMan) PMHS CTs and contextualize their bone quality within the normative population. Site-specific comparisons appear to suggest the WIAMan samples have better bone quality on average than the general population, with the exception of the calcaneus. Future work by the collaboration will include using vBMD to inform scaling injury risk curves from experimental data to ultimately improve Soldier survivability through developing better injury mitigation tools.

This work has demonstrated that site-specific analysis of vBMD is critical for all investigations into fracture resistance in injury prevention. The creation of a normative population for males can enhance the field of injury biomechanics by contextualizing PMHS bone quality within a large sample. Using the IBRC's methods for vBMD quantification across the skeleton and comparing the results with the normative population would provide a more discriminant understanding of injury risk that outperforms current methods of DXA assessment. Lastly, the contribution of vBMD to injury risk during high-rate traumatic loading is relatively unknown. Future work must investigate the relationship between vBMD and injury outcomes across the skeleton.

1. INTRODUCTION

As warfare strategies evolve and/or new geographical regions produce conflicts, ensuring Soldier survivability in the face of new injury mechanisms is crucial. To design and implement survivability mechanisms for Soldiers, researchers utilize surrogates to assess the efficacy of new technologies in preventing injury. For any anthropomorphic test device to predict risk of injury, it must be biofidelic, reflecting the actual human biological response, with injury risk curves that correspond to real-world injuries incurred during a traumatic event. However, to scale injury risk curves and apply experimental data across the Soldier population, it is necessary to identify a metric that allows for these techniques. This research investigates the aspects of bone that correlate to fracture tolerance and their variation across anatomical sites and between individuals, with the goal of improving Soldier survivability through fracture prevention which subsequently affects soft tissue injury, long-term outcomes, and functionality.

The objective of this collaborative research is to enhance Soldier survivability by understanding important contributors to skeletal response and injury due to high-rate traumatic loading. This joint endeavor has combined the bone mineral density (BMD) and imaging expertise at Ohio State University (OSU) to develop a rigorous and standardized methodology for analyzing CT scans with the military injury risk research at the U.S. Army Combat Capabilities Development Command (DEVCOM) Analysis Center (DAC). This work successfully created a normative volumetric bone mineral density (vBMD) population for male postmortem human subjects (PMHS) across multiple anatomical sites for use by the Warrior Injury Assessment Manikin (WIAMan) program. This project was funded as part of the WIAMan program. Results will be used to inform WIAMan Injury Assessment Reference Curves and interpretation of experimental data.

2. MATERIAL AND METHODS

2.1 OSU Male PMHS Normative Population Demographics

The Injury Biomechanics Research Center at OSU curates a substantial CT scan database from PMHS. The scans in the image repository were acquired on standard hospital/clinical CT scanners (i.e., either a 384-slice Siemens Somatom Force or a 128-slice Siemens Somatom Definition Edge) with typical protocols and resolutions. Initial inquiries to identify scans to include in the normative population resulted in the exclusion of any male PMHS CT with reduced scan quality due to errors in acquisition, instrumentation, excessive decomposition, or field of view issues. Dual X-ray absorptiometry (DXA) scans were performed on all PMHS using standardized protocols to assess the lumbar spine, femoral neck, and radius for areal bone mineral density (aBMD). Table 1 demonstrates the demographics of the 200 male PMHS selected for analysis and inclusion in the normative population. Table 2 demonstrates the demographics of age-stratified cohorts along with the target of the 50th percentile male. Both the total sample ($n = 200$) and each age-stratified group well represented the 50th percentile male in measures of body size represented by height, weight, and body mass index (BMI; $\text{weight}/\text{height}^2$).

Table 1. PMHS male normative population demographics

Total Sample (n = 200)	Age (yr)	Height (cm)	Weight (kg)	BMI
Mean $\pm$ SD	65.2 $\pm$ 12.6	177.2 $\pm$ 6.8	75.2 $\pm$ 11.7	24.0 $\pm$ 3.5
Min	24	159	34	13.3
Max	102	192	102.1	32.8

Table 2. PMHS male normative population demographics by age decade

Decade	n =	Age (yr) Mean $\pm$ SD	Height (cm) Mean $\pm$ SD	Weight (kg) Mean $\pm$ SD	BMI Mean $\pm$ SD
20	3	25.0 $\pm$ 1.0	174.8 $\pm$ 9.9	75.4 $\pm$ 2.2	24.8 $\pm$ 2.8
30	4	34.5 $\pm$ 1.9	175.9 $\pm$ 6.4	81.3 $\pm$ 15.3	26.4 $\pm$ 5.4
40	13	46.0 $\pm$ 2.9	176.3 $\pm$ 6.0	70.3 $\pm$ 7.3	22.6 $\pm$ 2.6
50	41	55.7 $\pm$ 2.7	178.9 $\pm$ 6.7	76.4 $\pm$ 11.9	23.9 $\pm$ 4.0
60	67	65.2 $\pm$ 3.0	176.9 $\pm$ 6.8	76.2 $\pm$ 11.2	24.4 $\pm$ 2.9
70	50	73.9 $\pm$ 2.8	177.5 $\pm$ 6.9	74.9 $\pm$ 11.8	23.8 $\pm$ 3.5
80	21	84.3 $\pm$ 2.7	175.2 $\pm$ 6.6	71.8 $\pm$ 14.3	23.4 $\pm$ 4.6
90	0	-	-	-	-
100	1	102	167.6	78.4	27.9
50th percentile male	-	45	176	76	-

2.2 Skeletal Locations for Quantitative CT Analysis

Quantitative CT (QCT) allows for the 3D analysis of bone in multiple anatomical locations. Volumetric bone mineral density (vBMD), a proxy for mineralization and a reflection of material properties, is quantifiable using standard clinical QCT. Typical assessments of bone quality using BMD are often performed using DXA rather than QCT. Protocols for interpreting aBMD results are centered around the lumbar spine and hip anatomical regions¹⁻³ and the determination of fracture risk. Thus, most studies of vBMD attempt to assess bone quality using one of these sites rather than targeting skeletal elements throughout the body. However, previous work has demonstrated complex variation in vBMD within and between bones.⁴⁻⁷ Understanding and mitigating injury risk likely requires a more nuanced, site-specific (rather than global) approach to the components of bone quality.

To develop a rigorous and standardized method of vBMD assessment, we investigated the variance in vBMD across the body and determined the subsequent effects of utilizing a global assessment of bone quality. Multiple anatomical locations were selected for this work. Additionally, multiple measurements of vBMD were collected, where appropriate, due to the complex contribution of both trabecular (Tb) and cortical (Ct) bone to the whole bone or region (i.e., lumbar spine) response to loading. Bilateral analyses were conducted due to inherent asymmetry demonstrated in the human skeleton (most commonly a result of differences in mechanical loading environments). Table 3 outlines the anatomical site (elements), locations within the bone (expressed as a percentage of length relative to the distal end for long bones) and tissue compartments (Tb, Ct, and total) that were available for analysis at each site.

Table 3. Elements, locations within the bone measured relative to the distal end, and tissue type analyzed for vBMD

Skeletal element	Location (%)	Analyzed tissue
L2 vertebra	-	Tb and total
L3 vertebra	-	Tb and total
L4 vertebra	-	Tb and total
Femoral neck	-	Tb, total, Inf Ct, Sup Ct
Femur	50	Ct
Humerus	50	Ct
Radius	4	Tb and total
Radius	30	Ct
Radius	50	Ct
Tibia	4	Tb and total
Tibia	38	Ct
Tibia	50	Ct
Tibia	66	Ct
Calcaneus	-	Tb and total

2.3 QCT vBMD Method Development and Standardization

Standardized methods for QCT analysis of vBMD have been reported for typical anatomical locations such as the spine and hip⁸; however, little work has been done in other regions of interest (ROIs) across the skeleton. The gold standard for converting Hounsfield units (HU) for a given volume of interest (VOI) of bone to vBMD requires the inclusion of a phantom of known density values (i.e., phantom-based method) within each CT scan.⁹ Ideally, this allows for a scan-specific calibration curve to account for inherent variation in the grayscale values between individuals. However, in this retrospective sample, 175 male PMHS CTs included a phantom and 25 were imaged without a phantom. Thus, two methods, phantom-based (PB) and phantomless (PL), were developed and standardized to create the normative vBMD population and minimize variability due to acquisition parameters, differences in anatomical location VOI identification, or PMHS soft-tissue attenuation.

2.3.1 Phantom-based Method Development

PB vBMD calculation using Osirix MD (Pixmeo, Switzerland) requires three steps: isolation of each anatomical VOI, determining the average HU for only the bone within each VOI, and constructing site-specific calibration curves from the INTABLE phantom rods. The following outlines the steps taken to develop and standardize the phantom-based methodology for whole-body CT analysis of vBMD.

Standardized segmentation of each anatomical site VOI: All skeletal elements and locations were segmented into VOIs for analysis using Osirix MD software. Long bone locations (Table 3) were calculated as a percentage of total length of the bone relative to the distal end. Total lengths were measured in accordance with skeletal analysis standards¹⁰ by manually identifying the proximal and distal slice locations of each long bone. Segmented VOIs were isolated surrounding the 4%, 30%, 38%, 50%, and/or 66% locations relative to the distal end (Table 3). A total of five slices per VOI surrounding the “center slice” (located at the percentage location) were selected for 3D analysis. For lumbar spine and calcaneus sites, VOIs were identified at the 50% of the height of the bone rather than total length. Femoral neck ROIs are created using a combination of transverse and coronal planes to identify the appropriate position of an ROI that will encompass the entirety of the neck region. Using this similar methodology for each ROI, a VOI was produced that captured approximately 3.1 mm of bone for analysis at each location.

To quantify HU values from only bone tissue within each VOI (Tb, Ct, or total) at each site, two types of segmentation were applied. Initial blunt (manual) segmentation was used to delineate the spatial location within which a tissue-specific consistent

thresholding value (Table 4) was applied (see Haverfield et al.¹¹ for exemplar images). HU values were collected for each slice within a VOI and averaged to produce a mean HU value per tissue type.

Table 4. Threshold values by tissue type for all VOIs

Tissue type	Range	Units
Trabecular	150–660	HU
Cortical	661–3000	HU
Combined	150–3000	HU

To transform the mean HU values per VOI into vBMD values, the phantom-based construction of calibration curves required standardization. The WIAMan program had previously provided OSU with an INTable phantom consisting of rods of known densities (0, 75, and 150 mg/cm³) to quantify vBMD from PMHS whole body CT scans. INTable phantoms were present throughout the entirety of most CT scans included in the normative population. Initial investigations were conducted to quantify any variance in HU for each phantom rod due to the differential attenuation across the body. Improper methodology for the formation of calibration curves could result in erroneous vBMD values, especially when considering multiple anatomical sites. If the HU values of the phantom rods were consistent along the length of the body, one single *scan*-specific calibration curve could be used for all anatomical site vBMD calculations. However, it was suspected the HU values of the known density phantom rods would be inconsistent throughout the scan due to fluctuations in the x-ray tube as well as attenuation from varying densities of PMHS body tissues which would necessitate anatomical *site*-specific calibration curves. These initial investigations were performed on CTs from PMHS (n = 6) that spanned a wide range of BMIs as a proxy for tissue thickness (Table 5).

Table 5. Demographics for PMHS clinical CT scans chosen to investigate variance in phantom rod HU values along the length of the body

Sex	PMHS	Age (yr)	Height (cm)	Weight (kg)	BMI
Male	A	62	138.5	70	19.9
	B	49	177.8	68	21.5
	C	53	180.3	92.1	28.3
Female	D	54	163.8	40.6	15.1
	E	75	151.1	46	20.1
	F	94	152.4	54.9	23.6

HU values of each phantom rod (0, 75, and 150 mg/cm³) were quantified every 31.3 mm (or 50 axial slices) from head to foot using Osirix MD. The coefficient of variation (CV) was used to assess the level of variance in HU values per rod for each PMHS (Table 6). Given that the phantom rods consist of homogenous material, the HU values should be relatively consistent throughout the body if PMHS tissue attenuation

was not a factor; however, Figure 1 demonstrates the range of HU values for each PMHS (A–F) and each phantom rod from slice “0” (foot) towards the head. CV values ranging from 3.1% to 128.3% indicate varying levels of PMHS tissue densities affect X-ray photon attenuation. Homogeneity throughout the scan should not be assumed.

Table 6. Intra-scan variation (CV) per PMHS with respect to BMI

	Subject	0 mg/cm ³ CV (%)	75 mg/cm ³ CV (%)	150 mg/cm ³ CV (%)	BMI
Male	A	36.6	13.0	8.3	19.9
	B	24.1	13.2	7.2	21.5
	C	69.4	5.9	4.0	28.3
Female	D	128.3	19.6	11.8	15.1
	E	40.5	11.1	5.9	20.1
	F	63.6	3.8	3.1	23.6

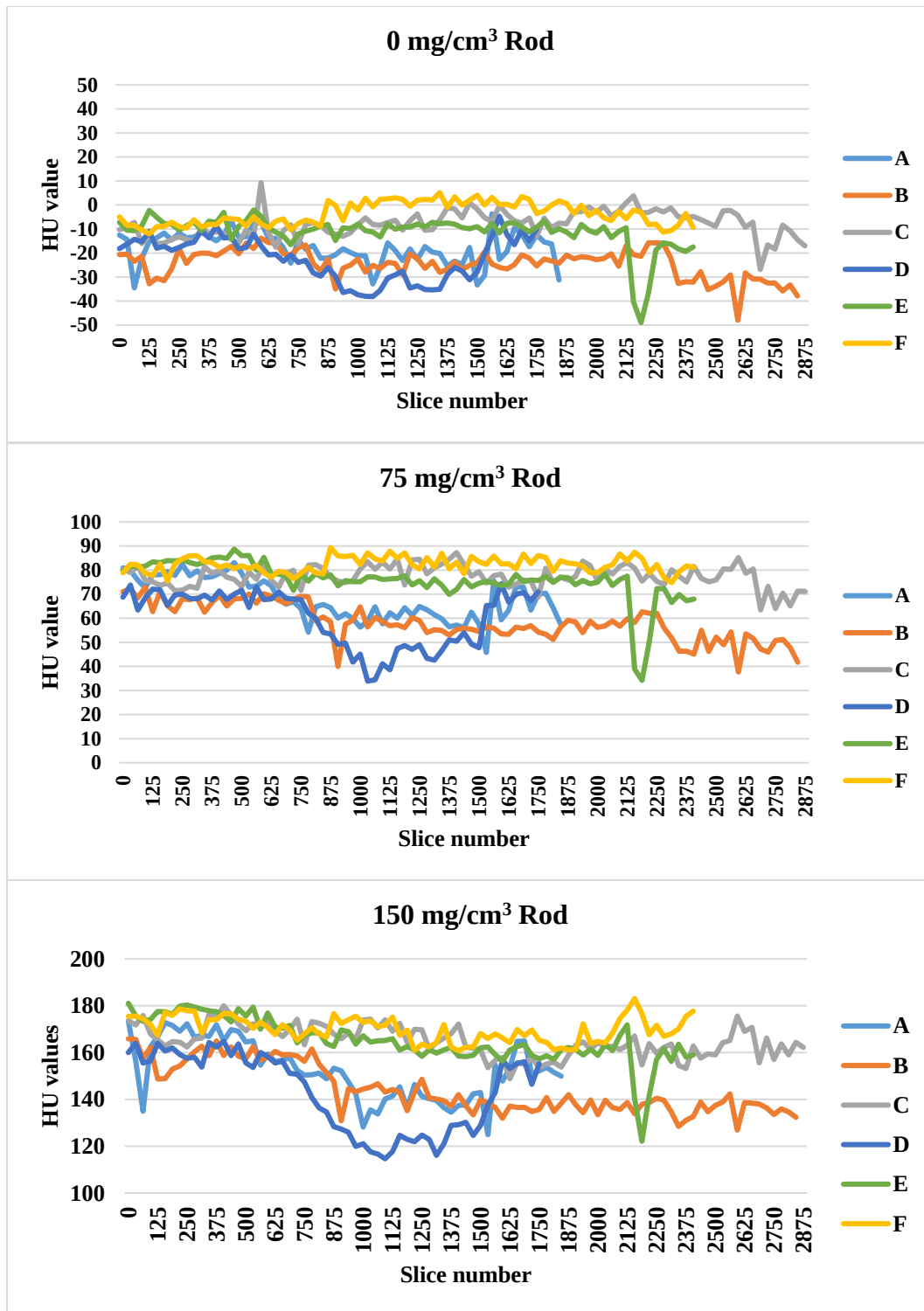


Figure 1. Variation in HU values (y-axis) for each phantom rod. X-axis represents the location/slice number along the length of the scan.

The amount that the HU values were affected by BMI varied across each rod (Table 6). It appears the lowest density rod (0 mg/cm^3) was more severely impacted (CV between 24.1% and 128.3%) by variation in density and thickness of PMHS tissue across the body than the 75 mg/cm^3 or 150 mg/cm^3 rods. The smallest PMHS (D) with a BMI of only 15.1 demonstrated the largest amount of variation along the length of the body and for all three INTable phantom rods. The resulting effects of this HU variation on the calculation of vBMD occurs due to differences in resulting calibration curves. As an exercise to quantify the severity of these effects on the resultant vBMD values, the vBMD for L4 was calculated for one PMHS using calibration curves from the highest (maximum) and lowest (minimum) HU values throughout the scan. The resultant Tb vBMD from a single L4 Tb volume of interest (VOI) was 200.3 mg/cm^3 (minimum value curve) and 242.3 mg/cm^3 (maximum value curve), representing a 19% difference in vBMD. Thus, it was determined that a *site-specific calibration curve* where the phantom rod HU values are quantified from the same axial slices as the anatomical VOI for analysis was necessary to reduce any variation in vBMD due to methodology.

MATLAB automation of phantom rod HU: Given that site-specific calibration curves are necessary for the standardized methodology and with as many as 25 calibration curves for each PMHS, manual collection of phantom rod HU was a time-consuming task (~6 h per scan to collect all sites). To maximize efficiency, a custom MATLAB code was written and validated to automate this process. The basic process of the code is as follows:

- a. Identify CT scan from designated folder and convert its grayscale to HU.
- b. Crop individual slices to include only the phantom rods.
- c. Identify the centers of each phantom rod and create identical 0.5 mm^2 ROIs within each (Figure 2).
- d. Quantify the mean HU for each ROI (phantom rod) throughout the entirety of the scan (per slice).
- e. Export all HU values (for every slice that contained a phantom rod) into an Excel spreadsheet organized by rod and per slice.

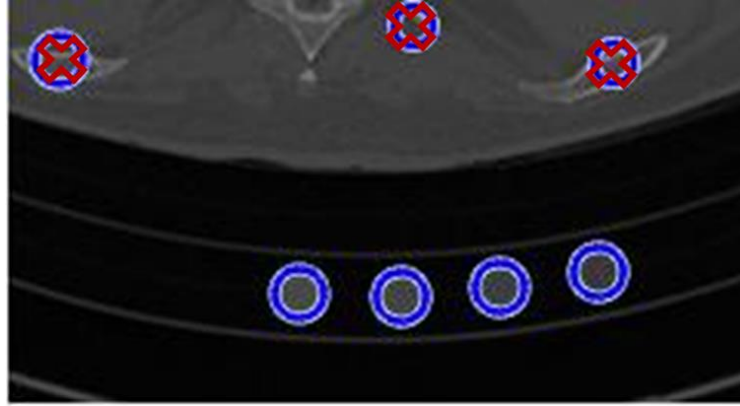


Figure 2. Phantom rod identification (ROI within blue circles) determined by mean X and Y coordinates, circular shape, and proximity to each other using customized MATLAB code

The automated phantom rod HU quantification using the customized MATLAB code was validated against manually constructed calibration curves for $n = 5$ PMHS. During this process, manual phantom rod HU collection in Osirix MD was performed for all 25 skeletal locations. Additionally, all anatomical skeletal HU values were collected to determine if the automated and manual phantom-based site-specific calibration curves produced comparable vBMD values. A total of 125 manual and 125 MATLAB automated calibration curves were constructed for vBMD calculation (Figure 3). The average %error between vBMD values at all anatomical locations calculated using the manual process (gold standard) and automated MATLAB code was 1.64% ($\pm 0.67\%$). Therefore, the MATLAB code was employed on all CT scans with INTABLE phantoms in the normative population to create site-specific calibration curves.

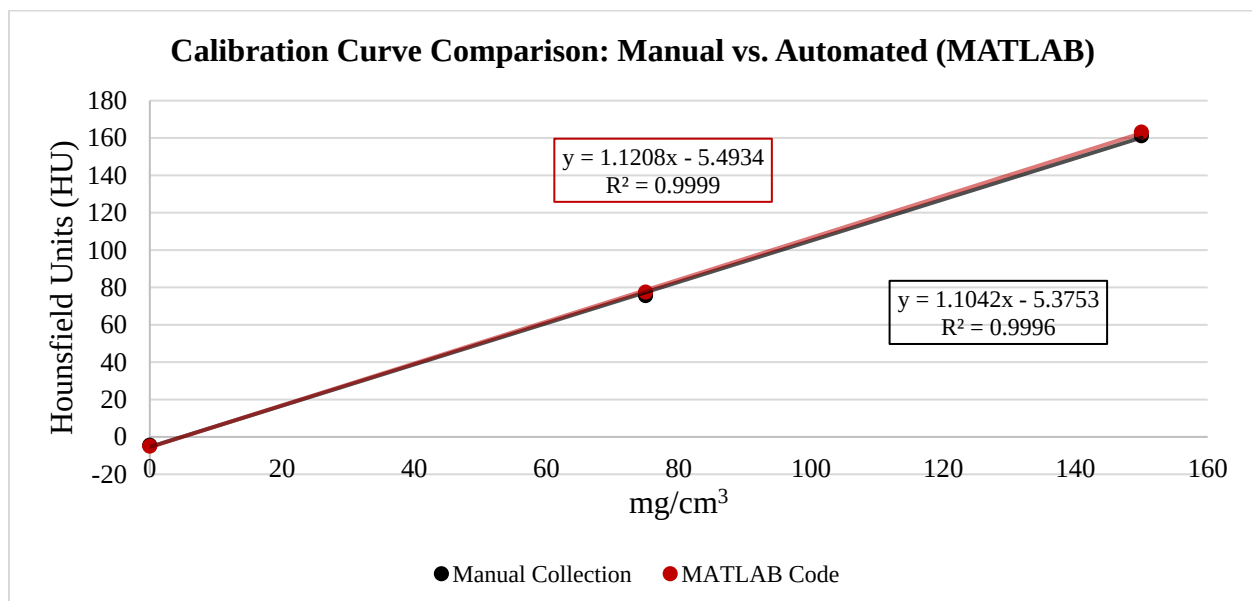


Figure 3. Example of minimal differences in calibration curves constructed from the automated MATLAB code compared to manual process

Calculation of phantom-based vBMD from HU values: Site-specific calibration curves were constructed using HU values and known densities (0, 75, and 150 mg/cm³) from the INTable phantom (produced by the MATLAB code). The site-specific HU values and known densities were plotted and a best fit line was applied (Figure 4). The equation for this line was used to calculate vBMD for each anatomical VOI HU value:

$$\text{vBMD} = [\text{HU}_{\text{VOI}} - \text{y-intercept}] / \text{slope} \quad (1)$$

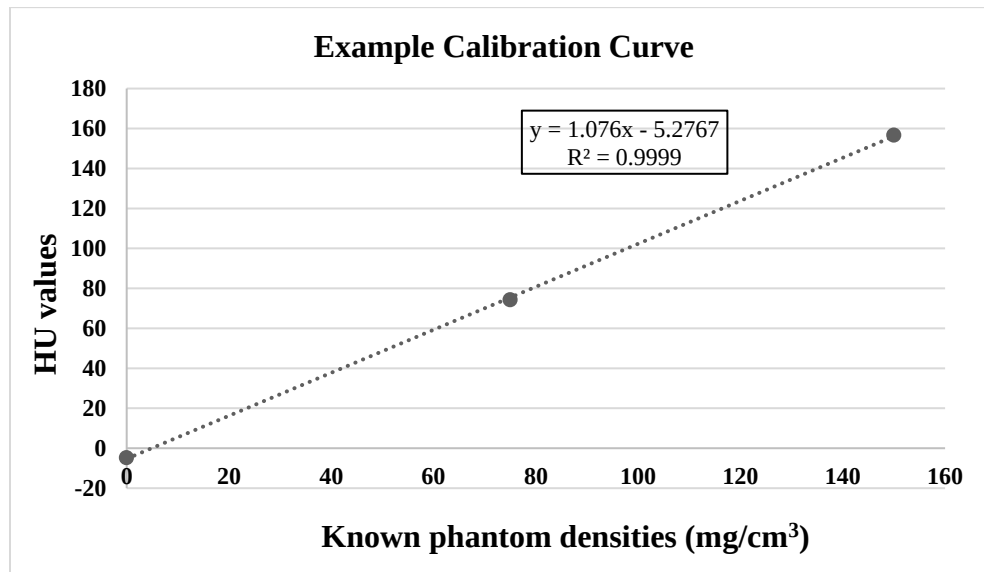


Figure 4. Exemplar site-specific calibration curve used to calculate vBMD. R^2 values near 0.999 (as represented) indicate good linearity within this range of density values when compared to the INTable phantoms.

All available skeletal elements, locations, and tissue types (Table 3) for CT scans that contained the INTable phantom rods ($n = 175/200$) were analyzed using the described standardized phantom-based vBMD methodology and reported in the normative population. This standardized phantom-based methodology was considered the gold standard against which phantomless methodologies were developed and validated; this afforded the opportunity to include male PMHS CT scans without INTable phantoms in the normative population as well as analyze CTs from WIAMan subjects across performers.

2.3.2 Phantomless Method Development

To complete the normative vBMD population, 25 male PMHS CTs required phantomless conversion of skeletal VOI HU into vBMD values. These retrospective CT scans were completed prior to the standardized acquisition parameter of including the INTable phantom yet are still available for vBMD analysis. Current literature on phantomless methods typically utilizes internal reference tissues such as air, fat, and

muscle to create scan-specific calibration curves under the assumption that the equivalent densities of each tissue (i.e., fat and muscle) are known and constant across individuals and scans. However, previous work has utilized inconsistent density values for reference tissues¹²⁻¹⁴ which suggests that the vBMD produced from these calibration curves may not be comparable. Additionally, these studies mainly focused on the lumbar spine, pelvis, and femoral neck; thus, it was unknown if this methodology could be applied to the additional skeletal sites included in this work. Therefore, an extensive process of phantomless method development and validation against the standardized phantom-based method was performed. Sections 2.4 and 2.5 outline results of two phantomless methods for calculating vBMD: internal reference tissue calibration curve (i.e., air, fat, muscle) and univariate and multiple regressions using subject and scan-specific variables.

2.4 Internal Reference Tissue Phantomless Method

As there is a lack of consensus in the literature on the equivalent densities of fat and muscle (Table 7), these values were investigated across a sample of 50 PMHS from the normative population. All QCT scans included the INTABLE phantom to calculate equivalent densities of each reference material (i.e., air, fat, and muscle) using the phantom-based calibration curve at each site. Consistency in equivalent density values is crucial for constructing accurate calibration curves in CT scans that do not contain the INTABLE phantom; thus, these values were calculated for specific body regions and averaged across the $n = 50$ male PMHS from the OSU sample (Table 8).

Table 7. Variation in vBMD equivalent densities (mg/cm³) reported across studies

Internal reference material	Equivalent density (mg/cm ³)	Study
Air	n/a	Weaver et al. ¹⁵
Fat	-69	
Muscle	77	
Air	-840	Eggermont et al. ¹⁴
Fat	-80	
Muscle	30	
Air	1.21	Winsor et al. ^{16,17}
Fat	950	
Muscle	1050	

Table 8. vBMD equivalent densities (mean $\pm$ SD) from OSU PMHS sample (n = 50)

Skeletal Site	Air vBMD (mg/cm ³)	Fat vBMD (mg/cm ³)	Muscle vBMD (mg/cm ³)
L2–L4	-906 $\pm$ 57	-51 $\pm$ 16	67 $\pm$ 16
Femoral neck	-865 $\pm$ 72	-52 $\pm$ 22	64 $\pm$ 17
Humerus	-888 $\pm$ 94	-62 $\pm$ 24	72 $\pm$ 17
Radius	-880 $\pm$ 77	-55 $\pm$ 26	70 $\pm$ 21
Tibia	-824 $\pm$ 48	-53 $\pm$ 22	55 $\pm$ 10

HU values from each skeletal site were converted to vBMD using calibration curves constructed from the above reference material equivalent density values (Table 8) on 10 PMHS from the normative population. The resulting PL vBMD was compared to the gold standard PB vBMD on the same PMHS. Specific sites were chosen where good consistency in muscle and subcutaneous fat tissue could be isolated in the same axial slices as the VOI (Table 8). There were no significant differences in vBMD values ($p > 0.542$) between methods at any site using paired t-tests. However, site-specific linear regressions between PL vBMD and PB vBMD varied widely in adjusted R^2 values ranging from 10.0% (tibia 50% Ct site) to 71.4% (L2 total) (Table 9). It appeared that although there were no differences between vBMD produced from both methods, the internal reference tissue PL method consistently demonstrated the weakest predications of the gold standard PB vBMD values on the denser Ct bone anatomical locations (Table 9).

Table 9. Accuracy of internal reference material PL vBMD compared to PB vBMD for n = 10

Skeletal site	PB mean vBMD (mg/cm ³)	PL mean vBMD (mg/cm ³)	Paired t-test p-value	Percent difference (%)	Univariate regression	
					R^2	p-value
L2 Tb	235.6	220.8	0.119	9.7	0.704	<0.001
L3 Tb	219.9	211.3	0.249	7.2	0.496	<0.001
L4 Tb	235.1	219.5	0.101	8.2	0.387	<0.001
L2 total	313.0	293.8	0.095	8.8	0.757	<0.001
L3 total	310.5	301.1	0.326	7.1	0.596	<0.001
L4 total	327.1	307.2	0.085	7.7	0.523	<0.001
Fem-neck Tb	296.6	270.0	0.078	11.1	0.709	<0.001
Fem-neck total	387.1	355.1	0.077	10.4	0.671	<0.001
Fem-neck Ct Inf	984.3	918.3	0.087	9.3	0.321	<0.001
Fem-neck Ct Sup	865.2	806.0	0.080	9.4	0.374	<0.001
Hum-50 Ct	1168.8	1083.9	0.027	8.7	0.268	<0.001
Rad-50 Ct	1126.0	1046.7	0.032	7.7	0.322	<0.001
Tib-50 Ct	1185.7	1161.8	0.340	5.3	0.165	0.016

Bold indicates p-values significant at $\alpha = 0.05$.

2.5 Regression Equation Phantomless Method

Due to the variable success of the internal reference tissue PL methodology, additional options were explored for calculating vBMD without the INTable phantom. The rationale for refining and standardizing a phantomless methodology was to be confident in incorporating the 25 PMHS CT scans without INTable phantoms into the normative population with PB values while maintaining a simple and universally applicable approach. Initial investigations involved extensive multiple regression models that included over nine subject- and scanner-specific independent predictors; however, these complex models were strategically simplified at each anatomical site and skeletal tissue type to reduce error associated with overfitting of the model. The preferred PL regression equations were developed for a CT scan acquired at 120 kV. Utilizing a sample of 50 phantom-based PMHS scans (referred to as the “method development sample”) from the normative population, the univariate, or in some cases multiple, regression equations presented in Table 10 were developed. All equations utilize skeletal element HU to predict vBMD. Equations are skeletal site and tissue specific.

Table 10. PL regression equations from method development sample (n = 50 PMHS)

Skeletal site	Slope	Intercept	R ²	Equation constant	Skeletal constant	Height constant	Weight constant	Method
L2 Tb	0.9907	4.76	0.747	-	-	-	-	Univariate
L3 Tb	0.889	30.43	0.680	-	-	-	-	Univariate
L4 Tb	0.897	32.14	0.606	-	-	-	-	Univariate
L2 total	0.961	14.36	0.504	-	-	-	-	Univariate
L3 total	0.969	6.87	0.563	-	-	-	-	Univariate
L4 total	0.804	48.49	0.432	-	-	-	-	Univariate
Fem-neck Tb	-	-	0.246	1077	0.433	-3.95	3.47	Multiple
Fem-neck total	0.937	24.9	0.707	-	-	-	-	Univariate
Fem-neck Ct Inf	-	-	0.336	873	0.654	-3.87	1.853	Multiple
Fem-neck Ct Sup	-	-	0.448	854	0.649	-3.98	1.756	Multiple
Fem-50 Ct	0.870	54.00	0.681	-	-	-	-	Univariate
Calc Tb	0.712	301.10	0.296	-	-	-	-	Univariate
Calc total	0.832	32.46	0.328	-	-	-	-	Univariate
Hum-50 Ct	0.832	39.82	0.510	-	-	-	-	Univariate
Rad-4 Tb	0.874	12.64	0.550	-	-	-	-	Univariate
Rad-4 total	0.885	7.90	0.606	-	-	-	-	Univariate
Rad-30 Ct	0.296	789.40	0.217	-	-	-	-	Univariate
Rad-50 Ct	0.362	693.60	0.200	-	-	-	-	Univariate
Tib-4 Tb	0.332	712.90	0.158	-	-	-	-	Univariate
Tib-4 total	0.826	51.30	0.476	-	-	-	-	Univariate
Tib-38 Ct	0.764	78.63	0.424	-	-	-	-	Univariate
Tib-50 Ct	0.535	483.50	0.456	-	-	-	-	Univariate
Tib-66 Ct	0.626	380.30	0.351	-	-	-	-	Univariate

To test the accuracy of vBMD calculated using these PL regression equations, 30 male PMHS (i.e., “method validation sample”) were chosen from the normative population. These individuals were not included in the method development sample, had INTable phantoms present in their CT scans, and had all skeletal sites represented. This allowed for PL vBMD values to be directly compared to the PB values from the same individuals using site-specific paired t-tests. Table 11 demonstrates no significant differences ($p > 0.0215$) between vBMD calculated from the PL regression equations in Table 10 and PB vBMD in the method validation sample. The percent difference ranged from 4.2% to 9.3% with an average across all anatomical sites of $6.7 \pm 5.4\%$. Overall, the regression PL method demonstrated generally smaller differences with the PB method and allowed greater confidence in the comparability of vBMD values across methods. This was due to the development of a regression PL method which avoids the error that could be introduced by the lack of consistent muscle or fat internal reference materials at each site. Thus, the regression equation was chosen to quantify site-specific phantomless vBMD for the 25 PMHS without INTable phantoms. This facilitated the completion of the normative OSU male population with confidence that the PL and PB methods were providing comparable results. Additionally, CTs from other university performers collected as part of the WIAMan program could be analyzed using the same methods to contextualize their site-specific vBMD within the normative population.

Table 11. Accuracy of regression PL vBMD compared to PB vBMD for n = 30 method validation sample

Skeletal site	PB mean vBMD (mg/cm ³)	PL mean vBMD (mg/cm ³)	Paired t-test p-value	Percent difference (%)	Univariate regression	
					R ²	p-value
L2 Tb	224.3	220.2	0.38	8.6	0.508	<0.001
L3 Tb	216.7	215.7	0.81	8.6	0.456	<0.001
L4 Tb	232.1	227.6	0.40	9.0	0.391	<0.001
L2 total	301.9	296.5	0.33	7.6	0.186	0.017
L3 total	304.9	304.1	0.87	7.4	0.228	0.008
L4 total	317.8	310.0	0.22	8.0	0.313	0.001
Fem-neck Tb	296.6	292.9	0.50	8.0	0.513	<0.001
Fem-neck total	402.1	387.8	0.53	7.4	0.440	<0.001
Fem-neck Ct Inf	1006.1	1000.4	0.65	5.2	0.177	0.021
Fem-neck Ct Sup	861.4	852.1	0.41	5.9	0.347	0.001
Fem-50 Ct	1207.4	1216.3	0.58	5.3	0.171	0.023
Calc Tb	226.9	229.2	0.60	6.9	0.518	<0.001
Calc total	359.3	362.0	0.62	6.2	0.717	<0.001
Hum-50 Ct	1142.7	1126.4	0.32	6.5	0.135	0.046
Rad-4 Tb	236.5	235.7	0.90	9.3	0.297	0.003
Rad-4 total	295.1	295.7	0.93	8.2	0.366	0.001
Rad-30 Ct	1089.0	1078.7	0.47	5.3	0.282	0.003
Rad-50 Ct	1095.2	1089.4	0.62	5.4	0.268	0.003
Tib-4 Tb	238.1	234.6	0.52	7.8	0.573	<0.001

Table 11. Accuracy of regression PL vBMD compared to PB vBMD for n = 30 method validation sample

Skeletal site	PB mean vBMD (mg/cm ³)	PL mean vBMD (mg/cm ³)	Paired t-test p-value	Percent difference (%)	Univariate regression	
					R ²	p-value
Tib-4 total	288.2	283.8	0.46	7.3	0.550	<0.001
Tib-38 Ct	1199.2	1200.4	0.92	4.2	0.102	0.085
Tib-50 Ct	1186.2	1187.3	0.93	4.2	0.246	0.005
Tib-66 Ct	1151.8	1144.8	0.60	5.0	0.108	0.076

Bold indicates p-values significant at $\alpha = 0.05$.

2.6 Statistical Analyses

vBMD was calculated for all available anatomical sites and tissue types using PB calibration curves or the validated PL regression equations for all 200 males to construct a site-specific normative male population. To characterize the variation in vBMD across skeletal elements, paired t-tests compared right and left sites as well as between lumbar spine levels. One-way analyses of variance (ANOVAs) with post hoc Tukey tests were used to investigate differences in vBMD within each tissue type (i.e., Ct, Tb, and total) across the body. Pearson correlations were used to understand systemic relationships of vBMD across skeletal elements (within tissue types).

To investigate the potential limitations of DXA in assessing PMHS for inclusion/exclusion criteria, interpreting injury outcomes, or scaling injury risk curves, aBMD and vBMD values from the normative population (n = 200) were compared across matched anatomical sites (i.e., lumbar spine, femoral neck, and radius). Both raw aBMD values as well as bone quality assessment values produced with respect to the standardized age and sex-matched National Health and Nutrition Examination Survey (NHANES) reference data were obtained from a GE Lunar system using typical protocols. To compare both aBMD and vBMD from the OSU normative population to DXA aBMD t-score and z-score output utilized for bone quality assessments, z-scores were calculated for the OSU PMHS using the following equation:

$$z - score = \frac{(x - \bar{X})}{\sigma} \quad (2)$$

where x = PMHSi aBMD or vBMD value

$\bar{X}$ = mean of OSU aBMD or vBMD normative population

σ = standard deviation of OSU aBMD or vBMD normative population

Pearson correlations and linear regressions were used to identify relationships between modalities (DXA and QCT) for the normative population across anatomical sites. Additionally, WIAMan subject CT scans were analyzed utilizing the validated and

appropriate phantom-based (PB) or phantomless methods such that vBMD (mg/cm^3) values could be transformed into z-scores with respect to the OSU normative population to investigate bone quality of WIAMan subjects across anatomical sites. Alpha level was set a priori at 0.05.

3. RESULTS AND DISCUSSION

3.1 Normative Male vBMD Population

Development of the male normative vBMD population across the skeleton included 175 phantom-based PMHS CT scans and 25 phantomless PMHS CT scans for a total of 200 male PMHS. The demographics of the normative population are summarized in Table 1. A complete list of average vBMD values with standard deviations for all anatomical sites and tissue types, as well as the number of PMHS with values from each site are listed in the Appendix within Table A-1. Initial investigations into the intra-individual variation in vBMD values included comparisons between bilateral elements, between lumbar vertebrae, and across all sites to understand the site-specific nature of bone quality.

Results of paired t-tests between right and left elements (Table 12) or between lumbar sites (Table 13) were used to determine if values could be combined into a single representative vBMD for each skeletal element/body region. Mean vBMD values included only individuals with each site in the comparison and without any surgical hardware or artifacts obscuring the VOI. Results indicate that only left and right femoral neck total vBMD were significantly different ($p < 0.001$) and should be reported and analyzed separately. For the lumbar spine, only L2 and L3 Tb vBMD were similar, indicating all lumbar spine vertebral values should be reported separately (see Table A-1 for complete element and tissue type specific values).

Table 12. Paired t-test comparisons between right and left vBMD values per site and tissue type (SDs reported in Table A-1)

Skeletal site	Left mean vBMD (mg/cm ³)	Right mean vBMD (mg/cm ³)	p-value
Fem-neck Tb	298.1	298.0	0.98
Fem-neck total	411.2	396.6	<0.001
Fem-neck Ct Inf	998.7	984.7	0.13
Fem-neck Ct Sup	826.9	817.0	0.10
Fem-50 Ct	1200.1	1199.7	0.93
Calc Tb	367.7	365.6	0.17
Calc total	367.7	365.6	0.33
Hum-50 Ct	1121.7	1119.6	0.68
Rad-4 Tb	236.9	232.4	0.06
Rad-4 total	297.9	300.1	0.41
Rad-30 Ct	1088.0	1095.8	0.13
Rad-50 Ct	1097.5	1103.7	0.27
Tib-4 Tb	248.2	245.5	0.18
Tib-4 total	292.4	291.4	0.60
Tib-38 Ct	1199.1	1197.4	0.60
Tib-50 Ct	1189.6	1192.7	0.39
Tib-66 Ct	1143.3	1142.7	0.87

Bold indicates p-values significant at $\alpha = 0.05$.

Table 13. Lumbar spine level comparison for vBMD per tissue site

Skeletal sites		Site 1 mean vBMD (mg/cm ³)	Site 2 mean vBMD (mg/cm ³)	p-value
L2 Tb	L3 Tb	217.4	220.5	0.08
L3 Tb	L4 Tb	219.6	229.74	<0.001
L2 Tb	L4 Tb	217.1	230.0	<0.001
L2 total	L3 total	298.5	308.6	<0.001
L3 total	L4 total	308.2	321.2	<0.001
L2 total	L4 total	297.8	322.0	<0.001

Bold indicates p-values significant at $\alpha = 0.05$.

For all sites that demonstrated no difference between right and left, vBMD values were averaged to create a combined value for each tissue type. Table 14 summarized all site-specific descriptive statistics for the normative population. The number of PMHS with anatomical sites available for inclusion in the normative population varied due to quality of scan (beam hardening), metal surgical implants, and field of view limitations. Table A-1 contains descriptive statistics for all bilateral sites as well as the combined values.

Table 14. Descriptive statistics for normative vBMD population by site and tissue type (all bilateral values were averaged except left and right femoral neck totals)

Skeletal site	n	Mean vBMD (mg/cm ³)	SD	Minimum	Maximum	95% CI
L2 Tb	179	217.4	32.8	151.0	330.2	(209.1, 225.6)
L3 Tb	184	219.7	29.1	125.7	296.7	(211.6, 227.9)
L4 Tb	185	229.6	30.0	151.5	341.6	(221.5, 237.7)
L2 total	179	298.3	40.3	205.8	467.4	(290.1, 306.6)
L3 total	184	308.2	36.5	219.9	420.2	(300.1, 316.3)
L4 total	185	321.1	37.5	224.2	471.0	(313.0, 329.2)
Fem-neck Tb	178	297.9	43.1	193.0	423.2	(289.6, 306.2)
Left fem-neck total	176	411.6	59.3	256.6	569.9	(403.3, 420.0)
Right fem-neck total	175	397.1	56.8	272.1	588.9	(388.7, 405.4)
Fem-neck Ct Inf	178	988.8	74.9	733.3	1183.6	(980.5, 997.1)
Fem-neck Ct Sup	178	820.9	73.9	606.0	1011.3	(812.6, 829.2)
Fem-50 Ct	177	1199.9	77.2	1001.5	1505.3	(1191.6, 1208.2)
Calc Tb	163	222.2	28.7	147.7	306.5	(213.6, 230.9)
Calc total	163	366.7	48.4	206.1	582.4	(358.0, 375.3)
Hum-50 Ct	154	1120.0	88.3	862.4	1352.0	(1111.1, 1128.9)
Rad-4 Tb	159	234.8	32.6	167.7	361.3	(226.1, 243.6)
Rad-4 total	159	298.7	41.2	199.6	412.0	(290.0, 307.5)
Rad-30 Ct	163	1092.8	76.7	851.8	1254.4	(1084.2, 1101.5)
Rad-50 Ct	164	1098.0	83.5	813.9	1332.1	(1089.4, 1106.6)
Tib-4 Tb	159	246.3	38.6	154.6	383.1	(237.5, 255.0)
Tib-4 total	159	291.7	43.7	194.7	419.5	(282.9, 300.5)
Tib-38 Ct	165	1197.2	62.7	999.6	1377.2	(1188.6, 1205.8)
Tib-50 Ct	166	1189.9	70.1	949.8	1419.3	(1181.3, 1198.5)
Tib-66 Ct	169	1141.0	73.7	887.8	1371.1	(1132.5, 1149.5)

vBMD varies across skeletal elements due to unique adaptations to mechanical loading environments across elements and site locations. Consequently, using a singular location to assess global bone quality of the PMHS may result in misleading assumptions of localized bony response to traumatic loading or difficulty in scaling injury risk curves. ANOVAs with post hoc Tukey tests were performed by tissue type (Tables 15–17) to investigate intra-skeletal variation. Overall, a majority of significant differences in vBMD across almost all sites and tissue types indicates the need for site-specific assessment of bone quality. Interestingly, the pattern of differences or similarities between sites was not always consistent across skeletal tissue type. For example, the L3 and Rad-4 Tb vBMD values were significantly different ($p < 0.001$; Table 15) but not different in total vBMD ($p = 0.55$; Table 16). It is likely important to account for the differential contribution of tissue type in each body region depending on the mechanism of loading. This approach may provide a more accurate basis for scaling injury risk curves rather than perpetuating assumptions about the biological meaningfulness of global representations of bone.

Table 15. Trabecular vBMD ANOVA (with post hoc Tukey tests) results

Trabecular comparisons		T-statistic	p-value	95% CI
Site 1	Site 2			
L3	L2	0.65	1.00	(-8.17, 12.81)
L4	L2	3.44	0.01	(1.73, 22.69)
Rad-4	L2	4.72	<0.001	(6.56, 28.34)
Fem-neck	L2	22.45	<0.001	(69.97, 91.13)
Tib-4	L2	7.82	<0.001	(17.98, 39.77)
Calc	L2	1.33	0.84	(-5.95, 15.69)
L4	L3	2.80	0.08	(-0.52, 20.30)
Rad-4	L3	4.12	0.001	(4.31, 25.95)
Fem-neck	L3	21.95	<0.001	(67.72, 88.73)
Tib-4	L3	7.23	<0.001	(15.73, 37.37)
Calc	L3	0.70	0.99	(-8.21, 13.29)
Rad-4	L4	1.43	0.79	(-5.57, 16.05)
Fem-neck	L4	19.20	<0.001	(57.84, 78.83)
Tib-4	L4	4.55	<0.001	(5.85, 27.47)
Calc	L4	-2.02	0.40	(-18.08, 3.39)
Fem-neck	Rad-4	17.06	<0.001	(52.19, 74.01)
Tib-4	Rad-4	3.01	0.04	(0.22, 22.63)
Calc	Rad-4	-3.33	0.02	(-23.72, -1.44)
Tib-4	Fem-neck	-13.97	<0.001	(-62.58, -40.77)
Calc	Fem-neck	-20.60	<0.001	(-86.52, -64.85)
Calc	Tib-4	-6.35	<0.001	(-35.15, -12.87)

Bold indicates p-values significant at $\alpha = 0.05$.

Table 16. Total vBMD ANOVA (with post hoc Tukey tests) results

Total comparisons		T-statistic	p-value	95% CI
Site 1	Site 2			
L3	L2	2.04	0.45	(-4.81, 24.58)
L4	L2	4.71	<0.001	(8.12, 37.47)
Rad-4	L2	0.08	1.00	(-14.84, 15.66)
L fem-neck	L2	23.14	<0.001	(98.47, 128.18)
R fem-neck	L2	20.14	<0.001	(83.89, 113.65)
Tib-4	L2	7.82	<0.001	(17.98, 39.77)
Calc	L2	-1.32	0.89	(-21.89, 8.62)
L4	L3	2.69	0.13	(-0.52, 20.30)
Rad-4	L3	-1.90	0.55	(-24.63, 5.68)
L fem-neck	L3	21.26	<0.001	(88.68, 118.20)
R fem-neck	L3	18.25	<0.001	(74.11, 103.67)
Tib-4	L3	-3.31	0.02	(-31.67, -1.36)
Calc	L3	11.78	<0.001	(43.43, 73.53)
Rad-4	L4	-4.49	<0.001	(-37.52, -7.25)
L fem-neck	L4	18.63	<0.001	(75.79, 105.27)
R fem-neck	L4	15.62	<0.001	(61.22, 90.73)
Tib-4	L4	-5.90	<0.001	(-44.56, -14.29)
Calc	L4	9.19	<0.001	(30.53, 60.60)
L fem-neck	Rad-4	22.37	<0.001	(97.60, 128.22)
R fem-neck	Rad-4	19.46	<0.001	(83.02, 113.69)
Tib-4	Rad-4	-1.36	0.88	(-22.74, 8.65)
Calc	Rad-4	13.21	<0.001	(52.35, 83.55)
Tib-4	L fem-neck	-23.76	<0.001	(-135.27, -104.64)
Calc	L fem-neck	-8.96	<0.001	(-60.18, -29.75)
Tib-4	R fem-neck	-20.85	<0.001	(-120.74, -90.07)
Calc	R fem-neck	-6.05	<0.001	(-45.64, -15.17)
Calc	Tib-4	14.85	<0.001	(59.40, 90.60)

Bold indicates p-values significant at $\alpha = 0.05$.

Table 17. Cortical vBMD ANOVA (with post hoc Tukey tests) results

Cortical comparisons		T-statistic	p-value	95% CI
Site 1	Site 2			
Rad-50	Hum-50	-2.58	0.193	(-48.41, 4.43)
Rad-30	Hum-50	-3.19	0.038	(-53.65, -0.74)
Fem-neck Sup	Hum-50	-35.83	<0.001	(-325.00, -273.18)
Fem-neck Inf	Hum-50	-15.72	<0.001	(-157.10, -105.28)
Fem-50	Hum-50	9.56	<0.001	(53.98, 105.87)
Tib-66	Hum-50	2.49	0.238	(-5.22, 47.23)
Tib-50	Hum-50	8.24	<0.001	(43.55, 96.23)
Tib-38	Hum-50	9.08	<0.001	(50.80, 103.56)
Rad-30	Rad-50	-0.62	1.000	(-31.24, 20.83)
Fem-neck Sup	Rad-50	-33.76	<0.001	(-302.58, -251.62)
Fem-neck Inf	Rad-50	-13.30	<0.001	(-134.68, -83.71)
Fem-50	Rad-50	12.40	<0.001	(76.40, 127.43)
Tib-66	Rad-50	5.17	<0.001	(17.19, 68.80)
Tib-50	Rad-50	11.00	<0.001	(65.96, 117.80)
Tib-38	Rad-50	11.86	<0.001	(73.21, 125.13)
Fem-neck Sup	Rad-30	-33.07	<0.001	(-297.42, -245.37)
Fem-neck Inf	Rad-30	-12.65	<0.001	(-129.51, -76.47)
Fem-50	Rad-30	13.01	<0.001	(81.57, 132.68)
Tib-66	Rad-30	5.79	<0.001	(22.36, 74.05)
Tib-50	Rad-30	11.61	<0.001	(71.13, 123.05)
Tib-38	Rad-30	12.46	<0.001	(78.38, 130.38)
Fem-neck Inf	Fem-neck Sup	20.89	<0.001	(142.95, 192.86)
Fem-50	Fem-neck Sup	47.08	<0.001	(354.03, 404.01)
Tib-66	Fem-neck Sup	39.30	<0.001	(294.81, 345.38)
Tib-50	Fem-neck Sup	45.09	<0.001	(343.58, 394.38)
Tib-38	Fem-neck Sup	45.91	<0.001	(350.83, 401.71)
Fem-50	Fem-neck Inf	26.22	<0.001	(186.12, 236.10)
Tib-66	Fem-neck Inf	18.68	<0.001	(126.91, 177.48)
Tib-50	Fem-neck Inf	24.57	<0.001	(175.68, 226.48)
Tib-38	Fem-neck Inf	25.42	<0.001	(182.93, 233.81)
Tib-66	Fem-50	-7.22	<0.001	(-84.24, -33.60)
Tib-50	Fem-50	-1.22	0.951	(-35.47, 15.40)
Tib-38	Fem-50	-0.33	1.000	(-28.22, 22.73)
Tib-50	Tib-66	5.90	<0.001	(23.16, 74.61)
Tib-38	Tib-66	6.77	<0.001	(30.41, 81.94)
Tib-38	Tib-50	0.87	0.994	(-18.59, 33.17)

Bold indicates p-values significant at $\alpha = 0.05$.

If site-specific quantification of vBMD is not available, the potential for characterizing the response of one element from another using vBMD values was investigated. Pearson correlations were performed within tissue types (Tb, Ct, and combined) (Table 18). L3 was chosen as the representative site to investigate lumbar spine relationships with other Tb and total vBMD sites. All tissue specific vBMD values were correlated across sites with the exception of total vBMD between L3 and 4% tibia (Tib-4) ($p=0.081$). Although these relationships were significant, correlations ranged from weak to moderate in strength suggesting proxy assumptions across the skeleton should be made with caution. Similarly, evidence from these intra-skeletal comparisons (Tables

12–18) suggest a global measurement of bone quality may be suboptimal for informing injury risk in PMHS, and analyzing specific anatomical sites of interest would prove more valuable.

Table 18. Pearson correlations between skeletal sites per tissue type

Skeletal site comparisons		% location	Tissue type	Pearson correlation (r)	p-value
Site 1	Site 2				
Radius	Tibia	4	Tb	0.497	<0.001
		30–38	Total	0.538	<0.001
			Ct	0.466	<0.001
			Ct	0.603	<0.001
Radius	Calcaneus	4	Tb	0.416	<0.001
			Total	0.432	<0.001
Tibia	Calcaneus	4	Tb	0.489	<0.001
			Total	0.597	<0.001
Femur	Humerus	50	Ct	0.524	<0.001
Femur	Tibia	50	Ct	0.607	<0.001
Femoral neck	Calcaneus	-	Tb	0.500	<0.001
L femoral neck	Calcaneus	-	Total	0.319	<0.001
R femoral neck	Calcaneus	-	Total	0.366	<0.001
L3	Radius	4	Tb	0.549	<0.001
			Total	0.266	0.001
L3	Femoral neck	-	Tb	0.481	<0.001
L3	L femoral neck	-	Total	0.369	<0.001
L3	R femoral neck	-	Total	0.352	<0.001
L3	Tibia	4	Tb	0.333	<0.001
			Total	0.144	0.081
L3	Calcaneus	4	Tb	0.401	<0.001
			Total	0.250	0.002

Bold indicates p-values significant at $\alpha = 0.05$.

3.2 Comparison Between Methods for Measuring Bone Mineral Density (DXA vs. QCT)

Having identified extensive variation in mineralization across the skeleton, it is necessary to understand the resulting effects on bone quality assessment across commonly employed methodologies (DXA and QCT). By normalizing each aBMD and vBMD value, the relative position of PMHS with respect to the OSU normative population ($n=200$ PMHS) or a standardized reference population (GE Lunar DXA NHANES data) can be used to investigate variation in bone quality assessments. PMHS aBMD is most commonly assessed using NHANES DXA t-scores for selection criteria and interpretation of experimental data but with varying success or consistency.¹¹ Given the ability of QCT to avoid some of the inherent measurement issues accompanying 2D DXA and the apparent superiority of site-specific QCT (vBMD) assessments,^{11,18} relationships between DXA and QCT assessments of the normative population were explored. When comparing NHANES DXA t-scores from standard GE Lunar DXA

protocol to the DXA z-scores that were calculated using *only* the site-specific DXA aBMD values from OSU normative (n = 200) PMHS population, we found that the OSU derived DXA z-scores are representative of the DXA t-scores derived in reference to NHANES. The extremely high correlation (Table 19) suggests that any individual categorized using either population (NHANES or OSU) would be similarly assessed in terms of bone quality status.

Table 19. NHANES DXA t-score compared to OSU calculated DXA z-score (Pearson correlations)

Skeletal sites	R	p-value
L2–L4	0.998	<0.001
Femoral neck	0.998	<0.001
Ultra-distal radius	0.998	<0.001
33% radius	0.995	<0.001

Bold indicates p-values significant at $\alpha = 0.05$.

To investigate the relationship across methodologies, Pearson correlations as well as linear regressions were performed between the NHANES derived DXA t-score assessment and OSU calculated QCT vBMD z-score. For the lumbar spine, femoral neck, and ultra-distal radius, the total vBMD values were used to be as comparable to DXA assessment as possible. For the 33% radius, the Ct vBMD values was used to calculate QCT vBMD z-scores to compare to DXA t-scores. Table 20 demonstrates the matched anatomical site-specific relationships. The lumbar spine and both radius sites were significantly correlated between methodologies. The weak R^2 values ranging from only 0.086 to 0.252 from the linear regression analyses indicated DXA was unable to explain the majority of variation present in the vBMD data. This would indicate a lack of biological relevance in these relationships and reflects the shortcomings of DXA methodology (including 2D analysis of 3D structures, superimposition of structures, and the influence of surrounding tissue). QCT vBMD values are more discriminatory due to their 3D nature, thresholding techniques to identify only bone, and ability to investigate the Ct and Tb bone compartments individually or as a combined unit (i.e., total vBMD). Given the differential sensitivities of tissue types to mechanical load adaptation and aging processes, separate analyses, only available in current QCT methodologies, of Ct and Tb bone would improve understanding of bony response to normal and injurious loading.

Table 20. NHANES DXA t-score compared to OSU QCT vBMD z-score (Pearson correlations and linear regressions)

Skeletal sites	R	R²	p-value
L2–L4	0.335	0.113	<0.001
Femoral neck	0.169	0.029	0.053
Ultra-distal radius	0.293	0.086	0.003
33% radius	0.502	0.252	<0.001

Bold indicates p-values significant at $\alpha = 0.05$.

Figures 5–8 demonstrate the normal histograms of DXA t-score (NHANES) and QCT z-score (OSU) and accompanying scatterplots with a trendline forced through zero to investigate whether DXA is consistently over or underpredicting vBMD values at each anatomical location. These analyses showed that data derived from DXA was likely capturing different aspects of bone due to limitations mentioned above but without consistently over/under predicting BMD relative to QCT. DXA t-score histogram distribution in the L2–L4 region suggests some slight over-estimation of BMD compared to the QCT z-score (Figure 5) which is likely due to the superimposition of the highly dense vertebral neural arch (DXA) which is excluded from the QCT VOI. Conversely, femoral neck, ultra-distal radius, and 33% radius did not demonstrate variance in histogram distribution across methodologies (Figures 6–8). Lastly, none of the scatterplots indicate a clear trend of consistent over/under estimation of BMD between methodologies including at the L2–L4 site.

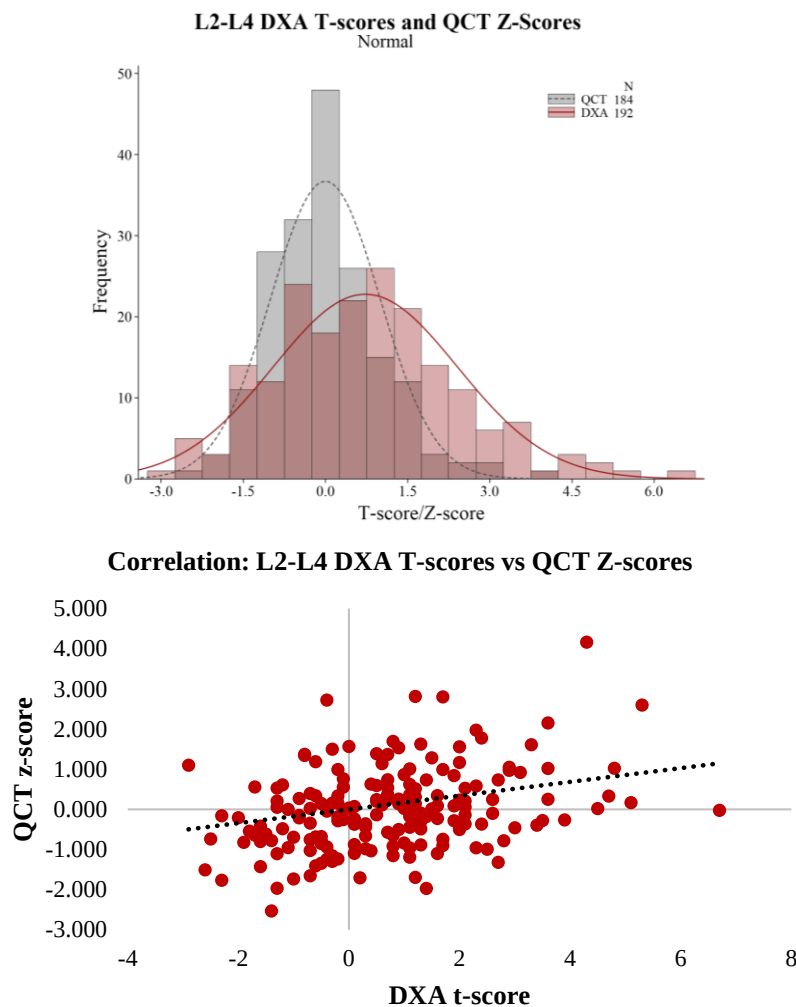


Figure 5. Lumbar (L2–L4) total QCT vBMD z-score (OSU) compared to L2–L4 DXA t-score derived from NHANES reference population

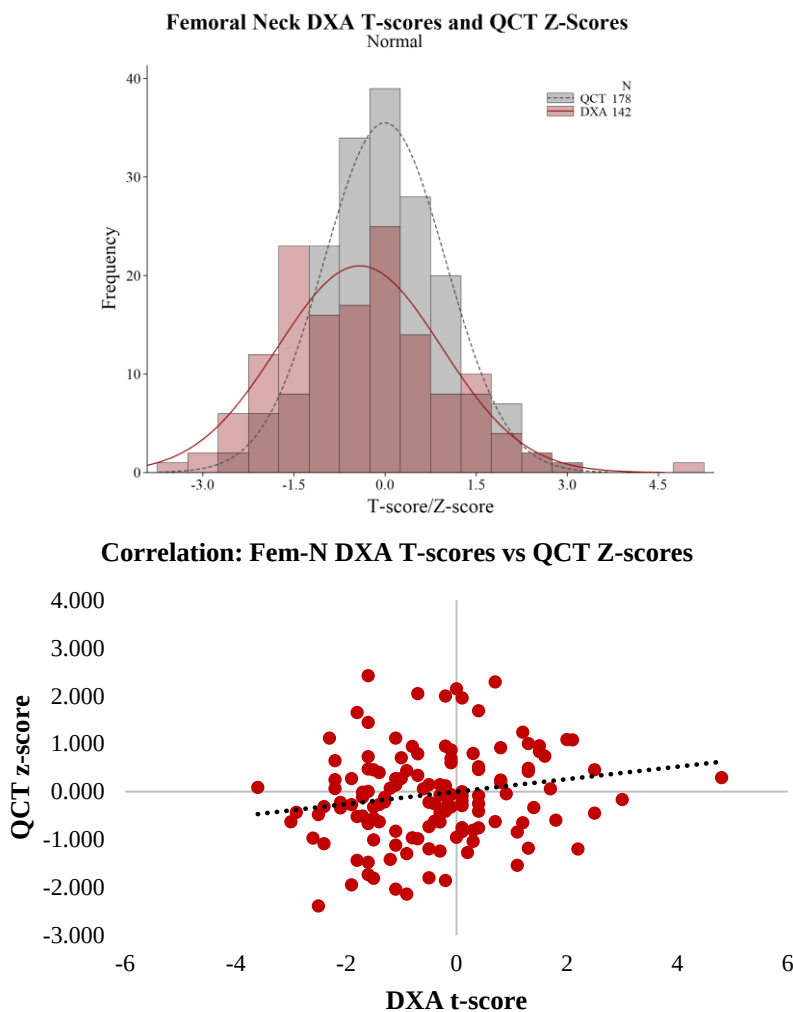


Figure 6. Femoral neck QCT vBMD z-score (OSU) compared to femoral neck DXA t-score derived from NHANES reference population

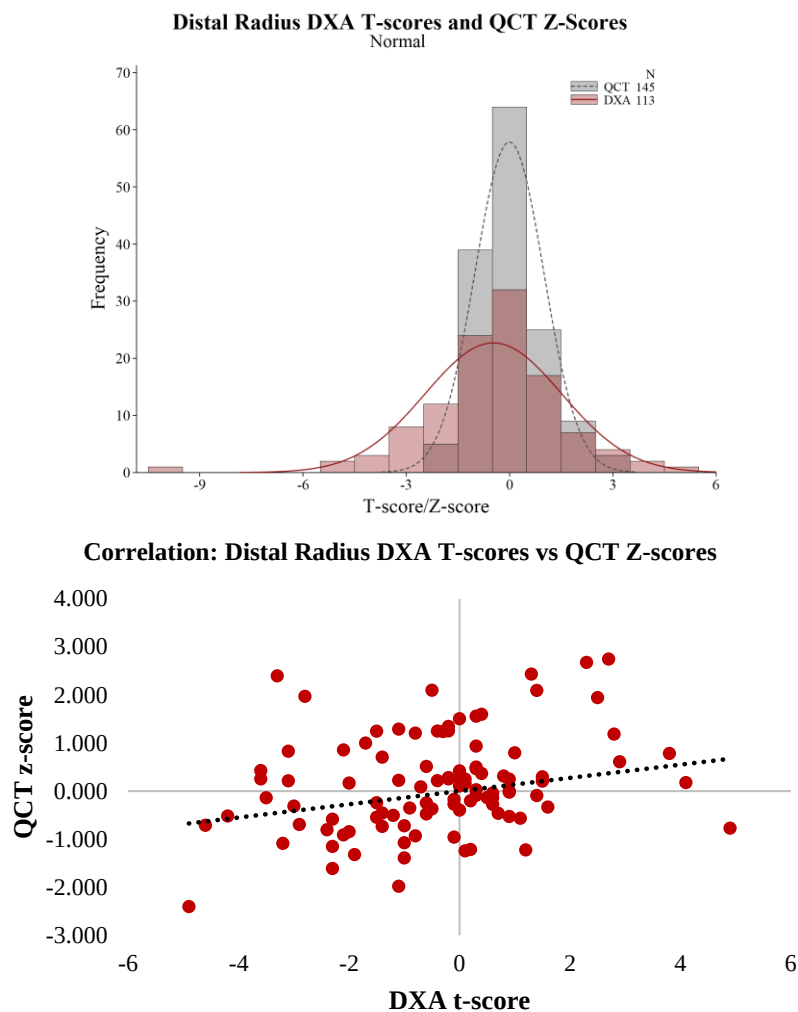


Figure 7. Distal radius QCT vBMD z-score (OSU) compared to distal radius DXA t-score derived from NHANES reference population

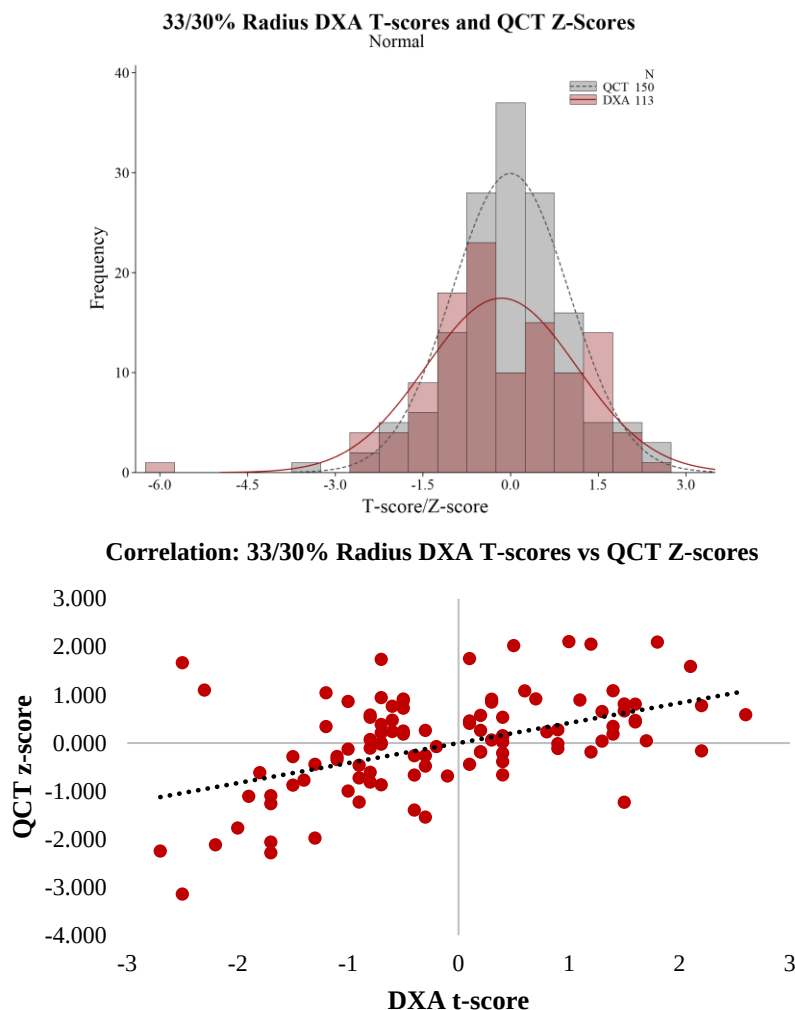


Figure 8. 30% radius QCT vBMD z-score (OSU) compared to 33% radius DXA t-score derived from NHANES reference population

To further investigate the relationship between DXA and QCT methodologies, the DXA z-scores for only the OSU normative population were compared to the QCT z-scores. We expected to find similar results as reported above due to the initial correlations identified between NHANES DXA t-scores and the OSU normative population calculated DXA z-scores. Again, significant correlations but weak relationships were found between the methodologies at comparable sites (Table 21; Figures 9–12). There was no clear over or under prediction of QCT vBMD z-scores by DXA z-scores. Similar to results summarized above, these data indicate that DXA and QCT are capturing different information about bone quality at least in the lumbar spine, femoral neck, and radius.

Table 21. OSU DXA z-scores compared to QCT z-scores for the normative population

Skeletal sites	R	R ²	p-value
L2–L4	0.343	0.118	<0.001
Femoral neck	0.171	0.029	0.050
Ultra-distal radius	0.292	0.085	0.003
33% radius	0.510	0.260	<0.001

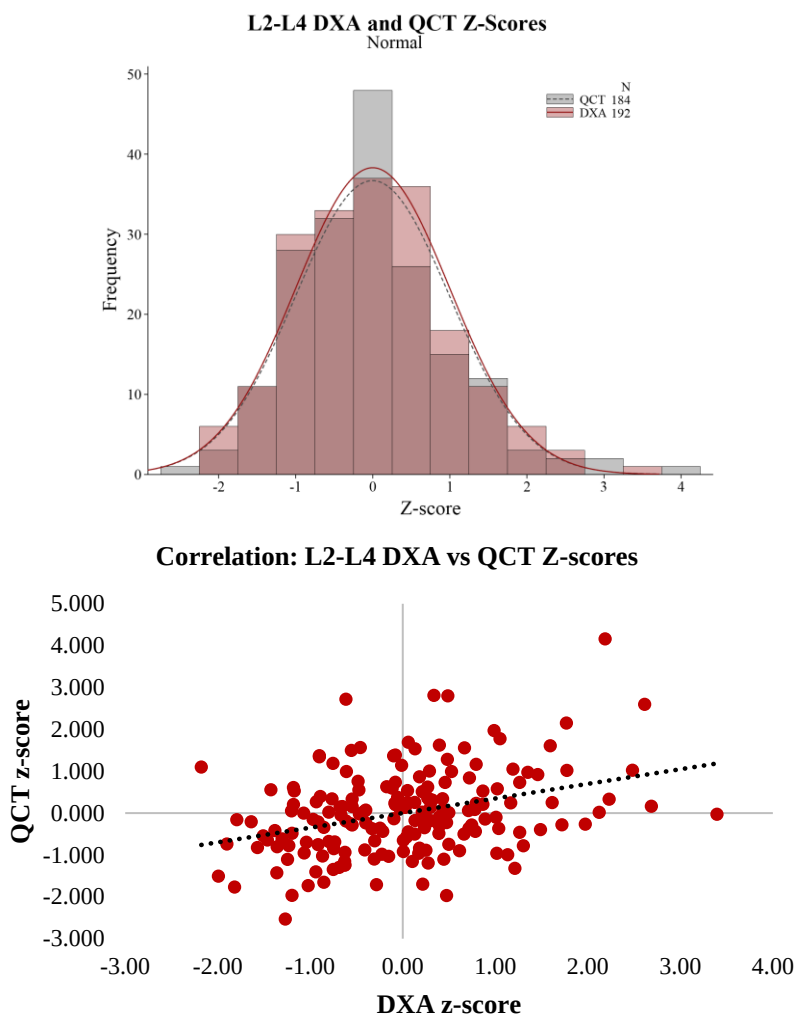


Figure 9. The distributions of the L2–L4 total vBMD z-score and L2–L4 DXA calculated z-score for the normative population appear to be more similar than the comparison with the t-score (Figure 5)

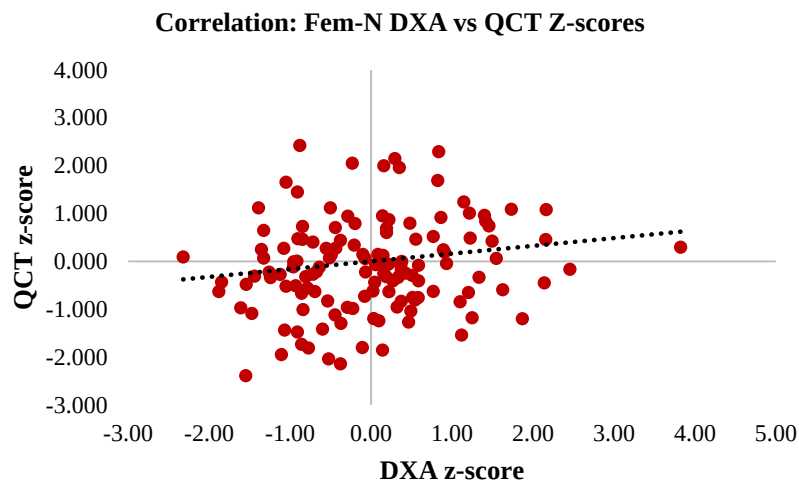
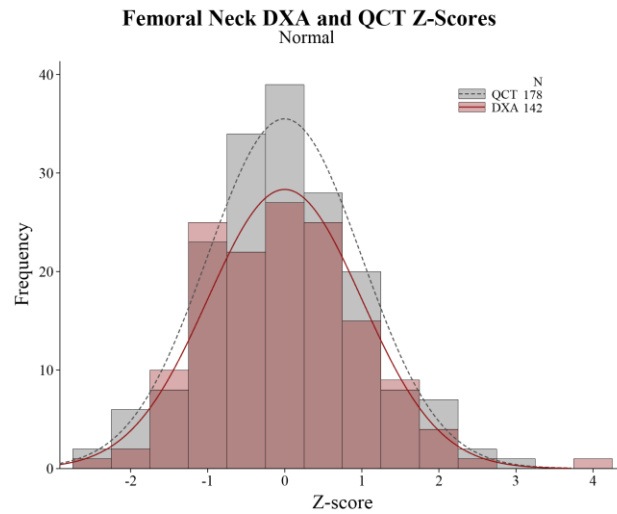


Figure 10. Femoral neck vBMD z-score compared to femoral neck DXA calculated z-score derived for the normative population

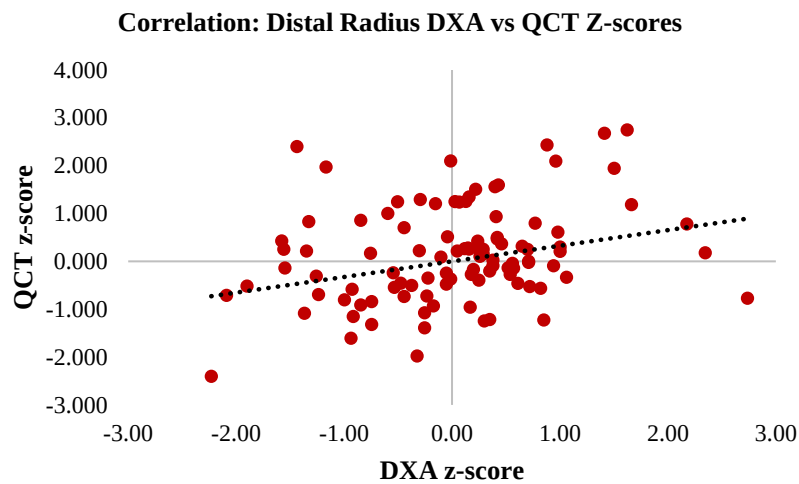
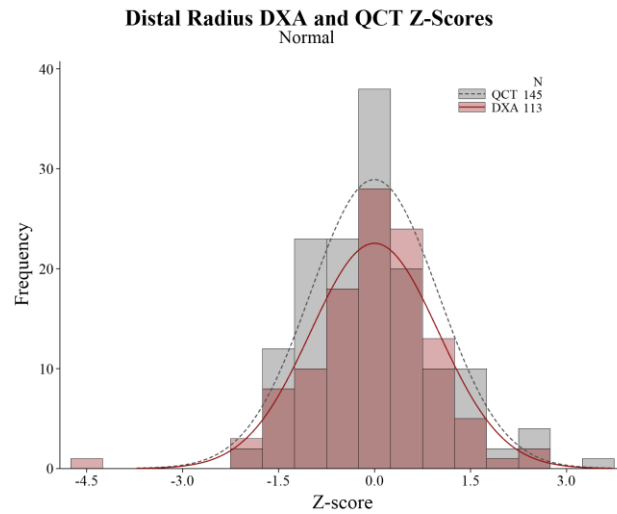


Figure 11. Distal radius vBMD z-score compared to distal radius DXA z-score calculated from normative population

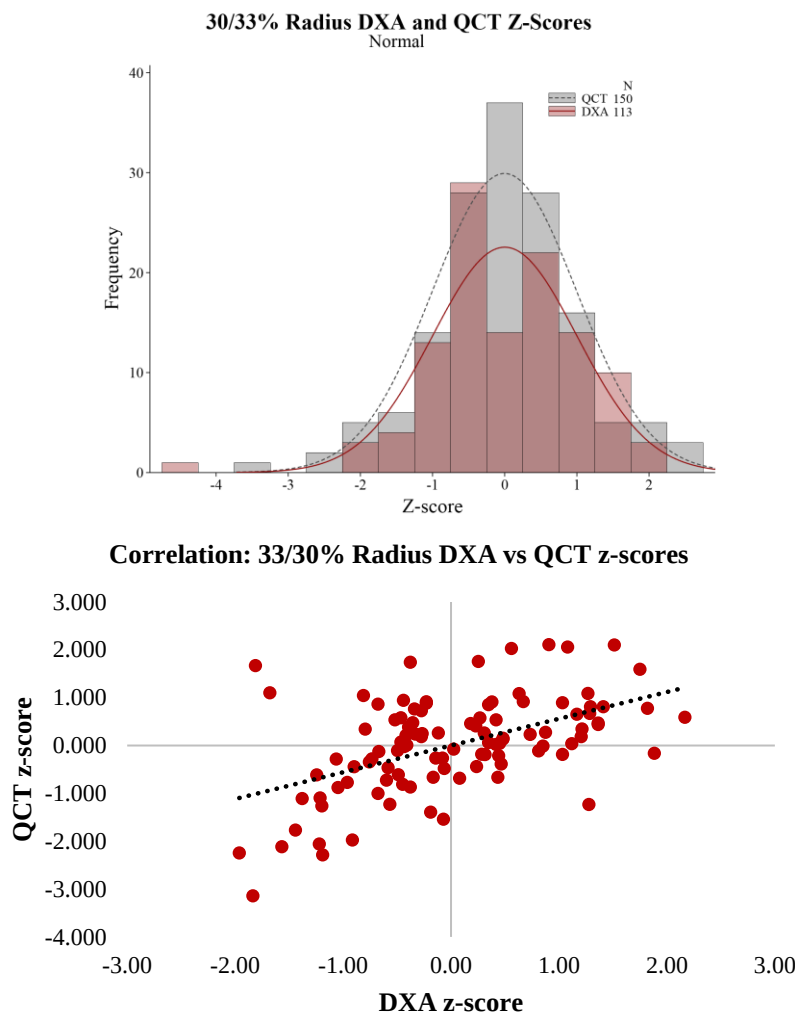


Figure 12. 30% radius vBMD z-score compared to 33% radius DXA z-score calculated from normative population

To demonstrate the impact of the differences in methodologies on the resulting categorization of bone quality with respect to a reference population (either NHANES for DXA or OSU QCT normative), some PMHS from the OSU normative population were identified on the site-specific histograms. Figures 13–16 demonstrate the inconsistent over/under prediction of bone quality with respect to the normative population when using DXA z-scores compared to QCT z-scores from the same individuals. Since 3D QCT vBMD has been established as the gold standard,¹⁹ these examples highlight a concerning trend with using DXA t-scores to evaluate PMHS for inclusion/exclusion criteria, to explain injury severity, or scale injury data.

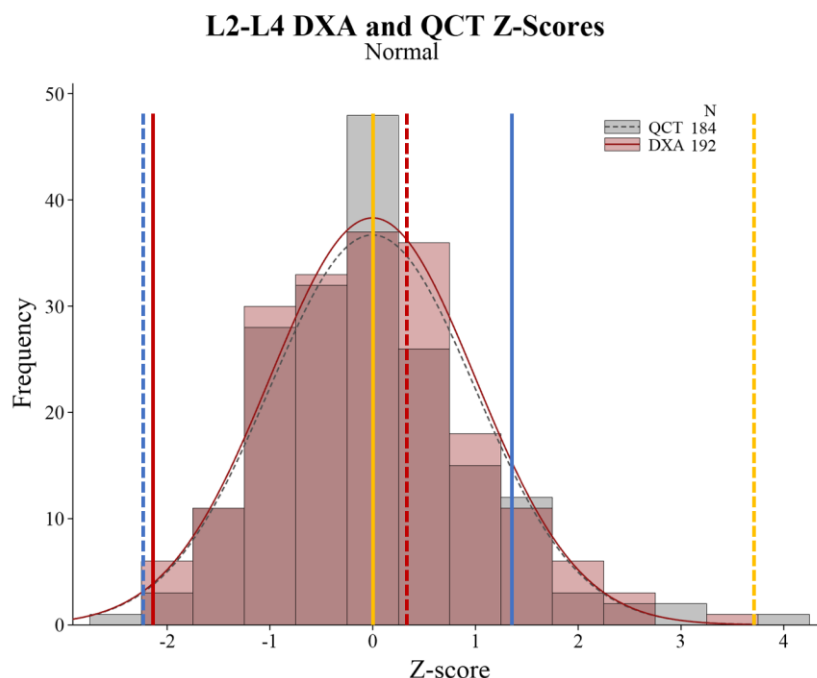


Figure 13. Bone quality assessment relative to the normative population of a 66-year-old (red), 58-year-old (blue), and 87-year-old (yellow) for L2–L4. Dotted lines are DXA z-scores specific to OSU sample. Solid lines are OSU QCT z-scores.

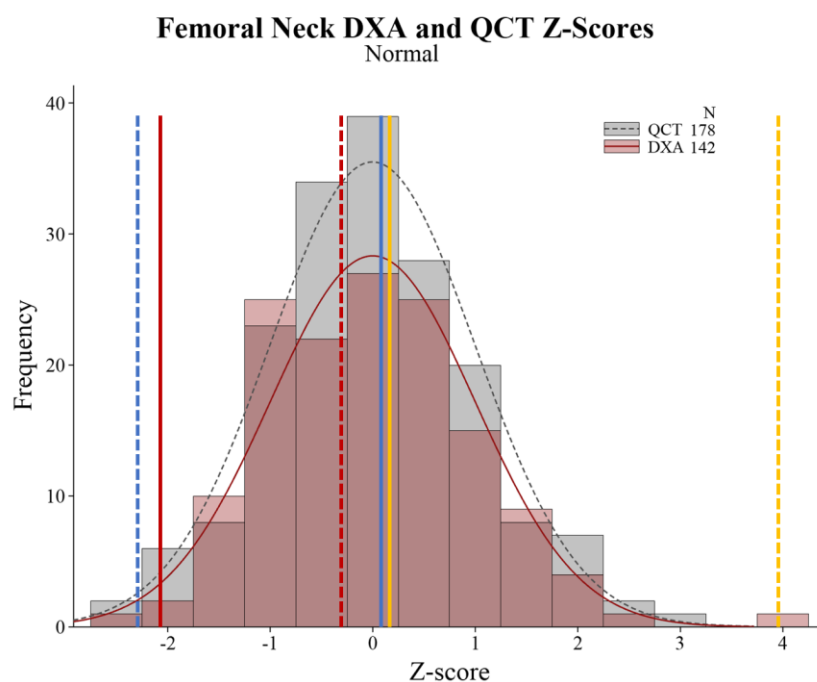


Figure 14. Bone quality assessment relative to normative population of a 66-year-old (red), 75-year-old (blue), and 26-year-old (yellow) for femoral neck. Dotted lines are DXA z-scores specific to OSU sample. Solid lines are OSU QCT z-scores.

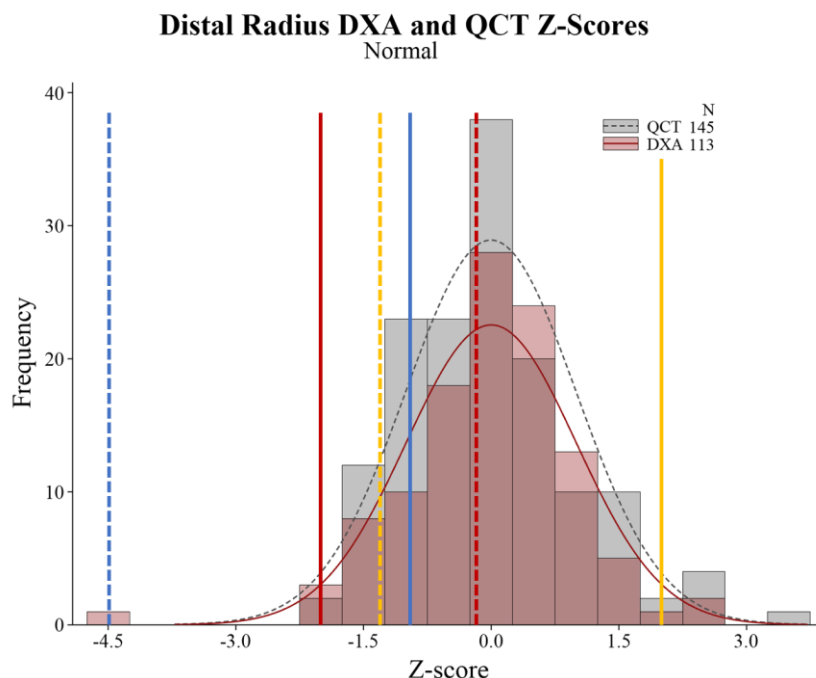


Figure 15. Bone quality assessment relative to normative population of a 102-year-old (red), 54-year-old (blue), and 35-year-old (yellow) for the distal radius. Dotted lines are DXA z-scores specific to OSU sample. Solid lines are OSU QCT z-scores.

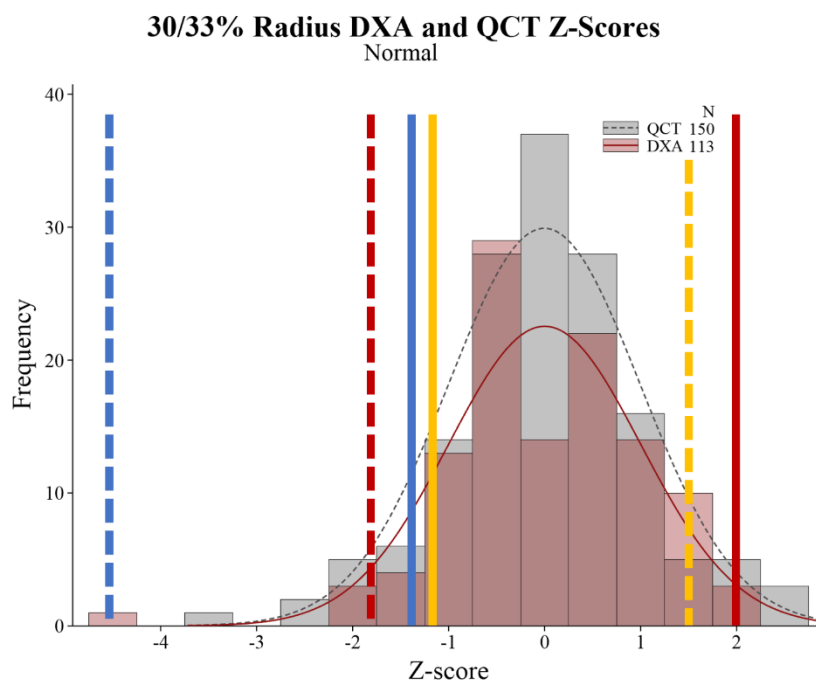


Figure 16. Bone quality assessment relative to normative population of a 35-year-old (red), 54-year-old (blue), and 62-year-old (yellow) for the distal diaphysis of the radius. Dotted lines are DXA z-scores specific to OSU sample. Solid lines are OSU QCT z-scores.

The concept of discordance, or mismatched assessments of bone quality, either across anatomical sites or between methodologies has been previously reported and attributed to both physiological differences in bone adaptation and limitations in DXA technology.^{20,21} Although correlations between aBMD and HU from QCT have been reported,²² the weakness of the relationships found in the present work indicate that suggests bone quality assessments across technologies are not identical. Although, Figures 13–16 highlight the effects of this discordance in only a few PMHS from this male normative population, it does suggest that assumptions of aBMD and vBMD providing similar insight into fracture risk are unfounded. Previous work has similarly identified correlations between aBMD and vBMD in the lumbar spine of females but with a discordance rate of 33%.²³ It is currently unknown if similar issues identified in this work for male PMHS would be identified in female PMHS or if the impact of the resulting effects of misleading assessments of bone quality given the prevalence of DXA values used in injury biomechanics. The QCT vBMD normative population data will be used to help scale injury risk curves in the WIAMan program to determine if this metric outperforms DXA aBMD input.

3.3 WIAMan Male PMHS vBMD Data Collection

A total of n=122 WIAMan male PMHS CT scans were available and met inclusion criteria for analysis using OSU's standardized PB or PL vBMD methodology. These analyses were performed on any available anatomical sites and tissue types included in the normative population that did not contain any artifacts. In the instance where a WIAMan performer may have included an alternative phantom (rather than the INTable phantom) in the CT scan, the PL regression method was chosen for calculating vBMD. For any anatomical locations that did not have the INTable phantom present in the VOI slices, the PL regression method was also utilized. vBMD and z-scores with respect to the OSU population were calculated for all available anatomical sites.

Figures 17–20 demonstrate the distribution of the calculated vBMD z-scores for the WIAMan samples compared to the OSU normative population. For the lumbar spine (L2–L4 total vBMD) and both femoral neck total vBMD, the WIAMan sample demonstrated higher average z-score values than the OSU normative population. However, the distributions for the z-scores of the WIAMan sample and the normative population for the calcaneus total vBMD appear very similar. This indicates that with respect to the OSU male normative vBMD population, WIAMan samples appear to have on average better bone quality than the general population (n=200 PMHS) except in the calcaneus.

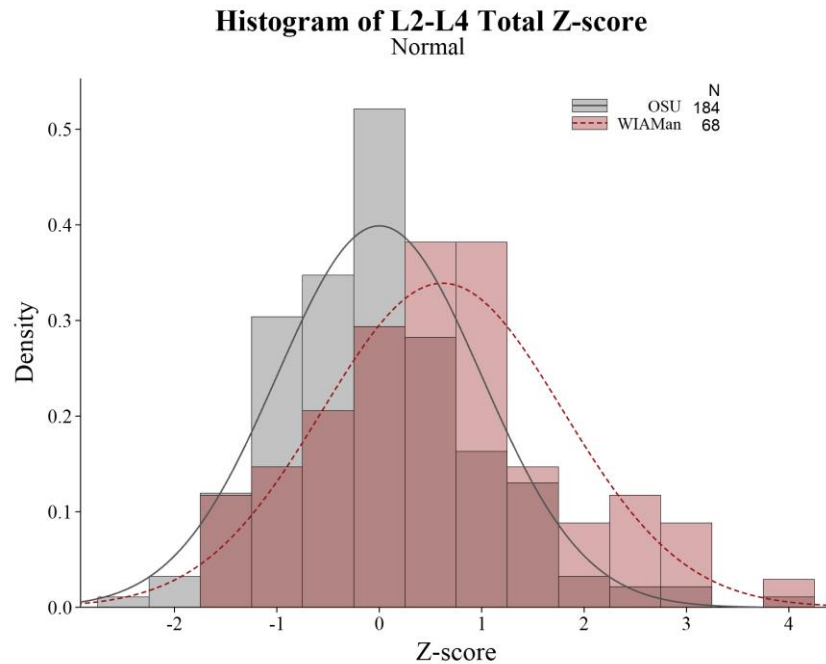


Figure 17. WIAMan vBMD z-score distribution (red) compared to OSU normative population z-score distribution (gray) for L2–L4 total vBMD values

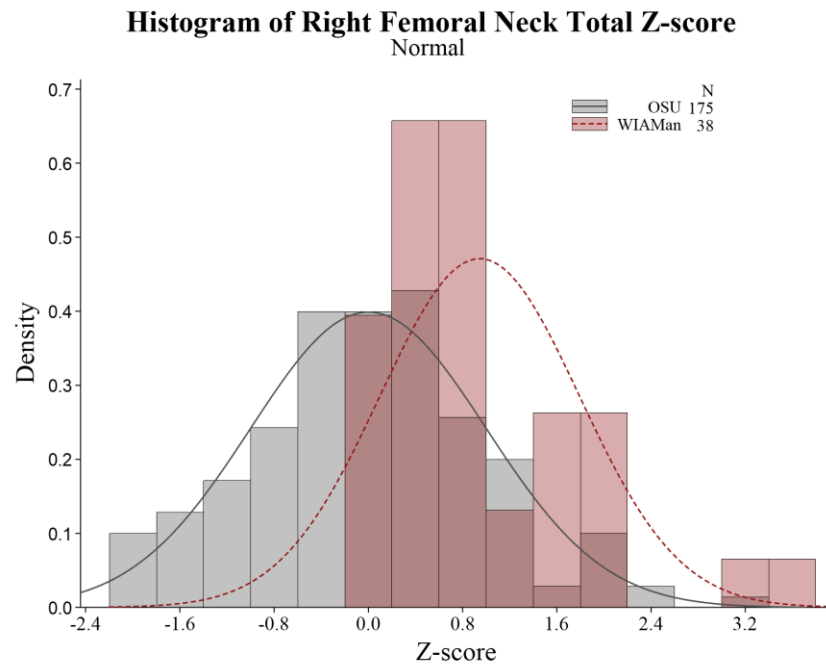


Figure 18. WIAMan vBMD z-score distribution (red) compared to OSU normative population z-score distribution (gray) for right femoral neck total values

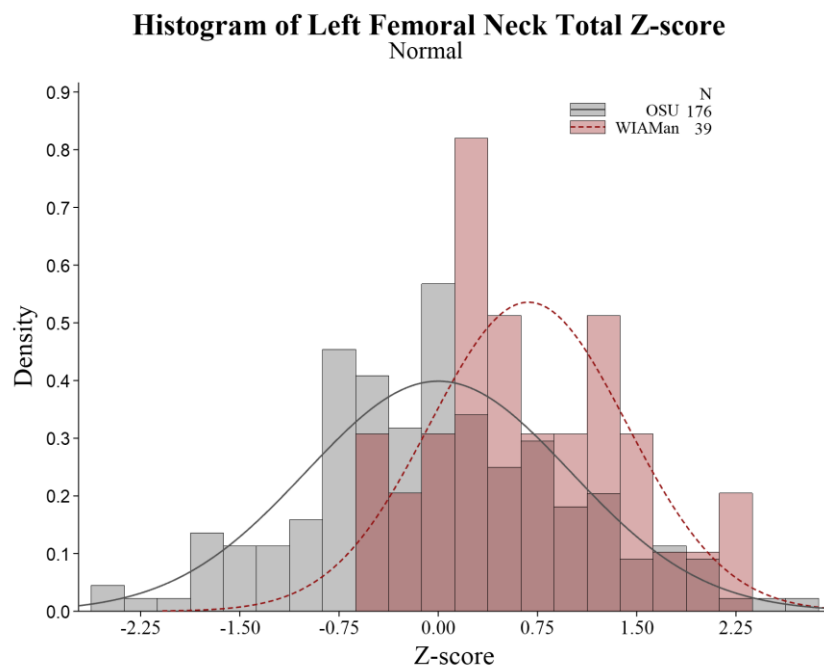


Figure 19. WIAMan vBMD z-score distribution (red) compared to OSU normative population z-score distribution (gray) for left femoral neck total values

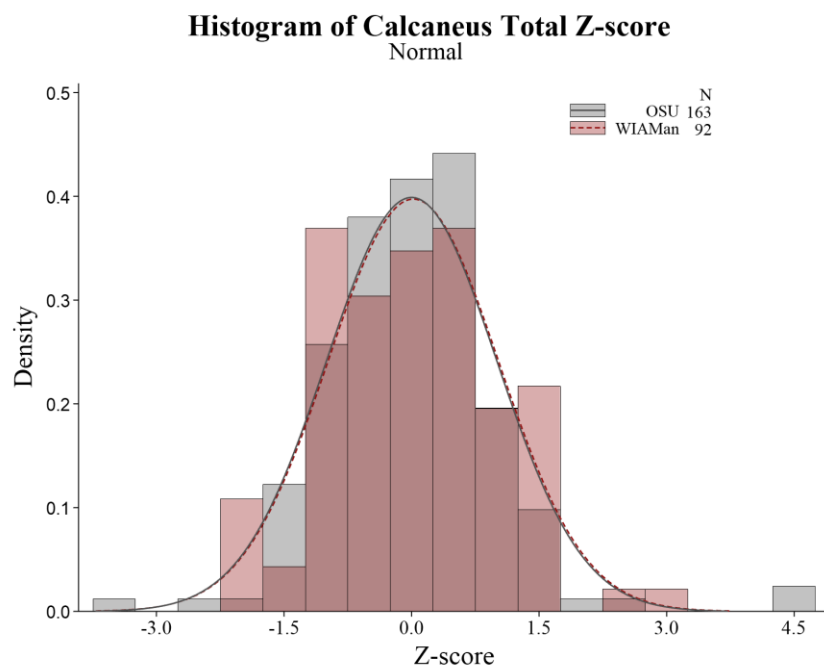


Figure 20. WIAMan vBMD z-score distribution (red) compared to OSU normative population z-score distribution (gray) for averaged calcaneus total values

4. CONCLUSIONS

This work extensively standardized the quantification of vBMD from CT scans using both a phantom-based and a fully validated phantomless methodology in a large sample of male PMHS. Identification of high levels of variability in mineralization across the skeleton suggest common practices employing global assessments of bone quality may be obscuring critical biological explanations for skeletal injury risk. Comparisons between DXA and QCT values of vBMD at identical anatomical sites indicate inherent differences between technologies in the biological aspects of bone represented in aBMD compared to vBMD. Preliminarily, this appears to create some discordance or mismatched determination of bone quality and vulnerability to injury when interpreting PMHS experimental data. However, the relevance of these findings will need to be determined through applications to injurious experimental data and will be performed by DEVCOM. The normative male PMHS vBMD population represents a large number of skeletal sites and can be used to contextualize WIAMan PMHS with respect to bone quality. Future work will include expansion and publication of the phantomless validation sample to ensure universal applicability of the regression equations. Additionally, the vBMD data collected here will be applied to the WIAMan program to inform scaling injury risk curves from experimental data to ultimately improve Soldier survivability through developing better injury mitigation tools.

5. REFERENCES

1. American College of Radiology. (2018). *ACR-SPR-SSR practice parameter for the performance of dual-energy X-ray absorptiometry (DXA)*. American College of Radiology. <https://www.acr.org/-/media/ACR/Files/Practice-Parameters/DXA.pdf>
2. Yu, J. S., Krishna, N. G., Fox, M. G., Blankenbaker, D. G., Frick, M. A., Jawetz, S. T. ... Beaman, F. D. (2022). ACR appropriateness criteria osteoporosis and bone mineral density: 2022 update. *Journal of the American College of Radiology*, 19(11, Supplement), S417–S432.
3. World Health Organization. (2004). *WHO scientific group on the assessment of osteoporosis at primary health care level: Summary meeting report, Brussels, Belgium, 5–7 May 2004*. World Health Organization. <https://www.dur-a-avaler.com/wp-content/uploads/2015/04/WHO-2004-Osteoporosis.pdf>
4. Haverfield, Z. A., Loftis, K. L., & Agnew, A. M. (2022). Skeletal site and method-dependent variability in bone mineral density in injury biomechanics research. *SAI International Journal of Transportation Safety*, 11(2), 177–185.
5. Sode, M., Burghardt, A. J., Kazakia, G. J., Link, T. M., & Majumdar, S. (2010). Regional variations of gender-specific and age-related differences in trabecular bone structure of the distal radius and tibia. *Bone*, 46(6), 1652–1660.
6. Haverfield, Z. A., Agnew, A. M., & Hunter, R. L. (2023). Differential cortical volumetric bone mineral density within the human rib. *Journal of Clinical Densitometry*, 26(2), 101358.
7. Chirvi, S., Pintar, F. A., Yoganandan, N., Stemper, B., & Kleinberger, M. (2020). Trabecular bone mineral density correlations using QCT: Central and peripheral human skeleton. *Journal of the Mechanical Behavior of Biomedical Materials*, 112, 104076.
8. American College of Radiology. (2022). *ACR–SPR-SSR practice parameter for the performance of quantitative computed tomography*. American College of Radiology. <https://www.acr.org/-/media/ACR/Files/Practice-Parameters/qct.pdf>
9. Engelke, K., Adams, J. E., Armbrecht, G., Augat, P., Bogado, C. E., Bouxsein, M. L. ... Lewiecki, E. M. (2008). Clinical use of quantitative computed tomography and peripheral quantitative computed tomography in the management of osteoporosis in adults: The 2007 ISCD official positions. *Journal of Clinical Densitometry*, 11(1):123–162.
10. Buikstra, J. E. & Ubelaker, D. H. (1994). *Standards for data collection from human skeletal remains: Proceedings of a seminar at the Field Museum of Natural History, organized by Jonathan Haas*. Arkansas Archeological Survey.

-
-
11. Haverfield, Z. A., Hunter, R. L., Loftis, K. L., & Agnew, A. M. (2022). Skeletal site and method-dependent variability of bone mineral density in injury biomechanics research. *2022 International Research Council on the Biomechanics of Injury conference proceedings*, 332–360.
<https://www.ircobi.org/wordpress/downloads/irc22/pdf-files/2249.pdf>
 12. Weaver, A. A., Beavers, K. M., Hightower, R. C., Lynch, S. K., Miller, A. N., & Stitzel, J. D. (2015). Lumbar bone mineral density phantomless computed tomography measurements and correlation with age and fracture incidence. *Traffic Injury Prevention*, 16(sup2), S153–S160.
 13. Weaver, A. A., Ronning, I. N., Armstrong, W., Miller, A. N., Kiani, B., Shayn Martin, R. ... Stitzel J. D. (2023). Computed tomography assessment of pelvic bone density: Associations with age and pelvic fracture in motor vehicle crashes. *Accident Analysis and Prevention*, 193, 107291.
 14. Eggermont, F., Verdonschot, N., van der Linden, Y., & Tanck, E. (2019). Calibration with or without phantom for fracture risk prediction in cancer patients with femoral bone metastases using CT-based finite element models. *PLoS One*, 14(7), e0220564.
 15. Weaver, A., Beavers, K., Caresse Hightower, R., Lynch, S., Miller, A., & Stitzel, J. (2015). Lumbar bone mineral density phantomless computed tomography measurements and correlation with age and fracture incidence. *Traffic Injury Prevention*, 16, S153–S160.
 16. Winsor, C., Li, X., Qasim, M., Henak, C. R., Pickhardt, P. J., Ploeg, H., & Viceconti, M. (2021). Evaluation of patient tissue selection methods for deriving equivalent density calibration for femoral bone quantitative CT analyses. *Bone*, 143, 115759.
 17. Hubbell, J. & Stephen, S. (2004). *Tables of X-ray mass attenuation coefficients and mass energy-absorption coefficients (version 1.4)*. National Institute of Standards and Technology. <http://physics.nist.gov/xaamdi>
 18. Hunter, R., Haverfield, Z., Kang, Y.-S., & Agnew, A. M. (2023). Potential consequences of contradictions in bone mineral density assessments in injury biomechanics. *2023 International Research Council on the Biomechanics of Injury conference proceedings*, 1031–1047.
 19. Kulkarni, A. G., Thonangi, Y., Pathan, S., Gunjotikar, S., Goparaju, P., Talwar, I. ... Kursija, G. (2022). Should Q-CT be the gold standard for detecting spinal osteoporosis? *Spine*, 47(6), E258–E264.
 20. Woodson, G. (2000). Dual X-ray absorptiometry t-score concordance and discordance between hip and spine measurement sites. *Journal of Clinical Densitometry*, 3(4), 319–324.
-
-

-
-
21. Faulkner, K. G., von Stetten, E., & Miller, P. (1999). Discordance in patient classification using t-scores. *Journal of Clinical Densitometry*, 2(3), 343–350.
 22. Gausden, E. B., Nwachukwu, B. U., Schreiber, J. J., Lorch, D. G., & Lane, J. M. (2017). Opportunistic use of CT imaging for osteoporosis screening and bone density assessment: A qualitative systematic review. *Journal of Bone and Joint Surgery*, 99(18), 1580–1590.
 23. Lin, W., He, C., Xie, F., Chen, T., Zheng, G., Yin, H. ... Wang, Z. (2023). Discordance in lumbar bone mineral density measurements by quantitative computed tomography and dual-energy X-ray absorptiometry in postmenopausal women: A prospective comparative study. *The Spine Journal*, 23(2), 295–304.

Appendix – Quantitative Computed Tomography Volumetric Bone Mineral Density Descriptive Statistics

Table A-1. QCT vBMD descriptive statistics per site used for calculation of vBMD z-scores of the normative population

vBMD (mg/cc) descriptive statistics				
Site	Average	SD	Minimum	Maximum
L2 total	298.313	40.337	205.751	467.390
L2 Tb	217.378	32.830	150.996	330.165
L3 total	308.197	36.481	219.896	420.151
L3 Tb	219.700	29.129	125.710	296.731
L4 total	321.109	37.533	224.161	470.982
L4 Tb	229.590	29.977	151.494	341.551
L Fem-50 Ct	1199.331	83.670	987.963	1548.787
R Fem-50 Ct	1200.470	81.208	993.298	1472.427
L fem-neck Tb	297.376	45.255	191.986	409.353
L fem-neck Ct Inf	992.906	77.241	704.859	1177.825
L fem-neck Ct Sup	826.052	78.107	611.629	1046.386
L fem-neck total	411.637	59.322	256.612	569.910
R fem-neck Tb	298.582	46.807	194.044	440.075
R fem-neck Ct Inf	984.594	86.211	761.787	1217.953
R fem-neck Ct Sup	816.772	89.073	537.211	1027.334
R fem-neck total	397.085	56.841	272.061	588.856
L Hum-50 Ct	1121.789	90.765	870.353	1422.925
R Hum-50 Ct	1118.865	92.324	862.353	1344.861
L Calc Tb	223.320	29.724	146.239	307.773
L Calc total	367.740	49.278	199.711	568.366
R Calc Tb	221.170	31.061	149.158	315.360
R Calc total	365.613	51.411	212.491	636.760
L Tib-4 Tb	247.583	39.968	151.591	373.012
L Tib-4 total	292.114	45.116	193.589	419.713
R Tib-4 Tb	245.480	41.132	130.351	430.923
R Tib-4 total	291.453	46.110	190.707	477.180
L Tib-38 Ct	1199.101	64.219	1006.405	1399.106
R Tib-38 Ct	1196.322	67.344	992.705	1414.035
L Tib-50 Ct	1189.397	68.201	972.771	1410.769
R Tib-50 Ct	1191.804	77.375	926.777	1472.699
L Tib-66 Ct	1142.479	75.123	889.752	1393.036
R Tib-66 Ct	1141.478	79.210	885.944	1410.342
L Rad-4 Tb	236.400	37.363	159.747	383.614
L Rad-4 total	297.160	45.385	199.637	448.079
R Rad-4 Tb	233.110	32.262	175.723	362.336
R Rad-4 total	300.546	40.611	215.420	405.442
L Rad-30 Ct	1087.888	84.260	808.981	1307.711
R Rad-30 Ct	1096.701	80.860	862.571	1282.186
L Rad-50 Ct	1094.230	89.990	819.876	1400.679
R Rad-50 Ct	1104.104	89.755	808.024	1407.098
L2-L4 total Comb	309.132	34.723	221.283	452.658
L2-L4 Tb Comb	222.633	27.835	155.580	297.862
Fem-neck total Comb	404.867	54.274	275.103	555.245
Fem-neck Tb Comb	297.928	43.094	193.015	423.229
Fem-neck Ct Sup Comb	820.913	73.918	606.022	1011.296

Table A-1. QCT vBMD descriptive statistics per site used for calculation of vBMD z-scores of the normative population

vBMD (mg/cc) descriptive statistics				
Site	Average	SD	Minimum	Maximum
Fem-neck Ct Inf Comb	988.816	74.901	733.323	1183.588
Calc total Comb	366.676	48.401	206.101	582.432
Calc Tb Comb	222.245	28.702	147.699	306.510
Hum-50 Ct Comb	1120.004	88.318	862.353	1351.970
Rad-4 Tb Comb	234.828	32.631	167.735	361.300
Rad-4 total Comb	298.726	41.242	199.637	411.973
Rad-30 Ct Comb	1092.807	76.658	851.817	1254.437
Rad-50 Ct Comb	1098.012	83.498	813.950	1332.111
Tib-4 Tb Comb	246.253	38.627	154.620	383.123
Tib-4 total Comb	291.680	43.716	194.666	419.479
Tib-38 Ct Comb	1197.184	62.682	999.555	1377.181
Tib-50 Ct Comb	1189.896	70.051	949.774	1419.319
Tib-66 Ct Comb	1141.011	73.716	887.848	1371.120
Fem-50 Ct Comb	1199.930	77.163	1001.546	1505.298

LIST OF ACRONYMS

2D/3D	two dimensional/three dimensional
aBMD	areal bone mineral density
ANOVA	analysis of variance
ARL	Army Research Laboratory
BMD	bone mineral density
BMI	body mass index
CT	computed tomography
Ct	cortical
CV	coefficient of variation
DAC	DEVCOM Analysis Center
DEVCOM	U.S. Army Combat Capabilities Development Command
DXA	dual X-ray absorptiometry
HU	Hounsfield units
Inf	inferior
NHANES	National Health and Nutrition Examination Survey
OSU	Ohio State University
PB	phantom-based
PL	phantomless
PMHS	postmortem human subjects
QCT	quantitative computed tomography
ROI	region of interest
SD	standard deviation
Sup	superior
Tb	trabecular
vBMD	volumetric bone mineral density
VOI	volume of interest
WIAMan	Warrior Injury Assessment Manikin